Official Title: A Phase III, Open-Label, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Compared With Gemcitabine+Cisplatin or Carboplatin for PD-L1-Selected, Chemotherapy Naive Patients With Stage IV Squamous Non-Small Cell Lung Cancer

NCT Number: NCT02409355

Document Date: Protocol Version 5: 24 June 2016

PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH GEMCITABINE+CISPLATIN OR CARBOPLATIN FOR PD-L1–SELECTED, CHEMOTHERAPY NAIVE PATIENTS WITH STAGE IV SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29432/ NCT02409355
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-003106-33
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
MEDICAL MONITOR:	[redacted], M.D., *Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 23 December 2014
DATES AMENDED:	Version 2: 24 April 2015 Version 3: 5 October 2015 Version 4: 16 December 2015 Version 5: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Jun-2016 18:50:34

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol GO29432 has been amended to remove the option for erlotinib switch maintenance for patients randomized to Arm B of the study (see Sections 1.4, 3.1, 3.3.2, 4.3.1.3, 4.3.2.2, 4.3.2.3, 4.4.1, 5.1.3.3). Recent data from Study BO25460 have demonstrated that patients with advanced or recurrent (Stage IIIB) or metastatic (Stage IV) non–small cell lung cancer (NSCLC) whose tumor did not harbor an epidermal growth factor receptor (EGFR)-activating mutation did not achieve benefit from maintenance therapy with erlotinib compared with placebo. Given the low incidence of EGFR-activating mutations in patients with squamous histology, the option of erlotinib switch maintenance therapy has been removed for all patients randomized to Arm B of the study. Patients already on switch maintenance therapy with erlotinib that was permitted under previous protocol versions may be allowed to continue to receive treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.

Furthermore, a recent communication (dated 18 April 2016) was sent to the investigators to inform of the Sponsor's decision to close enrollment into Study GO29432 and to enroll patients with squamous NSCLC into the ongoing Study GO29431 (IMpower110) in order to streamline and simplify the design of both studies. Patients already enrolled in Study GO29432 will remain on study and will be allowed to continue study treatment until radiographic disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1), withdrawal of consent, enrollment into an extension study, or death, whichever occurs first.

This amendment will reduce the number and type of protocol-specified assessments for evaluation of study treatment but will retain the requirements for reporting of adverse events and to monitor patient safety. Specifically, the following assessments have been removed:

- Pharmacokinetic
- Biomarker
- Anti-therapeutic antibody
- Tumor tissue sampling
- Patient-reported outcome assessments
- Survival follow-up

Additionally, this amendment includes the following changes:

- The recent approval in the United States of atezolizumab for the treatment of locally advanced or metastatic urothelial cancer has been added (see Sections 1.5 and 5).

- Objectives, endpoints, assessments noted above, and associated statistical analyses have been removed as they are no longer relevant (see Sections 2, 3.3.3, 3.4, 4.3.4, 4.5.6, 4.5.9, 4.5.11, 4.5.13.3., and 4.5.13.4, 5.3.5.8, and 6).
- The tumor tissue biopsy at the time of radiographic progression has been made optional (see Sections 3.1, 3.3.6, 4.5.7.2, and 8.2).
- The requirement for independent Data Monitoring Committee (iDMC) reviews has been removed due to the closeout of the study (Section 3.1.1).
- Study language has been revised to reflect the study's closure to enrollment due to a low number of patients (see Sections 3.2, 4.1, and 9.4).
- Based on the half-life of atezolizumab of 27 days, the use of contraception for female patients treated with atezolizumab has been extended from 90 days to 5 months after the last dose of atezolizumab, and female patients treated with atezolizumab should be instructed to inform the investigator of any pregnancy that occurs during study treatment and within 5 months after the last dose of atezolizumab (see Sections 4.1.1 and 5.4.3.1).
- Hormone replacement therapy or oral contraceptive have been removed from the exclusion criteria (see Section 4.1.2.3).
- Drug formulation and handling information for atezolizumab has been removed, and investigators should refer ro the Pharmacy Manual and Investigator's Brochure (see Section 4.3.1.1).
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer have been removed from the list of permitted therapy (see Section 4.4.1).
- Traditional herbal medicines have been removed from prohibited therapy, and language has been added to state that concomitant use of herbal therapies is not recommended because the pharmacokinetics, safety profile, and drug-drug interactions are unknown. However, use of herbal therapies not intended for the treatment of cancer for patients in the study is allowed at the discretion of the investigator (see Section 4.4.3).
- Language around other therapeutic options and continuation of atezolizumab at time of radiographic progression has been clarified (see Sections 4.5.1 and 4.6.2).
- The requirement for urinalysis to be performed at all treatment cycles and the treatment discontinuation visit has been removed. Urinalysis will be obtained during study treatment when clinically indicated (see Section 4.5.6).
- The Epstein-Barr virus serology sample testing for patients experiencing an acute inflammatory event has been removed (see Section 4.5.6).
- It has been clarified that tumor tissue samples collected at the time of clinical events are preferred (see Section 4.5.7.3).
- It is noted that the whole blood sample for DNA extraction may be collected at any time during the study (see Section 4.5.12.3).

- Screening assessments have been noted to be available in Version 4 of the protocol (see Section 4.5.13.1).
- The atezolizumab Investigator's Brochure was revised to include updated approaches for the management of atezolizumab-specific adverse events. To ensure consistent application of the most updated guidelines across atezolizumab protocols at all times, management guidelines and tables for atezolizumab-specific adverse events have been deleted from the protocol and replaced by cross-references to the guidelines in the current version of the Investigator's Brochure (see Sections 5.1.1, 5.1.5.1, 5.1.6, and 5.1.7).
- General guidelines regarding dose modifications have been added and that the investigator may use discretion in modifying or accelerating the dose modification guidelines depending on the severity of the toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care (see Section 5.1.5.1)
- Revisions have been made for consistency with the guidelines for management of atezolizumab-specific adverse events in the atezolizumab Investigator's Brochure (see Sections 5.1.1 and 5.1.7).The contraception requirements for male patients and pregnancy-reporting requirements for female partners of male patients who receive atezolizumab have been updated on the basis of the safety information for atezolizumab. Atezolizumab is not expected to be genotoxic. In addition, the anticipated concentrations of atezolizumab in seminal fluid as well as the potential risk to the developing conceptus is low following seminal transfer of atezolizumab to a female partner (see Section 5.4.3.2).

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

PROTOCOL AMENDMENT, VERSION 5: SUMMARY OF CHANGES

GLOBAL CHANGES

- The Medical Monitor contact information has been updated.
- Abbreviations have been spelled out in headings, where appropriate.
- The specific brand has been removed from references to prescribing information, where appropriate.
- References to the Independent Data Monitoring Committee have been removed from the text.
- The 12-month timepoint around tumor assessments has been clarified to be 48 weeks.
- The option of enrollment into the extension study has been added, where applicable.

PROTOCOL SYNOPSIS

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

SECTION 1.4: Maintenance Therapy for Non–Small Cell Lung Cancer

When the study was started, switch maintenance with erlotinib in unselected patients could be considered f~~F~~or patients with stable disease or continued response to therapy after four to six cycles *of chemotherapy*~~, switch maintenance treatment with erlotinib in unselected patients or pemetrexed in those with non-squamous histology can be considered~~ (NCCN Guidelines 2014). This recommendation ~~is~~*was* based on ~~two randomized Phase III trials, which have shown a PFS and OS benefit after the initiation of pemetrexed or erlotinib after induction treatment in patients with no disease progression~~*the Sequential Tarceva Unresectable NSCLC study (SATURN)* . In theSATURN ~~trial~~*study*, the median PFS in patients receiving maintenance therapy with erlotinib was significantly longer than in patients receiving placebo (12.3 vs. 11.1 weeks; hazard ratio [HR] 0.71, 95% CI: 0.62–0.81; p<0.0001). Maintenance treatment with erlotinib also yielded a statistically significant yet clinically modest improvement in OS (12.0 vs. 11.0 months; HR 0.81, 95% CI: 0.70–0.95; p=0.0088). A statistically significant improvement in PFS and OS was observed in patients with EGFR–wild-type and EGFR–mutation-positive tumors (Cappuzzo et al. 2010). ~~In the Phase III clinical trial evaluating pemetrexed maintenance therapy following four cycles of platinum based doublet chemotherapy, pemetrexed significantly improved PFS (4.3 vs. 2.6 months; HR 0.50, 95% CI: 0.42–0.61; p.<0.0001) and OS (13.4 vs. 10.6 months; HR 0.79, 95% CI: 0.65–0.95; p.=0.012) when compared with placebo (Ciuleanu et al. 2009). These~~ *This* Phase III trial~~s~~ resulted in regulatory approval *by the U.S. Food and Drug Administration (FDA) and European Medicines Agency* for erlotinib *in* ~~(~~unselected NSCLC~~) and pemetrexed (non squamous NSCLC), respectively~~, as maintenance therapy of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. *However, recent*

data from Study BO25460, a randomized, double-blind, placebo-controlled Phase III study, have demonstrated that patients with advanced or recurrent (Stage IIIB) or metastatic (Stage IV) NSCLC whose tumor did not harbor an EGFR-activating mutation did not achieve benefit from first-line maintenance therapy with erlotinib compared with placebo. OS was not superior in patients randomized to receive maintenance erlotinib followed by chemotherapy or best supportive care upon disease progression compared with patients randomized to receive maintenance placebo followed by erlotinib upon disease progression (HR =1.02, 95% CI, 0.85–1.22, p =0.82). In the maintenance phase, patients who received erlotinib also did not have superior PFS compared with patients who received placebo (HR =0.94, 95% CI, 0.80–1.11, p =0.48). This change in the benefit-risk assessment of erlotinib as switch maintenance therapy in patients whose tumors do not harbor an activating EGFR mutation has led to the removal of this treatment option from this protocol. Patients already receiving the switch maintenance therapy with erlotinib, permitted under previous protocol versions, may be allowed to continue to receive treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.

SECTION 1.5: Background on Atezolizumab (MPDL3280A)

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial cancer.

SECTION 1.6.2.1: Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer

Study PCD4989g is a Phase Ia dose escalation and expansion study, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, and provides the majority of data (with 558 safety evaluable patients as of the data ~~extraction~~ *cutoff* date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

SECTION 2: Objectives

The study is currently closed to enrollment due to a low number of patients; therefore, the objectives of this study are no longer applicable and formal analyses of efficacy or safety will not be performed.~~Analyses of all objectives specified below will be performed in chemotherapy naive patients with Stage IV squamous NSCLC who are selected on the basis of high PD-L1 expression on TCs and/or ICs (TC3 or IC3) using a centrally performed IHC assay (see Appendix 6).~~

~~SECTION 2.1: Efficacy Objectives~~

~~SECTION 2.1.1: Primary Efficacy Objective~~

~~The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with gemcitabine+cisplatin or carboplatin in PD-L1–selected patients with Stage IV squamous NSCLC, as measured by investigator-assessed PFS according to RECIST v1.1 (see Appendix 4).~~

SECTION 2.1.2: Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with gemcitabine+cisplatin or carboplatin as measured by investigator-assessed ORR (partial response [PR] plus complete response [CR]) according to RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with gemcitabine+cisplatin or carboplatin as measured by OS
- To determine the impact of atezolizumab compared with gemcitabine+cisplatin or carboplatin as measured by time to deterioration (TTD) in patient reported lung cancer symptom (cough, dyspnea, chest pain) score as assessed by the Symptoms in Lung Cancer (SILC) scale symptom score (Appendix 9)
- To evaluate the efficacy of atezolizumab compared with gemcitabine+cisplatin or carboplatin as measured by Independent Review Facility (IRF) assessed PFS according to RECIST v1.1
- To evaluate the efficacy of atezolizumab as measured by investigator assessed DOR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab as measured by investigator assessed time in response (TIR) according to RECIST v1.1
- To evaluate the OS rate at 1 and 2 years in each treatment arm
- To determine the impact of atezolizumab compared with gemcitabine+cisplatin or carboplatin as measured by TTD in patient reported lung cancer symptoms of cough, dyspnea (single item and multi item subscales), chest pain, arm/shoulder pain, or fatigue with use of the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (see Appendix 7) and the supplementary Lung Cancer Module (EORTC QLQ-LC13) (see Appendix 8)

SECTION 2.2: Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab compared with gemcitabine+cisplatin or carboplatin.
- To evaluate the incidence and titers of ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, pharmacodynamics, safety, and efficacy

SECTION 2.3: Pharmacokinetic Objective

The PK objective for this study is to characterize the pharmacokinetics of atezolizumab.

SECTION 2.4: Exploratory Objectives

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with gemcitabine+cisplatin or carboplatin as measured by IRF-assessed ORR, disease control rate (DCR), DOR, and TIR according to RECIST v1.1

- ~~To evaluate the efficacy of atezolizumab as measured by IRF assessed PFS, ORR, DCR, DOR, and TIR according to modified RECIST (ONLY in the atezolizumab arm; see Appendix 5)~~
- ~~To evaluate the efficacy of atezolizumab as measured by investigator assessed PFS, ORR, DCR, DOR, and TIR according to modified RECIST (ONLY in the atezolizumab arm; see Appendix 5)~~
- ~~To evaluate the efficacy of atezolizumab as measured by investigator assessed DCR according to RECIST v1.1~~
- ~~Landmark PFS at 6 months and 1 year~~
- ~~To evaluate the OS rate at 3 years in each treatment arm~~
- ~~To evaluate the relationship between tumor biomarkers (including but not limited to PD-L1, PD-1, somatic mutations, and others), as defined by IHC, quantitative reverse transcriptase- polymerase chain reaction (qRT-PCR) next generation sequencing (NGS), and/or other methods and measures of efficacy~~
- ~~To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood, and their association with disease status, mechanisms of resistance, and/or response to atezolizumab~~
- ~~To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to the immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor immune infiltration) from true disease progression~~
- ~~To evaluate and compare patient's health status as assessed by the EuroQoL 5-Dimension, 3-Level (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement~~
- ~~To determine the impact of atezolizumab compared with gemcitabine + cisplatin or carboplatin as measured by change from baseline in patient reported outcomes (PROs) of health related quality of life, lung cancer related symptoms, and health status as assessed by the EORTC QLQ-C30 and LC13~~

SECTION 3.1: Description of Study

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

Patients in both treatment arms ~~will~~*may* undergo a*n optional*~~mandatory~~ tumor tissue ~~collection for~~ biopsy~~, unless not clinically feasible as assessed by investigators,~~ at the time of radiographic disease progression *if clinically feasible. To do this, patients must sign a separate consent.* (…) ~~Patients who are unable to undergo biopsy sample collection but otherwise meet criteria listed above may continue to receive atezolizumab.~~

~~For patients with non-progressive disease after the platinum based chemotherapy, switch maintenance with erlotinib can be considered by the investigator in accordance with the NCCN guidelines (see Section 1.4).~~

All patients will undergo tumor assessments at baseline and every 6 weeks thereafter, regardless of dose delays, for the first ~~12 months~~*48 weeks* following Cycle 1, Day 1, *regardless of treatment delays.* After ~~12 months~~*48 weeks*, tumor assessments will be required every 9 weeks *after completion of the Week 48 tumor assessment, regardless of treatment delays,* until disease progression per RECIST v1.1 (for patients in both treatment arms) or loss of clinical benefit (for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, ~~study termination by the Sponsor, or death,~~ *enrollment into an extension study, or death,* whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, ~~study termination by Sponsor, or~~ death, *or are eligible to roll over to an extension study,* whichever occurs first. ~~A secondary endpoint of this study is IRF-assessed PFS according to RECIST v1.1. Therefore, an IRF will conduct an independent review of the responses of all patients, including a review of blinded computed tomography (CT) scans. All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints. Independent reviews will be performed prior to the final efficacy analyses.~~

SECTION 3.1.1: Independent Data Monitoring Committee

~~An independent Data Monitoring Committee (iDMC) will be used to evaluate safety data during the study on a periodic basis, approximately every 6 months from the time when the first patient is enrolled. Members of the iDMC will be external to the Sponsor and will follow a Charter that outlines their roles and responsibilities.~~

~~All summaries and analyses by treatment arm for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC). The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.~~

~~Following the data review, the iDMC will provide a recommendation to the Sponsor as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.~~

~~Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).~~

~~No interim efficacy analysis is planned for the primary endpoint of PFS.~~*An independent Data Monitoring Committee (iDMC) was in place to evaluate the safety data during the study on a periodic basis. However, as of 20 April 2016 the study was closed to enrollment due to a low number of patients; therefore, an iDMC will no longer be used to evaluate safety data.*

SECTION 3.2: End of Study

The study is currently closed to enrollment due to a low number of patients.

The end of study will be when all enrolled patients have discontinued study treatment or all patients have been enrolled into an extension study. Patients already enrolled will remain on study and will be allowed to continue study treatment until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1), withdrawal of consent, enrollment into an extension study, or death, whichever occurs first. In addition, the Sponsor may decide to terminate the study at any time

If the Sponsor decides to end the study, patients still receiving study treatment may be offered enrollment in an extension study if, in the opinion of the investigator and in consultation with the Medical Monitor, the patient would potentially benefit from continuing therapy.

~~The primary PFS analysis will be performed when approximately 238 investigator assessed PFS events in the ITT population have occurred or when the last patient has been randomized, whichever occurs last.~~

~~The end of study is when approximately 291 deaths in the ITT population have been observed. In addition, the Sponsor may decide to terminate the study at any time.~~

SECTION 3.3.2: Rationale for Gemcitabine, Cisplatin, or Carboplatin as a Comparator

~~On the basis of results from a Phase III randomized trial, which has shown a PFS and OS benefit for erlotinib after induction treatment in unselected patients who have not progressed (Cappuzzo et al. 2010), erlotinib was approved as maintenance treatment for patients with NSCLC in the first line setting. Therefore, in accordance with the NCCN guidelines, switch maintenance therapy with erlotinib can be considered for patients randomized to the control arm in this study (see Section 1.4).~~

~~SECTION 3.3.3: Rationale for Progression Free Survival as Primary Endpoint~~

~~Investigator assessed PFS (which will be supported by an IRF assessed PFS analysis, one of the secondary endpoints of the study) is the primary endpoint for this study.~~

~~PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit risk of the new treatment compared to available therapies (Guidance for Industry 2007; European Medicines Agency 2012). A PFS HR of 0.60 will~~

be targeted in PD-L1–selected population, which constitutes a clinically meaningful benefit in this patient population.

New treatment modalities such as targeted therapies and immunotherapy are emerging as highly effective regimens that are providing improvements in patient outcomes far beyond what has been achieved prior (Ellis et al. 2014). In particular, immunotherapy has been correlated and/or associated with durable responses, significant prolongation of PFS, and improvement of quality of life. Additionally, meta-analyses have indicated that PFS can be considered a good measure of clinical benefit for patients with locally advanced/metastatic NSCLC (Laporte et al. 2013). This study will test the hypothesis/assumption that treatment with atezolizumab will provide prolonged PFS compared with treatment with platinum-based chemotherapy in patients with squamous Stage IV NSCLC.

SECTION 3.3.3: Rationale for Allowing Patients to Continue Atezolizumab Treatment until Loss of a Clinical Benefit

In addition, while the primary endpoint measure (PFS by investigator) and secondary endpoint measures (ORR, DOR, and TIR by investigator and PFS by IRF) comparing the atezolizumab and gemcitabine-/cisplatin or carboplatin arms will use RECIST v1.1, exploratory analyses of PFS, ORR, DCR, and DOR with use of modified RECIST criteria will be performed for patients randomized to receive atezolizumab. Modified RECIST allows the incorporation of new lesions into the calculation of total tumor burden after baseline and takes into account the potential for pseudoprogression/tumor immune infiltration.

SECTION 3.3.4: Rationale for Patient Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (HRQoL) (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for trials that use PFS as a primary endpoint, where it is important to translate the delay in disease progression into an endpoint that is meaningful to patients.

Chest pain, dyspnea, and cough have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. Therefore, in order to assess TTD of lung cancer symptoms (cough, dyspnea, and chest pain) in this study, the SILC scale will be used. The SILC scale will be used to assess the delay of onset of primary distressing lung cancer symptoms reported by patients with Stage IV squamous NSCLC in the first-line setting.

In addition, the BR.21 study (erlotinib vs. BSC in second- or third-line NSCLC) demonstrated that longer TTD in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and QLQ-LC13 was consistent with superior PFS, OS, and quality of life benefits in the erlotinib arm compared with the placebo arm

~~(Aaronson et al. 1993; Bergman et al. 1994; Bezjak et al. 2006). In addition, patients in the afatinib LUX Lung first line study reported significant delay of TTD in lung cancer symptoms (cough, pain, dyspnea) as measured by the EORTC QLQ-C30 and QLQ-LC13 (Yang et al. 2013). In order to assess the HRQoL *health- related quality of life* and symptom severity of patients in this trial, PRO data will be collected from patients enrolled in this study using the validated questionnaires EORTC QLQ-C30 and QLQ-LC13.~~

~~The EQ-5D-3L PRO instrument (see Appendix 10) is included in the trial to generate health related quality of life utility scores for use in economic models for reimbursement.~~

SECTION 3.3.6: Rationale for the Collection of ~~Mandatory~~*Optional* Tumor Specimens at Radiographic Progression

~~A mandatory tumor biopsy will be performed (both treatment arms), if clinically feasible, at the time of radiographic progression in order~~*Patients in both treatment arms may undergo an optional tumor biopsy at the time of radiographic disease progression if clinically feasible. To do this, patients must sign a separate consent. These data will be used* to evaluate the utility of the biopsy in distinguishing pseudoprogression/tumor immune infiltration from true progression.

SECTION 3.4: Outcome Measures

The study is currently closed to enrollment due to a low number of patients; therefore, the outcome measures of this study are no longer applicable and formal analyses of efficacy or safety will not be performed.

~~SECTION 3.4.1: Efficacy Outcome Measures~~

~~SECTION 3.4.1.1: Primary Efficacy Outcome Measure~~

~~The primary efficacy outcome measure for this study is as follows:~~

- ~~PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator with use of RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of last tumor assessment. Patients with no post baseline tumor assessment will be censored at the randomization date plus 1 day.~~

~~SECTION 3.4.1.2: Secondary Efficacy Outcome Measures~~

~~The secondary efficacy outcome measures for this study are as follows:~~

- ~~Objective response (PR plus CR) as determined by the investigator according to RECIST v1.1~~
- ~~OS, defined as the time from randomization to death from any cause~~
- ~~TTD in patient reported lung cancer symptoms (cough, dyspnea, or chest pain, whichever occurs first) with use of the SILC scale symptom score, defined as time from randomization to the first deterioration maintained for two assessments or one assessment followed by death from any cause within 1 week~~

- ~~PFS, defined as the time from randomization to the first occurrence of disease progression as determined by IRF with use of RECIST v1.1 or death from any cause, whichever occurs first~~
- ~~DOR, defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator with use of RECIST v1.1, or death from any cause, whichever occurs first~~
- ~~TIR, defined as the same as DOR for responders. For non responders, TIR is defined as date of randomization plus 1 day.~~
- ~~1 year OS and 2 year OS~~
- ~~TTD in patient reported lung cancer symptoms, defined as time from randomization to deterioration (10 point change) on each of the EORTC QLQ C30 and EORTC QLQ LC13 symptom subscales (cough, dyspnea [single item and multi item subscales], chest pain, arm/shoulder pain, or fatigue) maintained for two assessments or one assessment followed by death from any cause within 3 weeks~~
- ~~Change from baseline in patient reported lung cancer symptoms (chest pain, dyspnea, and cough) on the symptom severity score of the SILC scale~~

~~SECTION 3.4.2: Safety Outcome Measures~~

~~The safety outcome measures for this study are as follows:~~

- ~~Incidence, nature, and severity of adverse events graded according to the NCI CTCAE v4.0~~
- ~~Changes in vital signs, physical findings, and clinical laboratory test results during and following atezolizumab administration~~
- ~~Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters~~

~~SECTION 3.4.3: Pharmacokinetic Outcome Measures~~

~~The PK outcome measures for this study are as follows:~~

- ~~Maximum serum atezolizumab concentration observed (C_{max}) after infusion on Day 1 of Cycle 1~~
- ~~Minimum serum atezolizumab concentration observed (C_{min}) prior to infusion on Day 1 of Cycles 2, 3, 4, 8, 16, and every eight cycles thereafter, at treatment discontinuation, and at 120 (±30) days after the last dose of atezolizumab~~

~~SECTION 3.4.4: Exploratory Outcome Measures~~

~~The exploratory outcome measures for this study are as follows:~~

- ~~ORR, DCR, DOR, and TIR as determined by IRF according to RECIST v1.1~~
- ~~PFS, ORR, DCR, DOR, and TIR as determined by IRF according to modified RECIST (atezolizumab only; see Appendix 5)~~
- ~~PFS, ORR, DCR, DOR, and TIR as determined by the investigator according to modified RECIST (atezolizumab only; see Appendix 5)~~

- ~~DCR, defined as the rate of patients with a complete or partial response as best response or with stable disease maintained for ≥6 weeks, as determined by the investigator according to RECIST v1.1~~
- ~~PFS at 6 months and at 1 year~~
- ~~OS rate at 3 years~~
- ~~Status of immune cell infiltrate and other exploratory biomarkers in mandatory biopsy specimens collected at progression~~
- ~~Status of PD-L1 , immune , and NSCLC related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood (or blood derivatives) collected before, during, or after treatment with atezolizumab or at progression and association with disease status and/or response to atezolizumab~~
- ~~Utility scores of the EQ-5D-3L questionnaire~~
- ~~Change from baseline in PROs of health related quality of life, lung cancer related symptoms, and health status as assessed by the EORTC QLQ-C30 and LC13~~

SECTION 4.1: Patients

~~Approximately 155 sites globally will participate in the study, and approximately 400~~ PD-L1–selected chemotherapy naive patients with Stage IV squamous non–small cell lung cancer will be enrolled in this study.

SECTION 4.1.1: Inclusion Criteria

- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception during study treatment that results in a low failure rate of <1% per year when used consistently and correctly. Female ~~and male~~ patients treated with atezolizumab should continue contraception use for ~~90 days~~ *5 months* after the last dose.

SECTION 4.1.2.3: Exclusion Criteria Related to Medications

~~Hormone replacement therapy or oral contraceptives~~

SECTION 4.3.1.1: Atezolizumab (MPDL3280A)

The atezolizumab (MPDL3280A) drug product is provided *as a sterile liquid* in a single-use, 20-mL ~~USP/Ph. Eur. Type 1~~ glass vial ~~as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration~~. ~~The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.~~

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

For further details on the ~~storage and preparation~~*formulation and handling* of atezolizumab, see the Pharmacy Manual and Investigator's Brochure.

SECTION 4.3.1.3: Erlotinib

Switch maintenance to erlotinib is *no longer* permitted for patients randomized to Arm B. *However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.*

Erlotinib will be ~~obtained from commercial sources at each participating site~~*provided by the Sponsor if required by local health authority regulations.*

SECTION 4.3.2.2: Gemcitabine +Cisplatin or Carboplatin

~~For patients with non progressive disease after the platinum based chemotherapy, switch maintenance with erlotinib can be considered by the investigator in accordance with the NCCN guidelines.~~

SECTION 4.3.2.3: Erlotinib

~~For those patients who receive switch maintenance with erlotinib, institutions should follow the NCCN guidelines and dosage and administration instructions in the package insert.~~

~~See the package insert for erlotinib (TARCEVA®) for more information on erlotinib dosing~~*Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.*

SECTION 4.3.3: Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, gemcitabine, cisplatin, ~~and~~ carboplatin*, and erlotinib*) will be provided by the Sponsor where required by local health authority regulations.

SECTION 4.3.4: Post-Study Access to Atezolizumab Investigational Medicinal Product Accountability

The Sponsor will evaluate the appropriateness of continuing to provide atezolizumab to patients assigned to this treatment ~~after evaluating the primary and secondary efficacy outcome measures and safety data gathered in the study and~~ in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

~~These analyses may be conducted prior to completion of the study.~~

SECTION 4.4.1: Permitted Therapy

The following therapies should continue while patients are in the study:

- ~~Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer~~

~~All medications must be recorded on the appropriate Concomitant Medications electronic Case Report Form (eCRF).~~

Switch maintenance ~~therapy with erlotinib is permitted and can be considered for patients randomized to the control arm. Investigators should follow the NCCN guidelines and dosage and administration instructions in the package insert for erlotinib (TARCEVA®)~~*treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.* ~~Erlotinib use as the protocol allowed maintenance therapy for the control arm should be recorded on the specific erlotinib eCRF and not as a concomitant medication.~~

SECTION 4.4.2: Cautionary Therapy for Atezolizumab-Treated Patients

Guidelines for the management of immune-mediated adverse events are *provided in Section 6 (Guidance for the Investigator) of the atezolizumab Investigator's Brochure*~~described in Section 5.1.7~~.

SECTION 4.4.3: Prohibited Therapy

The following medications are prohibited while in the study, unless otherwise noted:

- ~~Traditional herbal medicines as their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity~~

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator, provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

SECTION 4.5.1: Informed Consent Forms and Pre-Screening/Screening Log

Patients who are treated with atezolizumab and who show apparent radiographic progression at a tumor response evaluation ~~and have alternative anti-cancer therapies available to them~~ must sign consent at that time to ~~have a biopsy of the progressing lesion and~~ acknowledge deferring ~~these~~*other* treatment options in favor of continuing atezolizumab.

Patients in both treatment arms may undergo an optional tumor biopsy at the time of radiographic disease progression if clinically feasible. To do this, patients must sign a separate consent.

SECTION 4.5.5: Tumor and Response Evaluations

Tumor assessments will be performed every 6 weeks (±7 days) for ~~12 months~~*48 weeks* following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (for patients in both treatment arms) or loss of clinical benefit (for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1), withdrawal of consent, ~~death, or study termination by the Sponsor,~~ *enrollment into an extension study, or death,* whichever occurs first.

~~Scans will be submitted for central review to an IRF.~~

SECTION 4.5.6: Laboratory, Biomarker, and Other Biological Samples

The schedule of laboratory assessments should be performed according to Appendix 1. PK, ATA, and biomarker evaluations are no longer required.

Samples for the following laboratory tests ~~will~~*are to* be sent to the study site's local laboratory for analysis:

- (…)
- ~~Epstein Barr virus serology~~

  ~~Screening sample collection only; serology tests to be performed only in patients who experience an acute inflammatory event such as systemic inflammatory response syndrome while receiving study treatment~~

~~A central laboratory will coordinate the sample collection of tissue and blood samples for research related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments. Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis:~~

- ~~ATA assays (patients assigned to atezolizumab only)~~

  ~~Serum samples will be assayed for the presence of ATAs to atezolizumab with use of validated immunoassays. Accompanying PK samples will be collected at the same timepoints.~~

- ~~PK assay (patients assigned to atezolizumab only)~~

  ~~Blood samples for PK assessments will be obtained according to the schedule in Appendix 2.~~

  ~~Serum samples will be assayed for atezolizumab concentration with use of a validated immunoassay.~~

- ~~Biomarker assays~~

  ~~Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to NSCLC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2. Samples will be processed to obtain plasma and serum for the determination of changes in blood based biomarkers (e.g., ctDNA). Whole blood samples may be processed to obtain their derivatives (e.g., RNA and DNA) and may be evaluated for immune related, tumor type related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms.~~

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

- *Blood biomarker samples will no longer be collected, but samples already collected will be kept and used per original signed informed consent.*

For patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR), any leftover material from *samples already collected* ~~the above sample collection~~ will be stored and used for exploratory analyses as indicated in Section 4.5.12.

SECTION 4.5.7.2: *Optional* Tumor Samples at the Time of Radiographic Progression

Patients in both treatment arms ~~will~~*may* undergo a*n optional*~~mandatory~~ tumor biopsy to obtain a tumor sample~~, unless not clinically feasible,~~ at the time of radiographic disease progression *(preferably within 40 days of radiographic progression or prior to start of the next anti-cancer treatment, whichever is sooner) if they have provided consent for optional biopsy and if clinically feasible.*

The preferred sample types include: resections, core needle, excisional, incisional, punch, or forceps biopsies. If such specimens are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens e.g., from pleural effusion, and lavage samples) can also be submitted.

~~Acceptable samples include:~~

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

SECTION 4.5.7.3: Tumor Samples at Other Timepoints

Patients with additional tissue samples from procedures performed at different times during the course of their study participation (during treatment ~~and during survival follow up~~) who have signed the RCR optional consent will be requested (but not required) to also submit these *optional fresh biopsy* samples for central testing. *Tumor tissue samples collected at the time of clinical events (e.g., clinical response) are preferred.*

SECTION 4.5.9: Anti-Therapeutic Antibody Testing

ATA testing will no longer be performed.

~~Treatment with atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see Appendix 1 and Appendix 2 for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.~~

SECTION 4.5.11: Patient-Reported Outcomes

PRO assessments are no longer required, and PRO data will no longer be collected.

~~PRO data will be collected via the SILC, EORTC QLQ C30, QLQ LC13, and EQ 5D 3L questionnaires to more fully characterize the clinical profile of atezolizumab.~~

~~The questionnaires will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to the performance of non-PRO assessments and the administration of study treatment.~~

~~Patients will use an electronic PRO (ePRO) device to capture PRO data. The ePRO device and/or instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed by appropriate study personnel securely via the Internet.~~

~~The SILC scale will be used to assess patient reported severity of lung cancer symptoms (cough, dyspnea, and chest pain; see Appendix 9). The SILC scale is a nine item content valid self report measure of lung cancer symptoms. It measures severity of cough, dyspnea, and chest pain with a total symptom severity score. This~~

~~questionnaire will be completed using an ePRO device at the patient's home on a weekly basis, then monthly during survival follow up for 6 months following radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1). For patients who discontinue treatment for any reason other than disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after disease progression according to RECIST v1.1), assessment should continue at the same frequency as would have been followed if the patient had continued to receive study treatment. The assessments should be continued until disease progression according to RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), then follow the survival follow up frequency.~~

~~The EORTC QLQ-C30 (see Appendix 7) is a validated and reliable self report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales.~~
~~The EORTC QLQ-C30 module takes approximately 10 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow up at 3 and 6 months following radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue treatment after disease progression according to RECIST v1.1). For patients who discontinue treatment for any reason other than disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue treatment after disease progression according to RECIST v1.1), assessment should continue at the same frequency as would have been followed if the patient had continued to receive study treatment. The assessments should be continued until disease progression according to RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue treatment after disease progression according to RECIST v1.1), then follow the survival follow up frequency.~~

~~The EORTC QLQ-LC13 (see Appendix 8) module incorporates one multiple item scale to assess dyspnea and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The EORTC QLQ-LC13 module takes approximately 5 minutes to complete. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow up at 3 and 6 months following radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue treatment after disease progression according to RECIST v1.1). For patients who discontinue treatment for any reason other than disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab treated patients who continue~~

~~treatment after disease progression according to RECIST v1.1), assessment should continue at the same frequency as would have been followed if the patient had continued to receive study treatment. The assessments should be continued until disease progression according to RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), then follow the survival follow-up frequency.~~

~~The EQ-5D-3L is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that is used to build a composite of the patient's health status (see Appendix 10). The EQ-5D-3L will be utilized in this study for economic modeling. This questionnaire will be completed on the ePRO tablet at each scheduled study visit during study treatment and during survival follow-up at 3 and 6 months following radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1). For patients who discontinue treatment for any reason other than disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), assessment should continue at the same frequency as would have been followed if the patient had continued to receive study treatment. The assessments should be continued until disease progression according to RECIST v1.1 (or loss of clinical benefit atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), then follow the survival follow-up frequency.~~

~~Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 4.5.11.~~

SECTION 4.5.12.3: Sample Collection

The following sample will be used for identification of genetic (inherited) biomarkers:

- Whole blood sample for DNA extraction (6 mL)*, which may be collected at any time during the course of the study* ~~(see Appendix 1 and Appendix 2)~~

SECTION 4.5.13.1: Screening/Baseline Assessments

See *Appendix 1 of the previous protocol Version 4* for the schedule of screening assessments~~ and Appendix 2 for the schedule of PK, ATA, and biomarker sampling~~.

SECTION 4.5.13.2: Assessments during Treatment

Tumor assessments should occur every 6 weeks (± 7 days) for ~~12 months~~*48 weeks* following Cycle 1, Day 1 and every 9 weeks (± 7 days) ~~thereafter~~*after completion of the Week 48 tumor assessment*, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1),

withdrawal of consent, ~~death, or study termination by the Sponsor,~~ *enrollment into an extension study, or death,* whichever occurs first.

See Appendix 1 for the schedule of assessments performed ~~during the treatment period and Appendix 2 for the schedule of PK, ATA, and biomarker sampling~~.

SECTION 4.5.13.3: Assessments at Treatment Discontinuation Visit

~~Patients who discontinue study treatment must be followed according to the follow-up visit schedule for progression and/or survival until death, loss to follow up, or withdrawal of consent, which will be defined as study discontinuation.~~

SECTION 4.5.13.4: Follow-Up Assessments

For patients who discontinue study treatment for any reason other than radiographic progressive disease per RECIST v1.1, tumor assessments should continue at the same frequency as would have been followed if the patient had continued study treatment until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, ~~death, or study termination by the Sponsor,~~ *enrollment into an extension study, or death,* whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 should continue tumor assessments according to the protocol schedule of response assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, ~~death, or study termination by the Sponsor,~~ *enrollment into an extension study, or death,* whichever occurs first.

~~Follow-up data collection will also include PROs (only for the first 6 months after disease progression per RECIST v1.1, or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1); SILC will be completed monthly using an ePRO device at the patient's home and EORTC QLQ-C30, EORTC QLQ-C30 LC13, and EQ-5D-3L will be completed at the site on the ePRO tablet at 3 and 6 months after disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1). For patients who discontinue study treatment for any reason other than radiographic progressive disease per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), PRO assessments should continue at the same frequency as would have been followed if the patient had continued study treatment until radiographic disease progression (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.~~

~~Survival follow-up should continue until death, withdrawal of consent, the patient is lost to follow up, or study termination by the Sponsor, whichever occurs first. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) when permissible, to obtain information about survival status and date only.~~

~~See Appendix 1 and Appendix 2 for assessments to be performed during Follow Up visits.~~

SECTION 4.6.2: Study Treatment Discontinuation

- Radiographic disease progression per RECIST v1.1

  Exception for atezolizumab treatment:

  Patients must provide written consent to acknowledge deferring ~~any standard~~*other* treatment options ~~that may exist~~ in favor of continuing atezolizumab treatment at the time of initial progression

  ~~Availability of a mandatory biopsy sample collection, unless not clinically feasible as assessed by the investigators, at the site of local or metastatic progression~~

SECTION 4.6.3: Study and Site Discontinuation

The study is currently closed to enrollment due to a low number of patients.

SECTION 5: Assessment of Safety

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma. ~~Atezolizumab is not approved and is currently in clinical development. Human experience is currently limited and the entire safety profile is not known at this time.~~ The following information is based on results from nonclinical and clinical studies *for atezolizumab* and published data on similar molecules.

SECTION 5.1.1: Risks Associated with Atezolizumab

Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, *pneumonitis,* myositis, and myasthenia gravis, have been observed in *the Phase Ia* Study PCD4989g. ~~A more comprehensive list of adverse events observed with atezolizumab is provided in Section 1.6.2.~~ For further details regarding clinical safety, *including a detailed description of anticipated safety risks for atezolizumab,* see the atezolizumab Investigator's Brochure.

SECTION 5.1.3.3: Risks Associated with Erlotinib

Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.

SECTION 5.1.5: *Dose Modification*

SECTION 5.1.5.1: *General Notes Regarding Dose Modification*

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events 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 considers it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during study 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 chemotherapy, the dose of the other chemotherapy component does not require modification and the other chemotherapy component(s) may be administered if there is no contraindication.*
- *The investigator 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.*

SECTION 5.1.6: Atezolizumab Dose Modifications, *Treatment Delays, or Treatment Discontinuation*

~~Management of atezolizumab-specific adverse events is present in Section 5.1.7.~~

SECTION 5.1.7: Management of Atezolizumab-Specific Adverse Events

Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, ~~mycophenolate, or TNF α inhibitors~~*or other immunosuppressive agents.*

The primary approach to Grade 1 and 2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade immune-mediated adverse events, atezolizumab should be withheld and oral/parenteral steroids administered. Recurrent Grade 2 immune-mediated adverse events may also mandate withholding atezolizumab or the use of steroids. Consideration for 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. ~~The investigator should consider the benefit risk balance a given patient may be experiencing prior to further administration of atezolizumab.~~

Management of systemic immune activation is presented below. ~~For the management of other adverse events associated with atezolizumab not provided in Sections 5.1.7.1–5.1.7.10. Refer to~~*See* the atezolizumab Investigator's Brochure *for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, infusion-related reactions, potential pancreatic or eye toxicity, and other immune-mediated adverse events.* ~~*Guidelines for infusion-related reactions are provided in Section 4.3.2.1 (*~~*See Appendix 12 for precautions for anaphylaxis*~~)~~.

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

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

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

~~SECTION 5.1.7.1: Pulmonary Events~~

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

~~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:~~

- ~~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 (diffusion capacity of the lung for carbon monoxide [DL_{CO}])~~

- ~~Pulmonary function testing with a pulmonary embolism protocol~~

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

Table 12: Management Guidelines for Pulmonary Events/Pneumonitis

Table 12 has been removed from the protocol.

~~SECTION 5.1.7.2: Hepatic Events~~

~~Immune mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment.~~

~~While in this study, patients presenting with right upper quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.~~

~~If LFTs increase, concurrent medications, viral hepatitis, and toxic or neoplastic 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 antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.~~

~~Table 13: Management Guidelines for Hepatic Events~~

Table 13 has been removed from the protocol.

~~SECTION 5.1.7.3: Gastrointestinal Events~~

~~Immune mediated colitis has been associated with the administration of atezolizumab.~~

~~If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased C reactive protein or platelet count or bandemia), the following is recommended:~~

- ~~Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates in order to confirm colitis diagnosis. If possible, one or two biopsy specimens should be snap frozen and stored.~~
- ~~Perform laboratory tests to rule out alternate etiology (i.e., WBCs and stool calprotectin)~~

~~Table 14: Management Guidelines for Gastrointestinal Events (Diarrhea/Colitis)~~

Table 14 has been removed from the protocol.

~~**SECTION 5.1.7.4: Endocrine Events**~~

~~Thyroid disorders or adrenal insufficiency 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. TSH and free thyroxine (T4) levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.~~

Table 15: Management Guidelines for Endocrine Events

Table 15 has been removed from the protocol.

~~**SECTION 5.1.7.5: Ocular Events**~~

~~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.~~

Table 16: Management Guidelines for Ocular Events

Table 16 has been removed from the protocol.

~~**SECTION 5.1.7.6: Infusion Related Reactions**~~

~~No premedication is indicated for the administration of atezolizumab in Cycle 1. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.~~

Table 17: Management Guidelines for Infusion-Related Reactions

Table 17 has been removed from the protocol.

SECTION 5.1.7.7: Pancreatic Events

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

Table 18: Management Guidelines for Pancreatitis

Table 18 has been removed from the protocol.

~~**SECTION 5.1.7.8: Dermatologic Events**~~

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

Table 19: Management Guidelines for Dermatologic Events

Table 19 has been removed from the protocol.

~~**SECTION 5.1.7.9: Neurologic Disorders**~~

~~Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternate etiologies.~~

Table 20: Management Guidelines for Neurologic Disorders

Table 20 has been removed from the protocol.

~~**SECTION 5.1.7.10: Systemic Immune Activation**~~

~~Systemic immune activation (SIA) is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when given in combination with other immunomodulating agents. SIA should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab.~~

~~Recommendations regarding early identification and management of SIA are provided below. In the event of suspected SIA, the Medical Monitor should be contacted immediately for additional guidance.~~

~~Early disease recognition is critical, and the clinician should consider SIA if, in the absence of alternate etiologies, the presence of ≥2 of the following are present:~~

- ~~Hypotension refractory to aggressive IV fluid challenge~~
  - ~~May/can require vasopressor support~~
- ~~Respiratory distress requiring aggressive supportive care~~
  - ~~Supplemental oxygen, possible intubation~~
- ~~Fever greater than 38.5°C~~
- ~~Acute renal or hepatic failure~~
- ~~Bleeding from coagulopathy~~
- ~~Unexplained laboratory test abnormalities (change from baseline):~~
  - ~~Cytopenias (≥Grade 2 in two or more lineages), significant transaminitis, coagulopathy, elevated creatinine~~

~~Initial evaluation should include CBC with peripheral smear, PT, PTT, fibrinogen, D-dimer, ferritin, triglyceride, AST/ALT, total bilirubin, LDH, and a complete neurologic and abdominal examination (assess for hepatosplenomegaly).~~

~~If cytopenias (≥2 lineages and change from baseline) are present or ferritin is ≥3000 ng/mL, the following evaluations should also be performed:~~

- ~~Bone marrow biopsy/aspirate (assess for evidence of hemophagocytosis)~~
- ~~sCD25 (soluble IL-2 receptor)~~
- ~~Natural killer cell activity~~
- ~~Cytomegalovirus, Epstein-Barr virus and herpes simplex virus evaluation (evaluate for reactivated or active disease)~~

~~SIA is a clinical syndrome characterized by the following:~~

- ~~Onset greater than 24 hours after exposure to drug~~

  ~~AND~~

- ~~Progressive clinical deterioration in an acutely ill patient (in the absence of an alternate etiology)~~

  ~~AND~~

- ~~Involving multiple organs (≥2)~~

  ~~AND~~

- ~~Demonstrating specific laboratory test abnormalities~~

~~Diagnosis of SIA should only be made in patients who present with a constellation of clinical findings as outlined above and who fulfill the following established diagnostic criteria in the absence of an alternate etiology.~~

~~The diagnostic criteria and recommended management for systemic immune activation are provided in Table 21 below.~~

Table 21: Diagnostic Criteria and Management for Systemic Immune Activation

Table 21 has been removed from the protocol.

SECTION 5.3.5.8: Deaths

~~For this protocol, mortality is an efficacy endpoint.~~

~~During survival follow-up, deaths attributed to progression of NSCLC should be recorded only on the Survival eCRF.~~

SECTION 5.4.3.1: Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within *5 months*~~90 days~~ after the last dose of atezolizumab or within 6 months after the last dose of cisplatin.

SECTION 5.4.3.2: 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 the last dose of atezolizumab or within~~ 6 months after the last dose of gemcitabine, cisplatin, or carboplatin.

SECTION 6: Statistical Considerations and Analysis Plan

The study is currently closed to enrollment due to a low number of patients; therefore, formal analysis of efficacy endpoints will not be performed.

~~Primary and secondary analyses (PFS, OS) will be performed on all randomized patients (i.e., ITT) irrespective of whether the assigned treatment was actually received. ORR, DCR, and TIR analyses will be performed on all randomized patients who have measureable disease at baseline. DOR analyses will be performed on the subset of patients who achieve an objective response. For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.~~

~~For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error.~~

~~For TTD analysis, only patients with a non missing baseline assessment will be included in the analyses. For change from baseline analysis, only patients with a non missing baseline assessment and at least one non missing post baseline assessment will be included in the analyses.~~

SECTION 6.1: Determination of Sample Size

The study is currently closed to enrollment due to a low number of patients; therefore, sample size estimation is no longer applicable.~~Estimates of the number of events required to demonstrate efficacy in terms of PFS (primary PFS analysis as defined in Section 6.4.1) and OS are based on the following assumptions:~~

- ~~Two-sided significance level of 5% for PFS~~
- ~~97.6% power to detect an HR of 0.6 for PFS, corresponding to an improvement in median PFS from 6 months to 10 months~~
- ~~Two-sided significance level of 3% for OS~~
- ~~80% power for OS to detect an HR of 0.7, corresponding to an improvement in median OS from 11 months to 15.7 months~~
- ~~Event times exponentially distributed~~

- Accrual ramp-up time of 12 months to reach 20 patients per month thereafter
- Dropout rate assumed for both treatment arms

  5% per 12 months for PFS

  5% per 24 months for OS

With these assumptions, approximately 238 PFS events are required. This number of events corresponds to a minimal detectable HR of approximately 0.776. Approximately 400 patients will be enrolled in the study. Primary analysis of PFS (as defined in Section 6.4.1 using the U.S. registration censoring rule) will occur when approximately 238 PFS events have occurred or after the last patient has been enrolled, whichever occurs last. This is expected at approximately 28 months after the first patient is randomized.

Given this sample size and the assumptions listed above, it is expected that approximately 291 deaths will be required for the final OS analysis.

SECTION 6.2: Summaries of Conduct of Study

Subject disposition will be provided in listing format due to the small sample size. Summaries will not be provided. Enrollment, study drug administration, and discontinuation from the study will be summarized by treatment arm. The incidence of study drug discontinuation for reasons other than disease progression will similarly be tabulated. Protocol deviations, including major deviations of inclusion/exclusion criteria, will be summarized in a similar manner by treatment arm.

SECTION 6.3: Summaries of Treatment Group Comparability

Demographic and baseline characteristics, such as age, sex, race/ethnicity, baseline disease characteristics, ECOG performance status, and number of prior cancer treatments, will be *provided in listing format* summarized by treatment arm.

Descriptive statistics (mean, median, SD, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

SECTION 6.4.1: Primary Efficacy Endpoint

The primary efficacy analysis is the comparison of PFS between the two treatment arms of atezolizumab and gemcitabine + cisplatin or carboplatin. The primary endpoint, PFS, is defined as the time (in months) between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined on the basis of investigator assessment per RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post baseline tumor assessment will be censored at the randomization date plus 1 day.

For U.S. registrational purposes, the primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients

with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits. Type I error control will be applied to this analyses of PFS.

The null and alternative hypotheses for PFS analysis can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in Arm A (atezolizumab) and Arm B (control), respectively:

$H_0: S_A(t) = S_B(t)$ versus $H_1: S_A(t) \neq S_B(t)$

The stratification factors will be those used during randomization, which include sex (male vs. female), ECOG performance status (0 vs.1), presence of liver metastases at baseline (yes vs. no), and PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC3). An unstratified analysis will also be performed. In case that the numbers of patients are too small in some strata, patients in these strata may be pooled for analysis according to a pre-specified method presented in the statistical analysis plan.

The HR will be estimated using a stratified Cox regression model including 95% CIs. The unstratified HR will also be presented.

Kaplan Meier methodology will be used to estimate the median PFS for each treatment arm and to construct survival curves for the visual description of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

The following analyses will be performed for both PFS endpoints described above:

- Analyses described in Section 6.7.7 (Analyses at Landmark Timepoints)
- Analyses described in Section 6.7.9 (Subgroup Analyses)
- Secondary endpoint of PFS by IRF assessment, per RECIST v1.1 in Section 6.4.7.2

SECTION 6.4.2: Secondary Efficacy Endpoints

The secondary endpoints include investigator assessed ORR, DOR, and TIR per RECIST v1.1, OS, IRF assessed PFS per RECIST v1.1, and TTD per SILC scale and EORTC scale. The final analyses of ORR, TTD per SILC scale and EORTC scale, DOR, and TIR, as well as the first interim analysis of OS, will occur at the time of the final PFS analysis. It is estimated approximately 175 death events (60% of full OS information) will be observed. The second OS interim analysis will be conducted when approximately 239 death events (82% of full OS information) have occurred. The final analysis of OS is planned when approximately 291 deaths have been observed.

If the primary endpoint of PFS is statistically significant at a 5% 2-sided significance level, the secondary endpoints of ORR and TTD (per SILC scale) will be tested simultaneously in the ITT population, each at a two-sided 1% significance level.

~~The OS endpoint will be tested next at a two-sided significance level depending on the outcome of the prior two tests, as follows:~~

1. ~~If both the ORR and the TTD per SILC scale endpoints are statistically significant at the 1% significance level, OS will be tested at a 5% significance level.~~
2. ~~Otherwise, if either the ORR or the TTD per SILC scale endpoint is statistically significant at a 1% significance level, OS will be tested at a 4% significance level.~~
3. ~~If neither the ORR nor the TTD per SILC scale endpoint is statistically significant at the 1% significance level, OS will be tested at a 3% significance level.~~

~~SECTION 6.4.2.1: Objective Response Rate~~

~~An objective response is defined as either an unconfirmed CR or PR, as determined by the investigator with use of RECIST v1.1. Patients not meeting these criteria, including patients without any post baseline tumor assessments, will be considered non-responders.~~

~~ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two arms using the stratified Cochran-Mantel-Haenszel test, stratified by the same factors used in the primary efficacy analysis.~~

~~SECTION 6.4.2.2: Overall Survival~~

~~OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died by the date of data cutoff date will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.~~

~~OS will be analyzed using the same methods as PFS.~~

~~SECTION 6.4.2.3: One-Year and Two-Year Landmark Overall Survival Analysis~~

~~The 1-year and 2-year survival rate is defined as the percentage of patients who are still alive at 1 year and 2 years after randomization. The analysis population for the 1-year and 2-year survival rate will be the ITT population. The Kaplan-Meier method will be used to estimate the 1-year and 2-year survival rate for each treatment arm, along with the 95% CIs with use of Greenwood's formula. The difference in 1-year and 2-year survival rates between treatment arms will be assessed using the normal approximation method.~~

~~**SECTION 6.4.2.1: Patient Reported Outcomes (Symptoms in Lung Cancer Scale)**~~

~~Only TTD using the SILC scale will be part of the alpha spending.~~

~~TTD with use of the SILC scale is defined as the time from randomization to the first documented deterioration of disease symptom in the SILC symptom score (cough, dyspnea, or chest pain, whichever occurs first). In order for the symptom to be considered "deteriorated," the symptom score change from baseline must be held for at least two consecutive assessment timepoints or an initial deterioration followed by death within 1 week from the last assessment. Patients will be censored at the last time when they completed an assessment for cough, dyspnea, or chest pain if they have not deteriorated. If no post baseline assessment is performed, patients will be censored at the date of randomization plus 1 day. TTD using the SILC scale will be analyzed using the same methods as PFS.~~

~~**SECTION 6.4.2.5: Additional Patient Reported Outcomes**~~

~~TTD with use of the EORTC is defined as the time from baseline to the first time the patient's score shows a ≥10 point increase above baseline in any of the following EORTC transformed scores for cough, dyspnea (single item), dyspnea (multi item subscale), chest pain, or arm/shoulder pain. In order for the symptom to be considered "deteriorated," a score increase of ≥10 points above baseline must be held for at least two consecutive cycles or an initial score increase of ≥10 points is followed by death within 3 weeks from the last assessment. A ≥10 point change in the score is perceived by patients as clinically significant (Osoba et al. 1998). Patients will be censored at the last time when they completed an assessment for cough, dyspnea (single item), dyspnea (subscale items), chest pain, and arm/shoulder pain if they have not deteriorated. If no post baseline assessment is performed, patients will be censored at the randomization date plus 1 day. TTD with use of the EORTC scale will be analyzed using the same methods as PFS.~~

~~PROs of HRQoL, lung cancer related symptoms, and health status will be measured using the SILC, EORTC QLQ C30, and EORTC QLQ LC13. Summary statistics (mean, SD, median, 25th and 75th percentiles, range, and change from baseline) of linear transformed scores will be reported for all the items and subscales of the SILC, EORTC QLQ C30, and the QLQ LC13 according to the EORTC scoring manual guidelines and the SILC scale symptom scores. Completion and compliance rates will be summarized at each timepoint by treatment arm. Only patients with a non missing baseline assessment and at least one non missing post baseline assessment will be included in the analyses.~~

~~**SECTION 6.4.2.6: Duration of Response**~~

~~DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented, whichever occurs first. Disease progression will be determined on~~

the basis of investigator assessment with use of RECIST v1.1. DOR will be assessed in patients who had an objective response during the study as determined by the investigator with use of RECIST v1.1. Patients who have not progressed and who have not died by the date of data cutoff for analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

DOR analysis is performed on the basis of a non randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. DOR will be estimated using Kaplan Meier methodology. Comparisons between treatment arms will be made for descriptive purposes only.

SECTION 6.4.2.7: Time in Response

The two treatment arms will be compared with respect to TIR. Non responders will be considered as having an event and TIR will be defined as date of randomization plus 1 day; and for responders TIR will be the same as DOR. The methodologies outlined for the primary analysis of PFS will be used for the analyses of TIR.

SECTION 6.4.2.8: Independent Review Facility–Assessed PFS per RECIST v1.1

To support the primary analysis of investigator assessed PFS, the analysis of PFS as assessed by the IRF will be performed. The methodologies outlined for the primary analyses of PFS (for both definitions of PFS as described in Section 6.4.1) per the investigator will be used for the analyses of PFS based on IRF assessment.

SECTION 6.5: Safety Analyses

*Listings of safety data will be provided for the safety population and will include study drug exposure, adverse events, and deaths.*Safety analyses will be performed on the safety population (see Section 6). Summaries will be presented for the safety evaluable population by treatment arm.

Study drug exposure, including treatment duration, number of doses, and dose intensity, will be summarized for each treatment arm using descriptive statistics.

All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade 3, 4, and 5), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment arm.

~~Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.~~

~~Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data and changes in vital signs will be summarized by treatment arm.~~

~~Serum levels and incidence of ATA against atezolizumab will be summarized to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy.~~

SECTION 6.6: Pharmacokinetic Analyses

The study is currently closed to enrollment due to a low number of patients; therefore, samples will no longer be collected, and formal analysis of PK and pharmacodynamics samples will not be performed.~~PK and pharmacodynamic samples will be collected in this study as outlined in Appendix 2.~~

~~Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate. Additional PK and pharmacodynamic analysis will be conducted based upon the availability of data.~~

SECTION 6.7: Exploratory Analyses

The study is currently closed to enrollment due to low number of patients; therefore, formal analysis of exploratory endpoints will not be performed.

~~SECTION 6.7.1: Independent Review Facility–Assessed ORR, DOR, TIR, and DCR per RECIST v1.1~~

~~DCR is defined as the rate of patients with complete or partial response as best response or stable disease that has been maintained for ≥6 weeks as assessed by the IRF per RECIST v1.1.~~

~~The methodologies outlined in Sections 6.4.1 and 6.4.2 for primary and secondary efficacy endpoint analyses will be used for the analyses of ORR, DOR, TIR, and DCR based on IRF assessment.~~

~~SECTION 6.7.2: Independent Review Facility–Assessed ORR, DOR, TIR, DCR, and PFS per Modified RECIST~~

~~IRF-assessed ORR, DOR, TIR, DCR, and PFS with use of modified RECIST criteria will be limited to the atezolizumab arm only, with no comparison to the control arm. The methods outlined for the primary and secondary efficacy endpoint analyses will be used for these analyses.~~

~~SECTION 6.7.3: Investigator Assessed ORR, DOR, TIR, DCR, and PFS per Modified RECIST~~

~~Investigator assessed ORR, DOR, TIR, DCR, and PFS with use of modified RECIST criteria will be limited to the atezolizumab arm only, with no comparison to the control arm. The methods outlined for the primary and secondary efficacy endpoint analyses will be used for these analyses.~~

~~SECTION 6.7.4: Investigator Assessed DCR per RECIST v1.1~~

~~DCR is defined as the rate of patients with complete or partial response as best response or stable disease that has been maintained for ≥6 weeks by the investigator per RECIST v1.1.~~

~~The methodologies outlined in Section 6.4.2.1 will be used for the analyses of DCR based on the investigator assessment.~~

~~SECTION 6.7.5: Exploratory Biomarker Analysis~~

~~Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. The tumor biomarkers include but are not limited to PD-L1 and CD8, as defined by IHC, qRT-PCR, or other methods. Additional pharmacodynamic analyses will be conducted as appropriate.~~

~~SECTION 6.7.6: EQ-5D-3L Health Status Data~~

~~The EQ-5D-3L health status data will be used for obtaining utility measures for economic modeling. Patients without post baseline assessments will be excluded from this analysis. These analyses will not be analyzed as an endpoint for the Clinical Study Report.~~

~~SECTION 6.7.7: Six Month and One Year Landmark PFS Analysis~~

~~Six month and 1 year PFS analysis will occur at the time of final PFS analysis.~~

~~The 6-month and 1-year PFS rate is defined as the percentage of patients who are still progression free at 6 months or 1 year after randomization. The analysis population will be the ITT population. The Kaplan Meier method will be used to estimate the 6-month and 1-year PFS rate for each treatment arm, along with the 95% CIs with use of Greenwood's formula. The difference in 6-month/1-year PFS rates between treatment arms will be assessed using the normal approximation method.~~

~~SECTION 6.7.8: Three Year Landmark OS Analysis~~

~~The methodologies for landmark OS analysis outlined in Section 6.4.2.2 will be used.~~

~~SECTION 6.7.9: Impact of Demographic and Baseline Characteristics on PFS and OS~~

~~To assess the consistency of the study results in subgroups defined by demographic (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., PD-L1~~

~~tumor expression status, presence of liver metastases at baseline, ECOG performance status, prior lines of therapy, smoking history, etc.), the duration of PFS assessed by the investigator and OS in these subgroups will be examined. Summaries of PFS and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan Meier estimates of median PFS and OS, will be produced separately for each level of the categorical variables.~~

SECTION 6.8: Sensitivity Analyses on the Primary Endpoint

The study is currently closed to enrollment due to low number of patients; therefore, a formal sensitivity analysis of the primary endpoint will not be performed.

~~SECTION 6.8.1: Analysis Accounting for Missing Data~~

~~To support the PFS analyses defined in Section 6.4.1, a sensitivity analysis will be performed to evaluate the potential impact of missing scheduled tumor assessments on the primary analysis of PFS, as determined by the investigator with use of a PFS event imputation rule. If a patient has missed two or more assessments scheduled immediately prior to the date of the PFS event (disease progression or death), the patient will be counted as having progressed on the date of the first of these missing assessments.~~

~~The imputation rule will be applied to patients in both treatment arms. Statistical methodologies analogous to those used in the primary analysis of PFS as specified in Section 6.4.1 will be used for this sensitivity analysis.~~

~~SECTION 6.8.2: Independent Review Facility–Determined and Investigator-Determined Concordance Analyses~~

~~Concordance between the IRF-determined and investigator-determined assessments will be conducted. Summaries of agreement between the IRF-determined and the investigator-determined progressive disease status (yes vs. no) and objective response (yes vs. no) will be provided by treatment arm.~~

~~Summaries of agreement between the IRF-determined and the investigator-determined progressive disease dates (PDD_{IRF} and PDD_{INV}) for patients experiencing progressive disease on the basis of both the IRF and the investigator assessments will be provided by treatment arm.~~

~~SECTION 6.8.3: Censoring for Non-Protocol Anti-Cancer Therapy~~

~~PFS data for patients receiving non-protocol anti-cancer therapy prior to documented disease progression will be censored at the time of the last tumor assessment prior to therapy initiation.~~

~~SECTION 6.8.4: Discontinuation Caused by Toxicity Impact Analysis~~

~~A sensitivity analysis will be performed to assess the impact of discontinuation because of toxicity on the primary PFS comparison. Patients in Study GO29432 who discontinue study drug may undergo disease assessments at intervals that are different from those~~

~~mandated during study treatment. In this analysis, the PFS for any patient who discontinued study treatment prior to disease progression because of adverse events will be censored at the time of the last tumor assessment prior to study drug discontinuation.~~

~~SECTION 6.9: Handling of Missing Data~~

~~For PFS, patients without a date of disease progression and death will be analyzed as censored observations on the date of the last tumor assessment. If no post baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day. In the analysis of PFS for U.S. registrational purposes, data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits (see Section 6.4.1).~~

~~For objective response, patients without any post baseline assessment will be considered non responders.~~

~~For OS, patients who are not reported as having died will be analyzed as censored observations on the date when they were last known to be alive. If no post baseline data are available, OS will be censored at the date of randomization plus 1 day.~~

~~For DOR, patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.~~

~~For responders, TIR is censored the same way as DOR. Non responders will be considered as having an event at the date of randomization plus 1 day.~~

~~For TTD with use of SILC scale analysis, patients will be censored at the last time when they completed an assessment for cough, dyspnea, and chest pain if they have not deteriorated. If no post baseline assessment is performed, patients will be censored at the date of randomization plus 1 day.~~

SECTION 6.9.1: Interim Safety Analyses

~~An iDMC will be used to evaluate interim safety on a regular basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. Members of the iDMC will be external to the Sponsor and will follow a Charter that outlines their roles and responsibilities.~~*The study is currently closed to enrollment due to a low number of patients; therefore, interim safety data will not be evaluated by an iDMC.*

~~SECTION 6.9.2: Planned Interim Analysis~~

~~No interim analyses are planned for PFS in this study.~~

~~The first OS interim analysis will be conducted at the time of final PFS analysis. It is projected that approximately 175 OS events in the ITT population will have been observed at the time of final PFS analysis, but the exact timing of this analysis will depend on the actual number of PFS events. The stopping boundaries are shown in Table 31, with the exact boundaries depending on the outcome of the ORR test and TTD (SILC) test.~~

~~The second OS interim analysis will be conducted when approximately 82% of the information (i.e., approximately 239 OS events in the ITT population) has been observed. This is expected at 34 months after the first patient is enrolled, but the exact timing of this analysis will depend on the accrual of OS events. The stopping boundaries are shown in Table 31, with the exact boundaries depending on the outcome of the ORR test and TTD (SILC) test.~~

~~The final OS analysis will be performed when approximately 291 OS events have occurred. This analysis is expected at 43 months after the first patient is enrolled, but the exact timing of this analysis will depend on the accrual of OS events. The stopping boundaries are shown in Table 31, with the exact boundaries depending on the outcome of the ORR test and TTD (SILC) test.~~

Table 31: Interim and Final Analysis for Overall Survival

~~Table 31 has been removed from the protocol.~~

~~SECTION 6.9.3: Optional Interim Analysis~~

~~To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the primary endpoint of PFS beyond what is specified in Section 6.10.1. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.~~

~~The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.~~

~~The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC Charter will also be made available to relevant health authorities.~~

SECTION 8.2: Informed Consent

The Informed Consent Form will also contain the following additional signature pages:

- *A signature page for patients to undergo an optional tumor tissue biopsy at the time of radiographic disease progression, if clinically feasible.*

SECTION 9.4: Administrative Structure

~~Approximately 155 sites globally will participate in the study and approximately 400 patients will be randomized.~~

APPENDIX 1: Schedule of Assessments

The appendix has been updated to reflect the changes to the protocol.

APPENDIX 2: Schedule of Pharmacokinetic, Biomarker, and Anti-Therapeutic Antibody Assessments

The appendix and all cross references have been removed from the protocol.

Appendix 7: EORTC QLQ-C30

The appendix and all cross references have been removed from the protocol.

Appendix 8: EORTC QLQ-LC13

The appendix and all cross references have been removed from the protocol.

Appendix 9: Symptoms in Lung Cancer Scale

The appendix and all cross references have been removed from the protocol.

Appendix 10: EuroQoL 5 Dimension, 3 Level Questionnaire

The appendix and all cross references have been removed from the protocol.

Appendix 13: Preexisting Autoimmune Diseases

The appendix and all cross references have been removed from the protocol.

SAMPLE INFORMED CONSENT FORMS

The sample Informed Consent Forms have been revised to reflect the changes to the protocol, where appropriate.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH GEMCITABINE + CISPLATIN OR CARBOPLATIN FOR PD-L1–SELECTED, CHEMOTHERAPY NAIVE PATIENTS WITH STAGE IV SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29432
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-003106-33
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
MEDICAL MONITOR:	[redacted], M.D., *Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy to the Sponsor or their designee. Contact details will be provided to the investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH GEMCITABINE + CISPLATIN OR CARBOPLATIN FOR PD-L1–SELECTED, CHEMOTHERAPY NAIVE PATIENTS WITH STAGE IV SQUAMOUS NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29432
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-003106-33
IND NUMBER:	117296
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267)
PHASE:	III
INDICATION:	Non–Small Cell Lung Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

The study is currently closed to enrollment due to a low number of patients; therefore, the objectives of this study are no longer applicable and formal analyses of efficacy or safety will not be performed.

Study Design

Description of Study

This is a randomized, Phase III, multicenter, open-label study designed to evaluate and compare the safety and efficacy of atezolizumab with gemcitabine + cisplatin or carboplatin in *programmed death–ligand 1 (*PD-L1*)*–selected patients who are chemotherapy-naïve *and have* Stage IV squamous *non–small cell lung cancer (*NSCLC*)*.

At screening, tumor specimens from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory. Only patients who are PD-L1–selected (tumor cell [TC]3 or tumor-infiltrating immune cell [IC]3) will be enrolled. Patients will be randomized 1:1 to receive either atezolizumab alone or gemcitabine + cisplatin or carboplatin, stratified by sex (male vs. female), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs.1), presence of liver metastases at baseline (yes vs. no), and PD-L1 tumor tissue expression by *immunohistochemistry (*IHC*;* TC3 and any IC vs. TC0/1/2 and IC3).

Given the toxicities associated with platinum-based chemotherapies (neutropenia, anemia) and the requirement for pre-medications, this will be an open-label study. No crossover will be allowed from the control arm (gemcitabine + cisplatin or carboplatin) to the experimental arm (atezolizumab). Approximately 400 patients will be randomized.

Atezolizumab (fixed dose of 1200 mg) will be administered intravenously on Day 1 of each 21-day cycle. Atezolizumab treatment may continue as long as patients are experiencing clinical benefit as assessed by 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) or until unacceptable toxicity or death.

During treatment, patients who are treated with atezolizumab and who show evidence of clinical benefit will be permitted to continue atezolizumab treatment at any timepoint after *Response*

Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- Patients must provide written consent to acknowledge deferring *other* treatment options in favor of continuing treatment *with atezolizumab* at the time of initial progression.

Patients in both treatment arms *may* undergo a*n optional* tumor tissue biopsy at the time of radiographic disease progression *if clinically feasible. To do this, patients must sign a separate consent*. These data will be used to explore if the radiographic findings are consistent with the presence of tumor or if the appearance of progression was pseudoprogression. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance and progression to atezolizumab when compared to such mechanisms after treatment with chemotherapy. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients randomized to receive gemcitabine + cisplatin or carboplatin (per investigator's choice) will receive chemotherapy intravenously on Day 1 (for cisplatin or carboplatin) and on Days 1 and 8 (for gemcitabine) of each 21-day cycle for four or six cycles, as per local standard-of-care. The intended number of cycles planned for the platinum-based chemotherapy will be specified by the investigator prior to study randomization. Treatment with gemcitabine + cisplatin or carboplatin will discontinue early if RECIST v1.1 criteria for progressive disease are met or if patient experiences unacceptable toxicity.

All patients will undergo tumor assessments at baseline and every 6 weeks thereafter, regardless of dose delays, for the first *48 weeks* following Cycle 1, Day 1 *regardless of treatment delays*. After *48 weeks*, tumor assessments will be required every 9 weeks *after completion of the Week 48 tumor assessment, regardless of treatment delays,* until disease progression per RECIST v1.1 (for patients in both treatment arms) or loss of clinical benefit (for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, *enrollment into an extension study, or death,* whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, death, *or are eligible to roll over to an extension study,* whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn.

Number of Patients

The study is currently closed to enrollment due to a low number of patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- Histologically or cytologically confirmed Stage (IV) squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition)
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

    No ongoing requirement for corticosteroids as therapy for CNS disease

    No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.

- Tumor PD-L1 expression (TC3 or IC3), as determined by an IHC assay performed by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening

  A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or a minimum of 15 unstained, freshly cut, serial sections from an FFPE tumor specimen is required for participation in this study. This specimen must be accompanied by the associated pathology report.

  If fewer than 15 slides are available at baseline (but no fewer than 10), the patient may still be eligible, upon discussion with the Medical Monitor.

  For freshly collected specimens, resections, core needle biopsies, excisional, incisional, punch, or forceps biopsies are acceptable.

  Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable.

  Tumor tissue from bone metastases is not acceptable.

  For core needle biopsy specimens, preferably, at least three cores embedded in a single paraffin block, should be submitted for evaluation.

  For patients whose initial archival tumor tissue sample is PD-L1 negative, a biopsy can be performed at screening to submit fresh tissue for the purposes of testing PD-L1 status. A positive test result in any tumor tissue sample will satisfy this eligibility criterion.

  For samples not meeting minimum requirements for size/slide number, contact the Medical Monitor to determine if patient is eligible for study participation.

- No prior treatment for Stage IV squamous NSCLC unless patient had a previously detected sensitizing epidermal growth factor receptor *(EGFR)* mutation or *anaplastic lymphoma kinase (ALK)* fusion oncogene.

  Patients having previously detected sensitizing *EGFR* mutation must have been previously treated with an EGFR tyrosine kinase inhibitor (TKI; erlotinib, gefitinib, etc.) and experienced disease progression (during or after treatment) or intolerance to treatment with an EGFR TKI. However, given that testing for EGFR mutations is not considered standard in this patient population due to its extremely low frequency, patients with an unknown status will not be required to be tested at screening.

  Patients having a previously detected *ALK* fusion oncogene must have been previously treated with crizotinib or another ALK inhibitor and experienced disease progression (during or after treatment) or intolerance to treatment with the ALK inhibitor. However, given that testing to detect ALK fusion oncogenes is not considered standard in this patient population due to its extremely low frequency, patients with an unknown status will not be required to be tested at screening.

- Patients who have received prior neo-adjuvant, adjuvant chemotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy or chemoradiotherapy cycle.

- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can only be considered measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of measurable disease.

- ECOG performance status of 0 or 1
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

  ANC ≥ 1500 cells/μL without granulocyte colony-stimulating factor support

  Lymphocyte count ≥ 500 cells/μL

  Platelet count ≥ 100,000 cells/μL without transfusion

  Hemoglobin ≥ 9.0 g/dL

  Patients may be transfused to meet this criterion.

  INR or aPTT ≤ 1.5 times the upper limit of normal (ULN)

  This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization.

  AST and ALT ≤ 2.5 × ULN

  If patient has liver metastases, AST and/or ALT ≤ 5 × ULN

  Alkaline phosphatase ≤ 2.5 × ULN

  If patient has liver or bone metastases, alkaline phosphatase ≤ 5 × ULN

  Serum bilirubin ≤ 1.5 × ULN

  Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.

  Calculated creatinine clearance (CrCl) ≥ 45 mL/min

  If using cisplatin, calculated CrCl must be ≥ 60 mL/min
- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception during study treatment that results in a low failure rate of < 1% per year when used consistently and correctly. Female patients treated with atezolizumab should continue contraception use for *5 months* after the last dose. Female patients treated with cisplatin should continue contraception use for 6 months after the last dose. Male patients treated with gemcitabine, cisplatin, or carboplatin should continue contraception use for 6 months after the last dose. Such methods include combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion or vasectomized partner (on the understanding that this is the only one partner during the entire study duration), and sexual abstinence.

  Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical trial if they have a partner of childbirth potential. Male patients must always use a condom.
- Women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

Exclusion Criteria

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

Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by *computed tomography* (CT) or magnetic resonance imaging evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. There is no required minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.
- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN)

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while in the study.
- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year *overall survival* > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

  Patients with controlled Type I diabetes mellitus on a stable insulin regimen are eligible for this study.

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

  Rash must cover less than 10% of body surface area

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months requiring treatment with either PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors or high potency or oral steroids.
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation

- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans), idiopathic pneumonitis or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive HIV test
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening).

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization.
- Patients with active hepatitis C

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<50\%$ must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Active tuberculosis
- Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- 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

Exclusion Criteria Related to Medications

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

  TKIs approved for treatment of NSCLC discontinued >7 days prior to randomization; the baseline scan must be obtained after discontinuation of prior TKIs.
- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to randomization
- Received therapeutic oral or *intravenous* antibiotics within 2 weeks prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Administration of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live attenuated vaccine will be required during the study

  Influenza vaccination should be given during influenza season. Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization or at any time during the study.

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies

    Patients who have had prior anti–cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:

    Minimum of 6 weeks from the last dose of anti–CTLA-4

    No history of severe immune related adverse effects from anti–CTLA-4 (*National Cancer Institute Common Terminology Criteria for Adverse Events* [NCI CTCAE] Grades 3 and 4)

- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomization

    Prior treatment with cancer vaccines is allowed.

- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization

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

    The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

Exclusion Criteria Related to Gemcitabine, Cisplatin or Carboplatin

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- CrCl < 60 mL/min (cisplatin)
- Grade ≥2 peripheral neuropathy as defined by *NCI CTCAE v*4.0 criteria (cisplatin)
- Known hypersensitivity to gemcitabine
- History of radiation therapy within 7 days prior to initiating gemcitabine

Length of Study

The study is currently closed to enrollment due to a low number of patients.

End of Study

The study is currently closed to enrollment due to a low number of patients.

Outcome Measures

The study is currently closed to enrollment due to a low number of patients; therefore, the outcome measures of this study are no longer applicable and formal analyses of efficacy or safety will not be performed.

Investigational Medicinal Products

Test Product (Investigational Drug)

Atezolizumab, at a dose of 1200 mg, will be administered by *intravenous* infusion every 21 days.

Comparator

The comparator arm includes gemcitabine+cisplatin or carboplatin to be administered every 21 days for four or six cycles in accordance with the local standard-of-care or at the suggested doses and/or infusion times indicated in the table below.

Table: Gemcitabine+Cisplatin or Carboplatin Regimen

Chemotherapy	Dose/Route	Treatment (Four or Six Cycles)
Gemcitabine	1250 mg/m^2 IV	Over 30 minutes on Days 1 and 8 q21d
Cisplatin	75 mg/m^2 IV	Over 1–2 hours on Day 1 q21d
Gemcitabine	1000 mg/m^2 IV	Over 30 minutes on Days 1 and 8 q21d
Carboplatin	AUC 5 IV	Over ~30–60 minutes on Day 1 q21d

AUC=area under the concentration curve; IV=intravenous; q21d=every 21 days.

Erlotinib

Erlotinib *is considered an Investigational Medicinal Product and will be provided by the Sponsor if required by local health authority regulations.* Switch maintenance *treatment to* erlotinib is *no longer* permitted for patients randomized to *Arm B. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the Investigator.*

Statistical Methods

Primary Analysis

The study is currently closed to enrollment due to a low number of patients; therefore, formal analysis of efficacy endpoints will not be performed.

Determination of Sample Size

The study is currently closed to enrollment due to a low number of patients; therefore, formal analysis of efficacy endpoints will not be performed.

Interim Analyses

The study is currently closed to enrollment due to a low number of patients; therefore, interim safety data will not be evaluated by an independent Data Monitoring Committee.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
BSC	best supportive care
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	Case Report Form
CT	computed tomography
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
C_{trough}	trough concentration
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ePRO	electronic PRO
FDA	U.S. Food and Drug Administration
FFPE	formalin fixed paraffin embedded
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug application
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent to treat
IV	intravenous
IxRS	interactive Web/voice response system
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	*progressive disease*
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
q21d	every 21 days
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SD	*stable disease*
TC	tumor cell
TKI	tyrosine kinase inhibitor
TNF	tumor necrosis factor
UBC	urothelial bladder cancer
ULN	upper limit of normal

1. BACKGROUND

1.1 NON-SMALL CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there would be 226,160 new cases of lung cancer and 160,340 lung cancer deaths in the United States alone (Siegel et al. 2012). Similar data from Europe estimate that there were 288,000 new cases of lung cancer and 253,000 deaths in 2008 (GLOBOCAN 2008).

Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Molina et al. 2008; Howlader et al. 2014). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% (Langer et al. 2010) of NSCLC. The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects.

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumors *are* commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways. Evaluation of NSCLC tumor tissue will reveal cytological differences between the squamous cell type (keratinization, intracellular bridges, and central necrosis) and adenocarcinoma (glandular architecture). In cases where the tumor sample is poorly differentiated or there is limited tissue available, immunohistochemical markers may support the histologic diagnosis. Thyroid transcription factor–1 is infrequently expressed in squamous cells and strongly expressed in adenocarcinoma. In contrast, p63, CK5/6, and 34βE12 are strongly expressed in squamous cell carcinoma and less frequently in adenocarcinoma (Travis et al. 2011).

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the epidermal growth factor receptor (EGFR), the rearrangement in the anaplastic lymphoma kinase (ALK) gene, and mutations in the GTPase Kras (K-ras) gene. The rates of these mutations differ between squamous cell carcinoma and

adenocarcinoma. For example, *EGFR* kinase domain mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). The *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is very rare in the squamous histology but observed in approximately 7% of patients with adenocarcinoma (Herbst et al. 2008; Langer et al. 2010). In addition, K-ras mutations are very rare in squamous NSCLC, while they can be observed in up to 30% of cases of adenocarcinoma NSCLC (Travis et al. 2011).

1.2 FIRST-LINE TREATMENT FOR NON–SMALL CELL LUNG CANCER

Patients with previously untreated NSCLC that does not harbor a driver mutation that confers sensitivity to a targeted agent are typically treated with chemotherapy. The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995; a meta-analysis showed that platinum-based doublet chemotherapy conferred a 2-month improvement in median survival over best supportive care (BSC) (NSCLC Collaborative Group 1995). More recently, the European Big Lung Trial demonstrated the potential benefits of chemotherapy. In this trial, 725 patients with advanced NSCLC were randomly assigned to BSC plus cisplatin-based chemotherapy or BSC alone (Spiro et al. 2004). Patients allocated to chemotherapy had a significantly longer median survival than did those managed with BSC (8 vs. 5.7 months).

The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in overall response rate (approximately 15%–22%) and median survival (7–10 months). More recently, the addition of bevacizumab to carboplatin and paclitaxel resulted in an increase in response rate from 15% to 35% and an increase in median overall survival (OS) from 10 to 12 months (see Table 1).

Despite the limited survival benefit conferred by cytotoxic chemotherapy, platinum-based regimens remain the standard first-line option for most patients with locally advanced and metastatic NSCLC not harboring an activating *EGFR* mutation or *ALK* gene rearrangement. In particular, for newly diagnosed advanced stage non-squamous NSCLC, standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, well-designed clinical trials conducted over the last decade have clearly demonstrated that bevacizumab and pemetrexed are not appropriate agents for the treatment of patients with squamous cell carcinoma of the lung (Johnson et al. 2004; Scagliotti et al. 2008; Sandler et al. 2009). The combination of gemcitabine and a platinum analog (either carboplatin or cisplatin) has demonstrated efficacy as first-line treatment for NSCLC and, as a result, is often a reference arm in clinical trials evaluating new therapeutics (Schiller et al. 2002; Treat et al. 2010). The median duration of progression-free survival (PFS) and OS in patients with squamous NSCLC is approximately 5.1–5.5 months and 10.3–10.8 months, respectively (see Table 1).

Overall, these regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy) and are generally poorly tolerated by elderly and poor–performance status patients. Therefore, novel therapies that deliver an improved therapeutic index are urgently needed for squamous NSCLC.

Table 1 Randomized Phase III Trials in Patients with Previously Untreated *Non–Small Cell Lung Cancer*

First-Line Therapy Regimen	ORR (%)	Median PFS (months)	Median OS (months)	OS HR (95% CI)
Chemotherapy [a]				
Cisplatin and paclitaxel (n=288)	21	3.4	7.8	
Cisplatin and gemcitabine (n=288)	22	4.2	8.1	
Cisplatin and docetaxel (n=289)	17	3.7	7.4	
Carboplatin and paclitaxel (n=290)	17	3.1	8.1	
Chemotherapy+biologic [b]				
Carboplatin and paclitaxel (n=444)	15	4.5	10.3	0.79
Carboplatin, paclitaxel, and bevacizumab (n=434)	35	6.5	12.3	0.67–0.92
Chemotherapy [c]				
Cisplatin and pemetrexed, overall (n=839)	31	4.8	10.3	0.94
Cisplatin and gemcitabine, overall (n=830)	28	5.1	10.3	0.84–1.05
Cisplatin and pemetrexed, non-squamous	NR	5.3	11.8	0.81
Cisplatin and gemcitabine, non-squamous	NR	4.7	10.4	0.70–0.94
Cisplatin and pemetrexed, squamous	NR	4.4	9.4	1.23
Cisplatin and gemcitabine, squamous	NR	5.5	10.8	1.00–1.51
Chemotherapy [d]				
Carboplatin and nab-paclitaxel, overall (n=521)	33	6.3	12.1	0.922
Carboplatin and paclitaxel, overall (n=531)	25	5.8	11.2	0.797–1.066
Carboplatin and nab-paclitaxel, non-squamous (n=221)	26	6.9	13.1	0.950
Carboplatin and paclitaxel, non-squamous (n=292)	25	6.5	13.0	NR
Carboplatin and nab-paclitaxel, squamous (n=300)	41	5.6	10.7	0.890
Carboplatin and paclitaxel, squamous (n=229)	24	5.7	9.5	0.719–1.101

Table 1 Randomized Phase III Trials in Patients with Previously Untreated Non–Small Cell Lung C (cont.)

First-Line Therapy Regimen	ORR (%)	Median PFS (months)	Median OS (months)	OS HR (95% CI)
Phase III trials [e]				
Cisplatin and vinorelbine (n=568)	29	4.8	10.1	0.871 0.762–0.996
Cisplatin, vinorelbine, and cetuximab (n=557)	36	4.8	11.3	

HR=hazard ratio; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

[a] Schiller JH, Harrington D, Belani CP, et al. Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002;346:92–8.

[b] Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non–small cell lung cancer. N Engl J Med 2006;355:2542–50.

[c] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small cell lung cancer. J Clin Oncol 2008;26:3543–51.

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1.3 TARGETED THERAPY FOR NON–SMALL CELL LUNG CANCER

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC (mainly non-squamous histology) characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC. Randomized Phase III trials of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (Lux-Lung 3) showed significant improvement of PFS and objective response rate (ORR) compared with platinum doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012; respectively). Similarly, the *ALK* inhibitor crizotinib has demonstrated efficacy in patients with NSCLC positive for *ALK* rearrangement as defined by fluorescence in situ hybridization (Crino et al. 2011; Camidge et al. 2012; Shaw et al. 2012; Shaw and Engelman 2014; Xalkori® U.S. Package Insert).

Despite current progress in treatment of patients with EGFR mutations and ALK rearrangements, survival rates for advanced disease remain low and acquired resistance to targeted agents is a major clinical problem. Therefore, alternative treatment options that yield durable responses and enhance OS remain an important focus of research. Against this background, immunotherapeutic agents, such as cancer vaccines and antibodies that modulate immune cell activity, offer an alternative treatment approach that could potentially improve the prognosis of patients with this disease. Therefore, patients with EGFR mutations or ALK mutations who have been treated with and whose disease progressed on an appropriate tyrosine kinase inhibitor (TKI) will be eligible for this trial.

1.4 MAINTENANCE THERAPY FOR NON–SMALL CELL LUNG CANCER

National Comprehensive Cancer Network (NCCN) guidelines on chemotherapy for Stage IV NSCLC recommend that cytotoxic regimens consisting of two drugs should be given for no more than six cycles. The guidelines also recommend stopping first-line cytotoxic chemotherapy at disease progression. *When the study was started, switch maintenance with erlotinib in unselected patients could be considered f*or patients with stable disease or continued response to therapy after four to six cycles *of chemotherapy* (NCCN Guidelines 2014). This recommendation *was* based on*the Sequential Tarceva Unresectable NSCLC study (SATURN).* In the SATURN *study*, the median PFS in patients receiving maintenance therapy with erlotinib was significantly longer than in patients receiving placebo (12.3 vs. 11.1 weeks; hazard ratio [HR] 0.71, 95% CI: 0.62–0.81; $p < 0.0001$). Maintenance treatment with erlotinib also yielded a statistically significant yet clinically modest improvement in OS (12.0 vs. 11.0 months; HR 0.81, 95% CI: 0.70–0.95; $p = 0.0088$). A statistically significant improvement in PFS and OS was observed in patients with EGFR–wild-type and EGFR–mutation-positive tumors (Cappuzzo et al. 2010). *This* Phase III trial resulted in regulatory approval *by the U.S.*

Food and Drug Administration (FDA) and European Medicines Agency for erlotinib *in* unselected NSCLC, as maintenance therapy of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. *However, recent data from Study BO25460, a randomized, double-blind, placebo-controlled Phase III study, have demonstrated that patients with advanced or recurrent (Stage IIIB) or metastatic (Stage IV) NSCLC whose tumor did not harbor an EGFR-activating mutation did not achieve benefit from first-line maintenance therapy with erlotinib compared with placebo. OS was not superior in patients randomized to receive maintenance erlotinib followed by chemotherapy or best supportive care upon disease progression compared with patients randomized to receive maintenance placebo followed by erlotinib upon disease progression (HR =1.02, 95% CI, 0.85–1.22, p =0.82). In the maintenance phase, patients who received erlotinib also did not have superior PFS compared with patients who received placebo (HR =0.94, 95% CI, 0.80–1.11, p =0.48). This change in the benefit-risk assessment of erlotinib as switch maintenance therapy in patients whose tumors do not harbor an activating EGFR mutation has led to the removal of this treatment option from this protocol. Patients already receiving the switch maintenance therapy with erlotinib, permitted under previous protocol versions, may be allowed to continue to receive treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.*

1.5 BACKGROUND ON ATEZOLIZUMAB (MPDL3280A)

Atezolizumab (MPDL3280A) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death–ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death–1 (PD-1) and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans. *Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial cancer.*

1.5.1 Summary of Nonclinical Studies

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

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

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

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

1.6 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

Refer to the Atezolizumab Investigator's Brochure for details on all clinical studies conducted to date.

1.6.1 Ongoing Clinical Studies

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

- Study PCD4989g: A Phase Ia, multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 21 days (q21d) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- Study GO28753 (POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1 unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.

Study GO28625 (FIR): A Phase II study assessing the clinical benefit of atezolizumab as a single agent in patients with locally advanced or metastatic NSCLC representing all lines of therapy (previously untreated to heavily pre-treated patients with exposure to multiple prior regimens).

1.6.2 Clinical Safety

1.6.2.1 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer

Study PCD4989g is a Phase Ia dose escalation and expansion study, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, and provides the majority of data (with 558 safety evaluable patients as of the data *cutoff* date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

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

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

Single-Agent Clinical Safety in Patients with NSCLC in Study PCD4989g

Of the 558 patients in Study PCD4989g, 520 (93.2%) patients experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly reported events (reported in $\geq$10% of all patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, and cough (see Table 2).

Table 2 Study PCD4989g: Adverse Events with Frequency ≥10% of Patients for All Grades

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

Note: "—" refers to missing Common Terminology Criteria grade.

Grade 3–4 adverse events (on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0]) were reported in 239 patients (42.8%), of which 66 (11.8%) were considered related. Grade 3 and 4 adverse events considered related by the investigator included dyspnea, pneumonitis, increased ALT, increased AST, increased gamma-glutamyl transferase (GGT), lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia.

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

1.6.2.2 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer in POPLAR Study GO28753

The Phase II Study GO28753 interim analysis, as of the 30 January 2015 data cutoff date, included data from 142 patients treated with atezolizumab as a fixed dose of 1200 mg IV every 3 weeks and 135 patients treated with docetaxel 75 mg/m^2 IV every 3 weeks. The frequency of patients in Study GO28753 who reported any adverse event regardless of attribution was 96.5% for the atezolizumab arm and 95.6% for the docetaxel arm. A higher number of Grade ≥3 adverse events were observed in the docetaxel arm (55.6% vs. 43.0%), explained primarily by the difference in adverse events due to bone marrow suppression. Adverse events reported in at least 10% of patients in either treatment arm are listed in Table 3.

Table 3 Adverse Events Reported in at Least 10% of Patients in POPLAR Study GO28753

	No. of Patients (%)	
MedDRA Preferred Term	Atezolizumab (n=142)	Docetaxel (n=135)
Fatigue	54 (38.0)	54 (40.0)
Decreased appetite	49 (34.5)	29 (21.5)
Dyspnoea	39 (27.5)	26 (19.3)
Cough	35 (24.6)	33 (24.4)
Nausea	31 (21.8)	45 (33.3)
Constipation	28 (19.7)	32 (23.7)
Pyrexia	24 (16.9)	17 (12.6)
Diarrhoea	24 (16.9)	38 (28.1)
Arthralgia	22 (15.5)	12 (8.9)
Anemia	21 (14.8)	27 (20.0)
Insomnia	19 (13.4)	11 (8.1)
Musculoskeletal pain	18 (12.7)	7 (5.2)
Vomiting	17 (12.0)	19 (14.1)
Back Pain	16 (11.3)	10 (7.4)
Asthenia	15 (10.6)	22 (16.3)
Pneumonia	15 (10.6)	4 (3.0)
Rash	15 (10.6)	16 (11.9)
Myalgia	8 (5.6)	18 (13.3)
Alopecia	3 (2.1)	52 (38.5)
Neuropathy peripheral	2 (1.4)	16 (11.9)
Neutropenia	2 (1.4)	17 (12.6)

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

1.6.2.3 Single-Agent Clinical Safety in Patients with *Non–Small Cell Lung Cancer* in FIR Study GO28625

As of the 23 October 2014 data cutoff date, the clinical database included preliminary safety data from 137 safety-evaluable patients in Study GO28625 with a median treatment duration of 88 days. Table 4 shows the overall safety findings in Study GO28625, which were consistent with those observed in Study PCD4989g (overall and NSCLC populations), as well as with the atezolizumab arm in Study GO28753.

Table 4 Adverse Events Reported in FIR Study GO28625

Parameter	No. of Patients (%)			
	Cohort 1 (n=31)	Cohort 2 (n=93)	Cohort 3 (n=13)	All Patients (n=137)
Any adverse event	31 (100.0%)	93 (100.0%)	13 (100.0%)	137 (100.0%)
Grade 3–5 adverse event [a]	15 (48.4%)	54 (58.1%)	8 (61.5%)	77 (56.2%)
Related adverse event	23 (74.2%)	60 (64.5%)	9 (69.2%)	92 (67.2%)
Adverse event leading to withdrawal from treatment	4 (12.9%)	8 (8.6%)	2 (15.4%)	14 (10.2%)
Serious adverse event	15 (48.4%)	45 (48.4%)	7 (53.8%)	67 (48.9%)
Related serious adverse event	2 (6.5%)	9 (9.7%)	1 (7.7%)	12 (8.8%)
Grade 5 adverse event [a]	3 (9.7%)	13 (14.0%)	4 (30.8%)	20 (14.6%)

NSCL non–small cell lung cancer.

[a] Deaths due to progression of NSCLC during the protocol-specified adverse event reporting period were captured as adverse events.

The most frequently observed adverse events (occurring in ≥10% of treated patients) of the 137 patients (100.0%) reporting any adverse event included fatigue, dyspnea, cough, nausea, and decreased appetite. In 43.8% of patients, the adverse events were Grade 1 or 2 in severity. In 12 patients (8.8%), the serious adverse event reported was considered by the investigator as related to atezolizumab (diarrhea in 2 patients and 1 patient each for lower gastrointestinal hemorrhage, rectal hemorrhage, Guillain-Barré syndrome, monoparesis, pleural effusion, pneumonitis, cardiac tamponade, elevated AST and ALT, diabetes mellitus, and muscular weakness).

Overall, there were 54 patient deaths (39.4%) reported. Disease progression was the cause of death in 46 patients. The remaining 9 deaths were reported due to the following in 1 patient each: cardiac tamponade, cardiac arrest, disseminated intravascular coagulation, pericardial effusion, respiratory disorder, death due to euthanasia, pericarditis constrictive, pneumonia, and death not otherwise specified.

1.6.2.4 Immune-Mediated Adverse Events

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

See the Atezolizumab Investigator's Brochure for details regarding immune-mediated adverse events observed in patients treated with atezolizumab. Guidelines for the management of potential immune-mediated adverse events are described in Section 5.1.7.

1.6.3 Clinical Activity

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)–based responses (i.e., RECIST, Version 1.1 responses), have been observed in patients with different tumor types, including NSCLC, RCC, melanoma, gastric cancer, UBC, colorectal cancer (CRC), head and neck cancer, breast cancer, and sarcoma treated with atezolizumab in Study PCD4989g.

See the Atezolizumab Investigator's Brochure for details on clinical activity in all patients treated to date, regardless of tumor type.

1.6.3.1 Single-Agent Clinical Activity in Patients with *Non–Small Cell Lung Cancer* in Study PCD4989g

As of the clinical data cutoff date of 2 December 2014, the safety and efficacy evaluable population included 88 patients with locally advanced or metastatic NSCLC enrolled into Study PCD4989g who had received their first dose of atezolizumab by 21 October 2013 and were evaluable for efficacy. The median age was 60.5 years (range from 24 to 84 years); the group represented a heavily pre-treated patient population in that 97.7% of the patients had received ≥2 prior systemic therapies and 77.3% had received ≥4 prior systemic therapies. RECIST responses (confirmed) were observed in a total of 20 patients, inclusive of squamous and non-squamous histologies and across all treatment cohorts (treatment dose levels: 1 to 20 mg/kg).

Preliminary results suggest that PD-L1 expression in tumor tissue is likely to be associated with response to atezolizumab. A prototype immunohistochemistry (IHC) assay has been used that measures specific PD-L1 signals in tumor-infiltrating immune cells (ICs) and tumor cells (TCs). PD-L1 staining categories in ICs are defined as IC0, IC1, IC2, and IC3, and are defined in TCs as TC0, TC1, TC2, and TC3. Table 5 summarizes the ORR by PD-L1 tumor expression in patients with NSCLC.

An ORR of 50.0% (11 of 22 patients, 95% CI: 28.2%–71.8%) was observed in patients with high levels of PD-L1 staining in TCs or ICs (TC3 or IC3 group) compared with an ORR of 15.5% (9 of 58 patients, 95% CI: 7.4%–27.4%) in patients with low or no PD-L1 staining in TCs and ICs (TC0/1/2 and IC0/1/2).

As of the 2 December 2014 cutoff date, 8 of 20 patients have continued to respond after 7+ to 27+ weeks. The median duration of response is 17 months.

Refer to the atezolizumab Investigator's Brochure for details on the clinical activity of atezolizumab in patients with NSCLC treated to date.

Table 5 Patients with *Non–Small Cell Lung Cancer* in Study PCD4989g: Objective Response Rate by Tumor PD-L1 Expression and Best Overall Response Rate (per RECIST Version 1.1)

PD-L1 IHC Expression Category	ORR (n=88)	PR	SD
TC3 or IC3	50% (11 of 22) 95% CI: 28.2%–71.8%	50% (11 of 22)	18.2% (4 of 22)
TC3 or IC2/3	31.6% (12 of 38) 95% CI: 17.5%–48.6%	31.6% (12 of 38)	28.9% (11 of 38)
TC0/1/2 and IC0/1/2	12.1% (7 of 58) 95% CI: 5.7%–22.5%	12.1% (7 of 58)	36.2% (21 of 58)
TC0/1/2 and IC0/1	14.3% (6 of 42) 95% CI: 6.4%–27.7%	14.3% (6 of 42)	33.3% (14 of 42)

IC=tumor-infiltrating immune cells; IHC=immunohistochemistry;
NSCLC=non–small cell lung cancer; ORR=objective response rate;
PD-L1=programmed death–ligand 1; PR=partial response;
RECIST=Response Evaluation Criteria in Solid Tumors: SD=stable disease;
TC=tumor cell.

Notes: This table is based on a data cutoff date of 21 April 2014 of patients with NSCLC dosed by 21 October 2013. Objective response is per RECIST v1.1.

1.6.3.2 Single-Agent Clinical Activity in Patients with *Non–Small Cell Lung Cancer* in POPLAR Study GO28753

The interim OS analysis in Study GO28753 (POPLAR) was conducted when approximately 150 deaths (30 January 2015) were observed. Demographic characteristics were comparable between treatment arms in the intent-to-treat (ITT) population. The median age was 62 years (range: 42–82 years for the atezolizumab arm, range: 36–84 years for the docetaxel arm), and the majority of patients had one prior therapy (64.6% for atezolizumab and 67.1% for docetaxel), non-squamous histology (66.0% for atezolizumab and 66.4% for docetaxel), and Eastern Cooperative Oncology Group (ECOG) performance status of 1 (66.4% for atezolizumab and 67.8% for docetaxel). More females were enrolled in the docetaxel arm (46.9% vs. 35.4%).

Key efficacy results for the ITT population and the PD-L1–selected subgroup categories, are shown in the next sections. For this interim dataset, median follow-up was approximately 12 months in both arms. The ORR and PFS data are expected to be mature given the length of follow-up and the number of PFS events observed (119 of 144 events and 111 of 143 events in the atezolizumab and docetaxel arm,

respectively). The OS data are not yet mature, with 71 events of 144 patients and 80 events out of 143 patients in the atezolizumab and docetaxel arms, respectively, having occurred. Follow-up is ongoing.

Efficacy results for the ITT population are shown in Table 6. PFS and ORR for the atezolizumab arm were similar to those for the docetaxel arm. An initial indication of OS benefit in the atezolizumab arm was observed, with a stratified HR of 0.78 (95% CI: 0.59, 1.03).

Table 6 Efficacy Results in Study GO28753 (POPLAR): Intent-to-Treat Population

Efficacy Endpoint	Atezolizumab (n =144)	Docetaxel (n =143)
Overall survival		
No. of deaths (%)	71 (49.3)	80 (55.9)
Median (months)	11.4	9.5
95% CI	9.7, NE	8.6, 12.5
Stratified hazard ratio	0.78	
95% CI	0.59, 1.03	
Progression-free survival		
No. of events (%)	119 (82.6)	111 (77.6)
Median (months)	2.8	3.4
95% CI	2.1, 4.1	2.8, 4.1
Stratified hazard ratio	0.96	
95% CI	0.76, 1.20	
Objective response rate (confirmed)	14.6%	15.4%

NE =not estimable.

The efficacy results for combined PD-L1 selected subgroups at different combinations of TC and IC cutoff are provided in Table 7, and include the complementary groups corresponding to each of the PD-L1 selected subgroups for comparison. Benefit with respect to OS appears to extend to the TC2/3 or IC2/3 subgroup, as well as to the TC1/2/3 or IC1/2/3 subgroup. For PFS, there appears to be a numerically graded benefit with increasing TC and IC PD-L1 expression.

Table 7 Study GO28753 (POPLAR) Efficacy Results by Combination PD-L1 Diagnostic Subgroups with Complementary Comparison Subgroupings: Intent-to-Treat Population

Diagnostic Subgroup	HR (95% CI)		Atezolizumab/ Docetaxel ORR (%)	Total No. of Patients (Atezolizumab/ Docetaxel)
	OS	PFS		
TC3 or IC3	0.47 (0.20, 1.11)	0.56 (0.28, 1.11)	37.5/13.0	47 (24/23)
TC3 or IC2/3	0.52 (0.28, 0.95)	0.64 (0.38, 1.08)	25/16.2	77 (40/37)
TC2/3 or IC2/3	0.56 (0.33, 0.95)	0.70 (0.45, 1.08)	22.0/14.5	105 (50/55)

HR=hazard ratio; IC=tumor-infiltrating immune cell; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TC=tumor cell.

Notes: The HRs for OS and PFS are unstratified values. The ORRs are for confirmed responses.

1.6.3.3 Single-Agent Clinical Activity in Patients with Non–Small Cell Lung Cancer in FIR Study GO28625

Key efficacy data from NSCLC patients enrolled in Study GO28625 are summarized in Table 8. Among the 71 efficacy-evaluable patients in Cohort 2, the ORR was 17% (95% CI: 8.18, 25.62). The median duration of response was not reached. As of the data cutoff date, the median PFS for all Cohort 2 efficacy-evaluable patients was 2.7 months (95% CI: 1.4, 3.1), and the 24-week PFS was 34.91% (95% CI: 23.46, 46.36).

Analyses of the PD-L1–selected subgroups revealed that the TC3 or IC3 subgroups showed the highest ORR (27%), with reductions in ORR with the inclusion of the IC2 and TC2 subgroups. For the TC3 or IC3 subgroup of Cohort 2, the median duration of response was not reached, the median PFS was 3.1 months (95% CI: 1.6, 15.3), and the 24-week PFS was 49.23% (95% CI: 29.76, 68.70).

Table 8 Efficacy Results for Study GO28625 (FIR): Efficacy-Evaluable Patients by PD-L1 Diagnostic Subgroups

Efficacy Endpoint	Efficacy Evaluable (i.e., TC2/3 or IC2/3) (n =71)	TC3 or IC3 (n =26)	TC3 or IC2/3 (n =63)
ORR	17% (12 of 71)	27% (7 of 26)	18% (11 of 63)
Median DOR (months) (95% CI)	NE (10.4, NE)	NE (10.4, NE)	NE (10.4, NE)
Median PFS (months) (95% CI)	2.7 (1.4, 3.1)	3.1 (1.6, 15.3)	2.7 (1.4, 4.5)
24-week PFS (%) (95% CI)	34.91 (23.46, 46.36)	49.23 (29.76, 68.70)	34.49 (22.31, 46.67)
1 year OS (%) (95% CI)	NA	NA	NA

DOR=duration of response; IC=tumor-infiltrating immune cell; NA=not applicable; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed–death ligand 1; PFS=progression-free survival; TC=tumor cell.

[a] Data for the PD-L1 subgroup of TC2/3 or IC2/3 are currently not available for Study PCD4989g.

[b] Only Cohort 2 patients.

1.6.4 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 and the mean volume of distribution at steady state had a range of 3.11–4.14 mL/kg and 48.1–67.0 mL/kg, respectively, which is consistent with the expected 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 the detection of ATAs and adverse events or infusion reactions has been observed.

1.6.5 Rationale for Atezolizumab Dosage

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

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The target trough concentration (C_{trough}) was projected to be 6 mg/mL on the basis of several

assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Currently available PK and ATA data suggest that the 15-mg/kg atezolizumab q21d regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q21d regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab q21dregimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab q21d level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. Therefore, a fixed dose of 1200 mg has been selected (equivalent to an average body weight–based dose of 15 mg/kg). Selection of an every-21-day dosing interval is supported by this preliminary pharmacokinetics evaluation.

See the Atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

1.7 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with Stage IV cancer (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

Overexpression of PD-L1 on TCs has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression is associated with a poor prognosis in patients with NSCLC (Mu et al. 2011).

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies and who have failed standard-of-care therapies. In Study PCD4989g, a Phase Ia, dose-escalation and expansion study, objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UBC, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma. In addition, in the NSCLC cohort, patients with NSCLC who have a high level of PD-L1 expression in TCs or ICs (TC3 or IC3) were more likely to respond to atezolizumab than those with low or no PD-L1 expression in TCs or ICs (TC0/1/2 and IC0/1/2; see also Sections 1.6.3.1 and 3.3.1).

On the basis of these observations, Study GO29432 is designed to evaluate if this anti-tumor effect observed in atezolizumab-treated patients would translate into prolonged PFS and OS compared with gemcitabine + cisplatin or carboplatin in patients with squamous NSCLC whose tumors show high levels of PD-L1 expression. A PD-L1 IHC assay will be used to identify patients by their tumor PD-L1 expression (see Appendix 5).

Study GO29432 will enroll patients with Stage IV squamous NSCLC who are naive to chemotherapy treatment and for whom the experimental arm can represent a valuable treatment option and can offer a reasonable benefit-risk balance. Patients whose tumors are known to harbor sensitizing *EGFR* mutations or *ALK* rearrangements must have experienced disease progression during or after treatment with an EGFR tyrosine kinase or ALK inhibitor, respectively (see specific inclusion criteria in Section 4.1.1), before they can enroll in the study. For these patients, atezolizumab can provide a potential clinical benefit compared with a standard platinum-based chemotherapy.

In order to account for the possibility of pseudoprogression/tumor-immune infiltration (i.e., radiographic increase in tumor volume caused by the influx of immune cells; Hales et al. 2010) and the potential for delayed anti-tumor activity, this trial will allow patients treated with atezolizumab to receive treatment beyond the initial apparent radiographic progression (see Section 3.3.3 and Section 4.6.2) with use of modified RECIST criteria (in addition to RECIST v1.1) to evaluate clinical benefit. As it is not yet possible to reliably differentiate pseudoprogression/tumor-immune infiltration from true tumor progression, the risk exists that some patients who are not responding to treatment but yet continuing to receive atezolizumab may experience further progression of NSCLC and delay treatment with subsequent therapies for which they are eligible.

Investigators should make every effort to fully inform patients of this risk. Investigators should make a careful assessment of the potential benefit of continuing treatment with atezolizumab, considering radiographic data and the clinical status of the patient. If, after an integrated assessment of radiographic data and clinical status, the decision is made to continue treatment with atezolizumab following apparent radiographic progression, patients for whom alternative approved anti-cancer therapies exist must provide written consent at that time to acknowledge deferring these treatment options in favor of continuing study treatment.

Atezolizumab has been generally well tolerated (see Section 1.6.2). Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis have been observed in Study PCD4989g. To date, these events have been manageable with treatment.

In summary, treatment with atezolizumab offers the potential for clinical benefit in chemotherapy naive, squamous Stage IV NSCLC patients with high PD-L1 expression. Because most atezolizumab-related toxicities observed to date have been mild and transient in nature and do not overlap with those of chemotherapy, patients who do not respond to study treatment are considered likely to be able to subsequently receive standard therapies for which they would otherwise have been eligible. Patients will be fully informed of the risk of continuing study treatment in spite of apparent radiographic progression, and investigators should make a careful assessment of the potential benefit of doing so, considering radiographic data, biopsy results, and the clinical status of the patient.

2. OBJECTIVES

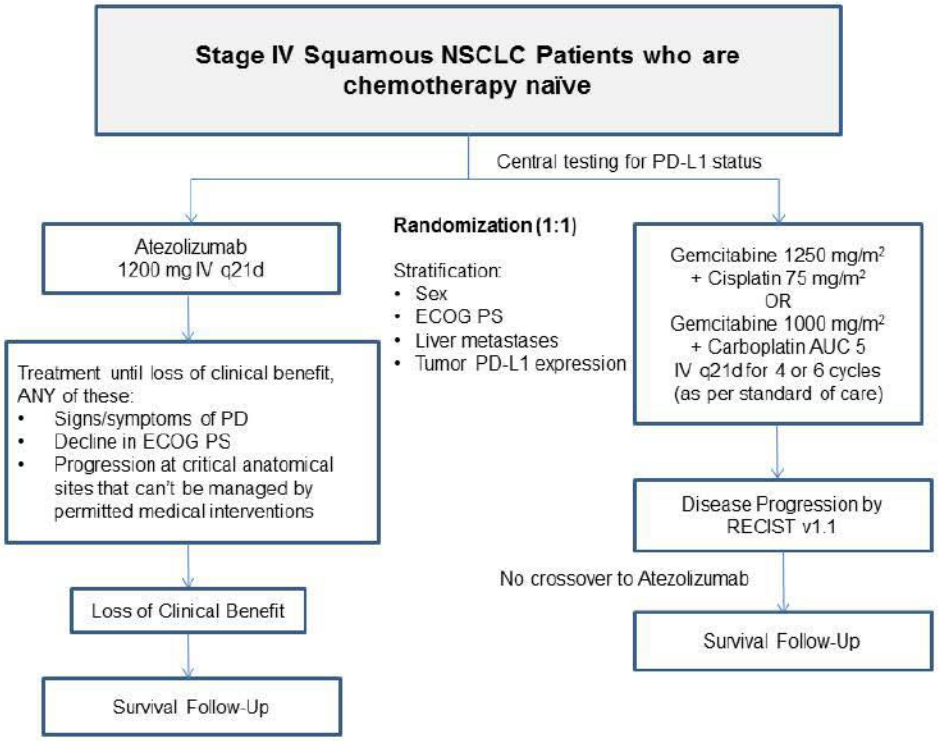
The study is currently closed to enrollment due to a low number of patients; therefore, the objectives of this study are no longer applicable and formal analyses of efficacy or safety will not be performed.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a randomized, Phase III, multicenter, open-label study designed to evaluate and compare the safety and efficacy of atezolizumab with gemcitabine + cisplatin or carboplatin in PD-L1–selected patients who are chemotherapy-naive and have Stage IV squamous NSCLC. Figure 1 illustrates the study design. The schedule of assessments is provided in Appendix 1.

Figure 1 Study Schema



AUC = area under the concentration–time curve; ECOG PS = Eastern Cooperative Oncology Group performance status; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; q21d = every 21 days; RECIST = Response Evaluation Criteria in Solid Tumors.

At screening, tumor specimens from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory using an IHC assay (see Appendix 5). Only patients who are PD-L1–selected (TC3 or IC3) will be enrolled. Patients will be randomized 1:1 to receive either atezolizumab alone or gemcitabine + cisplatin or carboplatin, stratified by sex (male vs. female), ECOG performance status (0 vs.1), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor tissue expression by IHC (TC3 and any IC vs. TC0/1/2 and IC3).

Given the toxicities associated with platinum-based chemotherapies (neutropenia, anemia) and the requirement for pre-medications, this will be an open-label study. No crossover will be allowed from the control arm (gemcitabine + cisplatin or carboplatin) to the experimental arm (atezolizumab). Approximately 400 patients will be randomized.

Atezolizumab (fixed dose of 1200 mg) will be administered intravenously on Day 1 of each 21-day cycle. Atezolizumab treatment may continue as long as patients are experiencing clinical benefit as assessed by 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) or until unacceptable toxicity or death.

During treatment, patients who are treated with atezolizumab and who show evidence of clinical benefit will be permitted to continue atezolizumab treatment at any timepoint after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring *other* treatment options in favor of continuing treatment *with atezolizumab* at the time of initial progression.

Patients in both treatment arms *may* undergo a*n optional* tumor tissue biopsy at the time of radiographic disease progression *if clinically feasible. To do this, patients must sign a separate consent*. These data will be used to explore if the radiographic findings are consistent with the presence of tumor or if the appearance of progression was pseudoprogression. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance and progression to atezolizumab when compared to such mechanisms after treatment with chemotherapy. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients randomized to receive gemcitabine + cisplatin or carboplatin (per investigator's choice) will receive chemotherapy intravenously on Day 1 (for cisplatin or carboplatin) and on Days 1 and 8 (for gemcitabine) of each 21-day cycle for four or six cycles, as per local standard-of-care (see Section 4.3.2.2 for treatment administration details). The intended number of cycles planned for the platinum-based chemotherapy will be specified by the investigator prior to study randomization. Treatment with gemcitabine + cisplatin or carboplatin will discontinue early if RECIST v1.1 criteria for progressive disease are met or if patient experiences unacceptable toxicity.

All patients will undergo tumor assessments at baseline and every 6 weeks thereafter, regardless of dose delays, for the first *48 weeks* following Cycle 1, Day 1 *regardless of treatment delays*. After *48 weeks*, tumor assessments will be required every 9 weeks *after completion of the Week 48 tumor assessment, regardless of treatment delays,* until disease progression per RECIST v1.1 (for patients in both treatment arms) or loss of

clinical benefit (for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, *enrollment into an extension study, or death*, whichever occurs first. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, death, *or are eligible to roll over to an extension study,* whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn.

3.1.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) was in place to evaluate the safety data during the study on a periodic basis. However, as of 20 April 2016 the study was closed to enrollment due to a low number of patients; therefore, an iDMC will no longer be used to evaluate safety data.

3.2 END OF STUDY

The study is currently closed to enrollment due to a low number of patients.

The end of study will be when all enrolled patients have discontinued study treatment or all patients have been enrolled into an extension study. Patients already enrolled will remain on study and will be allowed to continue study treatment until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1), withdrawal of consent, enrollment into an extension study, or death, whichever occurs first. In addition, the Sponsor may decide to terminate the study at any time

If the Sponsor decides to end the study, patients still receiving study treatment may be offered enrollment in an extension study if, in the opinion of the investigator and in consultation with the Medical Monitor, the patient would potentially benefit from continuing therapy.

3.3 RATIONALE FOR STUDY DESIGN

This Phase III study design is based on the assumption that in patients with Stage IV squamous NSCLC, who are chemotherapy naive and whose tumors are selected for high levels of PD-L1 expression, treatment with atezolizumab may prolong PFS compared with treatment with gemcitabine + cisplatin or carboplatin.

3.3.1 Rationale for Testing Atezolizumab in PD-L1–Selected Patients with Non–Small Cell Lung Cancer

Despite recent improvements in treatment, the prognosis for patients with advanced NSCLC remains dismal, with a median OS of approximately 12.5 months (Sandler et al. 2006). Patients who receive second-line treatment for their disease have

an even more limited prognosis, with a median survival duration of approximately 8–9 months (Stinchcombe et al. 2008). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life. Therefore, there is a continuing need for more efficacious, better tolerated treatments.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients, and expression of PD-L1 by TCs in several tumor types (including NSCLC) correlates with response to therapy (Topalian et al. 2012).

Data from Phase Ia Study PCD4989g suggest that tumor PD-L1 status as determined by IHC in patients with NSCLC correlates with response to atezolizumab (see Section 1.6.3).

Patients whose tumors were characterized as high TCs or ICs exhibited an ORR of 50% (TC3 or IC3 group; 11 of 22, 95% CI: 28.2%–71.8%) compared with an ORR of 12.1% in patients whose tumors expressed low or no PD-L1 staining in TCs and ICs (TC0/1/2 and IC0/1/2 group; 7 of 58, 95% CI: 5.7%–22.5%).

These data provide a rationale for evaluating the efficacy of atezolizumab in patients with Stage IV squamous NSCLC selected on the basis of tumor PD-L1 expression.

3.3.2 Rationale for Gemcitabine+Cisplatin or Carboplatin as a Comparator

In the first-line treatment setting for non-squamous NSCLC that does not harbor a driver mutation, standard of care is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. However, well-designed clinical studies conducted over the last decade have clearly demonstrated that bevacizumab and pemetrexed are not appropriate agents for the treatment of patients with squamous cell carcinoma of the lung (Johnson et al. 2004; Scagliotti et al 2008; Sandler et al. 2009). The combination of gemcitabine and a platinum analog (either carboplatin or cisplatin) has demonstrated efficacy as first-line treatment for NSCLC and, as a result, is often a reference arm in clinical trials evaluating new therapeutics (Schiller et al. 2002; Scagliotti et al. 2008; Treat et al. 2010). The control group in this study will receive gemcitabine+cisplatin or carboplatin, which is a standard of care regimen for patients with squamous NSCLC. This control group will be instrumental in assessing the relative benefit and safety of atezolizumab compared with chemotherapy in the front-line treatment setting.

3.3.3 Rationale for Allowing Patients to Continue Atezolizumab Treatment until Loss of Clinical Benefit

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 (see Section 1.7). Because of

the potential for pseudoprogression/tumor immune infiltration, this study will allow patients randomized to receive atezolizumab to continue to receive study treatment after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 3.1).

3.3.4 Rationale for Collection of Archival and/or Fresh Tumor Specimens

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Topalian et al. 2012). This correlation is also observed with atezolizumab in preliminary data from Study PCD4989g. In this study, archival and/or fresh tumor specimens from patients will be prospectively tested for PD-L1 expression by a central laboratory during the screening period. Only patients with PD-L1–selected tumors (defined by expression of PD-L1 in TCs or ICs) will be enrolled.

In addition to the assessment of PD-L1 status, other exploratory markers, such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed. DNA and/or RNA extraction may be performed to enable *next-generation sequencing* (NGS) to identify somatic mutations to increase understanding of disease pathobiology.

3.3.5 Rationale for Blood Biomarker Assessments

An exploratory objective of this study is to evaluate surrogate biomarkers (that may include circulating tumor DNA) in blood samples. The evaluation of blood biomarkers may provide evidence for biologic activity of atezolizumab in patients with NSCLC and may allow for the development of blood-based biomarkers to help predict which patients may benefit from atezolizumab.

In addition, potential correlations of these biomarkers with the safety and activity of atezolizumab will be explored.

3.3.6 Rationale for the Collection of *Optional* Tumor Specimens at Radiographic Progression

Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed and can be preceded by initial apparent radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumor activity and/or robust immune infiltration of the tumor with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional imaging (i.e., micrometastatic disease) may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010).

Patients in both treatment arms may undergo an optional tumor biopsy at the time of radiographic disease progression if clinically feasible. To do this, patients must sign a

separate consent. These data will be used to evaluate the utility of the biopsy in distinguishing pseudoprogression/tumor immune infiltration from true progression. In addition, mechanisms relating to progression, resistance, predictive, prognostic, and pharmacodynamic relationships in tumor biomarkers (including but not limited to PD-L1, CD8, mutation status, and others) and their efficacy will be evaluated. DNA and/or RNA extraction may be performed to enable NGS to identify somatic mutations that are associated with disease progression or acquired resistance to atezolizumab and to increase understanding of disease pathobiology.

3.4 OUTCOME MEASURES

The study is currently closed to enrollment due to a low number of patients; therefore, the outcome measures of this study are no longer applicable and formal analyses of efficacy or safety will not be performed.

4. MATERIALS AND METHODS

4.1 PATIENTS

PD-L1–selected chemotherapy naive patients with Stage IV squamous non–small cell lung cancer will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Male or female, 18 years of age or older
- Histologically or cytologically confirmed Stage IV squamous NSCLC (per the Union Internationale contre le Cancer/American Joint Committee on Cancer staging system, 7th edition; Detterbeck et al. 2009; see Appendix 2)
- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

    Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

    No ongoing requirement for corticosteroids as therapy for CNS disease

    No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization

    No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

        Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met.

- Tumor PD-L1 expression (TC3 or IC3), as determined by an IHC assay performed by a central laboratory on previously obtained archival tumor tissue or tissue obtained from a biopsy at screening

  A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or a minimum of 15 unstained, freshly cut, serial sections from an FFPE tumor specimen is required for participation in this study. This specimen must be accompanied by the associated pathology report.

    If fewer than 15 slides are available at baseline (but no fewer than 10), the patient may still be eligible, upon discussion with the Medical Monitor.

  For freshly collected specimens, resections, core needle biopsies, excisional, incisional, punch, or forceps biopsies are acceptable.

  Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable.

  Tumor tissue from bone metastases is not acceptable.

  For core needle biopsy specimens, preferably, at least three cores embedded in a single paraffin block, should be submitted for evaluation.

  For patients whose initial archival tumor tissue sample is PD-L1 negative, a biopsy can be performed at screening to submit fresh tissue for the purposes of testing PD-L1 status. A positive test result in any tumor tissue sample will satisfy this eligibility criterion.

  For samples not meeting minimum requirements for size/slide number, contact the Medical Monitor to determine if patient is eligible for study participation.

- No prior treatment for Stage IV squamous NSCLC unless patient had a previously detected sensitizing *EGFR* mutation or *ALK* fusion oncogene.

  Patients having previously detected sensitizing *EGFR* mutation must have been previously treated with an EGFR TKI (erlotinib, gefitinib, etc.) and experienced disease progression (during or after treatment) or intolerance to treatment with an EGFR TKI. However, given that testing for EGFR mutations is not considered standard in this patient population due to its extremely low frequency, patients with an unknown status will not be required to be tested at screening.

  Patients having a previously detected *ALK* fusion oncogene must have been previously treated with crizotinib or another ALK inhibitor and experienced disease progression (during or after treatment) or intolerance to treatment with the ALK inhibitor. However, given that testing to detect ALK fusion oncogenes is not considered standard in this patient population due to its extremely low frequency, patients with an unknown status will not be required to be tested at screening.

- Patients who have received prior neo-adjuvant, adjuvant chemotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy or chemoradiotherapy cycle.

- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can only be considered measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of measurable disease.

- ECOG performance status of 0 or 1 (see Appendix 6)
- Adequate hematologic and end-organ function, defined by the following laboratory test results obtained within 14 days prior to the first study treatment:

  ANC $\geq$1500 cells/μL without granulocyte colony-stimulating factor support

  Lymphocyte count $\geq$500 cells/μL

  Platelet count $\geq$100,000 cells/μL without transfusion

  Hemoglobin $\geq$9.0 g/dL

  Patients may be transfused to meet this criterion.

  INR or aPTT $\leq$1.5 times the upper limit of normal (ULN)

  This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization.

  AST and ALT $\leq 2.5 \times$ ULN

  If patient has liver metastases, AST and/or ALT $\leq 5 \times$ ULN

  Alkaline phosphatase $\leq 2.5 \times$ ULN

  If patient has liver or bone metastases, alkaline phosphatase $\leq 5 \times$ ULN

  Serum bilirubin $\leq 1.5 \times$ ULN

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

  Calculated creatinine clearance (CrCl) $\geq$45 mL/min

  If using cisplatin, calculated CrCl must be $\geq$60 mL/min

- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception during study treatment that results in a low failure rate of $<$1% per year when used consistently and correctly. Female patients treated with atezolizumab should continue contraception use for $5\ months$ after the last dose. Female patients treated with cisplatin should continue contraception use for 6 months after the last dose. Male patients treated with gemcitabine, cisplatin, or carboplatin should continue contraception use for 6 months after the last dose. Such methods include combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD), intrauterine hormone-releasing system (IUS),

bilateral tubal occlusion or vasectomized partner (on the understanding that this is the only one partner during the entire study duration), and sexual abstinence.

Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this study if they have a partner of childbirth potential. Male patients must always use a condom.

- Women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

4.1.2 Exclusion Criteria

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

4.1.2.1 Cancer-Specific Exclusions

- Active or untreated CNS metastases as determined by CT or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to randomization
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to randomization. There is no required minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.
- Uncontrolled or symptomatic hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN)

  Patients who are receiving denosumab prior to randomization must be willing and eligible to discontinue its use and replace it with a bisphosphonate instead while in the study.
- Malignancies other than NSCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized

prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)

4.1.2.2 General Medical Exclusions

- Women who are pregnant, lactating, or intending to become pregnant during the study
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

  Patients with controlled Type I diabetes mellitus on a stable insulin regimen are eligible for this study.

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

  Rash must cover less than 10% of body surface area (BSA)

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months requiring treatment with either PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors or high potency or oral steroids.
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation
- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans), idiopathic pneumonitis or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive HIV test
- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening).

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization.

- Patients with active hepatitis C

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Active tuberculosis
- Severe infections within 4 weeks prior to randomization including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- 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

4.1.2.3 Exclusion Criteria Related to Medications

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

  TKIs approved for treatment of NSCLC discontinued $>$7 days prior to randomization; the baseline scan must be obtained after discontinuation of prior TKIs.

- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to randomization
- Received therapeutic oral or IV antibiotics within 2 weeks prior to randomization

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

- Administration of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live attenuated vaccine will be required during the study

  Influenza vaccination should be given during influenza season. Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization or at any time during the study.

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti–cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:

  Last dose of anti–CTLA-4 at least 6 weeks prior to randomization

  No history of severe immune related adverse effects from anti–CTLA-4 (CTCAE Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to randomization

  Prior treatment with cancer vaccines is allowed.

- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to randomization

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

  The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

4.1.2.4 Exclusion Criteria Related to Gemcitabine, Cisplatin or Carboplatin

- History of allergic reactions to cisplatin, carboplatin, or other platinum-containing compounds
- Patients with hearing impairment (cisplatin)
- CrCl $<$60mL/min (cisplatin)
- Grade $\geq$2 peripheral neuropathy as defined by NCI CTCAE v4.0 criteria (cisplatin)
- Known hypersensitivity to gemcitabine
- History of radiation therapy within 7 days prior to initiating gemcitabine

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study.

After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 status by central testing), personnel at the study site will enter demographic and baseline characteristics in the interactive Web/voice response system (IxRS). For patients who are eligible for enrollment, the study site will

obtain the patient's randomization number and treatment assignment from the IxRS. Randomization to one of two treatment arms will occur in a 1:1 ratio.

Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization will be stratified by the following criteria:

- Sex (male vs. female)
- ECOG performance status (0 vs. 1)
- Presence of liver metastases at baseline (yes vs. no)
- Tumor tissue PD-L1 expression by IHC (TC3 and any IC vs. TC0/1/2 and IC3)

Patients should receive their first dose of study treatment on the day of randomization if possible. If this is not possible, the first dose should occur within 5 days after randomization.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab (MPDL3280A)

The atezolizumab (MPDL3280A) drug product is provided *as a sterile liquid* in a single-use, 20-mL glass vial. 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.

For further details on the *formulation and handling* of atezolizumab, see the Pharmacy Manual and Investigator's Brochure.

Atezolizumab (MPDL3280A) will be supplied by the Sponsor.

4.3.1.2 Gemcitabine + Cisplatin or Carboplatin

The comparator study drugs, gemcitabine + cisplatin or carboplatin (based on investigator's choice), will be used in commercially available formulations. They will be provided by the Sponsor if they are considered Investigational Medical Products (IMPs) by local regulations (see Section 4.3.4).

For information on the formulation, packaging, and handling of gemcitabine, cisplatin and carboplatin see the local prescribing information for each drug.

4.3.1.3 Erlotinib

Switch maintenance to erlotinib is *no longer* permitted for patients randomized to Arm B. *However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.*

Erlotinib will be *provided by the Sponsor if required by local health authority regulations.* For information on the formulation, packaging, and handling of erlotinib, see the local prescribing information.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab

Patients who are randomized to be treated with atezolizumab will receive 1200 mg atezolizumab administered by IV infusion q21d in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions.

Atezolizumab infusions will be administered per the instructions outlined in Table 9.

Table 9 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No pre-medication is allowed. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse atezolizumab (1200 mg in a 250 mL 0.9% NaCl intravenous infusion bag) over 60 (±15) minutes • If clinically indicated, record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes (±5-minute windows are allowed for all timepoints). • If clinically indicated, record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, pre-medication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. • If no reaction occurs, continue subsequent infusions over 30 (±10) minutes Continue to record vital signs within 60 minutes before starting infusion and during and after the infusion if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be delivered over 60 (±15) minutes. Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated or if patient experienced symptoms during the previous infusion. Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 30 (± 10) minutes after the infusion, if clinically indicated or if patient experienced symptoms during previous infusion.

NaCl = sodium chloride.

Dose modifications to atezolizumab are not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.6 and 5.1.7.

See the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

4.3.2.2 Gemcitabine + Cisplatin or Carboplatin

Each study site will administer gemcitabine + cisplatin or carboplatin according to local practice. The selected chemotherapy combination should remain the same for all cycles (i.e., patients who start on gemcitabine + cisplatin remain on this combination and not switch to gemcitabine + carboplatin during treatment and vice versa). Treatment can be given for four or six cycles as per local standard of care. The intended number of cycles of carboplatin or cisplatin will be specified by the investigator prior to study randomization.

Patients should receive anti-emetic and IV hydration for platinum-based treatments according to the local standard-of-care and manufacturer's instruction. Table 10 lists the suggested doses and infusion times for gemcitabine + cisplatin or carboplatin. Gemcitabine + cisplatin or carboplatin may be administered in accordance with the local standard-of-care in lieu of the suggested doses and/or infusion times in Table 10. If there is a significant difference between the protocol guidelines and institutional standard of care, call the Medical Monitor to discuss.

Table 10 Gemcitabine + Cisplatin or Carboplatin Regimen

Chemotherapy	Dose/Route	Treatment (Four or Six Cycles)
Gemcitabine	1250 mg/m^2 IV	Over 30 minutes on Days 1 and 8 q21d
Cisplatin	75 mg/m^2 IV	Over 1–2hours on Day 1 q21d
Gemcitabine	1000 mg/m^2 IV	Over 30 minutes on Days 1 and 8 q21d
Carboplatin	AUC 5 IV	Over ~30–60 minutes on Day 1 q21d

AUC = area under the concentration curve; IV = intravenous; q21d = every 21 days.

The guidelines for dose modification and treatment interruption or discontinuation for gemcitabine + cisplatin or carboplatin are provided in Section 5.1.8.

4.3.2.2.1 Gemcitabine

Institutions should follow their standard administration regimens for gemcitabine. In general, gemcitabine will be administered intravenously at a dose of 1250 mg/m^2 (in combination with cisplatin) 1000 mg/m^2 (in combination with carboplatin) or over 30 minutes on Days 1 and 8 of each 21 day cycle followed by cisplatin or carboplatin at approximately 30 minutes after the completion of the gemcitabine infusion on Day 1 only.

Gemcitabine injection must be diluted prior to infusion. The recommended diluent for reconstitution of gemcitabine is 0.9% sodium chloride injection without preservatives.

The administration of gemcitabine should be done in accordance with local practice and manufacturers' instructions; sites should follow their institutional standard-of-care for

determining the gemcitabine dose for obese patients and for dose adjustment in the event of patient weight changes.

4.3.2.2.2 Cisplatin/Carboplatin

Each site will choose to treat a given patient with either cisplatin or carboplatin according to local practice.

Cisplatin

Cisplatin should be administered by IV infusion approximately 30 minutes after completion of the gemcitabine infusion at a dose of 75 mg/m² over 1–2 hours or per standard-of-care at the institution. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin.

Refer to local clinical practice guidelines for further details.

Carboplatin

Carboplatin should be administered by IV infusion, immediately after the completion of the gemcitabine administration over 30–*60* minutes to achieve an initial target area under the concentration–time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 5 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

Total dose (mg) = (target AUC) × (glomerular filtration rate [GFR] + 25)

NOTE: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the CrCl. The CrCl is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age})\ (\text{wt})}{72 \times \text{Scr}}\ (\times 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate GFR using a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated on the basis of serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity caused by overdosing. On the basis of the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg} \bullet \text{min/mL)} \times (\text{GFR} + 25 \text{ mL/min})$$

The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is $6 \times 150 = 900$ mg.
For a target AUC = 5, the maximum dose is $5 \times 150 = 750$ mg.
For a target AUC = 4, the maximum dose is $4 \times 150 = 600$ mg.

See the FDA's communication regarding carboplatin dosing for more details at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm228974.htm.

4.3.2.3 Erlotinib

Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, gemcitabine, cisplatin carboplatin*, and erlotinib*) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of the IMPs with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Study Access to Atezolizumab Investigational Medicinal Product Accountability

The Sponsor will evaluate the appropriateness of continuing to provide atezolizumab to patients assigned to this treatment in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

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

Premedication with antihistamines may be administered for any atezolizumab infusions after Cycle 1.

The following therapies should continue while patients are in the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low–molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain only after the induction phase with chemotherapy is complete) provided it does not interfere with the assessment of tumor target lesions (e.g., if the lesion to be irradiated is not the only site of disease as that would render the patient not evaluable for response by tumor assessments according to RECIST v1.1)

  It is not a requirement to withhold atezolizumab during palliative radiotherapy.
- Inactive influenza vaccinations
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine 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 7).

Switch maintenance *treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.*

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance; see Section 5.1.7).

Systemic corticosteroids are recommended, with caution at the discretion of the treating physician, for the treatment of specific adverse events when associated with atezolizumab therapy. Guidelines for the management of immune-mediated adverse events are *provided in Section 6 (Guidance for the Investigator) of the atezolizumab Investigator's Brochure.*

4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment depending on the anti-cancer agent (see Section 4.1.2) and during study treatment until disease progression is documented and patient has discontinued study treatment. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (unless otherwise noted).

The following medications are prohibited while in the study, unless otherwise noted:

- Denosumab; patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study.
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, or within 90 days following the last atezolizumab dose (for patients randomized to atezolizumab).
- Use of steroids to pre-medicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in

such patients, non-contrast CT of the chest and non-contrast CT or MRIs of the abdomen and pelvis should be performed.

The concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator, provided that there are no known interactions with any study treatment. As noted above, herbal therapies intended for the treatment of cancer are prohibited.

4.5 STUDY ASSESSMENTS

See Appendix 1 for the schedules of assessments to be performed during the study.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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

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

4.5.1 Informed Consent Forms and Pre-Screening/Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and may be obtained more than 28 days before initiation of study treatment.

Prior to signing the main consent form for the study, patients will specifically allow for the collection and testing of archival or fresh tumor tissue by signing the pre-screening consent form.

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 randomization. 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.

Patients who are treated with atezolizumab and who show apparent radiographic progression at a tumor response evaluation must sign consent at that time to acknowledge deferring *other* treatment options in favor of continuing atezolizumab.

Patients in both treatment arms may undergo an optional tumor biopsy at the time of radiographic disease progression if clinically feasible. To do this, patients must sign a separate consent.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, non-NSCLC cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

NSCLC cancer history will include prior cancer therapies and procedures.

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

4.5.3 Physical Examinations

A complete physical examination, according to local practice, should be performed at screening. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions *electronic Case Report Form (*eCRF).

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital signs will be measured and recorded as described in Table 11.

Table 11 Vital Sign Measurements at Cycle 1 and All Subsequent Cycles

	Cycle 1
Treatment Arm	Timepoints
Arm A	Within 60 minutes prior to atezolizumab infusion
	During the infusion (every 15 [±5] minutes) and within 30 (±10) minutes after atezolizumab infusion if clinically indicated
Arm B	Within 60 minutes prior to gemcitabine infusion
	As clinically indicated prior, during, or after carboplatin or cisplatin infusion
	Subsequent Cycles
Treatment Arm	Timepoints
Arms A and B	Within 60 minutes prior to infusion
	During the infusion if clinically indicated or if symptoms occurred during the prior infusion
	Within 30 (±10) minutes after infusion if clinically indicated or if symptoms occurred during the prior infusion

For patients in the atezolizumab arm, see Table 9 *in Section 4.3.2.1.*

4.5.5 Tumor and Response Evaluations

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the chest and abdomen. A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard-of-care at subsequent response evaluations. A spiral CT scan of the chest may be obtained but is not a requirement.

A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with active or untreated CNS metastases are not eligible for this study (see Section 4.1.2.1 for CNS-related exclusions).

If a CT scan for tumor assessment is performed in a positron emission tomography/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.

Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests.

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. 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). Response will be assessed by the investigator with use of RECIST v1.1 and modified RECIST (see Appendix 3 and Appendix 4). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Tumor assessments will be performed every 6 weeks (±7 days) for *48 weeks* following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (for patients in both treatment arms) or loss of clinical benefit (for atezolizumab-treated patients who continue treatment beyond disease progression according to RECIST v1.1), withdrawal of consent, *enrollment into an extension study, or death,* whichever occurs first. At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected.

Patients treated with atezolizumab continuing to experience clinical benefit, despite evidence of radiographic progression per RECIST v1.1, will continue tumor assessments as per the schedule listed above.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

The schedule of laboratory assessments should be performed according to Appendix 1. *PK, ATA, and biomarker evaluations are no longer required.*

Samples for the following laboratory tests *are to* be sent to the study site's local laboratory for analysis:

- 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 or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- Coagulation (INR or aPTT)

- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed on Day 1 of each cycle during treatment prior to administration of study treatment. A serum pregnancy test must be performed if the urine pregnancy test result is positive.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥12 months of amenorrhea).
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick permitted
- Thyroid function testing (thyroid-stimulating hormone, free T3, free T4)
- HIV testing

  All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.
- HBV serology: HBsAg, antibodies against HBsAg, total HBcAb

  HBV DNA test must be performed prior to randomization if patient has negative serology for HBsAg and positive serology for HBcAb.
- HCV: hepatitis C virus antibody (anti-HCV)

  HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV
- *Blood biomarker samples will no longer be collected, but samples already collected will be kept and used per original signed informed consent.*
- For patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR), any leftover material from *samples already collected* will be stored and used for exploratory analyses as indicated in Section 4.5.12.

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

4.5.7 Tumor Tissue Samples

A central laboratory will coordinate the sample collection of tissue samples for research-related testing at central laboratories or at the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments.

See the laboratory manual for additional details on tissue sample handling.

4.5.7.1 Archival and Freshly Collected Tumor Tissue Samples for Screening

Representative tumor specimens in paraffin blocks (preferred) or at least 15 serial-cut, unstained slides with an associated pathology report must be submitted for determination of PD-L1 status to ensure patient meets eligibility criteria prior to randomization. In addition, exploratory biomarkers (including but not limited to markers

related to immune or NSCLC biology, such as T-cell markers or non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) may be evaluated.

Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status).

An archival tumor specimen should be submitted if available. If an archival specimen is not available, the patient may still be eligible, with the assumption that the patient is willing to consent to and undergo a pre-treatment biopsy or resection of the tumor. For freshly collected biopsy specimens, acceptable samples include:

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

Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are deemed ineligible to enroll in the study will be returned no later than 6 weeks after eligibility determination.

4.5.7.2 *Optional* Tumor Samples at the Time of Radiographic Progression

Patients in both treatment arms *may* undergo a*n optional* tumor biopsy to obtain a tumor sample at the time of radiographic disease progression *(preferably within 40 days of radiographic progression or prior to start of the next anti-cancer treatment, whichever is sooner) if they have provided consent for optional biopsy and if clinically feasible.*

The preferred sample types include: resections, core needle, excisional, incisional, punch, or forceps biopsies. If such specimens are not available, any type of specimens (including fine-needle aspiration, cell pellet specimens e.g., from pleural effusion, and lavage samples) can also be submitted.

The status of immune-related, tumor type–related and other exploratory biomarkers (including but not limited to T-cell markers and non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) in tumor tissue samples may be evaluated.

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the

patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by the FDA; results from these investigational tests should not be used to guide future treatment decisions.

4.5.7.3 Tumor Samples at Other Timepoints

If a patient undergoes a medically indicated procedure (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) any time during the course of the study that has the likelihood of yielding tumor tissue, any remaining samples or a portion of the sample not necessary for medical diagnosis (leftover tumor tissue) may be obtained for exploratory analysis.

Patients with additional tissue samples from procedures performed at different times during the course of their study participation (during treatment) who have signed the RCR optional consent will be requested (but not required) to also submit these *optional fresh biopsy* samples for central testing. *Tumor tissue samples collected at the time of clinical events (e.g., clinical response) are preferred.* Tissue samples obtained at multiple times from individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

4.5.8 Use and Storage of Remaining Samples from Study-Related Procedures

The remainder of samples obtained for study-related procedures (including blood samples and tumor tissues) will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples in the RCR for future research (see Section 4.5.12), the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.9 Anti-Therapeutic Antibody Testing

ATA testing will no longer be performed.

4.5.10 Electrocardiograms

A twelve-lead ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must 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.

4.5.11 Patient-Reported Outcomes

PRO assessments are no longer required, and PRO data will no longer be collected.

4.5.12 Samples for Roche Clinical Repository

4.5.12.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's *institutional review board/ethics committee (*IRB/EC*)* and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.12.1) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples may be collected for patients who have signed the RCR optional consent:

- Optional fresh biopsy samples
- Leftover tumor tissue samples
- Remaining fluids (serum, plasma, blood cell derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed

The following sample will be used for identification of genetic (inherited) biomarkers:

- Whole blood sample for DNA extraction (6 mL)*, which may be collected at any time during the course of the study*

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 4.5.12. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.12.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.12.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO29432 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29432.

4.5.12.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system to ensure compliance with data confidentiality, as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.13 Timing of Assessments

4.5.13.1 Screening/Baseline Assessments

Screening tests and evaluations will be performed within 28 days prior to Cycle 1, Day 1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening.

See *Appendix 1 of the previous protocol Version 4* for the schedule of screening assessments.

4.5.13.2 Assessments during Treatment

All treatment visits must occur within ±3 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.

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 and visits continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

After completion of the induction phase (for patients in the control arm) or after five cycles (for patients in the atezolizumab arm), one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations/holidays. Following the delay, the next cycle must be delivered 21 days from the previous dose administration. Two consecutive 28-day cycles are not permitted.

If a dose modification is required due to toxicity, refer to Section 5.1.6.

Tumor assessments should occur every 6 weeks (± 7 days) for *48 weeks* following Cycle 1, Day 1 and every 9 weeks (± 7 days) *after completion of the Week 48 tumor assessment*, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, *enrollment into an extension study, or death,* whichever occurs first.

The following assessments may be performed ≤96 hours before Day 1 of each cycle (for Cycle 1, Day 1, the following Day 1 procedures should occur after randomization but before study treatment is administered):

- ECOG performance status
- Limited physical examination
- Local laboratory tests

See Appendix 1 for the schedule of assessments performed.

4.5.13.3 Assessments at Treatment Discontinuation Visit

Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. The visit at which a response assessment shows radiographic progressive disease according to RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue

treatment after disease progression according to RECIST v1.1) may be used as the treatment discontinuation visit.

See Appendix 1 for assessments to be performed at the treatment discontinuation visit.

4.5.13.4 Follow-Up Assessments

After the Treatment Discontinuation Visit, adverse events should be followed as outlined in Section 5.3.

For patients who discontinue study treatment for any reason other than radiographic progressive disease per RECIST v1.1, tumor assessments should continue at the same frequency as would have been followed if the patient had continued study treatment until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, *enrollment into an extension study, or death,* whichever occurs first.

Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 should continue tumor assessments according to the protocol schedule of response assessments until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, *enrollment into an extension study, or death,* whichever occurs first.

Ongoing or new serious adverse events, adverse events of special interest or adverse events thought to be related to study treatment will be followed until the event has resolved to the baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse events.

4.5.13.5 Assessments at Unscheduled Visits

Assessments for unscheduled visits related to a patient's underlying NSCLC, study treatment, or adverse events should be performed as clinically indicated and entered into Unscheduled Visit eCRFs.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

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

4.6.2 Study Treatment Discontinuation

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

- 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 immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Intolerable toxicity related to study treatment
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Use of another non-protocol anti-cancer therapy (see Section 4.4.3)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

  Exception for atezolizumab treatment: patients randomized to atezolizumab treatment will be permitted to continue study treatment after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria (see Figure 2 for schematic representation):

  Evidence of clinical benefit as assessed by the investigator

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

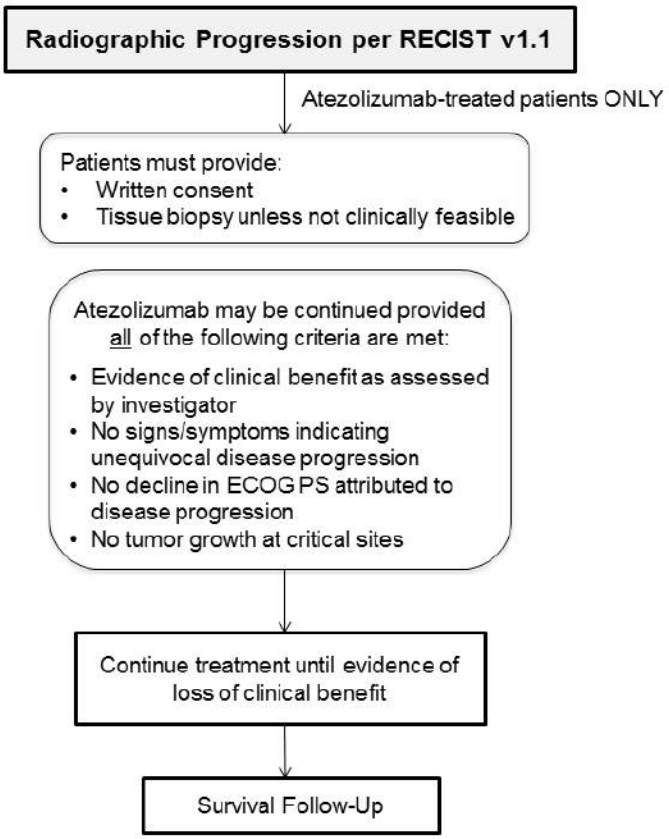
  No decline in ECOG performance status that can be attributed to disease progression

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

  Patients must provide written consent to acknowledge deferring *other* treatment options in favor of continuing atezolizumab treatment at the time of initial progression

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

Figure 2 Criteria for Continuing Atezolizumab in the Presence of Increased Radiographic Tumor Size (Atezolizumab Arm)



ECOG PS = Eastern Cooperative Oncology Group performance status; RECIST = Response Evaluation Criteria in Solid Tumors.

4.6.3 Study and Site Discontinuation

The study is currently closed to enrollment due to a low number of patients.

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

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

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

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the 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)

5. ASSESSMENT OF SAFETY

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma. The following information is based on results from nonclinical and clinical studies *for atezolizumab* and published data on similar molecules.

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). See Section 5.3 for complete details regarding safety reporting for this study.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. All serious adverse events and adverse events of special interest will be recorded during the trial and for up to 90 days after the last dose of study treatment or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or enhancement of autoimmune conditions. Adverse events with potentially immune-mediated causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, *pneumonitis,* myositis, and myasthenia gravis, have been observed in *the Phase Ia* Study PCD4989g. For further details regarding clinical safety, *including a detailed description of anticipated safety risks for atezolizumab,* see the atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup and management guidelines for suspected immune-mediated

adverse events are provided in Section 5.1.7 and in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

5.1.2 Risks Associated with Gemcitabine

Infusion times of gemcitabine longer than 60 minutes and more frequent than weekly dosing have been shown to increase toxicity.

Pulmonary toxicity has been reported with the use of gemcitabine. In cases of severe lung toxicity, gemcitabine therapy should be discontinued immediately and appropriate supportive care measures instituted.

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs. Monitoring for myelosuppression should occur prior to each cycle.

Hemolytic-uremic syndrome and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to *hemolytic-uremic syndrome*.

Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Use caution in patients with pre-existing renal impairment or hepatic insufficiency.

For more details regarding the safety profile of gemcitabine, see the *gemcitabine prescribing information*.

5.1.3 Risks Associated with Platinum-Based Chemotherapy

5.1.3.1 Risks Associated with Cisplatin Chemotherapy

Cisplatin is known to cause myelosuppression, ototoxicity, and nephrotoxicity. Cisplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for cisplatin-related adverse events.

For more details regarding the safety profile of cisplatin, see the *carboplatin prescribing information*.

5.1.3.2 Risks Associated with Carboplatin Chemotherapy

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 adverse events.

For more details regarding the safety profile of carboplatin, see the *carboplatin prescribing information*.

5.1.3.3 Risks Associated with Erlotinib

Switch maintenance treatment with erlotinib is no longer permitted. However, patients who had already started switch maintenance treatment with erlotinib under previous protocol versions may be allowed to continue treatment with erlotinib upon discussion of the risks, potential benefits, and alternative treatment options with the investigator.

The most commonly reported adverse drug reactions with erlotinib were rash and diarrhea. Most were Grade 1 or 2 in severity and were manageable without intervention. In general, rash manifests as a mild or moderate erythematous and papulopustular rash and may occur or worsen in sun-exposed areas. For patients who are exposed to the sun, protective clothing and/or the use of sunscreen (e.g., mineral-containing) may be advisable.

For more details regarding the safety profile of erlotinib, refer to the erlotinib *prescribing information*.

5.1.4 General Plan to Manage Safety Concerns

5.1.4.1 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non–serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Laboratory values must be reviewed prior to each infusion.

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).

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Section 5.2.2 and Section 5.2.3, *respectively*) will be reported in an expedited fashion (see Section 5.4.2). In addition, the Medical Monitor will review and evaluate observed adverse events on a regular basis.

Patients will be followed for serious adverse events and adverse events of special interest for 90 days following their last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. For all other adverse events, patients will be followed for 30 days after their last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study.

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

5.1.5 *Dose Modification*

5.1.5.1 *General Notes Regarding Dose Modification*

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF. The severity of adverse events 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 considers it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during study 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 chemotherapy, the dose of the other chemotherapy component does not require modification and the other chemotherapy component(s) may be administered if there is no contraindication.*
- *The investigator 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.*

5.1.6 Atezolizumab Dose Modifications, *Treatment Delays, or Treatment Discontinuation*

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 105 days beyond the last dose if they experience an adverse event that requires a dose to be withheld. If atezolizumab is withheld because of adverse events for $>$105 days beyond the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed for safety and efficacy as specified in Section 5.5.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab may be withheld for additional time $>$105 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) $\leq$10 mg/day. The

acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

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

5.1.7 Management of Atezolizumab-Specific Adverse Events

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

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

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

Management of systemic immune activation is presented below. See the atezolizumab Investigator's Brochure *for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, infusion-related reactions, potential pancreatic or eye toxicity, and other immune-mediated adverse events. See* Appendix 7 *for precautions for anaphylaxis.*

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

- *CBC with peripheral smear*

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

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

5.1.8 Gemcitabine + Cisplatin or Carboplatin Dose Modification and Management of Specific Adverse Events

Dose modification guidelines for gemcitabine + cisplatin or carboplatin are described in Table 12, Table 13, and Table 14. Additionally, manufacturer's instructions as well as local hospital or clinical practice *should* also be followed.

5.1.8.1 Hematologic Toxicity

Dose adjustments for hematologic toxicity may be required for gemcitabine and for cisplatin or carboplatin. Gemcitabine dosage adjustments for hematologic toxicity are based on the granulocyte and platelet counts taken on Days 1 and 8 of therapy. Patient receiving gemcitabine should be monitored prior to each dose with a CBC, including differential and platelet counts. If bone marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 12. For cisplatin or carboplatin dosage adjustment, see also Section 5.1.9 and the manufacturer's prescribing information.

Table 12 Dose Modification Guidelines for Hematological Toxicities on Day 1 of Gemcitabine + Cisplatin or Carboplatin

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	Gemcitabine/Cisplatin or Carboplatin % of full dose
≥1500	and	≥100,000	100%
less than 1,500	or	Less than100,000	Withhold

Table 13 Dose Modification Guidelines for Hematological Toxicities on Day 8 of Gemcitabine

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	Gemcitabine % of full dose
≥1000	and	≥100,000	100%
500-999	or	50,000–99,999	75%
<500	or	<50,000	Withhold

5.1.8.2 Dose Modifications Guidelines of Non-Hematological Toxicity

In general, for severe (Grade 3 or 4) non-hematological toxicity, and nausea/vomiting, therapy with gemcitabine should be held or dose reduced by 50% depending on the judgment of the investigator.

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary-leak syndrome
- Posterior reversible encephalopathy syndrome

Table 14 summarizes dose modifications guidelines for non-hematologic toxicities based on grade and severity.

Table 14 Gemcitabine Dose Modification Guidelines for Non-Hematological Toxicities

	Grade 2	Grade 3	Grade 4
First appearance	Interrupt treatment until resolved to Grade 0–1 then continue at same dose with prophylaxis where possible	Interrupt treatment until resolved to Grade 0–1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment unless investigator considers it to be in the best interest of the patient to continue at 50% of original dose, once toxicity has resolved to Grade 0–1 (after approval by the Sponsor)
Second appearance of same toxicity	Interrupt treatment until resolved to Grade 0–1, then continue at 75% of original dose	Interrupt treatment until resolved to Grade 0–1, then continue at 50% of original dose	
Third appearance of same toxicity	Interrupt treatment until resolved to Grade 0–1, then continue at 50% of original dose	Discontinue treatment permanently	
Fourth appearance of same toxicity	Discontinue treatment permanently		

5.1.9 Platinum Chemotherapy Dose Modification and Management of Specific Adverse Events

5.1.9.1 Cisplatin

Treatment with cisplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions (except alopecia, which does not warrant treatment discontinuation) or immediately if a Grade 3 or 4 neurotoxicity is observed.

Hematologic Toxicity

Treatment can be delayed for up to 3 weeks until the Day 1 ANC is $\geq 1500/mm^3$ and the platelet count is $> 100{,}000\ mm^3$. However, if the counts have not recovered in 3 weeks, the patient's chemotherapy will be dose reduced, held until adequate neutrophil recovery, or discontinued, according to physician judgment and local standard practice.

The cisplatin doses may be either administered at full dose (in the absence of toxicity) or at a reduced dose, as described in Table 15.

Table 15 Cisplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Cisplatin Dose
ANC $<500/mm^3$ and platelets $\geq 50,000/mm^3$	75% of previous dose
Platelets $<50,000/mm^3$, regardless of ANC	75% of previous dose
Platelets $<50,000/mm^3$ with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<1000/mm^3$ plus fever of $\geq 38.5°C$	75% of previous dose

[a] Nadir prior cycle.

Non-Hematologic Toxicity

If a patient develops a Grade ≥ 3 non-hematologic toxicity (excluding alopecia, which does not warrant treatment discontinuation, and neurotoxicity), cisplatin should be withheld until resolution to less than or equal to the patient's pre-treatment value. Treatment should be resumed according to the guidelines in Table 16.

Table 16 Cisplatin Dose Modification for Non-Hematologic Toxicities (Excluding Neurotoxicity)

Toxicity	Cisplatin Dose
Any Grade 3 or 4 toxicity (except alopecia)	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75% of previous dose

Nephrotoxicity

Impairment of renal function has been reported with cisplatin as single agent or in combination with other cytotoxic agents. CrCl must be ≥ 60 mL/min prior to the start of any cycle of cisplatin. If there is a drop in CrCl between cycles, but the CrCl is still ≥ 60 mL/min at the time of the next cycle, the treating physician should use his/her clinical judgment regarding continuing cisplatin, dose reduction, or delaying the cycle. If a patient's CrCl value has not returned to ≥ 60 mL/min within 42 days following last study drug administration, the patient must be discontinued from study treatment.

Ototoxicity

Ototoxicity has been observed with cisplatin as single agent or in combination with other cytotoxic agents. If the patient develops ototoxicity, subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits (http://www.drugs.com/pro/platinol.html).

Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 17. Patients should discontinue therapy if Grade 3 or 4 neurotoxicity is observed.

Table 17 Cisplatin Dose Modification for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 0–1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	50% of previous dose
Grade 3 or 4 neurotoxicity	Permanent discontinuation

5.1.9.2 Carboplatin

Hematologic Toxicity

At the start of each cycle, the ANC must be $\geq 1500/mm^3$ and the platelet count must be $\geq 100,000/mm^3$. Treatment should be delayed for up to 42 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines (Smith et al. 2006; NCCN 2012). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 18).

Table 18 Carboplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Carboplatin Dose
ANC $<500/mm^3$ and platelets $\geq 50,000/mm^3$	75% of previous dose
Platelets $<50,000/mm^3$, regardless of ANC	75% of previous dose
Platelets $<50,000/mm^3$ with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<1000/mm^3$ plus fever of $\geq 38.5°C$	75% of previous dose

[a] Nadir prior cycle.

All dose reductions for the first episode of neutropenic fever or thrombocytopenia (platelet count $<25,000$ or $<50,000$ with bleeding or that requires transfusion) are permanent. If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, the dose of carboplatin or cisplatin will be reduced according to physician judgment and local standard practice. Colony-stimulating factors, such as granulocyte colony-stimulating factor, may be used instead of dose reduction for neutropenic fever or Grade 4 neutropenia, according to the local standard practice and ASCO guideline. Patients who require a third dose reduction will immediately discontinue chemotherapy.

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Treatment should be delayed for up to 3 weeks until the Day 1 ANC is $\geq 1500/mm^3$ and the platelet count is $\geq 100,000/mm^3$. However, if the counts have not recovered in 3 weeks, the patient's chemotherapy will be dose-reduced, held until adequate neutrophil recovery, or discontinued, according to physician judgment and local standard practice. If chemotherapy is held longer than 42 days, all study treatment should be discontinued.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy must be withheld because of hematologic toxicity, full blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicity

For Grade 3 or 4 non-hematologic toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 19 provides the relevant dose adjustments for non-hematologic toxicities.

Table 19 Carboplatin Dose Modification on the Basis of Non-Hematologic Toxicities in the Preceding Cycle

Toxicity		Adjusted Carboplatin Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	100%
Oral mucositis	Grade 3 or 4	75%
Nausea/vomiting	Grade 3 or 4	75%
Neurotoxicity (motor or sensory)	Grade 2	100%
	Grade 3 or 4	75%
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue
Other	Grade 3 or 4	75%

AUC = area under the concentration curve.

[a] If deemed appropriate by the treating physician, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] Or any grade of diarrhea requiring hospitalization.

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs in spite of anti-emetics, the dose should be reduced by 25% for the next cycle. If tolerated, the dose should be increased back to 100% as soon as possible.

If, on Day 1 of any treatment cycle, the patient has oral mucositis, the treatment should be withheld until the oral mucositis is cleared. If the oral mucositis has not cleared in 3 weeks, the patient's chemotherapy will be discontinued. If acute Grade 3 oral mucositis occurs at any time, the dose should be given at a 75% dose when the oral mucositis is completely cleared. This is a permanent dose reduction.

Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, carboplatin should be withheld until the patient recovers completely or to Grade 1 toxicity. The treatment should then be resumed at 50% dose (permanent dose reduction). If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Sections 5.3.5.9 and 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported immediately by the investigator to the Sponsor (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include:

- The following confirmed treatment-emergent autoimmune conditions:

  Pneumonitis

  Hypoxia or dyspnea Grade ≥ 3

  Colitis

  Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency

  Vasculitis

  Hepatitis

  Transaminitis: Grade ≥ 2 (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN) OR AST/ALT $> 10 \times$ ULN

  Systemic lupus erythematosus

  Guillain-Barré syndrome

  Skin reactions: vitiligo, pemphigoid

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system, or infusion-reaction syndromes
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an

infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 to 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 20 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 20 Adverse Event Severity Grading Scale for Events Not Specifically Listed in the NCI CTCAE

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

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

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

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF; colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a

descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq$ 35% is direct bilirubin)

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Worsening of Non–Small Cell Lung Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 criteria. In rare cases, the determination of

clinical progression will be on the basis of symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is caused by disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization caused solely by progression of the underlying cancer

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded in the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.2.2 for further details)
- Adverse events of special interest (see Section 5.2.3 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D., *Ph.D.*

E-Mail: [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk as well as Medical Monitor contact information will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained, but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study treatment, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. Investigators are instructed to report all serious adverse events and adverse events of special interest considered related to study treatment regardless of time after study. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within $5\ months$ after the last dose of atezolizumab or within 6 months after the last dose of cisplatin. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancies should not be recorded on the Adverse Event eCRF. 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 the 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 eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 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 6 months after the last dose of gemcitabine, cisplatin, or carboplatin. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. 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 eCRF 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.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

Investigators are instructed to report all serious adverse events or adverse events of special interest that occur after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug for serious adverse events and adverse events of special interest, and 30 days after the last dose of study drug for all other adverse events or initiation of new anti-cancer therapy, whichever occurs first), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the atezolizumab Investigator's Brochure as a reference.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The study is currently closed to enrollment due to a low number of patients; therefore, formal analysis of efficacy endpoints will not be performed.

The safety population will include all randomized patients who received any amount of study treatment. Patients who are randomized into the study but did not receive any amount of study drug will not be included in the safety population.

6.1 DETERMINATION OF SAMPLE SIZE

The study is currently closed to enrollment due to a low number of patients; therefore, sample size estimation is no longer applicable.

6.2 SUMMARIES OF CONDUCT OF STUDY

Subject disposition will be provided in listing format due to the small sample size. Summaries will not be provided.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, baseline disease characteristics, ECOG performance status, and number of prior cancer treatments, will be *provided in listing format*. Baseline measurements are the last available data obtained prior to patients receiving the first dose of study drug.

6.4 EFFICACY ANALYSES

The study is currently closed to enrollment due to low number of patients; therefore, formal analysis of efficacy endpoints will not be performed.

6.5 SAFETY ANALYSES

Listings of safety data will be provided for the safety population and will include study drug exposure, adverse events, and deaths.

Verbatim description of adverse events will be mapped to thesaurus terms and graded according to NCI CTCAE v4.0.

6.6 PHARMACOKINETIC ANALYSES

The study is currently closed to enrollment due to a low number of patients; therefore, samples will no longer be collected, and formal analysis of PK and pharmacodynamics samples will not be performed.

6.7 EXPLORATORY ANALYSES

The study is currently closed to enrollment due to low number of patients; therefore, formal analysis of exploratory endpoints will not be performed.

6.8 SENSITIVITY ANALYSES ON THE PRIMARY ENDPOINT

The study is currently closed to enrollment due to low number of patients; therefore, a formal sensitivity analysis of the primary endpoint will not be performed.

6.9 INTERIM ANALYSIS

6.9.1 Interim Safety Analyses

The study is currently closed to enrollment due to a low number of patients; therefore, interim safety data will not be evaluated by an iDMC.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC with use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

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. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

Patient-reported data will be collected electronically with use of electronic devices provided by an *electronic PRO (*ePRO*)* vendor. The electronic device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with the FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted to a centralized database at the ePRO vendor. The data from the ePRO devices are available for view access only via secure access to a Web portal provided by the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The Sponsor will receive all data entered by patients on the e-diary and tablet device and all study documentation.

Details regarding patient reported data and the electronic device is available in the Study Reference Manual. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 (paper or electronic) are those in which 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, PROs, 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 pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be

entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data, as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug application (IND) will comply with the FDA regulations

and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason. A separate, specific signature will be required to document a patient's agreement to allow the collection of optional samples and any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Informed Consent Form will also contain the following additional signature pages:

- A signature page for patients receiving atezolizumab who wish, if approved by the treating physician, to continue treatment beyond initial radiographic disease progression and meet criteria specified in Section 4.6.2. This separate consent is to be signed after initial radiographic disease progression has occurred and patients have discussed other available treatment options and the potential risks of continuing treatment.
- *A signature page for patients to undergo an optional tumor tissue biopsy at the time of radiographic disease progression, if clinically feasible.*

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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 for use and disclosure of personal health information) signed by the patient, 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 national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd.

Randomization will occur through an IxRS. Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Procedure	All Treatment Cycles [a]	Treatment Discontinuation Visit
	Every 21 days (± 3 Days) [b]	≤30 Days after Last Dose
Vital signs [c]	x [c]	x [c]
Weight	x	x
Limited physical examination [d]	x	x
ECOG performance status	x	x
12-lead ECG	x [e]	x [e]
Hematology [f]	x	x
Serum chemistry [g]	x	x
Coagulation test (INR or aPTT)		x
Pregnancy test (women of childbearing potential ONLY)	x [h]	x [h]
TSH, free T3, free T4 [i]	x [j]	x [j]
Urinalysis [k]	x [k]	x [k]
Study treatment administration	x [l]	
Tumor response assessment [m]	x [n]	x
Informed consent to continue treatment beyond radiographic progression-(atezolizumab patients only)	At time of radiographic progression	
Optional tumor biopsy at radiographic progression (separate consent required) [o]	*At time of radiographic progression*	
Adverse events	x	x [p]
Concomitant medications	x	x
Optional RCR Blood (for DNA extraction) *RCR consent required*	At any time during the study	

CT = computerized tomography; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin fixed paraffin embedded; ICF = Informed Consent Form; IV = intravenous; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; TSH = thyroid-stimulating hormone.

[a] Assessments should be performed before study drug infusion unless otherwise noted.

[b] Except for Cycle 1, which must be performed within 5 days after the patient is randomized. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤96 hours before Day 1 of each cycle as specified in Section 4.5.13.2.

[c] Vital signs include pulse rate, respiratory rate, blood pressure, and temperature. For both study treatment arms, the patient's vital signs should be recorded within 60 minutes before infusion, and 30 (±10) minutes after the infusion if clinically indicated. For *the second atezolizumab infusion and beyond* in both arms, vital signs will be collected within

60 minutes prior to the infusion and should be collected during the infusion and 30 (±10) minutes after the infusion, if clinically indicated or if symptoms occurred in the prior infusion.

[d] Symptom-directed physical examinations; see Section 4.5.3 for details.

[e] ECG recordings will be obtained when clinically indicated.

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

[g] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

[h] Urine pregnancy tests; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[i] *Total T3 will be tested only at sites where free T3 is not performed.*

[j] Thyroid function testing (TSH, free T3, free T4) every fourth cycle *after Cycle 1, Day 1.*

[k] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). *Urinalysis will be obtained during study treatment when clinically indicated.*

[l] If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes until disease progression per RECIST v1.1 or loss of clinical benefit. For gemcitabine + cisplatin/carboplatin, study drug will be administered according to the local prescribing information, including premedication with steroids (see Section 4.3.2.2.2).

[m] *Perform every 6 weeks (±7 days; approximately every two cycles) for 48 weeks following Cycle 1, Day 1, regardless of treatment delays, and then every 9 weeks (±7 days) after completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression, (or loss of clinical benefit for atezolizumab-treated patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, death, or are eligible to roll over to an extension study, whichever occurs first. CT scans may be repeated at any time if progressive disease is suspected. See Section 4.5.5 for details.*

[n] CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest and abdomen. A CT scan of the pelvis is required as clinically indicated or as per local standard-of-care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. See Section 4.5.5 for details.

[o] *Optional tumor biopsy at radiographic disease progression, if clinically feasible, preferably within 40 days of radiographic progression or prior to start of the next anti-cancer therapy, whichever occurs is sooner.*

[p] All serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any serious adverse events or adverse events of special interest believed to be related to prior study drug treatment.

Appendix 2
American Joint Committee on Cancer
Non–Small Cell Lung Cancer Staging, 7th Edition

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____ LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Tis Carcinoma *in situ*	☐ Tis
☐ T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*	☐ T1
☐ T1a	Tumor ≤2 cm in greatest dimension	☐ T1a
☐ T1b	Tumor > 2 cm but ≤3 cm in greatest dimension	☐ T1b
☐ T2	Tumor > 3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≥2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	☐ T2
☐ T2a	Tumor > 3 cm but ≤5 cm in greatest dimension	☐ T2a
☐ T2b	Tumor > 5 cm but ≤7 cm in greatest dimension	☐ T2b
☐ T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (< 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe	☐ T3
☐ T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe	☐ T4
	* The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.	
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	☐ N1
☐ N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	☐ N2
☐ N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	☐ N3
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐ M1	Distant metastasis	☐ M1
☐ M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion**	☐ M1a
☐ M1b	Distant metastasis (in extrathoracic organs)	☐ M1b
	**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.	

Appendix 2
American Joint Committee on Cancer
Non–Small Cell Lung Cancer Staging, 7th Edition (cont.)

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
❑ Occult	TX	N0	M0	❑ Occult	TX	N0	M0
❑ 0	Tis	N0	M0	❑ 0	Tis	N0	M0
❑ IA	T1a	N0	M0	❑ IA	T1a	N0	M0
	T1b	N0	M0		T1b	N0	M0
❑ IB	T2a	N0	M0	❑ IB	T2a	N0	M0
❑ IIA	T2b	N0	M0	❑ IIA	T2b	N0	M0
	T1a	N1	M0		T1a	N1	M0
	T1b	N1	M0		T1b	N1	M0
	T2a	N1	M0		T2a	N1	M0
❑ IIB	T2b	N1	M0	❑ IIB	T2b	N1	M0
	T3	N0	M0		T3	N0	M0
❑ IIIA	T1a	N2	M0	❑ IIIA	T1a	N2	M0
	T1b	N2	M0		T1b	N2	M0
	T2a	N2	M0		T2a	N2	M0
	T2b	N2	M0		T2b	N2	M0
	T3	N1	M0		T3	N1	M0
	T3	N2	M0		T3	N2	M0
	T4	N0	M0		T4	N0	M0
	T4	N1	M0		T4	N1	M0
❑ IIIB	T1a	N3	M0	❑ IIIB	T1a	N3	M0
	T1b	N3	M0		T1b	N3	M0
	T2a	N3	M0		T2a	N3	M0
	T2b	N3	M0		T2b	N3	M0
	T3	N3	M0		T3	N3	M0
	T4	N2	M0		T4	N2	M0
	T4	N3	M0		T4	N3	M0
❑ IV	Any T	Any N	M1a	❑ IV	Any T	Any N	M1a
	Any T	Any N	M1b		Any T	Any N	M1b
❑ Stage unknown				❑ Stage unknown			

Reference: Lung. In: Edge S, Byrd DR, Compton CC, et al, editors. AJCC Cancer Staging Manual, Seventh Edition. Chicago: Springer, 2010:267–70.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

a. Measurable Tumor Lesions

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

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

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

b. Non-Measurable Tumor Lesions

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

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

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

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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

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

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

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 during the study (nadir), including baseline

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

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

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum during the 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 during the study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

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

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

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. Although 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. Although 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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 PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

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

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

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

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

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

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

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

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

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

c. Special Notes on Response Assessment

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "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.

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

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 CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (v1.1) conventions[3] and immune-related response criteria[4] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST = Response Evaluation Criteria in Solid Tumors.

A. DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression.

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[3] Eisenhauer et al. Eur J Cancer 2009;45: 228–47; Topalian et al. N Engl J Med 2012;366:2443–54; and Wolchok et al., Clin Can Res 2009;15:7412–20.

[4] Wolchok et al. Clin Can Res 2009;15:7412–20; Nishino et al J Immunother Can 2014;2:17; Nishino et al. Clin Can Res 2013;19:3936–43.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

A.1 MEASURABLE 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 as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (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)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$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 follow-up, only the short axis will be measured and followed.

A.2 NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 but $<$15 mm), 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 mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

A.3 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 for measuring 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 as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Cystic Lesions

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

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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.

B. TUMOR RESPONSE EVALUATION

B.1 DEFINITIONS OF TARGET/NON-TARGET LESIONS

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 that, for instances in which 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 in addition, 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 $\geq$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, 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 $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Non-Target Lesions

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.

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”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non–lymph node lesions must be $\geq$10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum

of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

B.2 CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion $\geq$15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to $<$15 mm (or even $<$10 mm). However, if it subsequently decreases to $<$10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of $<$10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter $\geq$15 mm).

The appearance of new lymph nodes with diameter $<$10 mm should not be considered pathological and not considered a new lesion.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

B.3 RESPONSE CRITERIA

Timepoint 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.

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum during the study (nadir SLD; this includes the baseline sum if that is the smallest during the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is considered not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE 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 only happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but

those gave a sum of 80 mm, the patient will be assigned PD status, regardless of the contribution of the missing lesion.

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to <+20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; SLD=sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.

Appendix 5
Anti–PD-L1 Immunohistochemistry

OVERVIEW

The Ventana anti–programmed death ligand–1 (PD-L1) (SP142) rabbit monoclonal primary antibody immunohistochemistry (IHC) assay will be used to determine PD-L1 IHC status. The anti–PD-L1 (SP142) rabbit monoclonal antibody IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to atezolizumab. For Study GO29432, the anti–PD-L1 (SP142) IHC assay will be used for investigational purposes only.

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody is intended for laboratory use in the semi-quantitative immunohistochemical assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded non–small cell lung cancer (NSCLC) tissue stained on a Ventana BenchMark ULTRA automated slide stainer. It is indicated as an aid in the selection of patients with NSCLC with locally advanced or metastatic disease who might benefit from treatment with atezolizumab.

This assay is for investigational use only. The performance characteristics of this product have not been established.

DEVICE DESCRIPTION

The Ventana anti–PD-L1 (SP142) rabbit monoclonal primary antibody is a pre-dilute, ready-to-use antibody product optimized for use with the Ventana Medical Systems OptiView DAB IHC Detection Kit and the OptiView Amplification Kit on Ventana Medical Systems automated BenchMark ULTRA platforms. One 5-mL dispenser of anti–PD-L1 (SP142) rabbit monoclonal primary antibody contains approximately 36 μg of rabbit monoclonal antibody directed against the PD-L1 protein and contains sufficient reagent for 50 tests. The reagents and the IHC procedure are optimized for use on the BenchMark ULTRA automated slide stainer, utilizing Ventana System Software (VSS).

SCORING SYSTEM

PD-L1 staining with anti–PD-L1 (SP142) rabbit monoclonal primary antibody in NSCLC can be observed in both tumor cells and tumor-infiltrating immune cells.

Appendix 6
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

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