PROTOCOL

TITLE:	**AN OPEN LABEL, RANDOMIZED PHASE I/II TRIAL OF CARBOPLATIN PLUS ETOPOSIDE WITH OR WITHOUT ATEZOLIZUMAB IN UNTREATED EXTENSIVE STAGE SMALL CELL LUNG CANCER**
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Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
ATA	anti–therapeutic antibody
AUC	area under the concentration-time curve
BSA	body surface area
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CBC	complete blood count
CMP	complete metabolic panel
CNS	central nervous system
CR	complete responses
CRC	colorectal cancer
CRF	Case Reporting Form
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DSMB	Data Safety and Monitoring Board
EBNA	Epstein-Barr nuclear antigen
EC_{50}	50% effective concentrations
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IFN	interferon

Abbreviation	Definition
IHC	immunohistochemistry
irAE	immune-related adverse event
IRB	Institutional Review Board
irRC	immune-related response criteria
irSAE	immune-related serious adverse event
IV	intravenous
LFT	liver function test
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NSCLC	non–small cell lung cancer
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCI	prophylactic cranial irradiation
PD	progressive disease
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic
PR	partial response
PS	performance status
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	response rate
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
TBNK	T, B, and natural killer [cells]
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cells
WBRT	whole brain radiation therapy

1. INTRODUCTION

1.1 SMALL CELL LUNG CANCER

Lung cancer remains the most lethal cancer in the United States, responsible for nearly 160,000 deaths per year [1]. Small cell lung cancer (SCLC), which comprises approximately 13% of these cases, is a particularly lethal subtype characterized by rapid growth and dissemination [2]. Patients with early, limited-stage SCLC can be treated with chemoradiation with the potential for long-term survival [3]. However, the majority of patients with SCLC (~70%) will present with extensive-stage disease (ED-SCLC) where efforts are palliative in nature.

1.1.1 Current Management

The current standard treatment for patients with ED-SCLC is platinum-based chemotherapy [4]. The combination of cisplatin plus etoposide emerged as an efficacious regimen in the early 1980s. While this regimen is still employed today, carboplatin has demonstrated equal efficacy with a more favorable toxicity profile [5]. Multiple trials employing these platinum doublets (at various doses) have shown fairly consistent outcomes (Table 1). Overall response rates (ORR) are high, on the order of 60-70%, but the benefit from treatment is transient. Progression free survival (PFS) is approximately 6 months and median overall survival (OS) with standard treatment remains under a year.

	Platinum Dosing	Etoposide Dosing	RR	PFS (m)	OS (m)
Roth , 1992 [4]	Cisplatin 20 mg/m2 days 1-5	80 mg/m2 days 1-5	61%	4.3	8.6
Pujol, 2001 [6]	Cisplatin 100 mg/m2 day 2	100 mg/m2 days 1-3	61%	6.3	9.3
Noda, 2002 [7]	Cisplatin 80 mg/m2 day 1	100 mg/m2 days 1-3	68%	4.8	9.4
Eckardt, 2006 [8]	Cisplatin 80 mg/m2 day 1	100 mg/m2 days 1-3	69%	6.3	10.1
Hanna, 2006 [9]	Cisplatin 60 mg/m2 day 1	120 mg/m2 days 1-3	44%	4.6	10.2
Okamoto, 2007 [10]	Cisplatin 25 mg/m2 days 1-3	80 mg/m2 days 1-3	73%	4.7	9.9
Okamoto, 2007 [10]	Carboplatin AUC 5 day 1	80 mg/m2 days 1-3	73%	5.2	10.6
Socinski, 2009 [11]	Carboplatin AUC 5 day 1	100 mg/m2 days 1-3	52%	5.4	10.6
Rudin, 2008 [12]	Carboplatin AUC 5 day 1	80 mg/m2 days 1-3	60%	7.6	10.6
Nagel, 2011 [13]	Carboplatin AUC 6 day 1	120 mg/m2 days 1-3	67%	7.0	11.0
Schmittel, 2011 [14]	Carboplatin AUC 5 day 1	140 mg/m2 days 1-3	52%	6.0	9.0

Table 1. Representative results from randomized trials using platinum-based chemotherapy for SCLC.

There have been many unsuccessful efforts to improve the durability of response to chemotherapy in SCLC. While identification of actionable driver mutations has led to more effective treatment algorithms in non-small cell lung cancer (NSCLC), genomic analyses of SCLC have not revealed consistent actionable targets. Novel therapeutic strategies for SCLC remain an unmet need.

1.1.2 Evidence in Support of Targeting PD-1 and PD-L1

One of the more promising paradigms to emerge in the treatment of advanced cancer is the use of agents targeting programmed death-1 (PD-1) and its ligands (PD-L1, PD-L2). Encouraging clinical data emerging in the field of tumor immunotherapy have

demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced cancer [15].

PD-L1 is one of two ligands that binds PD-1, an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as chronic infection or cancer [16]. Ligation of PD-1 with PD-L1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion [17]. Therefore, interruption of the PD-1/PD-L1 pathway represents an attractive strategy to re-invigorate tumor-specific T-cell immunity. PD-L1 expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, and colon carcinoma), and elevated PD-L1 expression is often associated with a worse prognosis. Furthermore, in murine tumor models, interruption of the interaction between PD-1 and PD-L1 resulted in anti-tumor effects [18, 19].

Early clinical data demonstrated efficacy of PD-1 antibodies in the treatment of different epithelial carcinomas. Two of these agents have been approved for the treatment of advanced NSCLC. Nivolumab, an anti-PD-1 antibody, was compared to docetaxel in patients with pretreated, advanced squamous NSCLC [20]. Patients randomized to receive nivolumab experienced an improvement in median overall survival (9.2 vs. 6.0 months). A similar outcome was seen in non-squamous NSCLC [21], where nivolumab again improved survival as compared to docetaxel (12.2 vs. 9.4 months). Nivolumab has also been associated with durable tumor regression in patients with advanced melanoma and renal cell carcinoma [22]. Pembrolizumab is another anti-PD-1 antibody now approved for treatment in melanoma [23] and NSCLC. In patients whose tumors express PD-L1, the response rate of pemetrexed was over 45% [24]. MEDI4736, which targets PD-L1, has shown activity in various cancers, including NSCLC, melanoma, head and neck squamous cell carcinoma (SCC), gastroesophageal cancer, breast cancer and pancreatic cancer [25, 26].

This strategy also shows promise in SCLC. The CheckMate 032 study explored an immunotherapy strategy in SCLC [27]. This phase I/II trial explored the activity of nivolumab with or without ipilimumab in patients with refractory small cell lung cancer. In the 40 patients who received nivolumab 3mg/kg every 2 weeks, the disease control rate was 38% with an acceptable toxicity profile. In addition, there were many patients who achieved a durable response.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (MPDL3280A) is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected

concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor, PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans. Atezolizumab has been approved for locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy.

1.2.1 Summary of Nonclinical Experience

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

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

Refer to the atezolizumab (MPDL3280A) Investigator's Brochure for details on the nonclinical studies. A brief summary is provided below.

1.2.1.1 Nonclinical Pharmacology

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

In more detail, equilibrium binding analysis demonstrated that atezolizumab binds to human and murine PD-L1 expressed on transfected 293 cells with sub-nanomolar affinities ($K_d = 0.433$ nM and 0.134 nM, respectively). These high affinities were confirmed in flow cytometry experiments with use of human T cells and murine PD-L1–expressing 293 cells, showing 50% effective concentrations (EC_{50}) of 0.395 ± 0.030 nM and 0.519 ± 0.025 nM for human and mouse, respectively. A comparable affinity to PD-L1 was determined in cynomolgus monkey T cells ($EC_{50} = 0.704 \pm 0.084$ nM).

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

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

1.2.1.2 Nonclinical Pharmacokinetics

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

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

Human PK parameters were projected using the species invariant-time method [28], incorporating results from the single-dose PK study in cynomolgus monkeys (Study 08-0598). The estimated mean CL value in humans was 1.98 mL/day/kg (range, 1.92–2.09 mL/day/kg). The estimated mean elimination half-life in humans was 21.5 days (range, 20.3–23.1 days). These parameters were used in calculating safety factors to support the starting dose in humans.

The proposed starting dose of atezolizumab in humans was 0.01 mg/kg administered intravenously. This dose was adequately supported by the 8-week, nonclinical toxicology study in cynomolgus monkeys (Study 08-1148). With use of the no observed adverse effect level (NOAEL) of 5 mg/kg and a human CL value of 1.98 mL/day/kg, the exposure (area under the concentration-time curve [AUC])-based safety factor is 268-fold. The single-dose, body weight-normalized, dose-based safety factor at the proposed Phase I starting dose of 0.01 mg/kg is 500-fold, and the safety factor based on the body surface area (BSA)-normalized dose is approximately 160-fold. These safety factors were considered adequate to support the proposed Phase I starting dose of 0.01 mg/kg.

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

1.2.1.3 Nonclinical Toxicology

The toxicology program was designed to support IV administration of atezolizumab to patients up to every week for at least 2 months. The program included an 8-week,

repeat-dose study in cynomolgus monkeys, a 15-day exploratory study in mice, an *in vitro* hemolytic potential evaluation, and a tissue cross-reactivity analysis of human and cynomolgus monkey tissues.

Atezolizumab was well tolerated in cynomolgus monkeys following IV doses of up to 50 mg/kg for 8 weeks (total of nine doses). Minimal-to-mild arteritis/periarteritis was observed in 1 of 12 and 3 of 12 cynomolgus monkeys following administration of 15 and 50 mg/kg atezolizumab, respectively. These findings were not present on Day 141, indicating apparent resolution during the recovery period. Spontaneous, sporadic arteritis/periarteritis has been observed in cynomolgus monkeys, suggesting that the monkeys may be predisposed to this form of autoimmune disorder [29].

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

In human tissues, biotin- atezolizumab–specific staining was detected in the placenta, lymph node, tonsil, and thymus. In cynomolgus monkey tissues, biotin-atezolizumab–specific staining was detected only in the lymph node. This staining is consistent with the reported expression of PD-L1 on lymphoid and nonlymphoid tissues [30, 31].

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

1.2.1.4 Scientific Rationale

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with stage IV cancer [15, 32]. Therefore, immunomodulation represents a promising new strategy for cancer therapy resulting in improved anti-tumor activity.

PD-L1 expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, glioblastoma multiforme, malignant lymphoma, multiple myeloma, and colon carcinoma), and elevated PD-L1 expression is often associated with a worse prognosis in patients with several cancers including renal cell carcinoma (RCC), melanoma, colorectal cancer (CRC), lung cancer, ovarian cancer, and others. Furthermore, in mouse tumor models, interruption of the interaction between PD-1 and PD-L1 resulted in anti-tumor effects [18, 19]: single-agent activity of PD-L1 blockade in the syngeneic CRC model MC-38, expressing the foreign antigen ovalbumin, resulted in complete responses (CRs) in all animals tested in fewer than 2 weeks of treatment (unpublished Genentech data). Finally, reports from three Phase I clinical trials testing cancer therapies targeting the PD-L1/PD-1 pathway have demonstrated activity in late-stage, standard-of-

care–refractory patients with cancer. In a Phase I dose-escalation study of 207 patients treated with BMS-936559, an IgG4 anti–PD-L1 monoclonal antibody, Brahmer et al. [33] observed a response rate of approximately 17% in patients with melanoma, 12% in patients with RCC, 10% in patients with non–small cell lung cancer (NSCLC), and 6% in patients with ovarian cancer. A Phase I dose-escalation study of 296 patients treated with nivolumab, an IgG4 anti–PD-1 monoclonal antibody, reported a response rate of approximately 28% in patients with melanoma, 27% in patients with RCC, and 18% in patients with NSCLC [34]. In a Phase I study in which 17 patients were treated with CT-011, a humanized antibody interacting with PD-1, clinical benefit was observed in 33% of patients, with one CR (non-Hodgkin's lymphoma) and one major response (acute myelogenous leukemia) [35].

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

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

1.2.2 Clinical Experience with Atezolizumab

1.2.2.1 Ongoing Clinical Studies

Current studies of atezolizumab include an ongoing Phase Ia monotherapy study, three ongoing combination studies, and three Phase II studies in patients with solid tumors. Details of all ongoing studies may be found in the atezolizumab (MPDL3280A) Investigator's Brochure.

Phase Ia Study PCD4989g

Study PCD4989g is a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks to patients with locally advanced or metastatic solid malignancies or hematologic malignancies. Ongoing expansion cohorts are studying the efficacy in patients with pancreatic cancer, bladder cancer, breast cancer, esophageal cancer, prostate cancer, SCLC, malignant lymphoma, multiple myeloma, and other less common tumor types.

Phase Ib Study GP28328

Ongoing Phase Ib Study GP28328 is evaluating the safety and pharmacology of atezolizumab administered with bevacizumab alone (Arm A) or with bevacizumab plus leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX; Arm B) in patients with advanced solid tumors. Additional cohorts have been included to investigate atezolizumab in

combination with carboplatin plus paclitaxel, in combination with carboplatin plus pemetrexed, and in combination with carboplatin plus nab paclitaxel, pemetrexed, and cisplatin in patients with advanced or metastatic NSCLC.

Phase Ib Study GP28384

Ongoing Phase Ib Study GP28384 is evaluating the safety and pharmacology of atezolizumab administered in combination with vemurafenib in patients with previously untreated $BRAF^{V600}$–mutation positive metastatic melanoma.

Phase Ib Study GP28363

Ongoing Phase Ib Study GP28363 is evaluating the safety and pharmacology of atezolizumab administered in combination with cobimetinib (MEK inhibitor) in locally advanced or metastatic solid tumors.

Phase II Study GO28625 (FIR)

Ongoing, single-arm, Phase II Study GO28625 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. In particular, this study is evaluating whether archival or fresh tumor tissue is more predictive of response to atezolizumab. Safety and efficacy data are not yet available for this study.

Phase II Study GO28753 (POPLAR)

Study GO28753 is a randomized, open-label, Phase II study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28753 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is OS for both the PD-L1–positive population and the overall study population.

Phase II Study GO28754 (BIRCH)

Ongoing, single-arm, Phase II Study GO28754 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. Safety and efficacy data are not yet available for this study.

Phase III Study GO28915 (OAK)

Study GO28915 is a randomized, open-label, Phase III study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28915 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is OS for both the PD-L1–positive population and the overall study population.

Phase II Study WO29074

Ongoing Phase II Study WO29074 is evaluating the safety and efficacy of atezolizumab monotherapy or the combination of atezolizumab and bevacizumab versus sunitinib in

treatment-naïve patients with RCC. Safety and efficacy data are not yet available for this study.

1.2.2.2 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.

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 $\geq$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 $\geq$3 AEs were reported by 199 of 412 patients (48.3%). There were 51 patients (12.4%) who reported Grade $\geq$3 AEs that were assessed as related to study drug by the investigators. The most frequently reported related Grade $\geq$3 AEs included fatigue (5 patients [1.2%]), increased alanine aminotransferase and increased aspartate aminotransferase (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 adverse events 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 and influenza-like illness, which are considered potential adverse drug reactions associated with atezolizumab.

For further details, see the atezolizumab (MPDL3280A) Investigator's Brochure.

1.2.2.3 Clinical Activity

As of the data cutoff of 19 September 2013 (dosing cutoff 8 August 2013), efficacy data are available for 301 patients treated in Phase Ia Study PCD4989g. Patients with multiple tumor types were included in the study, with the largest cohorts consisting of patients with NSCLC, RCC, and melanoma. In the overall efficacy-evaluable population,

the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) was 19.3%. Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, breast cancer, colorectal cancer, head and neck cancer, gastric cancer, and sarcoma. The majority of responses have been durable, with 78% of responses still ongoing. Overall, a total of 58 responders were identified with a median duration of response of 73.9 weeks.

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

For further details, see the atezolizumab (MPDL3280A) Investigator's Brochure.

1.2.2.4 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03−20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state (Vss) had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected PK profile of an IgG1 antibody in humans. The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10, 15, and 20 mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

1.3 STUDY RATIONALE

Platinum-based chemotherapy such as carboplatin plus etoposide remains the current standard for advanced SCLC but the benefit from this therapy has reached a plateau (Table 1). While initial response rates are high, new strategies to maintain the response and prolong survival are needed. Tumor cell death after cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens. Invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-1/PD-L1 signaling may result in deeper and more durable responses compared to standard chemotherapy alone.

Early efforts incorporating checkpoint inhibition in SCLC have been promising. A randomized Phase II trial compared six cycles of standard chemotherapy (carboplatin and paclitaxel) with two different schedules of ipilimumab, a CTLA-4 inhibitor in 103 patients with SCLC. In the concurrent schedule, ipilimumab was given with cycle 1 to 4 of chemotherapy followed by two doses of placebo; in the phased schedule, placebo was given with the first two cycles of chemotherapy and ipilimumab was added with cycle 3 to 6. Eligible patients were given maintenance ipilimumab or placebo every 12 weeks until progression. The primary endpoint was immune relate progression free survival (irPFS). This trial noted an improvement in irPFS in patients treated with the phased ipilimumab schedule compared to chemotherapy alone (6.4 vs. 5.3 months, HR 0.64, P=0.03) with a non-significant trend towards improvement in RR (57% vs. 49%) and OS (12.9 vs. 9.9 months) [36]. The CheckMate 032 explored an immunotherapy strategy in SCLC [27]. This phase I/II trial explored the activity of nivolumab with or without ipilimumab in patients with refractory small cell lung cancer. In the 40 patients who received nivolumab 3mg/kg every 2 weeks, the disease control rate was 38% with an acceptable toxicity profile. In addition, there were many patients who achieved a durable response.

Combining standard chemotherapy with a PD-1/PD-L1 inhibitor holds great appeal in the treatment of SCLC. While this approach may be appropriate for many cancer types, SCLC may be particularly vulnerable to this treatment strategy. Early studies have suggested greater efficacy with agents targeting PD-1/PD-L1 in tumors that are more mutationally complex, such as those associated with tobacco use. SCLC has a strong association with tobacco use and indeed, genome-wide sequencing studies have consistently shown that SCLC carries one of the highest rates of non-synonymous mutations [37, 38]. In addition, atezolizumab has been safely combined with platinum based chemotherapy doublets in the treatment of NSCLC [39]. Thus, a combination of carboplatin, etoposide and atezolizumab may significantly improve outcomes in the treatment of SCLC.

2. OBJECTIVES

2.1 PRIMARY

PHASE I

To evaluate the safety and tolerability of atezolizumab administered with carboplatin and etoposide.

PHASE II

To evaluate the hazard ratio (HR) for PFS according to modified RECIST v1.1 in patients receiving first-line carboplatin, etoposide and atezolizumab for ED-SCLC compared with patients receiving carboplatin and etoposide alone.

2.2 SECONDARY

- **To evaluate PFS with carboplatin, etoposide and atezolizumab compared to chemotherapy alone according to RECIST v1.1**
- **To evaluate the complete response rate with carboplatin, etoposide and atezolizumab compared to chemotherapy alone according to RECIST v1.1**
- **To evaluate ORR with carboplatin, etoposide and atezolizumab compared to chemotherapy alone according to RECIST v1.1**
- **To evaluate the HR for OS in patients receiving first-line carboplatin, etoposide and atezolizumab for ED-SCLC compared with patients receiving carboplatin and etoposide alone**
- **To evaluate the safety and tolerability of atezolizumab when given with carboplatin plus etoposide**
- **To evaluate the 6 month and 12 month survival with carboplatin, etoposide and atezolizumab compare to chemotherapy alone**

2.3 EXPLORATORY

- **To evaluate the ORR and PFS with atezolizumab alone in patients with ED-SCLC who progress after initial therapy with carboplatin plus etoposide**
- **To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, PD-1 and others) as defined by IHC or quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) and efficacy**

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label study with two parts, a Phase I study and a randomized Phase II study. This study will be conducted at approximately ten sites in the United States. Approximately 178 patients will be enrolled in this trial.

3.1.1 Phase I

The Phase I portion will assess the safety and tolerability of atezolizumab with carboplatin and etoposide. The first dose-level will employ carboplatin plus etoposide at standard doses with the recommended Phase II dose of atezolizumab determined for single agent use. Standard 3+3 rules will apply. If there are 0-1 DLTs, the cohort will be expanded to 6 patients. If 0-1 out of 6 patients experience a DLT, this will be the dose used in the randomized Phase II portion. If 2 or more patients develop a DLT from the first cohort, the dose of atezolizumab will be reduced. If there are 0-1 DLTs in this second cohort, the cohort will be expanded to 6 patients. If 0-1 out of these 6 patients experiences a DLT, this will be the dose used in the randomized Phase II portion. If 2 or more patients in this cohort develop a DLT, the combination will be deemed intolerable without further modification to the protocol. Carboplatin plus etoposide will be given for 4 cycles and atezolizumab will be continued as long as patients are experiencing clinical benefit in the opinion of the investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression) after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

3.1.2 Phase II

The Phase II portion will assess the efficacy of carboplatin and etoposide with atezolizumab as compared to carboplatin and etoposide alone. The dose of carboplatin and etoposide given with atezolizumab will be established by the Phase I portion. Patients will be randomized in a 1:1 fashion to receive chemotherapy alone or with atezolizumab; there will be no placebo. Carboplatin plus etoposide will be given for 4 cycles either alone or with atezolizumab and then patients in the experimental arm will receive atezolizumab alone until progression. At the time of progression, patients in the standard arm may receive atezolizumab alone until progression provided certain eligibility criteria are met.

All patients will return to the clinic for an end of treatment visit within 30 days after the last dose of study treatment. All AEs will be recorded until 60 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, only ongoing serious AEs determined by the investigator to be treatment related will be recorded. Additionally, patients with unresolved AEs or abnormal laboratory values deemed to be related to study treatment may be contacted by telephone for follow up of these events. AEs will be graded according to NCI CTCAE v4.0. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until the patient dies, experiences disease progression, or initiates further systemic cancer therapy, whichever occurs first. Following completion and/or discontinuation of study treatment, all patients will be followed for survival.

3.2 RATIONALE FOR STUDY DESIGN

The starting dose of atezolizumab in this study will be 1200 mg administered once every 3 weeks (q3w). No DLTs have been encountered at this dose in ongoing studies. Simulations do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight [40].

Given that nonclinical and available Phase IA and IB data for atezolizumab have shown minimal overlap with the well defined safety profiles of cytotoxic chemotherapy agents including carboplatin, it is anticipated that a dose level at the single-agent MTD is an appropriate starting dose to evaluate the proposed treatment combination. Because standard therapy is effective, at least initially, carboplatin and etoposide will be administered at standard, published doses: carboplatin AUC 5 plus etoposide 100 mg/m^2 given intravenously on day 1 and days 1-3, respectively, q3w [11]. If this initial dose is not well tolerated, de-escalation of atezolizumab will commence.

The ethical conduct of a study of cancer therapy requires that a patient has the opportunity to continue study treatment for as long as such treatment is effective and tolerable. Therefore, patients who comply with the requirements of the protocol, are tolerating study treatment, and have not developed progressive disease per modified

(during Phase II) RECIST v1.1 criteria will be offered dosing beyond the DLT assessment window, as described in Section 3.3.

Based on prior combination studies, there is no expectation that atezolizumab will significantly alter the pharmacokinetics of carboplatin or etoposide.

Development of a predictive diagnostic assay that enables prospective identification of patients with SCLC who are likely to respond to treatment with atezolizumab in combination with carboplatin plus etoposide may allow for preselection of patients likely to benefit from treatment with these regimens in future clinical studies. Preliminary results suggest that tumor expression of PD-L1 correlates with response to anti-PD-1 therapy [41]. Archival paraffin-embedded tumor tissue will be used to assess PD-L1 expression by IHC and qPCR assays. In addition, other potential predictive and prognostic markers that are related to PD-L1 activity, tumor immune biology, and type of disease may be analyzed. Patients who cannot provide a specimen may still be eligible, upon discussion with the Principal Investigator. Analysis of these specimens may help determine which marker is more predictive of potential response to atezolizumab.

3.3 DOSE ESCALATION

3.3.1 Dose Escalation Rationale

There will be no dose adjustments of atezolizumab, which will be given at a dose of 1200 mg every 3 weeks, as dose reductions would not be expected to reduce toxicity.

Ongoing studies of atezolizumab with platinum-based chemotherapy in patients with NSCLC have demonstrated tolerability with no overlapping toxicities. Because chemotherapy is effective in patients with SCLC, and because we expect the combination to be well tolerated, treatment will start with standard chemotherapy dosing. If this combination is poorly tolerated, we will de-escalate the doses of chemotherapy. Asymptomatic neutropenia or grade 3 neutropenic fever are often encountered with standard chemotherapy and can be prevented with the use of myeloid growth factors. These specific toxicities should not limit the dose of this regimen. Thus, if the DLTs at dose level 1 are related to asymptomatic neutropenia that resolves or grade 3 neutropenic fever (with no other non-neutropenia related DLTs), patients will be enrolled to a cohort employing the same doses but mandating the use of G-CSF or pegylated G-CSF.

3.3.2 Phase I Dose Escalation Design

Atezolizumab is planned to be tested at a flat dose of 1200 mg. Carboplatin will be given at a dose of AUC 5 and etoposide will be given at a dose of 100 mg/m^2. Dose reduction of atezolizumab is not permitted. Dose de-escalation of carboplatin and etoposide, if necessary, will occur in accordance with the following rules:

- A minimum of 3 patients will be initially enrolled in the first cohort.
- If 0-1 of the first 3 patients enrolled in the first cohort experiences a DLT, 3 additional patients (for a total of 6 evaluable patients) may be enrolled in that cohort.
- If fewer than one-third of the evaluable patients in the first cohort experiences a DLT (i.e., DLT in 0-1 of the 6 patients), the Phase I portion will be complete and this dose level will be used for the Phase II portion.
- If a DLT is observed in one-third or more of the patients in the first cohort (i.e., 2 or more of the 6 patients), the MTD will have been exceeded and dose de-escalation will commence.
- For dose level -1 and -2, evaluation will proceed in the same fashion as above. If dose level -2 exceeds the MTD, alternate dosing or schedules may be evaluated after consultation with the Principal Investigator and creation of a study amendment.

Intra-patient dose escalation or re-escalation will not be allowed in this study. Patients will receive 4 cycles of chemotherapy plus atezolizumab followed by atezolizumab therapy until progression. In the event of intolerable toxicity, the investigator will have the option of discontinuing chemotherapy before cycle 4 and continuing treatment with atezolizumab alone, if the investigator feels the patient is deriving clinical benefit.

3.3.3 Dose Levels

Dose Schedule for Cohorts			
	Dose		
	Atezolizumab	**Carboplatin**	**Etoposide**
Level 1	1200 mg	AUC 5	100 mg/m^2
Level 1A[*]	1200 mg	AUC 5	100 mg/m^2
Level -1	1200 mg	AUC 5	80 mg/m^2
Level -2	1200 mg	AUC 4	80 mg/m^2

Table 2. *Dose schedules. Atezolizumab will be given on day 1, carboplatin will be given on day 1, etoposide will be given on days 1-3, and cycle length is 21 days.*

[*] *If there are 2 or more patients with DLTs in Level 1 and at least one of the patient's only DLTs were related to asymptomatic neutropenia or grade 3 neutropenic fever, patients will then be enrolled to dose level 1A, where dosing is the same as in Level 1 but the use of G-CSF or pegylated G-CSF is mandated. If other DLTs are responsible for de-escalation, patients will be enrolled to level -1. Use of myeloid growth factors will stop once carboplatin and etoposide are complete (i.e., no myeloid growth factors will be mandated with atezolizumab alone).*

3.3.4 Definition of Dose-Limiting Toxicity (DLT)

DLT is defined as one of the following toxicities occurring during the DLT assessment window (Days 1-21 of Cycle 1) that is at least possibly related to atezolizumab (see Section 6.6.2). Dose reductions or delays of carboplatin or etoposide will not, in themselves, constitute DLTs.

- Grade ≥ 4 neutropenia (ANC < 500/μL) lasting > 7 days
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 3 thrombocytopenia associated with acute hemorrhage
- Grade ≥ 4 thrombocytopenia lasting > 7 days
- Any Grade ≥ 3 non-hematologic or non-hepatic major organ adverse event, with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 1 within 7 days of implementing maximal supportive care
  - Grade 3 skin rash that resolves to Grade ≤ 2 within 7 days with appropriate supportive care
  - Grade 3 laboratory abnormality that is asymptomatic and also deemed by the investigator not to be clinically significant
- Grade ≥ 3 hepatic toxicity lasting for > 48 hours with the following exception: For patients with Grade 2 AST, ALT, and/or alkaline phosphatase abnormalities at baseline, only an increase to > 8x the upper limit of normal (ULN) lasting > 48 hours will be considered a DLT.
- Any toxicity leading to a delay in treatment for > 3 weeks

3.3.5 Patients Evaluable for Assessment of DLTs

For patients enrolled in the dose-finding stage (the Phase I portion), DLTs will be assessed during the DLT assessment window (Days 1-21 of Cycle 1). Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT will not be considered evaluable for DLTs and will be replaced.

3.4 PHASE II DOSING

Dosing for the Phase II portion will be determined by results from the Phase I dose escalation.

In the experimental arm, patients will receive 4 cycles of chemotherapy plus atezolizumab followed by atezolizumab therapy alone as long as patients are experiencing clinical benefit. In the event of intolerable toxicity, the investigator will have the option of discontinuing chemotherapy before cycle 4 and continuing treatment with atezolizumab alone, if the investigator feels the patient is deriving clinical benefit.

In the standard arm, patients will receive 4 cycles of chemotherapy alone and enter observation. At the time of progression, patients may receive atezolizumab, provided they continue to meet the eligibility criteria with respect to hematologic and end organ function, general exclusions, and exclusion criteria related to medications. Patients approved for treatment may receive atezolizumab as long as patients are experiencing clinical benefit. Patients must re-sign the main informed consent to acknowledge deferring standard treatment options that may exist in favor of initiating atezolizumab.

3.5 SURVIVAL FOLLOW UP

Following early discontinuation or completion of treatment, all patients will be followed for survival every 3 months via telephone calls, patient medical records, and/or clinical visits until death, loss to follow-up, or study termination by the Sponsor.

3.6 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., progression) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur within 12 months after the last patient is enrolled.

3.7 OUTCOME MEASURES

3.7.1 Primary Efficacy Outcome Measure (Phase II)

- Progression-free survival (PFS), defined as the time from the first study treatment to the first occurrence of progression using RECIST v1.1 or death, whichever occurs first

3.7.2 Secondary Efficacy Outcome Measures

- Overall survival (OS), defined as the time from the first study treatment to death
- Survival at 6 months and 12 months
- Objective response, defined as a complete or partial response using RECIST v1.1

3.7.3 Safety Outcome Measures

The safety and tolerability of atezolizumab administered in combination with carboplatin plus etoposide will be assessed using the following primary safety outcome measures:

- Incidence and nature of DLTs
- Incidence, nature, and severity of AEs and laboratory abnormalities graded per NCI CTCAE v4.0

Additional safety outcome measures will include the number of cycles and the dose intensity of each component of the treatment regimen, as well as changes in vital signs and clinical laboratory test results during and following atezolizumab administration in combination with carboplatin and etoposide.

3.7.4 Exploratory Measures

The following exploratory biomarker endpoints will be assessed when appropriate:

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

4. MATERIALS AND METHODS

4.1 STUDY POPULATION

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Ability and willingness to comply with the requirements of the study protocol
- Age ≥ 18 years.
- Histological or cytological diagnosis of ES-SCLC (Note: Extensive-stage disease is defined as disease beyond the ipsilateral hemithorax, mediastinum and ipsilateral supraclavicular area and including malignant pleural or pericardial effusion or hematogenous metastases)
    - Patients with mixed histology SCLC and NSCLC are permitted
- Representative tumor specimens in paraffin blocks (preferred) or at least 10 unstained slides, with an associated pathology report, requested at any time prior to study entry. Tissue from core needle, punch, or excisional biopsy sample collection is preferred but slides from fine-needle aspiration, brushing, and lavage samples are acceptable. Patients without available tissue may still be eligible if permitted by the study PI.
- 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 ≥ 1000 cells/μL
    - WBC counts $> 2500/\mu L$
    - Lymphocyte count $\geq 500/\mu L$
    - Platelet count $\geq$ 100,000/μL
    - Hemoglobin ≥ 9.0 g/dL (transfusion to meet this criterion is permitted)
    - Serum sodium $\geq$ 120 mmol/L
    - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

      Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.
    - AST and ALT $\leq 3.0 \times$ ULN with the following exception:

      Patients with liver involvement: AST and/or ALT $\leq 5 \times$ ULN
    - Alkaline phosphatase $\leq 2.5 \times$ ULN with the following exception:

      Patients with liver or bone involvement: alkaline phosphatase $\leq 5 \times$ ULN
    - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

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

- Measurable disease per RECIST v1.1 (see Appendix 6)
- Patients with asymptomatic CNS metastases are allowed
- 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 6 months after the last dose of atezolizumab
- ECOG performance status of 0 or 1 (see Appendix 8)
  - Patients with ECOG performance status of 2, secondary to the underlying disease, may be enrolled in the Phase II portion of the study
- INR and aPTT $\leq 1.5 \times$ ULN
  - This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low–molecular weight heparin or warfarin) should be on a stable dose.

4.1.2 Exclusion Criteria

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

- Inability to comply with study and follow-up procedures
- Limited stage SCLC appropriate for definitive treatment with chemoradiation
- Prior systemic anti-cancer therapy for small cell lung cancer
- Prior palliative radiation therapy < 2 weeks prior to administration of study treatment or prior whole brain radiation therapy (WBRT) < 4 weeks prior to study treatment
- Symptomatic brain metastases (patients with asymptomatic brain metastases may be eligible provided other criteria are met)
- Leptomeningeal disease or carcinomatous meningitis
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab (patients receiving bisphosphonate therapy or denosumab to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible, though patients receiving denosumab must be willing and eligible to receive bisphosphonates instead)
- Malignancies other than SCLC within 2 years prior to administration of study treatment with the exception of those with a negligible risk of metastases or death treated with expected curative outcome (such as adequately treated carcinoma *in situ* of the cervix or breast, basal or squamous cell skin cancer, or localized prostate cancer treated definitively)
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease
- Pregnancy, lactation, or breastfeeding

- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
  - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
  - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
  - Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition in the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologics, oral calcineurin inhibitors, high potency oral steroids)
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- 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 HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active, clinically serious infections of NCI CTCAE v4.0 Grade 2 or higher within 4 weeks prior to Cycle 1, Day 1
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina. Patient with known coronary artery disease, congestive heart failure not meeting the above criteria, or known left ventricular ejection fraction less than 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician

- 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
- History of stroke or transient ischemic attack (TIA) within 6 months prior to Cycle 1, Day 1
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study
  - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.
- Treatment with systemic immunostimulatory agents (including but not limited to IFN-α, IL-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Prior treatment with anti–PD-1, or anti–PD-L1 therapeutic antibody or pathway targeting agents
  - Patients who have received prior treatment with anti–CTLA-4 may be enrolled, provided the following requirements are met:
    - Minimum of 12 weeks from the first dose of anti–CTLA-4 and $>$ 6 weeks from the last dose
    - No history of severe immune-related adverse effects from anti–CTLA-4 (CTCAE Grade 3 and 4)
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1, Day 1
  - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation
- 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

4.2 STUDY TREATMENT

4.2.1 Method of Treatment Assignment

This is an open-label study with two parts, a Phase I study and a randomized Phase II study.

For the Phase I portion, patients will be assigned to dose levels in the order in which they were enrolled. Upon completion of all screening evaluations, the site eligibility packet reviewed by the study coordinator. Upon approval, a patient number, cohort, and dose will be assigned for patients in the Phase I portion.

For the Phase II portion, patients will be assigned to the standard arm (carboplatin plus etoposide) or the experimental arm (carboplatin, etoposide, plus atezolizumab) by stratified randomization via via Georgetown Lombardi Comprehensive Cancer Center Department of Biostatisics.

4.2.2 Study Drug: Atezolizumab

Once marketing authorization is received commercial atezolizumab will be used and will not be provided by Genentech for “on label” studies. For studies done before marketing authorization and/or "out of label", atezolizumab will be provided free of charge by Genentech but switched to commercial drug once marketing authorization is received. Genentech will replace any atezolizumab drug that is not reimbursed. For studies done “out of label,” atezolizumab will be provided free of charge by Genentech. (This may also apply to other chemotherapeutic agents if the trial is a combination therapy trial. The Sponsor Investigator should discuss with other corporate sponsors.) 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.

4.2.2.1 Formulation

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

For further details, see the atezolizumab (MPDL3280A) Investigator’s Brochure.

4.2.2.2 Dosage, Administration, and Storage

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion q3w (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 adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No steroid 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 infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event.
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or

life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix 9.

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

4.2.3 Carboplatin and Etoposide

4.2.3.1 Formulation and Storage

Please refer to the carboplatin (PARAPLATIN) and etoposide (ETOPOPHOS) Package Inserts for details on respective formulations and storage. Carboplatin and etoposide will be sourced commercially by individual study sites. Anti-emetic premedication with a 5HT3 antagonist (such as ondansetron) 30 minutes prior to administration of chemotherapy is recommended, though sites should follow their institutional standard of care. **The use of dexamethasone as a premedication is prohibited in Cycle 1.** Use in subsequent cycles is strongly discouraged but may be permitted after discussion with the Principal Investigator.

4.2.3.2 Etoposide Dosing

Etoposide will be dosed according to Table 1 for the Phase I portion and the dose for the Phase II portion will be determined by the Phase I study. Sites may follow their own institutional practice for determining the etoposide dose for obese patients and for dose adjustments in the event of patient weight changes.

4.2.3.3 Carboplatin Dosing

Carboplatin will be dosed according to Table 1 for the Phase I portion and the dose for the Phase II portion will be determined by the Phase I study. The Calvert formula will be used to calculate the dose. Creatinine clearance will be capped at 125 ml/min when calculating carboplatin doses using the Calvert formula.

4.2.4 Administration

The induction phase of the study will consist of four cycles of atezolizumab plus chemotherapy, with each cycle being 21 days in duration. On Day 1 of each cycle, all eligible patients will receive drug infusions in the following order:

Atezolizumab → carboplatin → etoposide

For Cycle 1, premedication administered for atezolizumab/placebo is not permitted. Patients should receive anti-emetics and IV hydration for platinum-based treatments according to the local standard of care and manufacturer's instruction. However,

because of the immunomodulatory effects of steroids, premedication with steroids is not permitted with cycle 1.

On Day 1 of scheduled infusions of atezolizumab, carboplatin and etoposide (Cycles 1−4), study treatment should be administered in the following manner:

1. Atezolizumab (omitted for patients in the Phase II portion randomized to chemotherapy alone) administered intravenously over 60 (± 15) minutes (for the first infusion, shortening to 30 [± 10] minutes for subsequent infusions) followed by

2. Carboplatin administered intravenously over 30−60 minutes to achieve an initial target area under the concentration−time curve (AUC) of 5 mg/mL/min (Calvert formula dosing), followed by

3. Etoposide (100 mg/m_2) administered intravenously over 60 minutes. On Days 2 and 3 of Cycles 1−4, etoposide (100 mg/m_2) will be administered intravenously over 60 minutes.

Chemotherapy may be administered in accordance with local standard of care in lieu of the suggested infusion times. If there is a significant difference between the protocol guidelines and institutional standard of care, contact the study PI.

4.3 CONCOMITANT AND EXCLUDED THERAPIES

4.3.1 Concomitant Therapy

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

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 9).

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 $\geq$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. Megestrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low–molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.1.2) should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

Prophylactic Cranial Irradiation (PCI)

PCI is permitted but not mandated for patients. For patients in the phase II portion who are randomized to the experimental arm, PCI can be administered within 8 weeks of completion of chemotherapy at a total dose of 25 - 30 Gy in 10 fractions. Atezolizumab will continue every 21 days as scheduled but will be held for PCI. PCI should not begin within 2 weeks of atezolizumab administration. Upon completion of PCI, atezolizumab will resume at least 14 days after the last day of radiation. Patients will discontinue study treatment if there is evidence of CNS metastasis.

4.3.2 Excluded Therapy

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

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 4.1.2 and Section 4.3.1 and except for PCI as outlined in Section 4.3.1)

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

  Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment after discussion with the PI.

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 with Cycle 1 except for patients enrolled on dose level 1A.

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.

4.4 GENERAL PLAN TO MANAGE SAFETY CONCERNS

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Section 4.1.1 and Section 4.1.2) and close monitoring (as indicated below and in Section 4.8.1). See Section 6.7 for complete details regarding safety reporting for this study.

Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial (see Section 4.1.2). Results from the nonclinical toxicology studies with atezolizumab as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors were taken into account.

Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Patients will be followed for safety for 90 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 for the list and timing of study assessments). All SAEs and protocol-defined events of special interest (see Section 6.5.3 and Section 6.7.2.11) will be reported in an expedited fashion (see Section 6.7). In addition, investigators will review and evaluate observed AEs on a regular basis.

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

4.4.1 Management of Specific Safety Concerns with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, 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, 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.

4.4.2 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded on the eCRF. The severity of AEs will be graded according to the NCI CTCAE v4.0 grading system.

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab, carboplatin or etoposide) and the dose of that component is delayed or modified in accordance with the guidelines

below, other components may be administered if there is no contraindication. If chemotherapy is being delayed, atezolizumab should be delayed to allow concurrent administration for patients in the experimental arm.

- When treatment is temporarily interrupted because of toxicity caused by atezolizumab, carboplatin and/or etoposide, the treatment cycles will be restarted such that the atezolizumab and carboplatin plus etoposide infusions remain synchronized.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.
- In the event of intolerable toxicity, the investigator will have the option of discontinuing chemotherapy before cycle 4 and continuing treatment with atezolizumab alone, if the investigator feels the patient is deriving clinical benefit.

The treating physician may use discretion in modifying or accelerating the dose modification guidelines described below, depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

Modification of the atezolizumab dose will not be permitted. 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, then the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in Section 6.6.1.

Atezolizumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.5.

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.

If a patient must be tapered off steroids used to treat adverse events, 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 $\leq$ 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 investigator.

Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented later in this section as they have been observed in this study and are potentially immune related. See Section 4.3.1 for guidelines for the management of infusion-related reactions (see Appendix 9 for precautions for anaphylaxis).

4.4.2.1 Dose Modifications of Carboplatin and Etoposide

Dose modifications of carboplatin and etoposide are allowed as described below. Patients should not begin a new cycle of treatment unless the ANC is $\geq$ 1000 cells/mm^3 and the platelet count is $\geq$ 100,000 cells/mm^3. Patients who permanently discontinue combination carboplatin/etoposide chemotherapy for toxicity may still be considered for maintenance atezolizumab, depending on the nature of the toxicity and after discussion with the Principal Investigator.

Hematologic Toxicity

Table 2 summarizes dose modifications for carboplatin and etoposide based on ANC and platelets.

Table 3. Carboplatin and Etoposide Dosing Based on Hematologic Toxicity

	Etoposide dose (mg/m^2/day)	**Carboplatin dose (AUC)**
Febrile neutropenia	75% of previous dose	Decrease previous AUC by 1.5
ANC < 1.0	Hold chemotherapy until ANC ≥ 1.5 then resume at 75% of previous dose if recurs then reduce to 50% of initial dose	Hold chemotherapy until ANC ≥ 1.5 and then decrease previous AUC by 1.5
Nadir platelets < 50,000/mm^3 without bleeding	Hold until platelets > 100,000/ m^3 then reduce to 75% of previous dose	Hold until platelets > 100,000/ m^3 then decrease previous AUC by 1.5
Nadir platelets < 50,000/mm^3 with bleeding	Hold until platelets > 100,000/ m^3 then reduce to 50% of previous dose	Hold until platelets > 100,000/ m^3 then decrease previous AUC by 1.5

** Patients experiencing neutropenia-related toxicities as defined above will receive myeloid growth factor (G-CSF or pegylated G-CSF) on day 4 or 5 of the subsequent cycle and maintain the original doses. If any neutropenia-related toxicities recur with subsequent cycles, the dose reductions listed above will be employed. Use of myeloid growth factors will stop once carboplatin and etoposide are complete (i.e., no myeloid growth factors will be mandated with atezolizumab alone). If patients are receiving treatment on dose level 1A, which mandates G-CSF use, dose reductions above should be immediately employed.*

Dose reductions for neutropenia and/or thrombocytopenia are permanent. Patients who require a third dose reduction will permanently discontinue combination (carboplatin and etoposide) chemotherapy. Combination chemotherapy should also be discontinued if ANC and platelets do not recover to $\geq$ 1000/μL and $\geq$ 100,000/mm^3, respectively, after treatment is delayed by 3 weeks. For the Phase II portion, patients experiencing neutropenia-related toxicities as defined above will receive myeloid growth factor (G-CSF or pegylated G-CSF) on day 4 or 5 of the subsequent cycle. If any neutropenia-related toxicities recur with subsequent cycles, the dose reductions listed above will be employed. Use of myeloid growth factors will stop once carboplatin and etoposide are complete (i.e., no myeloid growth factors will be used with atezolizumab alone).

In cases of anemia, no dose reductions are required. The investigator may use supportive transfusions, other measures or dose delays as deemed appropriate.

Non-Hematologic Toxicity

If patients develop non-hematologic toxicities Grade ≥ 3, treatment should be withheld until resolution to Grade ≤ 2. Exclusions include alopecia and nausea and/or emesis controlled on adequate anti-emetic therapy.

Table 4. Carboplatin and Etoposide Dosing Based on Non-Hematologic Toxicity

NCIC-CTCAE v4.0	Chemotherapy
Grade ≤ 2	No dose adjustment required
Grade 3	Delay until grade < 2 then reduce by 1 dose level
Grade 4	Delay until grade < 2 then reduce by 1 dose level, consider permanent discontinuation of chemotherapy

Dose reductions for Grade 3 or 4 non-hematologic toxicities are permanent. Patients who require a third dose reduction will permanently discontinue combination (carboplatin and etoposide) chemotherapy.

4.4.2.2 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. If possible, one or two biopsy specimens should be snap frozen and stored.

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 provides a summary of dose modification guidelines for gastrointestinal toxicities.

Table 5. 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 ≤ 10mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening immune-related diarrhea or colitis.

TNF = tumor necrosis factor.

4.4.2.3 Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of atezolizumab.

While on this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and 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 for the 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 .

Table 6. 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 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 ≤ 10mg oral prednisone equivalent per day Permanently discontinue atezolizumab for life-threatening immune-related hepatic events.
	AST/ALT ≥ 3 × ULN with bilirubin > 2 × ULN	Hold atezolizumab. Consult 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.

4.4.2.4 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 .

Table 7. 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 higher potency topical steroids if rash unresolved
	Grade 3: Severe $>$30% BSA	Hold atezolizumab. 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 $\leq$10mg oral prednisone equivalent per day Permanently discontinue atezolizumab for life-threatening immune-related dermatologic toxicity.

BSA = body surface area; PRN = as needed.

4.4.2.5 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 .

Table 8. Dose Modification Guidelines for Endocrine Toxicity

Toxicity	Description	Management
Hypothyroidism	TSH elevated, asymptomatic	Continue atezolizumab. Start thyroid replacement hormone. Monitor TSH weekly
	TSH elevated, symptomatic	Hold atezolizumab. Consider referral to an endocrinologist. Restart atezolizumab when symptoms are controlled by thyroid replacement and TSH levels are decreasing

TSH = thyroid-stimulating hormone.

4.4.2.6 Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumaband 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, or pulmonary hypertension and the following should be performed:

- 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 (see Section 4.8.1).

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

Table 9. 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 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.

4.4.2.7 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 preexisting 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.

4.4.2.8 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.

4.4.2.9 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 .

Table 10. Dose Modification Guidelines for Ocular / 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

4.5 PATIENT DISCONTINUATION

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study
- Investigator determines it is in the best interest of the patient
- Patient non-compliance, defined as repeated non-compliance with study protocol

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 CRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

See Section 4.8.1 and Section 4.8.2 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

4.6 STUDY TREATMENT DISCONTINUATION

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

- Pregnancy
- Unmanageable toxicity due to atezolizumab
- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab, including development of an irAE determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anti-cancer therapy (except for PCI)
- Delay of atezolizumabdosing by > 84 days

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

4.7 STUDY AND SITE DISCONTINUATION

The Sponsor Investigator or 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:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor Investigator will notify Genentech if the Sponsor Investigator decides to discontinue the study, and vice versa.

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

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

4.8 CLINICAL AND LABORATORY EVALUATIONS

4.8.1 Study Assessments

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

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

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

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

4.8.1.1 Medical History and Demographic Data

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

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

4.8.1.2 Vital Signs

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

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

4.8.1.3 Physical Examination

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

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

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

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

4.8.1.4 Tumor and Response Evaluation

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis (when appropriate). If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

For subsequent tumor assessments, procedures for tumor assessment should be performed as clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans) when possible. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response will be assessed by the investigator using RECIST v1.1 and modified RECIST criteria (see Appendices 6 and 7). The same evaluator should perform assessments if possible to ensure internal consistency across visits. At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected.

Scans will be performed every two cycles during the administration of chemotherapy and for the first 4 cycles (12 weeks) of maintenance atezolizumab for patients in the experimental arm, and every 6 weeks for patients in the standard arm and for the first 4 cycles (12 weeks) of observation. Thereafter scans will be performed ever 9 weeks until disease progression or study discontinuation.

4.8.1.5 Laboratory Assessments

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (aPTT and INR)
- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (TSH, free T3, and free T4)
- EBV serology (EBNA IgG)
- HBV serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen)
  - HBV DNA test is required for patients who have positive serology for anti-HBc
- HCV serology (anti-HCV)
  - HCV RNA test is required for patients who have positive serology for anti-HCV
- Auto-antibody testing
  - Anti-nuclear antibody
  - Anti–double-stranded DNA
  - Circulating anti-neutrophil cytoplasmic antibody
  - Perinuclear anti-neutrophil cytoplasmic antibody
- Archival tumor tissue sample

  Representative tumor specimens in paraffin blocks (preferred) or at least 10 unstained slides, with an associated pathology report, are requested but not mandatory for enrollment of patients on study. In addition, exploratory biomarkers (including but not limited to markers related to immune or SCLC biology) may be evaluated. Tumor tissue should be of good quality based on total and viable tumor content. Instructions on tissue shipping will be provided at conclusion of the study.

4.8.1.6 Cardiac Function Tests

Electrocardiograms

Twelve-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

Echocardiograms

Echocardiograms will be obtained in patients with a known history of pericardial effusions during screening, Day 1 of Cycle 2, as clinically indicated or per standard of care thereafter during treatment, and at the treatment discontinuation visit.

4.8.2 Treatment Discontinuation Visit

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

4.8.3 Follow-Up Assessments

All visits must occur within -2 or +7 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

Please see the study flowchart provided in Appendix 1 for the schedule of treatment period assessments.

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

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 2 days, the patient can resume the original schedule.

After concurrent chemotherapy with atezolizumab for patients in the experimental arm, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

4.8.4 Post-Treatment Evaluations

Patients who discontinue early from treatment or who complete the initial study treatment in full will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease prompting patient discontinuation may be used as the treatment discontinuation visit.

Please see the study flowcharts provided (see Appendix 1) for assessments to be performed at the treatment discontinuation visit.

Female patients of reproductive potential must practice adequate birth control for a minimum of 12 months post-treatment. Male patients who are not surgically sterile must practice adequate birth control for a minimum of three months post-treatment.

5. STATISTICAL CONSIDERATIONS

The primary objective of the Phase I portion of this study is to establish the safety and tolerability of atezolizumab administered with carboplatin and etoposide. The primary objective of the Phase II portion of the trial is to evaluate the PFS according to RECIST v1.1 in patients receiving first-line carboplatin, etoposide and atezolizumab for ED-SCLC compared with patients receiving carboplatin and etoposide alone. The final study analysis will be based on patient data collected through study discontinuation. Analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment. In general, data will be summarized as warranted, and listings will be provided in place of tables when sample sizes are small. All summaries will be presented by the assigned dose regimen and, where applicable, treatment arm. Kaplan-Meier estimates will be used to describe the PFS and OS distribution and logrank statistic will be used to compare the PFS and OS of patients receiving atezolizumab with carboplatin and etoposide and those receiving carboplatin and etoposide alone. The response rate and its confidence interval will be calculated using exact binomial calculation given the small sample size. The analysis of biomarkers will also be descriptive given the limited sample sizes.

Analysis of the Conduct of the Study

Enrollment and major protocol violations, study treatment administration, and reasons for patient discontinuations from the study will be described and listed or summarized. Demographic and baseline characteristics, such as age, sex, race/ethnicity, weight, and baseline ECOG performance status, will be summarized.

5.1 SAFETY ANALYSES: ADVERSE EVENTS, LABORATORY TESTS, ECGS, AND VITAL SIGNS

Safety will be assessed through summaries of DLTs, AEs, changes in laboratory test results, changes in vital signs and ECGs, and exposure to components of study treatment. All patients who receive any amount of study treatment will be included in the analyses. Verbatim descriptions of AEs will be mapped to thesaurus terms. AE data will be listed by study site, dose cohort, treatment arm, patient number, and study day. Events occurring on or after treatment on Cycle 1 Day 1 will be summarized by thesaurus term, appropriate thesaurus level, and NCI CTCAE v4.0 grade. Serious AEs, including deaths, will be listed separately and summarized.

AEs leading to treatment discontinuation will be listed. AEs meeting the criteria for DLT will be listed. Patients who withdraw from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered unevaluable for DLT assessments.

Relevant laboratory and vital signs (heart rate, blood pressure, and temperature) and ECG data will be displayed by time, with NCI CTCAE v4.0 Grade 3 and 4 values identified where appropriate. Additionally, all laboratory data will be summarized by grade using NCI CTCAE v4.0.

5.2 ANTI-TUMOR ACTIVITY ANALYSES

The analyses described below will be based on definitions of responses according to RECIST v1.1. Response assessment data, duration of objective response (for responders), and PFS will be listed for all patients with measurable disease by dose level (in the Phase I portion) and study arm (in the Phase II portion).

Objective response is defined as a complete or partial response, as determined by investigator assessment using RECIST v1.1 and confirmed by repeat assessments $\geq$ 4 weeks after initial documentation. Patients with missing or no response assessments will be classified as non-responders. PFS will be defined as the time from study treatment initiation (Cycle 1 Day 1) to the first occurrence of documented disease progression or death from any cause during the study, whichever occurs first. For patients who do not have documented progressive disease or death during the study, PFS will be censored at the day of the last tumor assessment. OS is defined as the time from the first dose of study treatment to the time of death from any cause on study.

5.3 DETERMINATION OF SAMPLE SIZE FOR PHASE I

The sample size for the Phase I portion will be determined by the dose-escalation rules described above. Any patient who does not complete the DLT assessment window for any reason other than a DLT will be considered non-evaluable for dose-escalation

decisions and MTD assessment and will be replaced by an additional patient at that same dose level. It will require a minimum of 6 and a maximum of 24 evaluable patients.

Table 9 describes the probability of not observing any DLTs in 3 patients, and the probability of observing fewer than two DLTs in 6 patients for different underlying DLT rates.

Table 11. Probability of Observing DLTs for Different Underlying DLT Rates

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

For a given DLT with a true rate of 10%, 5%, or 1%, the probability of observing at least one such AE in a given cohort of 6 patients is 47%, 26.5%, and 5.8%, respectively.

5.4 DETERMINATION OF SAMPLE SIZE AND DATA ANALYSIS FOR PHASE II

The primary endpoint of the Phase II portion is progression free survival (PFS). The sample size estimation is completed using the log-rank test with the stochastic curtailment/conditional power adjusted type II error for one futility analysis. With the proposed sample size of 160 (80 patients per arm), it provides 80% power to detect a 2.7 months improvement of the PFS for the test arm, i.e. 8 months for carboplatin, etoposide and atezolizumab vs. 5.3 months for carboplatin and etoposide alone, with one-sided type I error = 5%. The total number of required events is 154. The assumptions of this power analysis are the accrual time is approximately 36 months and an additional follow-up time is about 18 months.

Interim analysis: The interim analysis will be based on the stochastic curtailment method. One interim analysis for futility will be performed at 77 events by calculation of conditional power, an estimate of the probability that the study shows a statistically significant effect on the primary endpoint given the results to date and assumptions regarding outcome through the end of the study. A recommendation to stop the trial for futility will require a conditional power below 10%, under the observed efficacy trend at the time of interim analysis, at the one-sided type I error less than 5%.

Data analysis plan for the primary endpoint: Demographic information such as age and race will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percents and frequencies for

categorical parameters, will be presented. Adverse medical events will be tabulated. NCI toxicity Grade 3 and Grade 4 laboratory abnormalities will be listed.

For the univariate analysis, i.e., the primary analysis of comparing the progression free survival between two arms, the two study groups will be compared for survival with Kaplan-Meier estimates and log-rank tests (two-sided) upon observing the full 154 events. When the test is used for claiming efficacy, the more stringent two-sided significance level of 5% will be used, namely, one-sided at 2.5%. For the multivariable data analysis, the proportional hazard model will be used for adjusted tests of significance and estimates of hazard ratios. The strategy to be used for developing multivariable models involves the following steps: apply multiple imputation for missing covariate values to make good use of partial information; choose an appropriate statistical model based on the nature of the response variable; decide on the allowable complexity of the model (i.e., the number of covariates) based on the effective sample size available; allow for nonlinear predictor effects using regression splines; incorporate pre-specified interactions; check distributional assumptions; adjust the variance-covariance matrix for multiple imputation; graphically interpret the model using partial effect plots; quantify the clinical utility (discrimination ability) of the model; internally validate the calibration and discrimination of the model using the bootstrap approach, i.e., .632+ bootstrap, to estimate the model's likely performance on a new set of subjects.

There are four secondary objectives of this trial.

1. To evaluate the response rate (RR) with carboplatin, etoposide and atezolizumab compared to chemotherapy alone according to RECIST v1.1,
2. To evaluate the hazard ratio (HR) for overall survival (OS) in patients receiving first-line carboplatin, etoposide and atezolizumab for ED-SCLC compared with patients receiving carboplatin and etoposide alone,
3. To evaluate the 6-month and 12-month survival in patients receiving carboplatin, etoposide and atezolizumab compared to chemotherapy alone,
4. To evaluate the safety and tolerability of atezolizumab when given with carboplatin plus etoposide.

Data analysis plan for the secondary endpoints: The Fisher's exact test will be applied to study the association between two treatment arms and the response rate. The exact two-sided 95% confidence intervals (CIs) of the RR rate will be reported for each treatment arm. For lifetime data analyses, e.g., overall survival, the possible risk factors will be compared for survival with Kaplan-Meier estimates and log-rank tests. The proportional hazard model will be used for adjusted tests of significance and estimates of hazard ratio. The 95% CIs for the 6-month and 12-month survival rate will be reported. The Fisher's exact test as well as the Wilcoxon rank sum test will be applied to examine the correlation between the treatment arms and the toxicities outcomes.

The standard reported OS is 10.9 months in the control arm (Spigel, JCO 2011). There is 80% statistical power to show a median survival difference of 6 months or hazard ratio of 0.645. See Table below.

Table1. Statistical determination of overall survival (OS)

Sample size	Alpha (one-sided)	Power	HR	median OS in control group (months)	median OS in treatment group (months)	Improvement of OS (months)	Expected Events in control group	Expected Events in treatment group
160	0.05	70%	0.684	10.9	15.93	5.03	70	62
160	0.05	80%	0.645	10.9	16.89	5.99	70	60
160	0.05	90%	0.594	10.9	18.35	7.45	70	58

The statistical analyses will be completed by either R 3.1.1 or SAS 9.4 statistical program in this project.

5.5 DATA QUALITY ASSURANCE

The data will be collected via EDC through use of eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this trial, including quality checking of the data.

6. ASSESSMENT OF SAFETY

This is an open-label study with two parts, a Phase I study and a randomized Phase II study. This study is the first trial in which atezolizumab will be administered to humans in combination with carboplatin plus etoposide. Nonclinical and Phase IA data for atezolizumab suggest that there is minimal overlap of the atezolizumab safety profile with the well-defined safety profiles of carboplatin plus etoposide. Specific potential safety issues anticipated in this trial, as well as measures intended to avoid, minimize, and manage such toxicities, are detailed in the protocol. Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to atezolizumab, all events of death, and any study specific issue of concern.

The definitions of DLT have been designed to keep the degree and frequency of severe toxicity observed in this study within acceptable limits for Phase I trials in oncology. As with any Phase I clinical trial, unpredicted safety issues may arise during the course of study. Eligibility criteria for this trial have been established to ensure the safety of participating patients. A number of exclusion criteria are specifically based on the well-

established safety profiles of carboplatin plus etoposide as well as nonclinical and clinical data for atezolizumab.

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs and laboratory abnormalities, defined and graded according to NCI CTCAE v4.0. General safety assessments will include interval histories, physical examinations, and specific laboratory studies, including serum chemistry and blood counts. Grade 3 or 4 AEs during the DLT assessment window and all SAEs will be reported in an expedited fashion to the Principal Investigator and to Drug Safety for entry into the safety database. In addition, the Sponsor and the investigators will review and evaluate observed AEs on a regular basis.

The PD-1/PD-L1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. 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. Suggested workup procedures for suspected irAEs are included in the protocol.

All patients will return to the clinic for an end of treatment visit within 30 days after the last dose of study treatment. All AEs will be recorded until 60 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, only ongoing SAEs determined by the investigator to be treatment related will be recorded. Additionally, patients with unresolved AEs or abnormal laboratory values deemed to be related to study treatment may be contacted by telephone for follow up of these events.

6.1 RISKS ASSOCIATED WITH ATEZOLIZUMAB

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. Whereas the MTD was not reached in a Phase I clinical study of an anti–PD-1 monoclonal antibody (nivolumab) in patients with cancer, evidence of autoimmune conditions including pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis were reported [34]. Another Phase I clinical study of an anti–PD-L1 monoclonal antibody (BMS-936559) reported drug-related AEs with potential immune-related causes including rash, hypothyroidism, hepatitis, adrenal insufficiency, sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis [33]. As of 10 May 2014, AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, and pneumonitis, have been observed. A more comprehensive list of observed AEs is provided in Section 1.2.2.

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 [42]. Suggested workup procedures for suspected irAEs are provided in Section 4.4.

Cynomolgus monkeys receiving weekly IV or subcutaneous doses of atezolizumab at 15 or 50 mg/kg in a repeat-dose toxicity study had histologic evidence of arteritis/periarteritis in medium-sized arteries. This finding is consistent with a known spontaneous condition in this species and may reflect an underlying predisposition to this autoimmune condition. Anti–PD-L1 therapy appears to have increased the incidence of this finding, which is compatible with the blocking of PD-L1 and the deregulation of peripheral tolerance. Of note, there were no apparent clinical sequelae of the arteritis in any of the animals. In addition, no toxicities were observed in cynomolgus monkeys that were given weekly IV doses of atezolizumab at 5 mg/kg (total nine doses). In an exploratory toxicology study in mice, findings attributed to atezolizumab were limited to minimal neuropathy of the sciatic nerve in C57Bl/6 mice at both doses tested (10 and 50 mg/kg). This observation is consistent with the observation that female PD-1–deficient mice develop autoimmune inflammation in multiple tissues, including peripheral nerves, whereas no such lesions were observed in age-matched PD-1–sufficient mice [43]. No microscopic findings related to atezolizumab were observed in CD-1 mice, suggesting that this strain may not be predisposed to autoimmune inflammation under PD-L1 blockade.

In an exploratory research study, mortality was observed in mice acutely infected with clone 13 variant of lymphocytic choriomeningitis virus (LCMV CL-13) when a chimeric derivative of atezolizumab was administered. However, additional data in the LCMV CL-13 acute infection model suggest that this mortality is not unique to this chimeric antibody or the inhibition of the PD-L1/PD-1 pathway, because similar mortalities were observed with other PD-L1 and PD-1 inhibitors, as well as with IL-2 administration. Mortality was not observed in LCMV CL-13 chronically infected mice when a chimeric derivative of atezolizumab was administered. Additionally, PD-L1 blockade did not result in mortality in other models of acute viral infections (LCMV Armstrong, adenovirus, or vaccinia). These data suggest that the coincident broad tissue tropism, the high, sustained viral burden, and the large LCMV-specific T-cell response, features that distinguish LCMV CL13 from known human infections, may account for the mortalities observed in LCMV CL13. Because of the potential risks associated with infections, the Phase I study will exclude patients with a history of HIV, hepatitis B, or hepatitis C (except for patients with HCC co-infected with HBV or HCV) or with or with evidence of significant active infection. Atezolizumab dosing will also be held for new clinically significant infections and may resume if the infection resolves within 42 days. Despite these potential risks, it should be noted that there is no reported evidence to date of an increased morbidity risk resulting from acute viral or bacterial infections in patients who have been treated with CT-011 or MDX-1106. There was no atezolizumab-dependent cytokine release detected following incubation with human PBMCs representing concentrations approximately 750-fold above the expected

maximum observed concentration at the proposed starting dose, suggesting that the risk for exaggerated cytokine release associated with atezolizumab administration is low.

Refer to the atezolizumab (MPDL3280A) Investigator's Brochure for additional details regarding the nonclinical studies.

6.2 RISKS ASSOCIATED WITH CARBOPLATIN

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related AEs. For more details regarding the safety profile of carboplatin, please refer to the carboplatin Package Insert.

6.3 RISKS ASSOCIATED WITH ETOPOSIDE

Etoposide is known to cause bone marrow suppression including myelosuppression, anemia, thrombocytopenia, diarrhea, hepatotoxicity and alopecia. Etoposide-based chemotherapy is considered to be moderately emetogenic. Etoposide carries a small risk of secondary hematologic malignancy. Patients will be monitored for etoposide-related AEs. For more details regarding the safety profile of etoposide, please refer to the etoposide Package Insert.

6.4 POTENTIAL OVERLAPPING TOXICITIES

The risk of overlapping toxicities between atezolizumab, carboplatin and etoposide is thought to be minimal. Nevertheless, the attribution and management of certain AEs that have been associated with each agent separately (e.g., hepatotoxicity, skin, and GI toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory AEs associated with carboplatin and etoposide (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of atezolizumab. Toxicities should initially be managed according to the protocol, with dose holds and modifications (if applicable) applied to the component of the study treatment judged to be the primary cause. For severe (Grade 3) or persistent Grade 1/2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for AEs listed above. If, in the opinion of the investigator, atezolizumab is a potential inciting factor, the dose of atezolizumab may be held for a maximum of 42 days beyond when next dose should have been given. Prompt symptomatic management is appropriate for mild IRAEs. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or tumor necrosis factor-alpha inhibitors.

6.5 SAFETY PARAMETERS AND DEFINITIONS

6.5.1 Overview

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements. Unexpected fatal or life-threatening events associated with the use of the study drug will also be reported to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Investigators are responsible for reporting other relevant SAEs associated with the use of the study medication to their IRBs per local requirements by a written safety report within 15 calendar days of notification.

6.5.2 Adverse Events

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

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated small cell lung cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

6.5.3 Serious Adverse Events

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as **nonserious AEs**. The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations. Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

6.5.4 Dose-Limiting Toxicities

AEs that meet the definition of a DLT (see Section 3.3.4) will be recorded on the AE eCRF. DLTs also meet the definition of an SAE or a protocol-defined event of special interest, and qualify for expedited reporting to the Sponsor (see Sections 6.7.2.11 and Section 6.7 for reporting instructions). Investigators will also participate in frequent teleconferences with the Sponsor during which they will report any DLTs observed during the DLT assessment window for each patient in the dose-escalation stage of the study.

6.6 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

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

6.6.1 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.

6.6.2 Assessment of Adverse Events

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

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

Yes

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

No

Evidence exists that the AE has an etiology other than the 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 AEs are those AEs that are listed or characterized in the Package Insert or current Investigator Brochure.

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

6.7 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

6.7.1 Eliciting Adverse Events

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

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

6.7.2 Specific Instructions for Recording Adverse Events

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

6.7.2.1 Diagnosis versus Signs and Symptoms

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

6.7.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 6.6.1), 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”.

6.7.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

6.7.2.4 Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for 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.

6.7.2.5 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the last dose of study drug. A Pregnancy Report Form should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) submitted to

Genentech/Roche Drug Safety. Pregnancy should not be recorded on the Adverse Event CRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF.

6.7.2.6 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 90 days after completing treatment with atezolizumab. Male patients who received study treatment should not attempt to father a child until end of study. A Pregnancy Report Form should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted to Genentech/Roche Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report CRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

6.7.2.7 Abortions

Any spontaneous/therapeutic abortion should be classified as a serious adverse event (as Genentech considers spontaneous abortions to be medically significant events), recorded on the Adverse Event CRF, and reported to Genentech/Roche Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

6.7.2.8 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF, and reported to Genentech/Roche Drug Safety immediately (i.e., no more than 24 hours after learning of the event).

6.7.2.9 Post-Study Adverse Events

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

6.7.2.10 Safety Reconciliation

The Sponsor Investigator agrees to conduct reconciliation for the product. Genentech and the Sponsor Investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the 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'.

6.7.2.11 Adverse Events of Special Interest

Protocol-defined events of special interest include SAEs and DLTs occurring during the DLT assessment window. For this protocol, "real-time" safety monitoring will be employed for DLT assessments and dose-escalation decisions. Investigators will be required to report all SAEs, DLTs, and Grade 3 or Grade 4 AEs to the Medical Monitor by e-mail or phone and via the EDC system within 24 hours of the event (see Section 6.7.2.12 for instructions on expedited reporting).

AEs of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP. The following events are events of special interest and will need to be reported to the Sponsor expeditiously (see Section 6.7.2.12 for reporting instructions) irrespective of regulatory seriousness criteria:

- Pneumonitis
- Colitis
- Endocrinopathies: e.g. diabetes mellitus, pancreatitis, thyroid dysfunction, adrenal insufficiency or hypothyroidism
- Hepatitis
- Transaminitis: AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN or AST/ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Guillain-Barré syndrome
- Myasthenia gravis
- Meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza like illness, SIRS, SIA (systemic inflammatory activation), or infusion-reaction syndromes
- Suspected Transmission of an Infectious Agent (STIAMP) by the study drug

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

6.7.2.12 Adverse Event Reporting

Investigators must report all SAEs to Genentech/Roche and the Georgetown University IRB within the timelines described below. The completed MedWatch/case report should be submitted immediately via fax / E-mail to Genentech/Roche Drug Safety at:

Email: welwyn.pds-pc@roche.com

Fax: +44 1707 377 967/ 373 779/ 373 793/ 390 959

The MedWatch/case report should also be faxed immediately to the Georgetown University IRB at:

(202) 687-4847

Relevant follow-up information should be submitted to Genentech/Roche Drug Safety and the Georgetown University IRB as soon as it becomes available.

SAE, AESIs and Pregnancy reports whether related or unrelated to atezolizumab will be transmitted to Genentech/Roche within 24 hours of the Awareness Date.

Additional reporting requirements to Genentech/Roche and the Georgetown University IRB include the following:

- All non-serious atezolizumab AEs originating from the study will be forwarded Genentech/Roche quarterly

Note: Investigators should also report events to the Coordinating Site at the Georgetown Lombardi Comprehensive Cancer Center (Giuseppe Giaccone: email: gg496@georgetown.edu; Fax 202-687-0313) and to their local IRB as required.

OR

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Principal Investigator immediately, followed by submission of written case details on an AE eCRF within 24 hours.

Principal Investigator Contact Information:
Medical Monitor: Giuseppe Giaccone, M.D., Ph.D.
Telephone No.: 202-687-7072

Investigators will submit reports of all SAEs, regardless of attribution, and all protocol-defined events of special interest to Genentech/Roche and the Georgetown University IRB within 24 hours of learning of the events. For initial SAE and protocol-defined events of special interest reports, investigators should record all case details that can be gathered within 24 hours on an AE eCRF and submit the report via the EDC system. A report will be generated and sent to Genentech/Roche Drug Safety by the EDC system.

In the event the EDC system is unavailable, a completed AE paper reporting form and fax coversheet should be submitted immediately upon completion to Genentech's/Roche's Drug Safety Department or its designee at the fax numbers or E-mail address indicated below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

E-mail: welwyn.pds-pc@roche.com

Fax: +44 1707 377 967/ 373 779/ 373 793/ 390 959

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

MedWatch 3500A Reporting Guidelines

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

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information

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

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally Genentech/Roche may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Genentech/Roche Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

6.7.3 Additional Reporting Requirements for IND

For investigator-sponsored 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 FDA as expedited IND Safety Reports according to the following guidance and timelines:

Seven Calendar Day Telephone or Fax Report

The investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of atezolizumab. An unexpected AE is one that is not already described in the atezolizumab Investigator's 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.

Fifteen 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 AE is one that is not already described in the atezolizumab (MPDL3280A) Investigator's 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).

Contact Information for IND Safety Reports

FDA fax number for IND safety reports:

Fax: (800) FDA-0178

All written IND safety reports submitted to the FDA by the investigator must also be submitted via fax/e-mail to the following:

E-mail: welwyn.pds-pc@roche.com

Fax: +44 1707 377 967/ 373 779/ 373 793/ 390 959

Site's IRB: 202-687-1506

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

Tel: (888) 835-2555

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

6.7.4 IND Annual Reports

Copies of all IND annual reports submitted to the FDA by the Sponsor-Investigator should be sent to Genentech/Roche Drug Safety via fax/E-mail at:

E-mail: welwyn.pds-pc@roche.com

Fax: +44 1707 377 967/ 373 779/ 373 793/ 390 959

6.8 STUDY CLOSE-OUT

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

Atezolizumab (MPDL3280A) Protocols

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

Fax: (866) 706-3927

7. ETHICAL CONSIDERATIONS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive atezolizumab treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 4.5.

This study will be conducted in accordance with the U.S. FDA regulations, the ICH E6 Guideline for GCP, and applicable local, state, and federal laws, as well as other applicable country laws.

7.2 INFORMED CONSENT

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

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

7.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific adverse event requirements that investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

7.4 CONFIDENTIALITY

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

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

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

8. STUDY MEDICAL MONITORING REQUIREMENTS

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

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

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

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

8.1 INVESTIGATOR REQUIREMENTS

8.1.1 Study Initiation

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

- U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all sub-investigators
- Complete financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572
- Federal-wide Assurance number or IRB statement of compliance
- Written documentation of IRB approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB -approved Informed Consent Form. A Clinical Research Agreement signed and dated by the study site
- Investigator's Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator

8.1.2 Study Completion

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

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

8.1.3 Informed Consent Form

A Sample Informed Consent Form will be provided to each site. Confirmation of IRB approval will be provided to Genentech.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB-approved Informed Consent Form must be provided to Genentech for regulatory purposes.

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

8.1.4 Communication with Institutional Review Board

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB. Investigators are also responsible for promptly informing the IRB of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others. In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB all unanticipated problems involving risk to human patients. Some IRBs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Genentech. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB and archived in the site's study file.

8.1.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

8.1.6 Study Monitoring Requirements

The Principal Investigator will permit Genentech monitors/representatives and collaborators, the U.S. FDA, other regulatory agencies, IRBs, and the respective national or local health authorities to inspect facilities and records relevant to this study

8.1.7 Electronic Case Report Forms

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator. In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

8.1.8 Source Data Documentation

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents. Source documents are where patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed. To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB review. The investigational site must also allow inspection by applicable regulatory authorities.

8.1.9 Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that 1) allows data entry only by authorized individuals; 2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); 3) protects the database from tampering; and 4) ensures data preservation. In collaboration with the study monitor, Genentech's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

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

8.1.10 Study Medication Accountability

All study drug required for completion of this study will be provided by Genentech. The recipient will acknowledge receipt of the drug by returning the appropriate

documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be recorded by using the Drug Inventory Log. Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to Genentech or designee with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented. Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

8.1.11 Data Management and Monitoring

The Principle Investigator and will conduct weekly safety monitoring with several co-investigators. The investigators shall meet on a weekly basis to review toxicities and follow up on results of patients enrolled on the study.

The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated study utilizing an FDA approved agent, it is considered a moderate risk study which requires real-time monitoring by the PI and study team and semi-annual reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly teleconferences.

All SAEs are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 6 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

8.1.12 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.1.13 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

8.1.14 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

8.1.15 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).
- An unplanned protocol variance is considered a violation if the variance:

Has harmed or increased the risk of harm to one or more research participants.
Has damaged the scientific integrity of the data collected for the study.
Results from willful or knowing misconduct on the part of the investigator(s).
Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by study personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

8.1.15 Disclosure of Data

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes. Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB for each study site, if appropriate.

8.1.16 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech for transfer of any records to another party or moving them to another location.

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency

regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an ICH region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.1.17 Obligations of Investigators

The PI is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The PI at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the PI will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

8.2 STUDY MEDICATION ACCOUNTABILITY

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

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

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

8.3 DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled on study and that data is recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted,

initialed and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the Georgetown University IRB.

8.4 MULTI-INSTITUTION STUDY COORDINATION

8.4.1 Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, at Lombardi-Georgetown, there will be a dedicated "multi-institutional" research coordinator who will play the primary role in coordinating the trial between Lombardi-Georgetown and additional sites. This coordinator will be the main point of contact for the overall PI and the other site PIs for any study related concerns, and to screen each patient being considered for enrollment (Including "remote" screening for the patients being screened at other sites). This coordinator will also be the point of contact for the data managers for data entry questions. Finally, this coordinator will play a major role in regulatory coordination of the study, specifically by: 1) Reviewing and confirming all study-related adverse events; 2) Submitting all SAE reports to the Georgetown IRB (The research coordinators at the other sites will prepare SAE reports for patients treated at their respective sites, but the "multi-institutional" coordinator will submit the final report); 3) Gathering and preparing all primary source data for review/audit by Genentech.

8.4.2. Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's name, to the local PI, to the overall study PI, and to the multi-institutional coordinator. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the multi-institutional research coordinator (by email or fax). Patients should not start therapy until both the overall study PI and the multi-institutional coordinator have reviewed the patient's records and confirmed that the patient is eligible for enrollment.

8.4.3. Data Collection and Management

Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data

should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit.

8.4.4 Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites to review patient enrollment, toxicity, and response assessment.

8.4.5. Trial Auditing

Lombardi-Georgetown will provide trial auditing. The multi-institutional coordinator will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.

8.5 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

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

9. CORRELATIVE STUDIES

Exploratory Biomarker Assessments

There are several factors which may potentially predict clinical response to atezolizumab. We will systematically investigate these factors as described below. Tumor tissue will be collected and analyzed for exploratory biomarkers to assess correlation with clinical outcomes from study participants. Informed consent will be obtained from all patients.

Tumor analysis

Formalin-fixed paraffin-embedded (FFPE) archival tumor specimens will be acquired. If a patient has multiple archival tumor tissue samples, the most recently obtained tissue sample is preferred.

A reference laboratory will receive the tumor samples and perform immunohistochemistry (IHC) using antibodies for PD-L1 and PD-L2. PD-L1 and PD-L2

status of both the tumor cells and the tumor infiltrating lymphocytes (TILs) will be quantified. In addition, the reference lab will perform IHC to characterize tumor infiltrating lymphocytes (TILs), including CD3, CD4, CD8, FoxP3, Granzyme B, PD-1, CD20, and CD68. The abundance of each protein(s) monitored will be correlated with clinical endpoints. Finally, a standard hematoxylin and eosin (H&E) stain will be obtained for each tumor sample to assess tumor histology, to quantify mitotic figures, and to evaluate for tumor necrosis.

In addition, the Genentech Immunochip assay will be obtained for each tumor sample. This assay, which has been previously described [44] measures expression levels of ~90 immune-related markers from paraffin. From this dataset, we hope to establish which gene(s) correlate with tumor response. An “inflammatory signature” (also called a “Th1 signature”) has previously been described to be important for response to atezolizumab in other tumor types [44].

FFPE tumor tissue may also be evaluated also by fluorescent *in-situ* hybridization (FISH), genetic mutation detection methods (such as targeted next generation sequencing, exome sequencing, and/or RNA sequencing), qPCR, epigenetic alterations detection methods (to determine gene methylation status), and/or proteomic studies (such as reverse phase protein array) as part of additional exploratory analyses of putative biomarkers thought to be associated with response or resistance. Such analyses will be completed retrospectively and within the scope of informed consent.

Appendix 1 Study Flowchart

	Screening[a]	Cycle 1					Cycles ≥ 2		End of Treatment [b]	Follow Up
Assessment Window (days)	-28 to -1	1	2	3	8	15	1 [c] (± 2-7)	15-21	≤ 30 days after last dose	
Signed Informed Consent Form	X[a]									
Review of eligibility criteria	X									
Medical, surgical, and cancer histories including demographic information [d]	X									
EBV, CMV, HBV, HCV serology [e]	X									
Concomitant medications [f]	X	X			X	X	X		X	
Tumor assessment	X							X	X	X
Complete physical examination [h]	X									
Limited physical examination [i]		X			X	X	X			
ECOG performance status	X	X			X				X	
Vital signs, height, weight [j]	X	X			X	X	X		X	
Echocardiogram[k]	X						X		X	
12-lead electrocardiogram [l]	X								X	
Hematology [m]	X	X	X		X	X	X		X	
Serum chemistry [n]	X	X	X		X	X	X		X	
Coagulation panel (aPTT, INR)	X								X	
Serum pregnancy test [o]	X									
TSH, free T3, free T4	X								X	
Auto-antibody testing [p]	X						X [q]		X	
Adverse events		X			X	X	X		X	X
Atezolizumab administration		X					X			
Carboplatin administration [r]		X					X [r]			
Etoposide administration [s]		X	X	X			X [s]			
Archival tumor tissue specimen [t]	X									
Survival follow up [u]										X [u]

a. Written informed consent is required before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests. Screening local laboratory assessments obtained ≤ 96 hours prior to Cycle 1, Day 1 do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment.

b. Patients will be asked to return to the clinic 30 days after the last dose of study treatment for an end of treatment visit. After this visit, all adverse events (including serious adverse events and protocol-defined events of special interest), regardless of attribution, will be recorded until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Patients will be contacted at 60 and 90 days after the last dose of study treatment to determine if any new adverse events have occurred. Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event. Scans performed within 6 weeks prior to the end of treatment visit do not need to be repeated.

c. The window for study treatment infusion on Cycle 2, Day 1 is + 2 days (not – 2 days). All subsequent Day 1 infusions and all examinations and labs may be administered with a window of -2 to +7 days.

d. Cancer history includes date of diagnosis, presence of brain metastases, and any prior radiation treatment. Demographic information includes age, sex, and self-reported race/ethnicity.

e. HBV DNA must be collected prior to Cycle 1, Day 1 in patients who have a positive serology for the anti-HBc antibody

f. Concomitant medications include any prescription or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used within the last documentation of medications will be recorded.

g. Tumor assessments will be performed at the end of cycles 2, 4, 6, 8, 12 and 16 and as clinically indicated. Patients who discontinue study treatment for reasons other than disease progression (e.g. toxicity) should continue to undergo scheduled tumor assessments every 12 weeks until the patient dies, experiences disease progression or initiates further systemic anti-cancer therapy, whichever occurs first. All measurable and evaluable lesions should be assessed and documented using physical examination and image-based evaluation. Screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI with contrast). Bone scans and CT of the neck should also be performed if clinically indicated. If a PET/CT is performed, the CT portion of the study must be consistent with standards for a full-contrast CT scan and the CT scan must be used to measure lesions selected for response assessment. Disease status will be assessed using RECIST v1.1. Other methods of assessment of measurable disease according to RECIST may be used. The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle.

h. A complete physical examination at screening and the end of treatment visit should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Changes in abnormalities noted at baseline should be recorded at the end of treatment visit. New or worsened abnormalities should be recorded as adverse events if appropriate. A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as adverse events if appropriate.

i. ECOG performance status, limited physical examination, and local laboratory assessments may be obtained $\leq$ 96 hours prior to Day 1 of each cycle

j. Vital signs include heart rate, blood pressure and temperature. For the first three infusions of atezolizumab, the patient's vital signs should be determined up to 60 minutes before, during (every 30 [$\pm$ 5] minutes during 90 and 60 minute infusions only). And at the end of atezolizumab infusion. For subsequent infusions, vital signs are required to be obtained only before and after atezolizumab infusion if the prior infusion was tolerated without symptoms. Vital signs will also be recorded after the last infusion on each clinic day. Height is only required for the screening visit.

k. Echocardiograms will be obtained in patients with a known history of pericardial effusions during screening, Day 1 of Cycle 2, then as clinically indicated or per standard of care thereafter during treatment, and at the treatment discontinuation visit

l. Twelve-lead ECGs are required as part of the screening assessment and at the end of treatment visit. ECGs will be reviewed by the investigator to determine patient eligibility at screening.

m. Hematology consists of CBC including hemoglobin, hematocrit, WBC count with automated or manual differential) and platelet count.

n. Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein and albumin.

o. Serum pregnancy test (for women of childbearing potential, including women who have had tubal ligation) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1.

p. Includes anti-nuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody and perinuclear anti-neutrophil cytoplasmic antibody.

q. On Day 1 of Cycle 3 and every 2 cycles thereafter

r. Carboplatin will be given for only 4 cycles

s. Etoposide will be given on days 1-3 of the first 4 cycles

t. Archival tumor tissue specimen may be obtained from any prior tumor excision or biopsy performed during the course of the patient's illness and does not need to be obtained during the 28 day screening window.

u. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor. All patients will be followed for survival unless the patient requests to be withdrawn from follow-up. This request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

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

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

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

Reference:

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

Appendix 3 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

GENENTECH SUPPORTED RESEARCH

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

Alternate Fax No: (650) 225-4630

Page 1 of ___

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

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix 4 FDA MedWatch 3500 Form

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

Appendix 5 Current NCI Common Terminology Criteria for Adverse Events (CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 6 Response Evaluation Criteria in Solid Tumors (RECIST)

Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a. Measurable Tumor Lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

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

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

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

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

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

b. Method of Assessment

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

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and $\geq$10 mm in diameter as assessed using calipers (e.g., skin nodules).

For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Appendix 6 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

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

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

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

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

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

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat

such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

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

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

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

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease

cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

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

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

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

Evaluation of Response

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1. Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

Table 2. Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

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

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3. Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 – 3.

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

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 7 Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{index\ lesions} + SPD_{new,\ measurable\ lesions}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$SPD = \sum_{i} \text{(Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i).}$$

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

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden $\geq 50\%$ relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden $\geq 25\%$ relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 8 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 9 Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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

Appendix 10 References

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2015.* CA Cancer J Clin, 2015. **65**(1): p. 5-29.
2. Govindan, R., et al., *Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database.* J Clin Oncol, 2006. **24**(28): p. 4539-44.
3. Turrisi, A.T., 3rd, et al., *Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide.* N Engl J Med, 1999. **340**(4): p. 265-71.
4. Roth, B.J., et al., *Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group.* J Clin Oncol, 1992. **10**(2): p. 282-91.
5. Rossi, A., et al., *Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data.* J Clin Oncol, 2012. **30**(14): p. 1692-8.
6. Pujol, J.L., et al., *Etoposide plus cisplatin with or without the combination of 4'-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study.* J Natl Cancer Inst, 2001. **93**(4): p. 300-8.
7. Noda, K., et al., *Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer.* N Engl J Med, 2002. **346**(2): p. 85-91.
8. Eckardt, J.R., et al., *Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer.* J Clin Oncol, 2006. **24**(13): p. 2044-51.
9. Hanna, N., et al., *Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer.* J Clin Oncol, 2006. **24**(13): p. 2038-43.
10. Okamoto, H., et al., *Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702.* Br J Cancer, 2007. **97**(2): p. 162-9.
11. Socinski, M.A., et al., *Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer.* J Clin Oncol, 2009. **27**(28): p. 4787-92.
12. Rudin, C.M., et al., *Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103.* J Clin Oncol, 2008. **26**(6): p. 870-6.

13. Nagel, S., et al., *Addition of darbepoetin alfa to dose-dense chemotherapy: results from a randomized phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide.* Clin Lung Cancer, 2011. **12**(1): p. 62-9.
14. Schmittel, A., et al., *A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer.* Ann Oncol, 2011. **22**(8): p. 1798-804.
15. Hodi, F.S., et al., *Improved survival with ipilimumab in patients with metastatic melanoma.* N Engl J Med, 2010. **363**(8): p. 711-23.
16. Blank, C., T.F. Gajewski, and A. Mackensen, *Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy.* Cancer Immunol Immunother, 2005. **54**(4): p. 307-14.
17. Blank, C. and A. Mackensen, *Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion.* Cancer Immunol Immunother, 2007. **56**(5): p. 739-45.
18. Iwai, Y., et al., *Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade.* Proc Natl Acad Sci U S A, 2002. **99**(19): p. 12293-7.
19. Strome, S.E., et al., *B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma.* Cancer Res, 2003. **63**(19): p. 6501-5.
20. Brahmer, J., et al., *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(2): p. 123-35.
21. Borghaei, H., et al., *Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(17): p. 1627-39.
22. Topalian, S.L., et al., *Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab.* J Clin Oncol, 2014. **32**(10): p. 1020-30.
23. Hamid, O., et al., *Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma.* N Engl J Med, 2013. **369**(2): p. 134-44.
24. Garon, E.B., et al., *Pembrolizumab for the treatment of non-small-cell lung cancer.* N Engl J Med, 2015. **372**(21): p. 2018-28.
25. Segal, N.H., et al., *Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody.* J Clin Oncol, 2014. **32**(5S): p. abstr 3002.
26. Lutzky, J., et al., *A phase 1 study of MEDI4736, an anti–PD-L1 antibody, in patients with advanced solid tumors.* J Clin Oncol, 2014. **32**(5S): p. abstr 3001.
27. Antonia, S.J., et al., *Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032.* J Clin Oncol, 2015. **33**: p. abstr 7503.
28. Dedrick, R.L., *Animal scale-up.* J Pharmacokinet Biopharm, 1973. **1**(5): p. 435-61.

29. Chamanza, R., et al., *Spontaneous lesions of the cardiovascular system in purpose-bred laboratory nonhuman primates.* Toxicol Pathol, 2006. **34**(4): p. 357-63.
30. Dong, H., et al., *B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion.* Nat Med, 1999. **5**(12): p. 1365-9.
31. Keir, M.E., G.J. Freeman, and A.H. Sharpe, *PD-1 regulates self-reactive CD8+ T cell responses to antigen in lymph nodes and tissues.* J Immunol, 2007. **179**(8): p. 5064-70.
32. Kantoff, P.W., et al., *Sipuleucel-T immunotherapy for castration-resistant prostate cancer.* N Engl J Med, 2010. **363**(5): p. 411-22.
33. Brahmer, J.R., et al., *Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.* N Engl J Med, 2012. **366**(26): p. 2455-65.
34. Topalian, S.L., et al., *Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.* N Engl J Med, 2012. **366**(26): p. 2443-54.
35. Berger, R., et al., *Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies.* Clin Cancer Res, 2008. **14**(10): p. 3044-51.
36. Reck, M., et al., *Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial.* Ann Oncol, 2013. **24**(1): p. 75-83.
37. Vogelstein, B., et al., *Cancer genome landscapes.* Science, 2013. **339**(6127): p. 1546-58.
38. Alexandrov, L.B., et al., *Signatures of mutational processes in human cancer.* Nature, 2013. **500**(7463): p. 415-21.
39. Liu, S.V., et al., *Safety and efficacy of MPDL3280A (anti-PDL1) in combination with platinum-based doublet chemotherapy in patients with advanced non-small cell lung cancer (NSCLC).* J Clin Oncol, 2015. **33**: p. abstr 8030.
40. Bai, S., et al., *A guide to rational dosing of monoclonal antibodies.* Clin Pharmacokinet, 2012. **51**(2): p. 119-35.
41. Brahmer, J.R., 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**(19): p. 3167-75.
42. Di Giacomo, A.M., M. Biagioli, and M. Maio, *The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications.* Semin Oncol, 2010. **37**(5): p. 499-507.
43. Yoshida, T., et al., *PD-1 deficiency reveals various tissue-specific autoimmunity by H-2b and dose-dependent requirement of H-2g7 for diabetes in NOD mice.* Proc Natl Acad Sci U S A, 2008. **105**(9): p. 3533-8.
44. Powderly, J.D., et al., *Biomarkers and associations with the clinical activity of PD-L1 blockade in a MPDL3280A study.* J Clin Oncol, 2013. **suppl; abstr 3001**.