Official Title: A Phase III, Open-Label, Randomized Study To Investigate The Efficacy And Safety Of Atezolizumab (Anti–PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy In Patients With Completely Resected Stage IB–IIIA Non–Small Cell Lung Cancer

NCT Number: NCT02486718

Document Date: Protocol Version 12: 24-May-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29527
STUDY NAME:	IMpower010
VERSION NUMBER:	12
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 117296 EudraCT Number: 2014-003205-15 EU CT Number: 2023-505981-26-00 NCT Number: NCT02486718 PS ID: RD002503 (SP142), RD005400 (SP263) CV ID: CIV-23-04-042935 (SP142), CIV-23-04-042936 (SP263)
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann–La Roche Ltd Grenzacherstrasse 124 4058 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Region-Specific Protocol		
Version	**Date Final**	**Region**	**Version**	**Date Final**
12	See electronic signature and date stamp on the final page of this document.	—	—	—
11	16 February 2023	—	—	—
10	3 February 2022	—	—	—
9	17 April 2021	—	—	—
8	11 February 2020	—	—	—
7	30 October 2018	—	—	—
5	29 June 2016	VHP	6	2 March 2018
4	5 October 2015	—	—	—
3	5 September 2015	—	—	—
2	8 June 2015	—	—	—
1	1 April 2015	—	—	—

PROTOCOL AMENDMENT, VERSION 12: RATIONALE

Protocol GO29527 has been amended primarily to update the risks and management guidelines for atezolizumab to align with the latest Atezolizumab Investigator's Brochure Version 20 and to reduce the requirements of the study for ongoing patients after the final disease free survival (DFS) analysis is conducted. Changes to the protocol, along with a rationale for each change, are summarized below:

- The requirement for tumor assessments/disease status assessments has been removed following the completion of the final DFS analysis to reduce burden on patients and investigators. After this, any recurrence or new primary non-small cell lung cancer (NSCLC) or new primary non-NSCLC malignancy diagnosed as a result of local standard of care is to be recorded in the electronic data capture system(Sections 3.1, 4.5.5, and 4.6.4.1, and Appendix 2).
- The requirement for biomarker sample collection at recurrence has been removed following the final DFS analysis to reduce burden on patients and investigators (Sections 3.1 and 4.5.8.1 and Appendices 2 and 3).
- Text in Section 4.3.6 has been modified to indicate that the Sponsor does not currently have any plans to provide atezolizumab or any other study treatments to participants who have completed the study and that the Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Products.
- The frequency for the collection of survival follow-up information has been updated from 3 months or more often to 6 months or more often to reduce the burden on patients and investigators during long term survival follow-up (Section 4.6.4.4 and Appendix 2).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Appendix 6).
- The adverse event management guidelines have been streamlined by removing standard of care information and restructured, for consistency with regulatory guidelines and industry standards (Appendix 9).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 9).
- The list of investigational, non-investigational, and auxiliary medicinal products has been corrected to include cisplatin and additional details for the non-investigational and auxiliary medicinal products (Appendix 10).

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.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
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SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann–La Roche Ltd Grenzacherstrasse 124 4058 Basel, Switzerland

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

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
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STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of atezolizumab, (MPDL3280A [anti–programmed death-ligand 1 [PD-L1] antibody]). This trial will enroll patients with Stage IB–Stage IIIA NSCLC following resection and adjuvant chemotherapy. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates.

OUTCOME MEASURES

EFFICACY OUTCOME MEASURES

Primary Efficacy Outcome Measure

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

- DFS, defined as the time from randomization to the date of occurrence of any of the following, whichever occurs first:
  - First recurrence of NSCLC, as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status
  - Occurrence of new primary NSCLC, as assessed by the investigator
  - Death from any cause

This efficacy outcome measure will be assessed in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay) within the Stage II-IIIA population, in all randomized patients with Stage II-IIIA NSCLC, and in the ITT population.

Secondary Efficacy Outcome Measures

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

- OS, defined as the time from randomization to death from any cause, in the ITT population
- DFS rates at 3 years and 5 years in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay), in the Stage II–IIIA population (i.e., all randomized patients with Stage II–IIIA NSCLC) and in the ITT population
- DFS in the PD-L1 subpopulation, defined as TC ≥50% by the SP263 IHC assay within patients with Stage II–IIIA NSCLC

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest graded according to the NCI CTCAE v4.0
- Changes from baseline in vital signs, physical findings, and targeted clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, safety, and efficacy parameters

OVERALL DESIGN AND STUDY POPULATION

This Phase III, open-label, randomized study will investigate the efficacy and safety of atezolizumab (anti–PD-L1 antibody) compared with the best supportive care following adjuvant cisplatin-based chemotherapy in patients with completely resected stage IB–IIIA non–small cell lung cancer.

Patients who fulfill the eligibility criteria will receive adjuvant cisplatin-based chemotherapy in the enrollment phase of the study. Patients will receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occur.

Patients who experience disease recurrence of their primary disease at any time up to completion of chemotherapy will not be eligible for the randomized phase of the study. Additionally, patients must fulfill the eligibility criteria of the randomized phase prior to randomization.

Eligible patients will go on to be randomized in a 1:1 ratio to receive either atezolizumab (Arm A) or BSC (Arm B).

All patients in the randomized phase will undergo safety, tolerability, and exploratory assessments on Day 1 of each 21-day cycle until recurrence of disease during the first 48 weeks, and patients who have experienced recurrence of disease will undergo these assessments within 30 days after the last dose of atezolizumab is administered.

All patients (irrespective of which arm they are randomized to) will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up. Patients assigned to either study arm who complete either the initial treatment or the initial observation period (16 cycles) will discontinue atezolizumab treatment or BSC and will continue follow-up tumor assessments. No patients are allowed to cross over.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Best supportive care	**Population Diagnosis or Condition:**	Stage IB-Stage IIIA NSCLC
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Compound{s}:	Atezolizumab	**Site Distribution:**	Multi-site
Active Comparator:	N/A	**Study Intervention Assignment Method:**	Randomized
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 1280 patients are expected to be accrued in the enrollment phase to meet the goal of approximately 1005 patients total in the randomized phase

STUDY TREATMENT

Four cycles of cisplatin-based chemotherapy will be administered prior to randomization with each cycle being 3 weeks (21 days) in length. The investigator will select the chemotherapy regimen (1, 2, 3, or 4) for the patient prior to enrollment.

Cisplatin-Based Chemotherapy Regimens

Regimen	Cisplatin 75 mg/m^2 IV, Day 1, Plus
1	Vinorelbine 30 mg/m^2 IV push, Days 1 and 8
2	Docetaxel 75 mg/m^2 IV, Day 1
3	Gemcitabine 1250 mg/m^2 IV, Days 1 and 8
4	Pemetrexed 500 mg/m^2 IV, Day 1 (non-squamous cell NSCLC only)

IV = intravenous; NSCLC = non–small cell lung cancer.

After randomization, in Arm A, atezolizumab will be administered intravenously on Day 1 of each 21-day cycle for a total of 16 cycles.

DURATION OF PARTICIPATION

Treatment will continue until disease recurrence, unacceptable toxicity, medical condition that may jeopardize the patient's safety, or withdrawal of consent. The total duration of study participation for each individual from screening until completion may vary depending on arm, tumor type, patient demographics, and availability of standard of care for specific tumor types. The total duration of study participation for each individual is expected to range from 1 day to more than 12 years.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ATA	anti–therapeutic antibody
BICR	blinded independent central review
BID	twice a day
BSA	body surface area
BSC	best supportive care
CALGB	Cancer and Leukemia Group B
C_{max}	maximum serum concentration observed
C_{min}	minimum serum concentration under steady–state conditions within a dosing interval
COVID-19	coronavirus disease 2019
CRCL	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
ctDNA	circulating–tumor DNA
C_{trough}	steady–state concentration at the end of a dosing interval (i.e., just prior to next drug administration)
DFS	disease–free survival
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ESA	erythropoietin–stimulating agents
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed paraffin–embedded
GGT	gamma–glutamyl transferase
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis

Abbreviation	Definition
HR	hazard ratio
HUS	hemolytic-uremic syndrome
IC	tumor–infiltrating immune cell
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
imAE	immune-mediated adverse event
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	Independent Review Facility
IRR	infusion-related reaction
ITT	intent to treat
IV	Intravenous
IxRS	interactive voice/Web response system
LACE	Lung Adjuvant Cisplatin Evaluation
LFT	liver function test
MAS	macrophage activation syndrome
MLND	mediastinal lymph node dissection
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
NSAIDS	nonsteroidal anti-inflammatory agents
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PO	by mouth

Abbreviation	Definition
PVC	polyvinylchloride
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
Q3W	every 3 weeks
QID	four times a day
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SARS CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
TC	tumor cell
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal

1. BACKGROUND

Lung cancer is the leading cause of cancer deaths worldwide. It was estimated that there would be 224,210 new cases of lung cancer (116,000 in men and 108,210 in women) and 159,260 deaths in the United States in 2014 (American Cancer Society 2014). Similar data from Europe estimate that there were 214,000 new cases of lung cancer and 268,000 deaths in 2012 (GLOBOCAN 2012).

Non–small cell lung cancer (NSCLC) is one of the two major types of lung cancer, accounting for approximately 85% of all lung cancer cases (Molina et al. 2008). The two predominant histologic types of NSCLC are adenocarcinoma, which accounts for more than half of cases, and squamous cell carcinoma, which accounts for approximately 25% of cases (Langer et al. 2010; Travis et al. 2011).

The overall 5-year survival rate for advanced NSCLC 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 Eastern Cooperative Oncology Group (ECOG) Performance Status, and a history of unintentional weight loss. More than half of the patients with NSCLC present with distant metastatic disease at the time of initial diagnosis, which directly contributes to poor survival prospects.

In its early stages, NSCLC is treated surgically with curative intent. However, 30%–70% of patients undergoing resection develop recurrence and die as a result of disease progression (Ponn et al. 2005). Adjuvant radiotherapy is no longer recommended after surgery as an adjuvant treatment option for patients with early-stage disease, specifically in Stage I and II patients because it has been shown to have a deleterious effect on long-term survival (PORT Meta-Analysis Trialists Group 1998).

1.1 ADJUVANT TREATMENT OPTIONS FOR PATIENTS WITH SURGICALLY RESECTED STAGE IB–IIIA NSCLC

Adjuvant chemotherapy is the standard of care for fully resected (Stage IB–IIIA) NSCLC. Additional studies are looking at the role of molecularly targeted adjuvant studies in relatively uncommon molecular subsets (epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase) that account for $<15\%$ of NSCLC.

The Lung Adjuvant Cisplatin Evaluation (LACE) reported on the results of a pooled analysis of data from several large studies of cisplatin-based adjuvant chemotherapy in patients with NSCLC. The pooled analysis of these data was used to identify treatment options associated with a higher degree of benefit or groups of patients benefiting more from adjuvant treatment (Pignon et al. 2008). With a median follow-up time of 5.2 years, the overall hazard ratio (HR) of death was 0.89 (95% CI: 0.82, 0.96; $p=0.005$), corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. Further analysis revealed no heterogeneity of chemotherapy effect among studies. The benefit varied

with stage, with the strongest effect seen in Stages II and III and a potential deleterious effect in Stage IA.

Of note, the effect of chemotherapy did not vary significantly (test for interaction, p = 0.11) with the associated drugs, including vinorelbine (HR = 0.80; 95% CI: 0.70, 0.91), etoposide or vinca alkaloid (HR = 0.92; 95% CI: 0.80, 1.07), or other treatment (HR = 0.97; 95% CI: 0.84, 1.13). In addition, there was no correlation between chemotherapy effect and sex, age, histology, type of surgery, planned radiotherapy, or planned total dose of cisplatin.

Table 1 from Heon and Johnson 2012 lists the five studies included in the LACE meta-analysis plus the Cancer and Leukemia Group B (CALGB) study of adjuvant paclitaxel and carboplatin in Stage IB NSCLC.

Table 1 Overview of Adjuvant Chemotherapy Studies

Study	Patients (n)	Stage Eligibility	Absolute Difference in 5-Year Survival (%)	HR for Death	95% CI	p-Value
IALT [a]	1867	I–III	4.1	0.86	0.76–0.98	< 0.03
JBR.10 [b]	482	IB–II	15	0.69	0.52–0.91	0.04
ANITA [c]	840	IB–IIIA	8.6	0.80	0.66–0.96	0.017
ALPI [d]	1088	I–IIIA	1	0.96	0.81–1.13	0.589
BLT [e]	381	I–III	NA	1.02	0.77–1.35	0.9
CALGB 9633 [f]	344	IB	2	0.83	0.64–1.08	0.125

ALPI = Adjuvant Lung Project Italy; ANITA = Adjuvant Navelbine International Trialist Association; BLT = Big Lung Trial; CALGB = Cancer and Leukemia Group B; HR = hazard ratio; IALT = International Adjuvant Lung Trial; NA = not applicable.

[a] Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non–small cell lung cancer. N Engl J Med 2004;350:351–60.

[b] Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352:2589–97.

[c] JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non–small cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006;7:719–27.

[d] Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected Stage, II, or IIIA non–small cell lung cancer. J Natl Cancer Inst 2003;95:1453–61.

[e] Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non–small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg. 2004;26:173–82.

[f] Strauss GM, Herndon JE II, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non–small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043–51.

Source: Heon S, Johnson BE. Adjuvant chemotherapy for surgically resected non–small cell lung cancer. Thorac Cardiovasc Surg 2012 Sep;144(3):S39–42.

The CALGB 9633 study was designed to evaluate the role of adjuvant paclitaxel/carboplatin in node-negative Stage I NSCLC. In this study, 344 patients were randomly assigned to observation or paclitaxel and carboplatin. Median follow-up was 74 months. Groups were well balanced with regard to demographics, histology, and extent of surgery. Survival was not significantly different (HR = 0.83; CI: 0.64, 1.08; p = 0.12). However, an exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for patients who had tumors ≥ 4 cm in diameter (HR = 0.69; CI: 0.48, 0.99; p = 0.043; Strauss et al. 2008). This study has formed the basis for subsequent adjuvant studies including patients with Stage IB whose tumors were ≥ 4 cm.

Study E1505 is a randomized study of chemotherapy, consisting of four cisplatin-based chemotherapy regimens (pemetrexed, gemcitabine, paclitaxel, or docetaxel) given for four cycles alone or with 1 year of bevacizumab beginning concurrently with chemotherapy (Wakelee et al. 2011; Wakelee et al. 2015). In this study, 1501 patients were enrolled. The interim analysis of the study, with a median follow-up of 41 months, was presented at the World Conference on Lung Cancer (WCLC) in 2015. This study did not meet its primary endpoint of overall survival (OS). The OS hazard ratio comparing the bevacizumab-containing arm (Arm B) to chemotherapy alone (Arm A) was 0.99 (95% CI: 0.81, 1.21, p = 0.93). The disease-free survival (DFS) HR was 0.98 (95% CI: 0.84, 1.14, p = 0.75). Statistically significant Grade 3–5 toxicities of note (all attributions) included overall worst grade (67% vs. 84%), hypertension (8% vs. 30%), and neutropenia (33% vs. 38%) for Arm A and Arm B, respectively. There was no significant difference in Grade 5 adverse events per arm, with 16 (2%) in Arm A and 19 (3%) in Arm B.

1.2 BACKGROUND ON ATEZOLIZUMAB (MPDL3280A)

Atezolizumab (MPDL3280A [anti–programmed death-ligand 1 [PD-L1] antibody]) is a humanized Ig G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its 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 for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

1.2.1 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 studies in patients.

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

1.3 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB

1.3.1 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 summarized below are 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 3 weeks (Q3W) to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.
- Study GO28753 (POPLAR): A randomized, Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1–unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.

- Study GO28754 (BIRCH): A Phase II, open-label study assessing the clinical benefit of atezolizumab as a single agent in patients with PD-L1–selected, locally advanced or metastatic NSCLC representing all lines of therapy (previously untreated to heavily pretreated patients with exposure to multiple prior regimens)

1.3.2 Clinical Safety

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

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. Study PCD4989g provides the majority of data (with 558 safety-evaluable patients as of the data extraction date of 11 May 2015) for the safety profile of atezolizumab as monotherapy.

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

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

Adverse Events

Of the 558 patients, 520 patients (93.2%) experienced at least one adverse event, including 376 patients (67.4%) who experienced one treatment-related adverse event. Commonly reported events (reported in $\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 (based on 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.

1.3.2.2 Single-Agent Clinical Safety in Patients with NSCLC in the Study GO28753

As of the 8 May 2015 data cutoff date, the Phase II POPLAR study (GO28753) included data from 142 patients treated with atezolizumab as a fixed dose of 1200 mg IV Q3W and 135 patients treated with docetaxel 75 mg/m^2 IV Q3W. The frequency of patients in Study GO28753 who reported any adverse event regardless of attribution was 96.3% for the atezolizumab arm and 95.8% for the docetaxel arm. A higher number of Grade ≥3 adverse events were observed in the docetaxel arm (56.3% vs. 44.4%). 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 Study GO28753

	No. of Patients (%)	
MedDRA Preferred Term	Atezolizumab (n=142)	Docetaxel (n=135)
Fatigue	55 (38.7)	54 (40.0)
Decreased appetite	49 (34.5)	28 (20.7)
Nausea	31 (21.8)	45 (33.3)
Cough	38 (26.8)	33 (24.4)
Dyspnoea	38 (26.8)	27 (20.0)
Diarrhoea	24 (16.9)	38 (28.1)
Constipation	29 (20.4)	32 (23.7)
Alopecia	3 (2.1)	52 (38.5)
Anaemia	23 (16.2)	26 (19.3)
Pyrexia	24 (16.9)	16 (11.9)
Asthenia	14 (9.9)	22 (16.3)
Vomiting	18 (12.7)	18 (13.3)
Arthralgia	22 (15.5)	12 (8.9)
Rash	15 (10.6)	16 (11.9)
Insomnia	19 (13.4)	11 (8.1)
Back pain	16 (11.3)	11 (8.1)
Musculoskeletal pain	19 (13.4)	7 (5.2)
Myalgia	8 (5.6)	18 (13.3)
Neutropenia	2 (1.4)	17 (12.6)
Pneumonia	15 (10.6)	4 (3.0)
Neuropathy peripheral	2 (1.4)	16 (11.9)

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

1.3.2.3 Single-Agent Clinical Safety in Patients with Non–Small Cell Lung Cancer in Study GO28754 (BIRCH)

As of the 28 May 2015 data cutoff date for the primary analysis, 659 patients were evaluable for safety. Table 4 shows the overall safety findings in Study GO28754.

Table 4 Adverse Events Reported in Study GO28754 (BIRCH)

Parameter	No. of Patients (%)			
	Cohort 1 1L (n=139)	Cohort 2 2L (n=267)	Cohort 3 3L+ (n=253)	All Patients (n=659)
All cause AEs	91%	92%	96%	94%
All cause Grade 3–4 AEs	40%	37%	39%	38%
Related adverse event	57%	63%	69%	64%
Related Grade 3–4 AEs	9%	12%	11%	11%
AE leading to withdrawal from treatment	6%	6%	4%	5%
Related Grade 5 (fatal) AE	0	0	0.4%[a]	0.2%

1L=first line; 2L=second line; 3L=third line; AE=adverse event; NSCLC=non–small cell lung cancer.

[a] One Grade 5 treatment-related event (pneumonia).

Adapted from Besse et al. 2015.

The most commonly reported adverse events (all grade) were fatigue, diarrhea, and nausea. The adverse event profile observed in Study GO28754 is consistent with that observed in Study PCD4989g (overall and NSCLC populations), as well as with the atezolizumab arm in Study GO28753 (POPLAR).

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

1.3.2.4 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 Appendix 9.

1.3.3 Clinical Activity

1.3.3.1 Single-Agent Clinical Activity in Patients with NSCLC in Study PCD4989g

As of the 2 December 2014 cutoff date, the efficacy-evaluable population included 88 patients with locally advanced or metastatic NSCLC. The median age was 60.5 years (range 24–84 years) and represented a heavily pre-treated patient population, with 97% of patients having received two or more prior systemic therapies, and 77.3% having received four or more prior systemic therapies.

Overall, responses were observed in 20 of 88 (22.7%) patients with NSCLC and included responses in patients with squamous and non-squamous NSCLC (4 in 21 patients and 16 in 67 patients, respectively). A total of 8 of the 20 responding patients have continued to respond at the time of the clinical data cutoff.

Table 5 displays the confirmed objective response rate (ORR), duration of confirmed response (DoR), and 6-month PFS rates by PD-L1 expression for patients with NSCLC. These results are based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) as assessed by the investigator. Analyses of tumor-infiltrating immune cells (ICs) and tumor cells (TCs) for PD-L1 expression on baseline tumor tissue from NSCLC patients have been performed. Higher ORRs were associated with higher PD-L1 expression.

See the Atezolizumab Investigator's Brochure for details on clinical activity in patients with NSCLC treated to date.

Table 5 Patients with NSCLC in Study PCD4989g: Investigator-Assessed Confirmed Objective Response Rate by Tumor PD-L1 Expression, Duration of Response, and 6-Month Progression-Free Survival Rates (per RECIST Version 1.1)

PD-L1 IHC Expression Category	ORR by RECIST, Version 1.1 n = 88	SD (n/N)	PD (n/N)	DOR (Range in Months)	6-Month PFS % (95% CI)
TC3 or IC3	50.0% (11 of 22) (95% CI: 28.22%, 71.78%)	13.6% (3/22)	31.8% (7/22)	7.16–25.26	50.0 (29.1, 70.9)
TC2/3 or IC2/3	33.3% (16 of 48) (95% CI: 20.40%, 48.41%)	22.9% (11/48)	37.5% (18/48)	7.16–26.74+	41.6 (27.6, 55.5)
TC0/1/2 and IC0/1/2	15.5% (9 of 58) (95% CI: 7.35%, 27.42%)	37.9% (22/58)	37.9% (22/58)	7.16–26.74+	41.1 (28.4, 53.8)
TC0/1 and IC0/1	12.5% (4 of 32) (95% CI: 3.51%, 28.99%)	43.8% (14/32)	34.4% (11/32)	9.92–24.74	46.7 (29.3, 64.0)

DOR = duration of response; IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; NSCLC = non–small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; SD = stable disease; PD = progressive disease; PD-L1 = programmed death–ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

Notes: This table is based on a data cutoff of 2 December 2014 of patients with NSCLC. ORR includes confirmed responses. The "+" denotes a censored value.

1.3.3.2 Single-Agent Clinical Activity in Patients with NSCLC in Study GO28753

The primary OS analysis in Study GO28753 (POPLAR) was conducted when 173 deaths (data cutoff date 8 May 2015) had occurred. 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 received one prior therapy (64.6% for atezolizumab and 67.1% for docetaxel), and had non-squamous histology (66.0% for atezolizumab and 66.4% for docetaxel) and ECOG Performance Status of 1 (67.6% for atezolizumab and 68.3% for docetaxel). More females were enrolled in the docetaxel arm (46.9% vs. 35.4%).

Efficacy results for the ITT population are shown in the following section. Atezolizumab showed significant improvement in overall survival compared with docetaxel in patients with advanced, previously treated NSCLC unselected for PD-L1 expression. OS in the ITT population was 12.6 months (95% CI: 9.7, 16.4) for atezolizumab versus 9.7 months (95% CI: 8.6, 12.0) for docetaxel (HR 0.73; 95% CI: 0.53, 0.99; p = 0.04). PFS was similar between groups (2.7 months with atezolizumab vs. 3.0 months with docetaxel). The ORR for the atezolizumab arm was similar to the docetaxel arm.

Objective responses with atezolizumab were durable, with a median duration of 14.3 months (95% CI: 11.6, not estimable) compared with 7.2 months (95% CI: 5.6, 12.5) for docetaxel (see Table 6) (Fehrenbacher et al. 2016). At the time of the clinical data cutoff, there was a minimum of 13 months of follow-up.

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

Efficacy Endpoint	Atezolizumab (n=144)	Docetaxel (n=143)
Overall survival		
No. of deaths (%)	78 (54.2)	95 (66.4)
Median (months) 95% CI	12.6 9.7, 16.4	9.7 8.6, 12.0
Stratified hazard ratio 95% CI	0.73 0.53, 0.99	
Progression-free survival		
No. of events (%)	124 (86.1)	121 (84.6)
Median (months) 95% CI	2.7 2.0, 4.1	3.0 2.8, 4.1
Stratified hazard ratio 95% CI	0.94 0.72, 1.23	
Objective response rate (confirmed)	14.6%	14.7%
Duration of response		
Median (months) 95% CI	14.3 11.6, NE	7.2 5.6, 12.5

NE=not estimable.

Improvement in OS increased with increasing PD-L1 expression, whereas patients with the lowest PD-L1 expression levels experienced OS similar to that in the docetaxel group (See Table 7).

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

Diagnostic Subgroup	HR (95% CI) OS	HR (95% CI) PFS	Atezolizumab/ Docetaxel ORR (%)	Total No. of Patients (Atezolizumab/ Docetaxel)
TC3 or IC3	0.49 (0.22, 1.07)	0.60 (0.31, 1.16)	37.5/13.0	47 (24/23)
TC2/3 or IC2/3	0.54 (0.33, .0.89)	0.72 (0.47,.1.10)	22.0/14.5	105 (50/55)
TC1/2/3 or IC1/2/3	0.59 (0.40, 0.85)	0.85 (0.63, 1.16)	18.3/16.7	195 (93/102)
TC0 and IC0	1.04 (0.62, 1.75)	1.12 (0.72, 1.77)	7.8/10.9	92 (51/44)

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.

In summary, the data from the POPLAR study show that atezolizumab provides survival benefit in previously treated patients with NSCLC.

1.3.3.3 Single-Agent Clinical Activity in Patients with Non–Small Cell Lung Cancer in Study GO28754 (BIRCH)

The primary analysis of Study GO28754 (BIRCH) was performed approximately 6 months after the last patient was enrolled (clinical cutoff 28 May 2015; Besse et al. 2015). Independent Review Facility (IRF)-assessed ORR by line of therapy is shown in Table 8.

Table 8 Study GO28754 (BIRCH) Independent Review Facility-Assessed Overall Response Rate: Treated Population

Primary Efficacy Endpoint IRF-ORR per RECIST v1.1	Cohort 1 (1L) N = 139	Cohort 2 (2L) N = 267	Cohort 3 (3L+) N = 253
TC3 or IC3 patients	n = 65	n = 122	n = 115
Responders (%)	17 (26.2%)	29 (23.8%)	31 (27.0%)
95% CI	16.0, 38.5	16.5, 32.3	19.1, 36.0
TC2/3 or IC2/3 patients	n = 139	n = 267	n = 253
Responders (%)	27 (19.4%)	46 (17.2%)	44 (17.4%)
95% CI	13.2, 27.0	12.9, 22.3	12.9, 22.6

1L = first line; 2L = second line; 3L = third line; IC = tumor–infiltrating immune cell; IRF = Independent Review Facility; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

Source: Besse et al. 2015.

The study met its primary objective of demonstrating a statistically significant and clinically meaningful ORR assessed by IRF per RECIST v1.1 compared with historical controls in the seven pre-specified subpopulations. At the clinical cutoff, more than 58% of responders assessed by IRF per RECIST v1.1 had an ongoing response in each line of therapy and each PD-L1 expression level. The estimated median DOR was 8.4 months in the TC2/3 or IC2/3 patients although follow-up is limited. OS data are not yet mature.

1.3.4 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 $\geq$ 1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent total clearance of drug (CL) and the mean volume of distribution under steady-state conditions (V_{ss}) had a range of 3.20 to 4.43 mL/day/kg and 48.1 to 64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

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

1.3.5 Additional Studies with Atezolizumab

Several studies that include targeted agents such as bevacizumab, erlotinib, and vemurafenib are being explored in combination with both atezolizumab and standard chemotherapy.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

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 Tcells 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 Tcells. B7.1 is a molecule expressed on antigen-presenting cells and activated T–cells. PD-L1 binding to B7.1 on Tcells 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). In mouse tumor models, interruption of the interaction between PD-L1 and PD-1 resulted in anti-tumor effects (Iwai et al. 2002; Strome et al. 2003).

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 (see Section 1.3.3). In addition, in the NSCLC cohort, patients who had a high level of PD-L1 expression in TCs or ICs were more likely to respond to atezolizumab than those with low or no PD-L1 expression in TCs or ICs (see Section 1.3.3).

Data from the randomized Phase II Study GO28753 (POPLAR) have suggested an OS benefit in the atezolizumab arm in a PD-L1–unselected population, with a stratified HR of 0.73 (95% CI: 0.53, 0.99). PFS and ORR for the atezolizumab arm were similar to those for the docetaxel arm (see Section 1.3.3.2 and Table 6).

Atezolizumab has been generally well tolerated (see Section 1.3.2). 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.

Given the evidence of the clinical activity of atezolizumab in previously treated NSCLC and the need to continue to improve upon the survival for patients with resected NSCLC treated with adjuvant cisplatin–based chemotherapy, the Sponsor proposes Study GO29527. Patients with completely resected Stage IB (tumors $\geq$4 cm)–IIIA NSCLC will receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occur, followed by randomization to either 16 cycles of atezolizumab treatment or best supportive care (BSC).

This trial will enroll patients with Stage IB–Stage IIIA NSCLC following resection and adjuvant chemotherapy. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit–risk ratio for atezolizumab is expected to be acceptable in this setting.

Covid-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merartin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021).

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID19 vaccines. When administered, COVID19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.2).

2. OBJECTIVES

The following objectives will be evaluated in patients with Stage IB–IIIA NSCLC.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective of the study is as follows:

- To evaluate the efficacy of atezolizumab monotherapy treatment compared with BSC as measured by DFS as assessed by the investigator in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay) within the Stage II–IIIA population, in all randomized patients with Stage II–IIIA NSCLC, and in the ITT population as detailed in Figure 2

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives of the study are to evaluate the efficacy of atezolizumab monotherapy treatment compared with BSC on the basis of the following outcome measures (see also Section 3.4.2):

- OS in the ITT population
- 3-year and 5-year DFS rates in the PD-L1 subpopulation (defined as ≥1%TC expression by the SP263 IHC assay) within the Stage II–IIIA population, in all randomized patients with Stage II–IIIA NSCLC, and in the ITT population
- DFS in the PD-L1 subpopulation (defined as ≥50% TC expression by the SP263 IHC assay) in patients with Stage II–IIIA NSCLC

2.2 SAFETY OBJECTIVES

The safety objectives of the study are as follows:

- To evaluate the safety and tolerability of atezolizumab treatment after up to four cycles of cisplatin-based chemotherapy in the adjuvant setting

- To evaluate the incidence and titers of ATAs against atezolizumab in the adjuvant setting and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective of the study is as follows:

- To characterize the pharmacokinetics of atezolizumab treatment in the adjuvant setting

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate DFS in TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by PD-L1 SP142 IHC in both the Stage II–IIIA and the ITT populations
- To evaluate DFS in the PD-L1 subpopulations defined by 22C3 TPS $\geq$1% and TPS $\geq$50% in both the Stage II–IIIA and the ITT populations
- To evaluate DFS in the PD-L1 subpopulations defined by SP263 TC $\geq$1% and TC $\geq$50% in the ITT population
- To evaluate the relationship between tumor and blood-based biomarkers (including but not limited to PD-L1, PD-1, somatic mutations, and others), as defined by IHC or quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR), nextgeneration 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 in the adjuvant treatment setting
- To evaluate biomarkers at the time of apparent recurrence of primary disease (i.e., NSCLC primary disease recurrence, occurrence of new primary NSCLCs) and to distinguish any immunomodulatory activity of atezolizumab (i.e., tumor-immune infiltration) in patients with confirmed recurrence of disease in patients assigned to atezolizumab

3. STUDY DESIGN

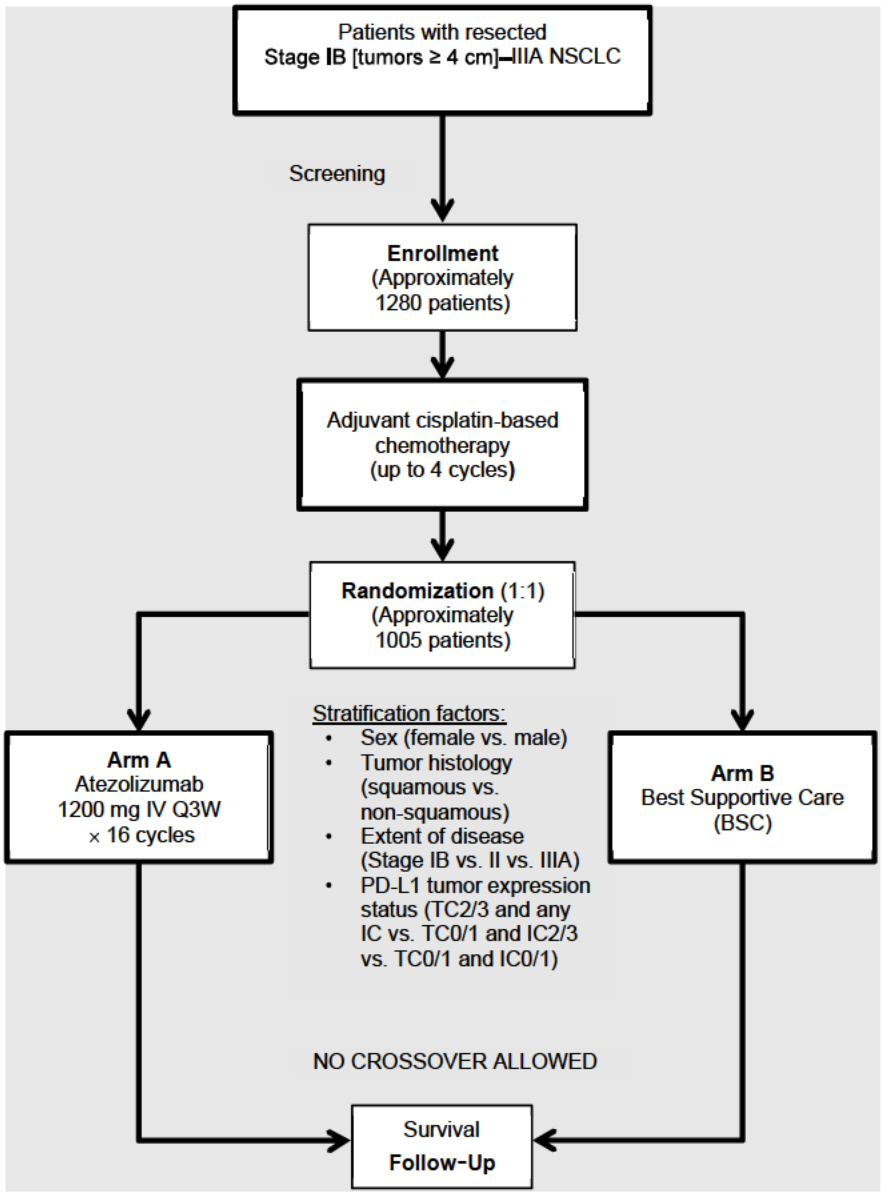
3.1 DESCRIPTION OF THE STUDY

This study is a Phase III, global, multicenter, open-label, randomized, study (IMpower010) comparing the efficacy and safety of atezolizumab versus BSC in patients with Stage IB–Stage IIIA NSCLC following resection and adjuvant chemotherapy, as assessed by DFS per the investigator and OS. The study consists of two phases: an enrollment phase and randomized phase.

In the enrollment phase, patients who have recently undergone complete resection of their NSCLC will be screened, and eligible patients will be enrolled to receive one of four regimens of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel,

gemcitabine, or pemetrexed; based on investigator choice). The randomized phase will start after patients have completed their cisplatin-based chemotherapy and are still considered eligible to proceed with randomization. Figure 1 illustrates the study design.

Figure 1 Study Schema



IC = tumor-infiltrating immune cell; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; Q3W = every 3 weeks; TC = tumor cell.
Note: Patients will receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occur.

Male and female patients age ≥18 years with ECOG Performance Status of 0 or 1 who have a complete surgical resection of histologically or cytologically confirmed Stage IB (tumors ≥4 cm)–IIIA NSCLC are potentially eligible. At screening, tumor specimens from each potentially eligible patient will be tested for PD-L1 expression by a central

laboratory with use of an IHC assay, but patients will be enrolled in the study regardless of the PD-L1 status. Patients who fulfill the eligibility criteria (see Section 4.1.1) will receive adjuvant cisplatin-based chemotherapy in the enrollment phase of the study. Patients will receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occur.

Patients who experience disease recurrence of their primary disease at any time up to completion of chemotherapy will not be eligible for the randomized phase of the study. Additionally, patients must fulfill the eligibility criteria of the randomized phase (see Section 4.1.1.2) prior to randomization.

Eligible patients will go on to be randomized in a 1:1 ratio to receive either atezolizumab (Arm A) or BSC (Arm B).

In Arm A, atezolizumab will be administered intravenously on Day 1 of each 21-day cycle for a total of 16 cycles. Patients randomized to Arm B will be continually followed starting on Day 1 of each 21-day cycle. To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will be required to undergo medical contacts Q3W for assessments during the first year, which will consist of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment. No crossover will be allowed from Arm B to Arm A.

All patients in the randomized phase will undergo scheduled tumor assessments at baseline and every 4 months starting at Cycle 1, Day 1 in the first year and every 6 months in the second year by computed tomography (CT) following randomization. Patients who have not experienced recurrence of disease will undergo tumor assessments every 6 months by CT *or* X-ray during Years 3–5 post-randomization. In the absence of disease recurrence, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

Before completion of the final analysis of DFS, patients from both treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed by investigators, at the first evidence of radiographic disease recurrence. These data will be used to explore whether the radiographic findings are consistent with the presence of tumor or, for patients treated with atezolizumab, if the appearance of recurrence was caused by tumor immune infiltration. In addition, these data will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome as well as to understand further the potential mechanisms of resistance and recurrence to atezolizumab compared with such mechanisms after treatment with

chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions. Tumor assessments will be performed by the investigator.

After Year 5 and the completion of the final analysis of DFS, there will no longer be a study requirement for tumor assessments to be completed and patients are to be followed according to the local standard as a part of their regular medical care. If a recurrence of the primary NSCLC, or a new second primary NSCLC or new primary non-NSCLC malignancy is diagnosed as a part of regular medical care, this data is to be entered in the study's electronic data capture (EDC) system.

Safety assessments will include the incidence, nature, and severity of adverse events; serious adverse events; adverse events of special interest; and laboratory abnormalities, graded per NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of ATAs to atezolizumab. Patient samples, including archival and fresh tumor tissues, as well as serum and plasma and whole blood, will be collected for future exploratory biomarker assessments.

All patients in the randomized phase will undergo safety, tolerability, and exploratory assessments on Day 1 of each 21-day cycle until recurrence of disease during the first 48 weeks, and patients who have experienced recurrence of disease will undergo these assessments within 30 days after the last dose of atezolizumab is administered (see Appendix 2).

Approximately 1280 patients are expected to be accrued in the enrollment phase to meet the goal of approximately 1005 patients total in the randomized phase, under the assumption that a dropout rate of approximately 21% is expected during adjuvant cisplatin-based chemotherapy treatment.

3.1.1 Independent Review Facility

An Independent Review Facility (IRF) may perform a blinded, independent central review (BICR) of images and other clinical data as needed. IRF membership and procedures will be detailed in a BICR charter.

3.2 END OF STUDY AND DURATION OF PARTICIPATION

The end of the study is defined as when approximately 564 OS events (the required number of deaths for the final OS analysis) have occurred in the ITT population (see Section 6.8.2). Additionally, the Sponsor may decide to terminate the study at any time (see Section 4.7.3).

Treatment will continue until disease recurrence, unacceptable toxicity, medical condition that may jeopardize the patient's safety, or withdrawal of consent. The total

duration of study participation for each individual from screening until completion may vary depending on arm, tumor type, patient demographics, and availability of standard of care for specific tumor types. The total duration of study participation for each individual is expected to range from 1 day to more than 12 years.

3.3 RATIONALE FOR STUDY DESIGN

This Phase III study is designed to test the hypothesis that 16 cycles of atezolizumab treatment following cisplatin–based adjuvant chemotherapy in patients with completely resected Stage IB–IIIA NSCLC will prolong DFS and OS compared with patients receiving adjuvant cisplatin–based chemotherapy alone. This hypothesis will be studied in the Stage IB–IIIA population as well as the Stage II–IIIA and PD-L1–selected subpopulations.

3.3.1 Rationale for Testing Atezolizumab in PD-L1–Unselected Patients with NSCLC

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 the Phase Ia study PCD4989g, evaluating single-agent atezolizumab in several tumor types including NSCLC, suggest that PD-L1 expression in TCs and ICs as determined by IHC correlates with response to atezolizumab. An ORR of 31.6% (12 of 38 patients, 95% CI: 17.5%, 48.6%) was observed in patients with high levels of PD-L1 staining in TCs or ICs (TC3 or IC2/3 group) compared with an ORR of 14.3% (6 of 42 patients, 95% CI: 6.4%, 27.7%) in patients with low or no PD-L1 staining in TCs and ICs (TC0/1/2 and IC0/1 group).

Data from the randomized Phase II Study GO28753 (POPLAR) have suggested an OS benefit in the atezolizumab arm in a PD-L1-unselected population, with a stratified HR of 0.73 (95% CI: 0.53, 0.99,) which suggest the benefit of atezolizumab might also occur in an unselected population.

3.3.2 Rationale for Best Supportive Care Arm (Arm B)

The standard of care for resected patients with NSCLC is four cycles of cisplatin-based chemotherapy followed by periodic chest X-rays and/or CT scans (see Section 1.1).

3.3.3 Rationale for Atezolizumab Dosage and Treatment Duration

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.

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 (steady-state concentration at the end of a dosing interval [i.e., just prior to next drug administration]; C_{trough}) was projected to be 6 μg/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 selection of the atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data (see Section 1.3.3.2). 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 Q3W regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6\mu g/mL$ and further safeguard against both inter-patient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab Q3W regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20-mg/kg atezolizumab Q3W regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15-mg/kg atezolizumab Q3W level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following 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.

A 1-year period of adjuvant treatment has been selected because this is believed to balance the expected benefit in the adjuvant setting with the risks and tolerability of therapy on the basis of an assessment of benefit versus risk observed in the metastatic cancer setting.

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

3.3.4 Rationale for Collection of Resected 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, tumor specimens from patients will be prospectively tested for PD-L1 expression by a central laboratory during the screening period and patients will be stratified by PD-L1 expression defined by the SP142 IHC assay. In addition, the PD-L1 status using the SP263 and 22C3 IHC assays will also be centrally evaluated. The study will allow for the evaluation of the efficacy of atezolizumab in both the ITT population, as well as in patients with PD-L1–selected tumors (defined by expression of PD-L1 in TCs). In addition to the assessment of PD-L1 status using the SP142, SP263, and 22C3 IHC assays, 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.

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 (ctDNA), gene expression, and others in blood samples. 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.

PD-L1 will be assessed *centrally* through the use of the VENTANA PD-L1 (SP263 *[also known as RD0827375]*, and also SP142 *[also known as RD0827376]* in earlier protocol versions) assays (Appendix 5 and Appendix 4, respectively), which may be considered investigational per local regulations.

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

3.3.6 Rationale for the Collection of Tumor Specimens at Disease Recurrence and/or Confirmation of a New Primary NSCLC

This initial apparent recurrence may occur as a result of either delayed anti-tumor activity and/or robust tumor-immune infiltration 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 from both treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease recurrence. These data will be used to explore whether the radiographic findings are consistent with the presence of tumor or, for patients treated with atezolizumab, if the appearance of recurrence was caused by tumor immune infiltration. In addition, these biopsies are important for the evaluation of predictive mechanisms related to tumor recurrence or occurrence, resistance, prognostic, and pharmacodynamic relationships in tumor biomarkers (including but not limited to PD-L1, CD8, mutation status, and others) as well as to efficacy in the adjuvant treatment setting. DNA and/or RNA extractions may be performed to enable the identification of somatic mutations by NGS to contribute to an improved understanding of the dynamics of PD-L1 expression, tumor immunobiology, and the relationship to disease recurrence and DFS in the adjuvant setting.

3.4 EFFICACY OUTCOME MEASURES

3.4.1 Primary Efficacy Outcome Measure

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

- DFS, defined as the time from randomization to the date of occurrence of any of the following, whichever occurs first:

  First recurrence of NSCLC, as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status

  Occurrence of new primary NSCLC, as assessed by the investigator

  Death from any cause

This efficacy outcome measure will be assessed in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay) within the Stage II-IIIA population, in all randomized patients with Stage II-IIIA NSCLC, and in the ITT population.

Of note, SP263 TC ≥1% is determined on the basis of PD-L1 expression in tumor cell membrane detected by Ventana PD-L1 (SP263) Assay (see Appendix 5).

3.4.2 Secondary Efficacy Outcome Measures

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

- OS, defined as the time from randomization to death from any cause, in the ITT population
- DFS rates at 3 years and 5 years in the PD-L1 subpopulation (defined as ≥1% TC expression by the SP263 IHC assay), in the Stage II–IIIA population (i.e., all randomized patients with Stage II–IIIA NSCLC) and in the ITT population
- DFS in the PDL1 subpopulation, defined as TC ≥50% by the SP263 IHC assay within patients with Stage II–IIIA NSCLC

3.5 SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest graded according to the NCI CTCAE v4.0
- Changes from baseline in vital signs, physical findings, and targeted clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, safety, and efficacy parameters

3.6 PHARMACOKINETIC OUTCOME MEASURES

The PK outcome measures for this study are as follows:

- Atezolizumab maximum serum concentration (C_{max}) observed after infusion on Day 1 of Cycle 1

- Atezolizumab minimum serum concentration (C_{min}) under steady–state conditions within a dosing interval prior to the infusion on Day 1 of Cycles 2, 3, 4, 8, and 16 and at study termination

3.7 EXPLORATORY OUTCOME MEASURES

The exploratory outcome measures for this study are as follows:

- DFS in TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by PD-L1 SP142 IHC in both the Stage II-IIIA and the ITT populations
- DFS in the PD-L1 subpopulations defined by 22C3 TPS $\geq$ 1% and TPS $\geq$ 50% in both the Stage II-IIIA and the ITT populations
- DFS in the PD-L1 subpopulations defined by SP263 TC $\geq$1% and TC $\geq$ 50% in the ITT population
- Status of PD-L1–, immune-, and NSCLC–related and other exploratory biomarkers in tumor tissues, and blood collected before, during, or after treatment with atezolizumab or at first evidence of radiographic disease recurrence or confirmation of new primary NSCLC
- Exploratory biomarkers in biopsy specimens and blood collected at the first evidence of radiographic disease recurrence or confirmation of new primary NSCLC

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients will be screened and enrolled if they have had a complete surgical resection of Stage IB (tumors $\geq$4 cm)–IIIA (per the Union Internationale Contre le Cancer [UICC]/American Joint Committee on Cancer [AJCC] staging system, Version 7) NSCLC and are eligible for the enrollment phase where they will receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse or patient's decision to discontinue occur. Patients who are enrolled will receive one of four chemotherapy regimens at the choice of the investigator. Provided that they still meet eligibility criteria, patients who complete chemotherapy will be randomized to receive either atezolizumab (Arm A) or BSC (Arm B).

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for Enrollment Phase

Patients must meet all of the following criteria to be eligible to enter the enrollment phase and receive cisplatin-based chemotherapy regimen in this study:

- A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or 15 (or more) unstained, freshly cut, serial sections (on slides) from an FFPE resected tumor specimen is required for participation in this study. This specimen must be accompanied by the associated pathology report.
- Signed Informed Consent Form
- Age $\geq$18 years

- ECOG Performance Status of 0 or 1
- Histological or cytological diagnosis of Stage IB (tumors $\geq$4 cm)–IIIA (T2–3 N0, T1–3 N1, T1-3 N2, T4 N0-1) NSCLC (per the UICC/AJCC staging system, 7th edition; Detterbeck et al. 2009)
- Patients must have had complete resection of NSCLC 4–12 weeks ($\geq$28 days and $\leq$84 days) prior to enrollment and must be adequately recovered from surgery

  Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

  Resection by segmentectomy or wedge resection is not allowed.
- If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred, though complete mediastinal lymph node dissection (MLND) is preferred. Systematic sampling is defined as removal of at least one representative lymph node at specified levels. MLND entails resection of all lymph nodes at those same levels. For a right thoracotomy, sampling or MLND is required at levels 4 and 7 and for a left thoracotomy, levels 5 and/or 6 and 7. **Exceptions will be granted for the following situations:**

  If there is clear documentation in the operative report or in a separately submitted addendum by the surgeon of exploration of the required lymph node areas, the patient will be considered eligible if no lymph nodes are found in those areas.

  If patients have documented N2 disease in one level (per the UICC/AJCC staging system, 7th edition; Detterbeck et al. 2009), not all levels need to be sampled.

  If the preoperative staging imaging results (contrast CT and PET scans) do not suggest evidence of disease in the mediastinum, the patient will be considered eligible if N2 nodal sampling is not performed per surgeon's decision.
- Eligible to receive a cisplatin-based chemotherapy regimen
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to enrollment:

  ANC $\geq$1500 cells/μL

  Platelet count $\geq$100,000 cells/μL

  Prothrombin time/INR $\leq$1.5, or, if patient is receiving therapeutic anticoagulation, prothrombin time/INR $\leq$3.0

  aPTT $\leq$institutional upper limit of normal (ULN) OR, if patient is receiving therapeutic anticoagulation, aPTT must be $<1.5\times$ULN

  Total bilirubin $\leq 1.25\times$ULN

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

  SGOT (AST) $\leq 2.5\times$ULN

SGPT (ALT) $\leq 2.5 \times$ ULN

Calculated creatinine clearance (CRCL) ≥ 60 mL/min, with use of institutional guidelines or the standard Cockcroft and Gault formula (1976) (see Appendix 8)

- For women of childbearing potential and men 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. Women and men should continue contraceptive use for 6 months after the last dose of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed). Women treated with atezolizumab should continue contraception use for 5 months after the last dose. Women must refrain from donating eggs during this same period.

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

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  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 cisplatin-based chemotherapy.

4.1.1.2 Inclusion Criteria for Randomized Phase

Patients must meet all of the following criteria to be eligible to be randomized to receive either atezolizumab or BSC after completion of the enrollment phase and up to four cycles of cisplatin-based chemotherapy:

- Adequate hematologic and end-organ function defined by the following laboratory results obtained within 14 days prior to randomization:

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

  Lymphocyte count ≥ 500 cells/μL

  Platelet count $\geq 100{,}000$ cells/μL

  Hemoglobin ≥ 9.0 g/dL

  Patients may be transfused to meet this criterion.

  INR or aPTT $\leq 1.5 \times$ ULN

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN

Serum bilirubin $\leq 1.25 \times$ ULN

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

Calculated CRCL ≥ 30 mL/min

The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault formula (1976) (see Appendix 8)

- Women who are not postmenopausal ($\geq$ 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 atezolizumab or BSC

4.1.2 Exclusion Criteria

4.1.2.1 Exclusion Criteria for Enrollment Phase

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

- Illness or condition that may interfere with a patient's capacity to understand, follow, and/or comply with study procedures
- Pregnant and lactating women
- Treatment with prior systemic chemotherapy, with the following exceptions:

  Chemotherapy for early stage of malignancy with curative intent, provided that the last dose received was more than 5 years prior to enrollment, is allowed.

  Low-dose chemotherapy for non-malignant conditions is allowed.
- Hormonal cancer therapy or radiation therapy as prior cancer treatment within 5 years before enrollment

  Prior surgery, biologic therapy, hormonal therapy, or radiation therapy for a malignancy over 5 years prior to enrollment that is now considered cured is acceptable.
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to enrollment
- A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies (audiometry will only be required for patients who have suspected or definitive hearing loss)
- Known sensitivity to any component of the chemotherapy regimen the patient will be assigned to, or to mannitol
- 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–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-mediated adverse effects from anti–CTLA-4 (NCI CTCAE Grades 3 and 4)

- Malignancies other than NSCLC within 5 years prior to enrollment, 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)
- 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 granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 6 for a more comprehensive list of autoimmune diseases)

  Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

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

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) 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.

- Positive test for HIV

  All patients will be tested for HIV prior to the inclusion into the study, and patients who are HIV-positive will be excluded from the clinical study.

- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HbsAg] test at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core (HBc) antibody and absence of HbsAg) are eligible only if they are negative for HBV DNA. HBV DNA must be obtained in these patients prior to enrollment.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Active tuberculosis
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the previous 3 months, 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.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-IKLinduced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Prior allogeneic bone marrow transplantation or solid organ transplant
- 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 renders the patient at high risk from treatment complications
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti–PD-1 or anti–PD-L1 antibodies but were not eligible are excluded)

Specific Exclusions for Pemetrexed Treatment

- Patients with squamous cell histology

4.1.2.2 Exclusion Criteria for Randomized Phase

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

- Signs or symptoms of infection within 14 days prior to randomization (severe infection within 28 days prior to randomization), including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

- Received therapeutic oral or IV antibiotics within 14 days 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.

- Major surgical procedure within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live attenuated vaccine will be required during the study
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFNs or IL-2) within 4 weeks or 5 drug-elimination half-lives of the drug, whichever is longer, prior to randomization

  Prior treatment with cancer vaccines is allowed.

- Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 14 days prior to randomization

  Patients who have received acute, low-dose ($\leq$10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be randomized in the study.

  The use of corticosteroids ($\leq$10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, or low dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. After written informed consent has been obtained and eligibility for both enrollment and randomization has been established (which includes completion of up to four cycles of cisplatin-based chemotherapy), the study site will enter demographic and baseline characteristics in the interactive voice/Web response system (IxRS). For those patients who are eligible for study randomization, the study site will obtain the patient's randomization number and treatment assignment from the IxRS. Randomization to the treatment and control arms will occur in a 1:1 ratio with use of a permuted-block randomization method. Randomization will be stratified by the following factors:

- Sex (female vs. male)
- Tumor histology (squamous vs. non-squamous)
- Extent of disease (Stage IB vs. Stage II vs. Stage IIIA)
- PD-L1 tumor expression status (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1 using the SP142 IHC assay)

Patients should undergo randomization within 3–8 weeks after receiving their last dose of induction treatment.

Patients should receive their first dose of study treatment (chemotherapy or atezolizumab) on the day of enrollment or randomization, respectively, if possible. If this is not possible, the first dose should occur within 5 days after enrollment or randomization.

4.3 STUDY TREATMENT

The term "study treatment" refers to all protocol-mandated treatments and includes atezolizumab and cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed. The investigational medicinal product (IMP) for this study is atezolizumab. Appendix 10 identifies all investigational, non-investigational, and auxiliary medicinal products for this study.

4.3.1 Cisplatin-Based Chemotherapy Regimens

Once patients are pre-screened to receive cisplatin-based chemotherapy and have been determined to be eligible, surgically resected patients will be enrolled to receive one of four cisplatin-based chemotherapy options (see Table 9). Patients will receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse or patient's decision to discontinue occur, with each cycle being 3 weeks (21 days) in length. The investigator will select the chemotherapy regimen (1, 2, 3, or 4) for the patient prior to enrollment.

Table 9 Cisplatin-Based Chemotherapy Regimens

Regimen	Cisplatin 75 mg/m^2 IV, Day 1, Plus
1	Vinorelbine 30 mg/m^2 IV push, Days 1 and 8
2	Docetaxel 75 mg/m^2 IV, Day 1
3	Gemcitabine 1250 mg/m^2 IV, Days 1 and 8
4	Pemetrexed 500 mg/m^2 IV, Day 1 (non-squamous cell NSCLC only)

IV = intravenous; NSCLC = non–small cell lung cancer.

4.3.2 Formulation, Packaging, and Handling of Cisplatin-Based Chemotherapy

4.3.2.1 Cisplatin

Cisplatin is commercially available as a 1 mg/mL solution in 50- and 100-mg vials. Intact vials of cisplatin are stored at room temperature. Solutions diluted with sodium chloride or dextrose are stable for up to 72 hours at room temperature. Because of the risk of precipitation, cisplatin solutions should not be refrigerated. In preparation, the desired dose of cisplatin is diluted with 250–1000 mL of saline and/or dextrose solution. Varying concentrations of 0.225%–5% sodium chloride and 5% dextrose may be used.

To maintain stability of cisplatin, a final sodium chloride concentration of at least 0.2% is recommended.

4.3.2.2 Vinorelbine

Vinorelbine is commercially available in 10 mg/mL ampules and 50-mg/5 mL vials. Intact vials are stored under refrigeration (2°C–8°C) and must be protected from light. Unopened vials are stable at temperatures up to 25°C for up to 72 hours. Vials should not be frozen. The drug must be diluted prior to administration. Diluted vinorelbine is stable for 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride (PVC) bags at 5°C–30°C).

For administration via syringe, the dose of the drug should be diluted to a concentration between 1.5 and 3.0 mg/mL with dextrose 5% or normal saline. For administration via IV bag, the dose of vinorelbine should be diluted between 0.5 and 2 mg/mL.
The following solutions may be used for dilution: 0.9% sodium chloride, 0.45% sodium chloride, 5% dextrose and 0.45% sodium chloride, Ringer's, and lactated Ringer's.

4.3.2.3 Docetaxel

Docetaxel is commercially available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous). Docetaxel is stored at 4°C protected from light. The solvent vials may be stored at room temperature or at 4°C. The premix solution is stable for 8 hours at room temperature (15°C–25°C) or refrigerated (at 2°C–8°C). The final dilution is also stable for 8 hours. Note that the company (Aventis Pharmaceuticals) is no longer recommending that the final product be placed in PVC bags.

Just prior to use, allow the docetaxel vial to reach room temperature for 5 minutes. Add the entire contents of the ethanol diluent vial and mix by gently rotating the vial for 15 seconds. Allow to stand for 5 minutes at room temperature and check that the solution is homogeneous and clear (persistent foam is normal). The resulting solution contains 10 mg/mL of docetaxel. Note that the solution contains 15% overfill. Dosing amounts should be based in the concentration per extractable volume, not the total volume of the vial. The desired dose is diluted in 5% dextrose in water or normal saline (NS). The volume of the infusion should be adjusted in order to have a final docetaxel concentration of between 0.3 mg/mL and 0.9 mg/mL. Non–PVC-containing IV infusion bags and administration sets should be used to avoid patient exposure to the plasticizer DEHP.

4.3.2.4 Gemcitabine

Gemcitabine is commercially available in 200-mg and 1-g vials. Un-reconstituted drug vials are stored at controlled room temperature. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated because this could cause crystallization to occur. The unused portion should be discarded. In preparation, reconstitute the 200-mg vial with 5 mL and

the 1-g vial with 25 mL preservative-free normal saline to make a solution containing 38 mg/mL. Shake to dissolve.

4.3.2.5 Pemetrexed

Pemetrexed is supplied as a sterile lyophilized powder for IV infusion available in single-dose vials (100-mg and 500-mg vials). The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg mannitol. Each 100-mg vial of pemetrexed disodium contains equivalent to 100 mg pemetrexed and 106 mg mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH. Pemetrexed for injection should be stored at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F; see USP Controlled Room Temperature). Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2°C–8°C (36°F–46°F), or at 25°C (77°F), excursions permitted to 15°C–30°C (59°F–86°F; see USP Controlled Room Temperature). When prepared as directed, reconstituted and infusion solutions of pemetrexed contain no antimicrobial preservatives. Discard unused portion. Pemetrexed is not light sensitive.

4.3.3 Dosage, Administration, and Supportive Care Recommendations for Cisplatin-Based Chemotherapy

All doses will be based on patient's actual weight. The actual weight at screening will be used for calculating BSA. BSA should be recalculated only if a patient's weight changes by $>10\%$.

Institutions should follow their standard administration regimens (e.g., administration sequence or time) for the chemotherapy treatment. The premedication doses administered should be in compliance with prescribing information.

4.3.3.1 Chemotherapy Regimen 1: Cisplatin/Vinorelbine

Administer 30 mg/m^2 IV vinorelbine push over 6–10 minutes on Days 1 and 8. Administer 75 mg/m^2 IV cisplatin over 60 minutes on Day 1 immediately following vinorelbine. Institutional standards that require a prolonged cisplatin infusion are acceptable if the infusion does not exceed 4 hours.

Vinorelbine. Vinorelbine must be administered intravenously. The diluted vinorelbine is administered over 6–10 minutes into a running infusion via a side-arm port closest to the IV bag. The IV line should be flushed well with at least 75–125 mL of one of the solutions. **NOTE:** It is extremely important that the IV needle or catheter be properly positioned before any vinorelbine is injected. Leakage into surrounding tissue during IV administration of vinorelbine may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into

another vein. Because there are no established guidelines for the treatment of extravasation injuries with vinorelbine, institutional guidelines may be used.

Cisplatin. Cisplatin is usually administered as an IV infusion over 60 minutes.

See Section 4.3.3.5 for supportive care recommendations with cisplatin-based chemotherapy.

4.3.3.2 Chemotherapy Regimen 2: Cisplatin/Docetaxel

Administer 75 mg/m^2 IV docetaxel over 60 minutes on Day 1. Administer 75 mg/m^2 IV cisplatin over 60 minutes, Day 1, immediately following docetaxel.

Docetaxel. Docetaxel will be given by IV infusion at a dose of 75 mg/m^2 over 60 minutes on Day 1 (each cycle to be repeated every 3 weeks), immediately prior to cisplatin administration. It is recommended that docetaxel be administered with use of a peristaltic infusion pump.

Cisplatin. Cisplatin is usually administered as an IV infusion over 60 minutes.

Premedications

Patients should receive steroid premedication for docetaxel according to local standard of care and manufacturer's instructions.

It is recommended to give a dexamethasone (or equivalent steroid) regimen of 8 mg by mouth (PO) every 12 hours for 5 doses starting 24 hours prior to docetaxel infusion, continuing the day of docetaxel infusion, and finishing the day after the docetaxel infusion.

Supportive Care

See Section 4.3.3.5 for supportive care recommendations with cisplatin-based chemotherapy.

Other Prophylaxis Treatments

Granulocyte colony-stimulating factor treatment is permitted for patients treated with the cisplatin/docetaxel regimen. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer, and European Society of Medical Oncology guidelines in patients who are $\geq$60 years of age and/or with comorbidities (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011). Anti-emetics, anti-allergic measures, and other treatments for concomitant docetaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Summary of Product Characteristics.

Refer to the Summary of Product Characteristics (Package Insert) for docetaxel for all boxed warnings and contraindications.

4.3.3.3 Chemotherapy Regimen 3: Cisplatin/Gemcitabine

Administer gemcitabine 1250 mg/m^2 IV over 30 minutes on Days 1 and 8. Administer cisplatin 75 mg/m^2 IV over 60 minutes on Day 1 immediately following gemcitabine.

Gemcitabine. Gemcitabine is administered over 30 minutes as prepared or further diluted with normal saline to a minimum concentration of 0.1 mg/mL. Gemcitabine is commonly diluted in 100 mL or 250 mL of saline. Reconstitution at greater than 40 mg/mL may result in incomplete dissolution of drug.

Cisplatin. Cisplatin is usually administered as an IV infusion over 60 minutes.

Supportive Care

See Section 4.3.3.5 for supportive care recommendations with cisplatin-based chemotherapy.

4.3.3.4 Chemotherapy Regimen 4: Cisplatin/Pemetrexed (For Patients with Non-Squamous Histology)

Administer pemetrexed 500 mg/m^2 IV over 10 minutes on Day 1. Administer cisplatin 75 mg/m^2 IV over 60 minutes on Day 1 immediately following pemetrexed.

Pemetrexed. Pemetrexed is administered as an IV infusion over 10 minutes.

Cisplatin. Cisplatin is usually administered as an IV infusion over 60 minutes.

Supportive Care

See Section 4.3.3.5 for supportive care recommendations with cisplatin-based chemotherapy.

Other Prophylaxis Treatments

Patients should receive corticosteroid, folic acid, and vitamin B-12 premedication for pemetrexed. The choice of steroid and timing of premedication can be administered according to the local standard of care and manufacturer's instructions. All patients on pemetrexed must receive 1000 μg of vitamin B-12 intramuscularly given within 2 weeks of the first dose of chemotherapy and repeated at least every 9 weeks until 3 weeks after the last dose of pemetrexed. All patients in the pemetrexed group must take 350–1000 μg of folate (folic acid) orally daily starting at least 5–7 days prior to initiation of pemetrexed and continuing for at least 3 weeks after completion of the last dose of pemetrexed. It is also recommended that patients receive dexamethasone 4 mg orally twice daily (or an equivalent corticosteroid) on the day before, day of, and day after each dose of pemetrexed to prevent the occurrence of rash. All patients receiving pemetrexed therapy should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following administration of pemetrexed.

4.3.3.5 Supportive Care Recommendations for Cisplatin-Based Chemotherapy

Anti-Emetics

It is strongly recommended that all patients receive adequate anti-emetics with cisplatin-based chemotherapy. The specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved. One potential regimen consists of 20 mg of oral dexamethasone and a high dose of oral or IV 5HT3 antagonist (such as 2 mg oral or 10 mcg/kg IV granisetron, or 32 mg oral or IV ondansetron) on the day of cisplatin administration, followed by additional anti-emetics consisting of 4 days of oral dexamethasone (8 mg PO twice a day [BID] for 2 days [Days 2 and 3] then 4 mg PO BID for 2 days [Days 4 and 5]) and scheduled metoclopramide or 5HT3 antagonist for Days 2–5 for delayed emesis. NOTE: Dexamethasone dose should be reduced by 50% when administered with aprepitant.

Hydration Requirements

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre- and post-cisplatin hydration is achieved and that renal function remains adequate. One suggested regimen consists of administering cisplatin in 500 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr $\times$ 1 liter and post-cisplatin hydration consist of 0.5L NS + 10 mEq KCl/L + 1 gram magnesium sulfate/L + 25 grams mannitol/L at 500 cc/hr for at least 1 hour, followed by additional hydration at the discretion of the investigator.

4.3.4 Atezolizumab

4.3.4.1 Atezolizumab Formulation, Packaging, and Handling

The atezolizumab (MPDL3280A) drug product is provided as a sterile liquid in 20 mL glass vials. 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 storage and preparation of atezolizumab, see the Atezolizumab Pharmacy Manual and Investigator's Brochure.

4.3.4.2 Atezolizumab Dosage, Administration, and Compliance

Patients who are randomized to be treated with atezolizumab will receive 1200 mg atezolizumab administered by IV infusion every 21 days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions (see Appendix 7).

Atezolizumab infusions will be administered per the instructions outlined in Table 10.

Table 10 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication 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 IV 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, premedication 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) 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 patient experienced symptoms during the previous infusion. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 30 min (±10) after the infusion, if clinically indicated or 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 Appendix 9.

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

4.3.5 Investigational Medicinal Product Accountability

All IMP required for completion of this study (atezolizumab) will be provided by the Sponsor. The investigational site will acknowledge receipt of atezolizumab with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP 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 upon 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 IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.6 Post-Study Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide Roche IMP (atezolizumab) or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

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

4.4.1 Contraindications and Use of Concomitant Medications with Cisplatin-Based Chemotherapy Regimens

4.4.1.1 Cisplatin

Cisplatin is highly contraindicated in patients with preexisting renal impairment and should not be administered in patients who have a history of myelosuppression or patients with hearing impairment (see Section 4.3.3 for further instructions for reducing cisplatin–related side effects).

Cisplatin is contraindicated in patients with a history of allergic reactions to cisplatin or other platinum-containing compounds. Incompatibilities with cisplatin include the following drugs: amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, and thiotepa. Cisplatin may react with aluminum, which is found in some syringe needles or IV sets, forming a black precipitate. Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy. In a randomized study in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin (see the Cisplatin Package Insert).

4.4.1.2 Docetaxel

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe

reactions, including anaphylaxis, have occurred [see the Docetaxel Package Insert for additional information]. Patients with bilirubin greater than ULN, or patients with AST and/or ALT $> 1.5 \times$ ULN and alkaline phosphatase $> 2.5 \times$ ULN should not be treated with docetaxel because patients with these liver enzyme abnormalities are at risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Additionally, patients with neutrophil counts of < 1500 cells/mm³ should not be dosed with docetaxel and frequent blood cell counts should be performed on all patients receiving this regimen.

Docetaxel is a CYP3A4 substrate. Patients who receive docetaxel must avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. In addition, concomitant treatment with CYP3A4 inducers may decrease plasma concentrations of docetaxel. Concomitant medications that are CYP3A4 inducers should therefore be used with caution.

4.4.1.3 Vinorelbine

Acute pulmonary reactions have been reported and can occur with vinorelbine and other anti-cancer vinca alkaloids used in conjunction with mitocycin. Vinorelbine pharmacokinetics are not affected with concurrent administration of cisplatin although granulocytopenia has been reported to occur when both are administered together as opposed to vinorelbine administered alone. Patient monitoring is suggested when vinorelbine is given with drugs that inhibit metabolism of the P450 isoenzyme (CYP3A) or in patients who have hepatic impairment because concurrent administration of vinorelbine with these drugs often causes additional and more severe side effects (see the Vinorelbine Package Insert).

4.4.1.4 Gemcitabine

No formal drug interaction studies have been conducted with gemcitabine or in post-marketing experience, but with concurrent administrations of gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) in patients with NSCLC, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2 (see the Gemcitabine Package Insert). The incidence of febrile neutropenia (9/262 vs. 2/260), sepsis (4% vs. 1%), Grade 3 cardiac dysrhythmias (3% vs. < 1%) were all higher in the patients who received concurrent combinations of gemcitabine with cisplatin compared with patients who received cisplatin alone. The two-drug combination was more myelosuppressive with 4 possibly treatment-related deaths (1.5%), including 3 resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection.

4.4.1.5 Pemetrexed

Cisplatin does not affect the pharmacokinetics of pemetrexed and the pharmacokinetics of total platinum is unaltered by pemetrexed. Co-administration of oral folic acid or intramuscular vitamin B-12 does not affect the pharmacokinetics of pemetrexed. Results from in vitro studies with human liver microsomes demonstrated that pemetrexed would not cause clinically significant inhibition of metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2. No studies were conducted to determine the cytochrome P450 isozyme induction potential of pemetrexed, because pemetrexed used as recommended (once every 21 days) would not be expected to cause any significant enzyme induction. Aspirin, administered in low to moderate doses (325 mg every 6 hours), does not affect the pharmacokinetics of pemetrexed. The effect of greater doses of aspirin on pemetrexed pharmacokinetics is unknown.

All patients receiving pemetrexed therapy should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following administration of pemetrexed. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

4.4.2 Permitted Therapy with Atezolizumab

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 for enrollment and randomization 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)
- Vaccinations (such as influenza, COVID19)

  Live, attenuated vaccines are not permitted (see Section 4.4.4).
- Megestrol administered as an appetite stimulant
- Corticosteroids (≤10 mg oral prednisone or equivalent) 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 H_2-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).

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

4.4.3 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids, immunosuppressive medications, 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, immunosuppressive medications, 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 4.4.4).

Systemic corticosteroids or immunosuppressive medications 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 management of immune-mediated adverse events are described in Appendix 9.

4.4.4 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 recurrence 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.

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

- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the final dose of atezolizumab (for patients randomized to atezolizumab)

- Use of steroids to premedicate 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/MRI of other locations (if needed) 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. As noted above, herbal therapies that are intended for the treatment of cancer are prohibited.

4.5 STUDY ASSESSMENTS

Flowcharts of scheduled study assessments are provided in Appendix 1, Appendix 2, and Appendix 3.

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 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 may 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 enrollment and 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.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, 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. Demographic data will include age, sex, and self-reported race/ethnicity. Cancer history will include an assessment of tumor mutational status, if the result is available (e.g., sensitizing EGFR mutation, ALK fusion status).

4.5.3 Physical Examinations

A complete physical examination should include a weight measurement and an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems at screening. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), 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 the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

For patients assigned to Arm A (atezolizumab treatment arm), at the first infusion, vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion and 30 (±10) minutes after the infusion, if clinically indicated. Vital signs will also be collected during the first infusion (every 15 [±5] minutes), if clinically indicated. For subsequent infusions, vital signs will be collected within 60 minutes prior to the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. See Table 10 for more details.

For patients in Arm B, vital signs will be collected as per standard of care.

4.5.5 Tumor and Response Evaluations

Patients must be disease free at screening and reassessed at each subsequent tumor evaluation once randomized into study. Tumor assessments are to be performed at the timepoints specified in Appendix 2, with a window of ±7 days in the first year, ±14 days for Year 2 and Year 3, and ±1 month after Year 3, regardless of drug delays or interruptions.

Screening assessments in the enrollment phase will include an X-ray of the chest, CT scans (with oral/IV contrast unless contraindicated) of the chest and abdomen and a CT/MRI of the brain to rule out CNS metastasis, especially if patient has Stage IIIA disease. A spiral CT scan of the chest may be obtained but is not a requirement. MRI of the chest and abdomen with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

Screening assessments in the randomization phase will include CT scan (with oral/IV contrast unless contraindicated) of the chest (including liver and adrenal).

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.

Subsequent tumor assessments will include CT scans (with oral/IV contrast unless contraindicated) of the chest (including liver and adrenal) every 4 months in the first year and every 6 months in the second year after randomization. During Years 3–5, tumor assessment will be conducted every 6 months, by chest X-ray *or* chest CT (including liver and adrenal), until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. *After Year 5 and the completion of the final analysis of DFS, there will no longer be a study requirement for tumor assessments to be completed and patients are to be followed according to the local standard as a part of their regular medical care. If a recurrence of the primary NSCLC, or a new second primary NSCLC or new primary non-NSCLC malignancy is diagnosed as a part of regular medical care, this data is to be entered in the study's electronic data capture (EDC) system.*

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). Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will 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 or total carbon dioxide (if considered standard of

care for the site), calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)

- Coagulation (aPTT and INR for the enrollment phase; aPTT or INR for the randomization phase)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed at each cycle during treatment. A serum pregnancy test must be performed if the urine pregnancy test 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 [TSH], free T3, free T4)

  Total T3 (instead of free T3) should be tested only at sites where free T3 testing cannot be performed.
- HIV

  All patients will be tested for HIV prior to the inclusion into the study and patients who are HIV-positive will be excluded from the clinical study.
- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)

  HBV DNA is required on or before enrollment (only patients negative for HBV DNA are eligible) if patient has negative serology for HBsAg and positive serology for anti-HBc.
- HCV serology: hepatitis C virus antibody (anti-HCV)

  HCV RNA should be obtained prior to enrollment if the patient tests positive for anti-HCV.

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 laboratories 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.
- PK assay (patients assigned to atezolizumab only)

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

- Biomarker assays in blood samples

  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 3. Samples will be processed to obtain EDTA plasma and serum for the determination of changes in blood-based biomarkers (e.g., cytokines, ctDNA). Whole blood samples may be processed to obtain their derivatives (e.g., RNA and DNA) and may be evaluated for immune-mediated, tumor type-related, and other exploratory biomarkers (e.g., alterations in gene expression or single nucleotide polymorphisms).

  Residual PK and ATA samples will be retained for further method development, assay validation, and characterization. Samples will be stored for up to 5 years after the final clinical study report has been completed.

- For patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR) any remaining material from the above sample collection will be stored and used for exploratory analyses as indicated in Section 4.5.11.
  For patients who consent to RCR optional future research on their whole blood samples collected at screening but are determined to be ineligible for study participation, these samples and their derivatives (e.g., DNA, RNA, protein) may be used for future development of biomarker and/or diagnostic tests as indicated in Section 4.5.11.

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

4.5.7 Resected Tumor Tissue Samples

A central laboratory will coordinate the sample collection of resected tumor 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.

4.5.8 Resected Tumor Tissue Samples for Screening

Representative tumor specimens in paraffin blocks (preferred) or 15 or more freshly cut, serial unstained sections (on slides) with an associated pathology report must be submitted for determination of PD-L1 status prior to study enrollment. Analysis of PD-L1 will be performed using the VENTANA PD-L1 (SP263, and also SP142 in earlier protocol versions) assays (Appendix 5 and Appendix 4, respectively), which may be considered investigational per local regulations.

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).

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 not eligible to enroll in the study will be returned no later than 6 weeks after eligibility determination.

4.5.8.1 Tumor Samples at the Time of Disease Recurrence

For patients in both arms, a tumor sample should be obtained at the time of first radiographic confirmation of disease recurrence or confirmation of a new primary NSCLC for patients randomized in both arms unless not clinically feasible (within 40 days of disease recurrence or prior to start of the next anti-cancer therapy, whichever is sooner).

Acceptable samples include:

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

The status of immune-mediated and 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 recurrence or occurrence 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 U.S. Food and Drug Administration (FDA); results from these investigational tests should not be used to guide future treatment decisions.

After the DFS final analysis is complete, tumor tissue samples will no longer be collected.

4.5.8.2 Tumor Samples at Other Timepoints

If a patient undergoes a medically indicated procedure (e.g., bronchoscopy, esophagogastroduodenoscopy, or 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 and during survival follow-up) who have signed the Roche Clinical Repository (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 response are preferred. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy.

4.5.8.3 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 into the RCR for future research (see Section 4.5.11), 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 (Atezolizumab-Treated Patients Only)

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

4.5.10 Electrocardiogram

A twelve-lead ECG is required at screening and as clinically indicated. ECGs for each patient should be obtained on the same machine whenever 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 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 Optional Tumor and Blood Samples for Roche Clinical Repository (Optional Future Research)

4.5.11.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities 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 recurrence
- 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

4.5.11.2 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 or 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 4.5.11) will not be applicable at that site.

4.5.11.3 Optional Samples for Roche Clinical Repository

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

- Whole blood samples collected at screening (for screen fail patients only)
- Optional fresh biopsy 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; see Appendix 2 and Appendix 3)

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 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described in Section 4.5.11.4.

4.5.11.4 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 only to third parties 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 regarding 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.

4.5.11.5 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 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.

4.5.11.6 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. However, if RCR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and must enter the date of withdrawal on the appropriate Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study GO29527 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 GO29527.

4.5.11.7 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. Roche 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.

4.6 TIMING OF STUDY ASSESSMENTS

Flowcharts of scheduled study assessments are provided in Appendix 1 and Appendix 2. 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.

4.6.1 Screening and Pre-Treatment Assessments

Written informed consent for participation in the study (enrollment/randomized phases) must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to enrollment into study (screening/enrollment phase). Patients who are eligible to receive adjuvant cisplatin-based chemotherapy will be treated for up to four cycles (approximately 12 weeks). Within 3 weeks to 8 weeks after completion of the last dose of chemotherapy treatment, eligible patients will then be randomized into study. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days (or as otherwise specified) prior to enrollment period may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before receiving both adjuvant chemotherapy and prior to randomization into study. 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.

See Appendix 1 and Appendix 2 for the schedules of screening and pre-treatment assessments for the enrollment phase and randomization phase, respectively.

4.6.2 Assessments during Treatment/Best Supportive Care Period

All visits must occur within $\pm$3 days from the scheduled date unless otherwise noted. 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.

For patients in Arm A, if scheduled dosing is precluded because of a holiday, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule. If scheduled study assessments cannot be obtained because of a holiday, these assessments should then be obtained at

the soonest following date, provided that the soonest following date is not within 3 days of other regularly scheduled study assessments.

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

For both the enrollment and randomization phases, screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. The following assessments may be performed ≤96 hours before Day 1 of each cycle:

- ECOG Performance Status
- Limited physical examination
- Local laboratory tests

See Appendix 1 and Appendix 2 for the schedule of screening and pre-treatment assessments for the enrollment phase and randomization phase.

For patients in Arm B, if medical visits are completed during the randomization phase instead of a telephone contact, additional assessments including limited physical exam and laboratory tests may be completed as clinically indicated, according to local standard of care. See Appendix 2 for the schedule of required assessments for the randomization phase.

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

4.6.3 Assessments at Treatment Discontinuation Visit

For the enrollment phase, patients who discontinue early from chemotherapy or who complete up to four cycles of chemotherapy will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., after completion of up to four cycles, or when disease recurrence is determined or confirmed) may be considered as the treatment discontinuation visit.

For randomized phase, atezolizumab-treated patients who discontinue early from treatment or who complete the study treatment in full (16 cycles) will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease recurrence is determined or confirmed) may be used as the treatment discontinuation visit.

Patients randomized to BSC (Arm B) and who discontinue early from the BSC period or who complete BSC in full (1 year) will also be asked to return to the clinic not

more than 30 days after the last BSC visit for a discontinuation visit. The visit at which the decision is made to discontinue patient from the BSC visit (e.g., disease recurrence is determined or confirmed) may be used as the BSC discontinuation visit.

See Appendix 2 for the schedule of assessments performed at the treatment and study discontinuation as well as the treatment or BSC discontinuation visit.

4.6.4 Follow-Up Assessments

4.6.4.1 Ongoing Tumor Assessments

All patients in the randomized phase will undergo scheduled tumor assessments at baseline and every 4 months in the first year and every 6 months in the second year by CT following randomization. Patients who have not experienced recurrence of disease will undergo tumor assessments every 6 months by CT *or* X-ray during Years 3–5 post-randomization. In the absence of disease recurrence, tumor assessments should continue regardless of whether patients start new anti-cancer therapy until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

Patients who discontinue treatment before completing the 16 cycles of atezolizumab for reasons other than disease recurrence (e.g., toxicity) should continue to undergo scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study treatment until the patient has disease recurrence, dies, withdraws consent, is lost to follow-up, or until the study closes, whichever occurs first.

Additionally, patients in either arm who start a new anti-cancer therapy in the absence of disease recurrence should be followed according to the protocol schedule unless they withdraw consent, die, experience disease recurrence, are lost to follow-up, or until the study closes, whichever occurs first.

After Year 5 and the completion of the final analysis of DFS, there will no longer be a study requirement for tumor assessments to be completed and patients are to be followed according to the local standard as a part of their regular medical care.

4.6.4.2 Adverse Events

During both the enrollment phase (cisplatin-based chemotherapy) and randomization phase (atezolizumab or BSC), all serious adverse events and adverse events of special interest will be recorded during the study and for 90 days after the last dose of study treatment (last study assessment for patients in Arm B) or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study and for 30 days after the last dose of study treatment (last study assessment for patients randomized to Arm B) or until the initiation of another anti-cancer therapy, whichever occurs first. Investigators are instructed to report all serious adverse events and events of special interest considered related to study treatment regardless of time after study.

After the treatment discontinuation visit, adverse events should be followed as outlined in Section 5.5.1.

4.6.4.3 Anti-Therapeutic Antibody and Pharmacokinetic Assessments

For patients assigned to atezolizumab only: a post-treatment ATA and PK sample should be collected 120 days (±30 days) after the last dose of atezolizumab received during the treatment period unless the patient withdraws consent, dies, or the study closes, whichever occurs first.

See the schedule of assessments provided in Appendix 3 for specified follow-up assessments.

4.6.4.4 Survival and Subsequent Anti-Cancer Therapy

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months or more often until death, loss to follow-up, consent withdrawal, or study termination by Roche, whichever occurs first. All patients will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator), is lost to follow-up, dies, or the study is terminated by the Sponsor, whichever occurs first. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study treatment or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason. 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 noncompliance

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.

4.7.2 Discontinuation from Study Treatment

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

- Any medical condition that may jeopardize the patient's safety if he or she continues to receive study treatment
- Use of another non-protocol anti-cancer therapy (see Section 4.4.4)
- Pregnancy
- Disease recurrence as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status
- Occurrence of new primary NSCLC, as assessed by the investigator
- 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 (for patients randomized to Arm A)

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

4.7.3 Study and Site Discontinuation

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 study is placed on hold or if the Sponsor decides to discontinue the study or development program.

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
- Noncompliance 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

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated in Section 5.1.3).

An independent Data Monitoring Committee (iDMC) that has been involved in the review of aggregate safety data (refer to the iDMC charter for a detailed monitoring plan) from prior and current atezolizumab studies will be employed for this study. This committee will conduct periodic reviews of safety data according to procedures outlined in an iDMC charter.

For patients randomized to the atezolizumab arm, administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personal and adequate equipment/medicine to manage potentially serious reactions. The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., ASCO or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. In addition, immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH). Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for managing patients who experience anticipated adverse events are provided in Appendix 9.

5.1.2 Risk and Side Effects Associated with Administration of Cisplatin-Based Chemotherapy

5.1.2.1 Cisplatin

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 Cisplatin Package Insert.

5.1.2.2 Vinorelbine

Common hematologic toxicities associated with vinorelbine therapy include leukopenia and neutropenia (dose limiting), and anemia. Thrombocytopenia has also occurred, but is considered rare. Neurological toxicities include peripheral neuropathy (decreased reflexes, paresthesia, hypoesthesia), infrequently tumor pain and jaw pain. The most commonly reported gastrointestinal toxicities include constipation, mild or moderate nausea/vomiting, anorexia, and stomatitis.

Dermatological toxicities often associated with vinorelbine therapy include alopecia, phlebitis, local reaction at the site of injection (erythema, pain, vein discoloration), and moderate vesicant. Liver enzyme toxicities are rare, but mild transient increases in liver enzymes have been reported. Hypersensitivity reactions that are reported include reversible bronchospasm. Cardiovascular toxicities such as chest pain have also been reported, but are often associated with patients with preexisting cardiovascular disease or tumors within the chest. Pulmonary toxicities that have been documented include shortness of breath and some interstitial pulmonary changes. Fatigue is also commonly reported with vinorelbine treatment.

5.1.2.3 Docetaxel

Cardiac toxicities reported with docetaxel use include arrhythmias, pericardial effusions, and palpitations. Hematological toxicities reported can be severe or life threatening and include dose–related neutropenia, leukopenia, thrombocytopenia, anemia, hypoglycemia, and hypernatremia. The most commonly reported gastrointestinal toxicities include nausea and vomiting, diarrhea, oral mucositis, pancreatitis, and esophagitis.

Neurological toxicities reported include reversible dysthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, and seizures.

Hypersensitivity reactions can be severe with docetaxel use. Reported cases include local or general skin rash, flushing, pruritus, drug fever, chills and rigors, low back pain,

and severe anaphylactoid reactions such as flushing with hypo- or hypertension, with or without dyspnea.

Dermatological toxicities include alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, and nail changes. Common hepatotoxicities reported include increased transaminase, alkaline phosphatase, and bilirubin. Less commonly reported hepatic events include hepatic failure and/or hepatic drug reactions. Pulmonary events reported include dyspnea with restrictive pulmonary syndrome and pleural effusions. Other associated toxicities include asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema fluid retention syndrome, ascites, flu-like symptoms, and fever.

5.1.2.4 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. Monitor for myelosuppression should occur prior to each cycle.

Hemolytic-uremic syndrome (HUS) 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 a result of HUS.

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 preexisting renal impairment or hepatic insufficiency.

For more details regarding the safety profile of gemcitabine, see the Gemcitabine Package Insert.

5.1.2.5 Pemetrexed

The most common side effects of pemetrexed include gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation), myelosuppression, infection, fatigue, stomatitis, loss of appetite, and rash.

For more details regarding the safety profile of pemetrexed, see the Pemetrexed Package Insert.

5.1.3 General Plan to Manage Safety Concerns

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 Appendix 1 and Appendix 2). 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 and Appendix 2 for the list and timing of study assessments. During the study, patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection. All serious adverse events and protocol-defined events of special interest (see Section 5.2) will be reported in an expedited fashion (see Section 5.4.2). In addition, the iDMC and Medical Monitor will review and evaluate observed adverse events on a regular basis.

Patients who have an ongoing study treatment-related adverse event upon study treatment 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.

5.1.4 Management of Chemotherapy-Specific Adverse Events

For all toxicities, if one drug in a chemotherapy regimen is held, the other chemotherapy agent must be held as well. In general, treatment could be held for up to 63 days after Day 1 of last cycle of last cycle to allow sufficient time for recovery from the toxicities listed in the following sections. If one drug in a chemotherapy regimen is discontinued, the other chemotherapy can be continued as a single agent.

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.

5.1.4.1 Cisplatin Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

The dose modification guidelines for cisplatin are provided below.

Treatment with cisplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or treatment is delayed for more than 21 days because of toxicities.

Hematologic Toxicities

At the start of each cycle, the ANC must be ≥1500/μL, and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days after Day 1 of the last cycle 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). No dose adjustment for cisplatin is allowed for hematologic toxicities.

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 can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicities

If a patient develops a non-hematologic toxicity (see Table 11), cisplatin should be withheld for up to 63 days after Day1 of the last cycle until resolution to less than or equal to the patient's baseline (or Grade ≤1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 11.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting should be controlled with adequate anti-emetics.

Table 11 Cisplatin Dose Modifications for Non-Hematologic Toxicities (Excluding Neurotoxicity and Nephrotoxicity)

Toxicity	Cisplatin 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
Grade 3 or 4 nausea/vomiting [a]	75% of previous dose
Any other Grade 3 or 4 toxicity	75% of previous dose

[a] Despite the use of anti-emetics.

Nephrotoxicity

CRCL must be ≥60 mL/min prior to the start of any cycle of cisplatin. If there is a decrease in CRCL between cycles, but the CRCL is still ≥60 mL/min at the time of the next cycle, the investigator should use clinical judgment regarding the continuation of cisplatin, dose reduction, or delaying of the cycle. If a patient's CRCL value has not

returned to ≥60 mL/min within 63 days after Day1 of the last cycle, the patient should be discontinued from cisplatin.

Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 12. For a Grade 3 or 4 neurotoxicity, cisplatin should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgment).

Table 12 Cisplatin Dose Modifications or Treatment Discontinuation for Associated Neurotoxicity

Toxicity	Cisplatin Dose
Grade 0–1 neurotoxicity	100% of previous dose
Grade 2 neurotoxicity	75% of previous dose
Grade 3 or 4 neurotoxicity	50% of previous dose or permanent discontinuation

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). See Table 12 for dose modifications.

5.1.4.2 Pemetrexed Dose Modifications, Treatment Delays or Treatment Discontinuation, and Management of Specific Adverse Events

The dose modification guidelines are applicable for pemetrexed used as a single agent or in combination with cisplatin.

Treatment with pemetrexed should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions, or if treatment is delayed for more than 63 days after Day 1 of the last cycle because of toxicities.

Hematologic Toxicity

At the start of each cycle, the ANC must be ≥1500/μL and the platelet count must be ≥100,000/μL. Treatment should be delayed for up to 63 days after Day 1 of the last cycle to allow sufficient time for recovery. Growth factors may be used in accordance with 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 (nadir) platelet and neutrophil values from the previous cycle (see Table 13).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 13 Pemetrexed Dose Modifications for Hematologic Toxicities

Toxicity [a]	Pemetrexed Dose
ANC $<500/\mu L$ and platelets $\geq 50,000/\mu L$	75% of previous dose
Platelets $<50,000/\mu L$, regardless of ANC	75% of previous dose
Platelets $<50,000/\mu L$ with Grade ≥ 2 bleeding, regardless of ANC	50% of previous dose

[a] Nadir of prior cycle.

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 can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicity

At the start of each cycle, the CRCL must be ≥ 45 mL/min. For enrollment and dosing decisions, CRCL will be estimated using the original, weight-based Cockcroft and Gault formula or measured using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA) to determine the GFR. The method of CRCL assessment used at baseline should be used throughout the study.

If a patient develops a non-hematologic toxicity (see Table 14), pemetrexed should be withheld for up to 63 days after Day 1 of the last cycle until resolution to equal or less than the patient's baseline (or Grade 1 or better if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 14. For a Grade 3 or 4 neurotoxicity, pemetrexed should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgment).

Table 14 Pemetrexed Dose Modifications for Non-Hematologic Toxicities

Toxicity	Pemetrexed 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
Neurotoxicity	
Grade 2	75% of previous dose
Grade 3 or 4	50% of previous dose or permanent discontinuation
Any other Grade 3 or 4 toxicities	75% of previous dose

Treatment Delays Caused by Insufficient Folic Acid or Vitamin B-12 Supplementation

Cycle 1 should not be started until both of the following requirements are met:

- The patient has taken folic acid for 5 to 7 days preceding the first dose of pemetrexed or as per local standard of care, but not later than Cycle 1, Day 1.
- The patient has received a vitamin B-12 injection (which can be given on Cycle 1, Day 1).

Delay subsequent cycles until the patient has taken folic acid for at least 14 of the 21 days before Day 1 of the subsequent cycle.

For more details regarding pemetrexed dose modification, see the pemetrexed prescribing information.

5.1.4.3 Gemcitabine Dose Modifications, Treatment Delays or Treatment Discontinuation, and Management of Specific Adverse Events

The dose modification guidelines are applicable for gemcitabine used as a single agent or in combination with cisplatin.

The dose modification guidelines for gemcitabine are provided below.

Treatment with gemcitabine should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions, or if treatment is delayed for more than 21 days due to toxicities.

Hematologic Toxicities

At the start of each cycle, the ANC must be $\geq$1500 cells/μL and the platelet count must be $\geq$100,000 cells/μL. Gemcitabine dose modifications for hematologic toxicity should be on the basis of the granulocyte and platelet counts taken on Days 1 and 8 of therapy (see Table 15 and Table 16). Patients receiving gemcitabine should be monitored prior to each dose with a full blood count, including differential and platelet counts. Treatment

should be delayed for up to 63 days after Day1 of the last cycle to allow sufficient time for recovery. Growth factors may be used in accordance with 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 (nadir) platelet and neutrophil values from the previous cycle (see Table 15).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 15 Gemcitabine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 1

Toxicity [a]	Gemcitabine Dose
ANC <500/μL and platelets ≥50,000/μL	75% of previous dose
Platelets <50,000/μL, regardless of ANC	75% of previous dose
Platelets <50,000/μL with Grade ≥2 bleeding, regardless of ANC	50% of previous dose
ANC <1000/μL plus fever of ≥38.5°C	75% of previous dose

[a] Nadir of prior cycle.

Table 16 Gemcitabine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 8

Absolute Granulocyte Count		Platelet Count	Gemcitabine % of Dose on Day 1
≥1000/μL	and	≥100,000/μL	100%
500–999/μL	or	50,000–99,999/μL	75%
<500/μL	or	<50,000/μL	Withhold

Note: Omitted Day 8 doses of gemcitabine will not be made up. Day 8 dose adjustment for neutropenia and/or platelets is not a permanent dose reduction.

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 can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Non-Hematologic Toxicities

In general, for Grade 3 or 4 non-hematologic toxicities, gemcitabine should be withheld or the dose reduced by 50%, according to physician judgment.

Permanent discontinuation should be considered for any of the following events:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary-leak syndrome
- Posterior reversible encephalopathy syndrome

Table 17 provides dose modification guidelines for non-hematologic toxicities.

Table 17 Gemcitabine Dose Modifications, Treatment Delays, or Treatment Discontinuation and Patient Management for Grade 2, 3, or 4 Non-Hematologic 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.
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.		

5.1.4.4 Docetaxel Dose Modification and Management of Specific Adverse Events

Treatment with docetaxel should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or if treatment is delayed for more than 63 days after Day1 of the last cycle because of toxicities.

Guidelines for docetaxel dose modifications to manage general toxicities are shown in Table 18. Guidelines for the management of hepatotoxicity for patients who are treated with are shown in Table 19. Guidelines for the management of edema for patients who are treated with docetaxel are shown in Table 20.

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils $<$500 cells/mm^3 for more than 1 week, platelets $<$25,000 cells/μL, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and treatment then resumed at 55 mg/m^2. Patients who develop Grade $>$3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Table 18 Guidelines for Management of Specific Docetaxel-Related Adverse Events

Adverse Event (Worst Grade in Previous Cycle)	Action to Be Taken
Febrile neutropenia/Grade 4 AGC $\geq$7 days or platelets $<$25,000 cells/μL	Withhold docetaxel until symptoms resolve. [a] Reduce docetaxel to 75% of previous dose (e.g., from 75 mg/m^2 to 55 mg/m^2)
Grade 3 skin/neuropathy/major organ/ non-hematologic toxicity	Withhold docetaxel until symptoms resolve Reduce docetaxel to 75% of previous dose
Grade 4 skin/neuropathy/major organ/ non-hematologic toxicity OR Recurrence of Grade 3 toxicity after prior dose reduction	Discontinue docetaxel treatment

AGC = absolute granulocyte count.

[a] Do not resume treatment until AGC $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and toxicity $\leq$Grade 2.

Table 19 Guidelines for Management of Hepatotoxicity in Patients Treated with Docetaxel

	AST/ALT		Alkaline Phosphatase		Bilirubin	Docetaxel Dose
Mild to moderate	$>1.5 \times$ ULN	AND	$>2.5 \times$ ULN			75%
Severe	$>3.5 \times$ ULN	AND	$>6 \times$ ULN	OR	$>$ULN	Do not treat. Discontinue if treatment already started.

ULN = upper limit of normal.

Other Specific Toxicities Not Requiring Dose Adjustment

Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely, fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be re-challenged with docetaxel.

Hypersensitivity reactions may occur within a few minutes following initiation of docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required.

Fluid Retention

Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel infusion to reduce the incidence and severity of fluid retention. Patients with preexisting effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. See Table 20 for the management of edema.

Table 20 Guidelines for the Management of Edema in Patients Treated with Docetaxel

Edema	Severity	Effusion
Asymptomatic	Mild, Grade 1	Asymptomatic, no intervention needed
Symptomatic	Moderate, Grade 2	Symptomatic, may require intervention
Symptomatic, resulting in interruption of treatment	Severe, Grade 2	Symptomatic, urgent intervention required

5.1.4.5 Vinorelbine Dose Modification and Management of Specific Adverse Events

The dose modification guidelines are applicable for vinorelbine used as a single agent or in combination with cisplatin.

Treatment with vinorelbine should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions, or if treatment is delayed for more than 63 days after Day1 of the last cycle because of toxicities.

Hematologic Toxicity

Day 1 dosing may only start for platelet count $>$100,000 cells/μL and ANC $>$1500 cells/μL. Vinorelbine dose modifications for hematologic toxicity should be based

on the granulocyte and platelet counts taken on Days 1 and 8 of therapy (Table 21, Table 22). Patients who are receiving vinorelbine should be monitored prior to each dose with a full blood count, including differential and platelet counts. Treatment should be delayed for up to 63 days after Day 1 of the last cycle to allow sufficient time for recovery. Growth factors may be used in accordance with 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 (nadir) platelet and neutrophil values from the previous cycle (see Table 21).

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Table 21 Vinorelbine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 1

Toxicity [a]	Vinorelbine Dose
ANC <500/μL and platelets ≥50,000/μL	75% of previous dose
Platelets <50,000/μL, regardless of ANC	75% of previous dose
Platelets <50,000/μL with Grade ≥2 bleeding, regardless of ANC	50% of previous dose
ANC <1000/μL plus fever of ≥38.5°C	75% of previous dose

[a] Nadir of prior cycle.

Table 22 Vinorelbine Dose Modifications or Treatment Delays for Hematologic Toxicities on Day 8

Absolute Granulocyte Count		Platelet Count	Vinorelbine % of Dose on Day 1
≥1000/μL	and	≥100,000/μL	100%
500–999/μL	or	50,000–99,999/μL	75%
<500/μL	or	<50,000/μL	Withhold

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 can then be resumed.

No dose reductions are recommended for anemia. Patients should be supported per the treating physician's institution's guidelines.

Hepatic Toxicity

Dose reduction levels of vinorelbine for hepatic toxicity are shown in Table 23. The Day 1 value should be used in determining dose.

Table 23 Dose Reduction of Vinorelbine for Hepatic Toxicity

SGOT/AST		Alkaline Phosphatase		Bilirubin	Vinorelbine Dose
≤1.5×ULN	and	<1.5×ULN	and	WNL	100%
>1.5–5×ULN	and	1.5–5×ULN	or	>ULN–1.5×ULN	75%
>5×ULN	and	>5×ULN	or	>1.5×ULN	Hold [a]

LFT=liver function tests; ULN=upper limit of normal; WNL=within normal limits.

[a] Repeat LFTs weekly. If recovered, reduce delayed dose by 25%. Dose reductions for hepatic toxicity are permanent. If not recovered within 3 weeks, discontinue chemotherapy. If vinorelbine is delayed as a result of hepatic toxicity, cisplatin should also be delayed and administered when vinorelbine is resumed.

Any elevation in bilirubin alone qualifies for a dose reduction. However, an elevation in both the SGOT/AST and alkaline phosphatase is required to qualify for a dose reduction.

Peripheral Neuropathy or Autonomic Neuropathy Causing Constipation

Vinorelbine dose modifications for constipation caused by peripheral neuropathy or autonomic neuropathy are recommended in Table 24.

Table 24 Vinorelbine Dose Reduction for Sensory or Motor Neuropathy

Grade of Toxicity	Dose of Cisplatin and Paired Chemotherapy
0	100%
1	100%
2	Delay treatment until patient recovers to Grade 1; then resume treatment at 75% dose
≥Grade 3	Delay treatment until patient recovers to Grade 1; then resume treatment at 50% dose

For any Grade 3 or 4 toxicities not mentioned above, vinorelbine should be withheld until the patient recovers completely or to Grade 1 toxicity. The treatment should then be resumed at 75% dose (permanent dose reduction) for Grade 3 toxicities and 50% of dose (permanent dose reduction) for Grade 4 toxicities or at the discretion of the investigator.

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 the monitoring and recording of adverse events, including serious adverse events and non-serious adverse events of special interest, the measurement of protocol-specified safety laboratory assessments, the measurement of protocol-specified vital signs, and 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 Section 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, Xray) 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 (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 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious 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:

- 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, is defined as follows:

  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.
- 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, IRRs, CRS, influenza like illness, HLH, and MAS

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 5.3.1, 5.3.5, 5.4, and 5.4.2.

For each adverse event, 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) on the Adverse Event eCRF.

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 the 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 treatment,** only serious adverse events caused by a protocol-mandated intervention (e.g., serious adverse events related to invasive procedures such as biopsies) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, during both the enrollment phase (cisplatin-based chemotherapy) and randomization phase (atezolizumab or BSC), all serious adverse events and adverse events of special interest will be recorded during the study and for 90 days after the last dose of study treatment (last study assessment for patients in Arm B) or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study and for 30 days after the last dose of study treatment (last study assessment for patients randomized to Arm B) or until the initiation of another anti-cancer therapy, whichever occurs first. Investigators are instructed to report all serious adverse events and 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 nondirective 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 25 will be used for assessing the severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 25 Adverse Event Severity Grading Scale

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 NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.0_2010-06-14_QuickReference_8.5x11.pdf.

[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 one's self, 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 treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment

- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable)
- Known association of the event with study treatment 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

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 Diagnosis versus Signs and Symptoms

For all adverse events, a diagnosis (if known) rather than individual signs and symptoms should be recorded on the Adverse Event eCRF (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.

5.3.5.2 Infusion-Related Reactions

An exception to the above is symptoms that occur during or within 24 hours after an atezolizumab infusion. These may be part of an acute infusion reaction and should not be recorded under the diagnosis of “infusion-related reaction.” Rather, non-serious symptoms should be recorded as separate adverse events on the Adverse Event eCRF.

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 subsequent 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 or not 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 be recorded only once on the Adverse Event eCRF. The initial severity (intensity) of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If a persistent adverse event becomes more severe, the most extreme severity 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 is a change from baseline and 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 a clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding if 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 cholecystitis), only the diagnosis (i.e., cholecystitis) 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 whether 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 (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 is a change from baseline and 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 if 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.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × 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 5.3.5.1) 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 a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to disease recurrence or from confirmation of a new primary NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on study deaths, regardless of relationship to study treatment, 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. 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. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

During post-study treatment survival follow-up, deaths attributed to disease recurrence of NSCLC or from confirmation of a new primary NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF.

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").

5.3.5.10 Lack of Efficacy or NSCLC Recurrence

Events that are clearly consistent with the expected pattern of disease recurrence should **not** be recorded as adverse events. These data will be captured as efficacy assessment data only. The expected pattern of disease recurrence will be based on determination by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status. Every effort should be made to document disease recurrence with use of objective criteria. If there is any uncertainty as to whether an event is due to disease recurrence, it should be reported as an adverse event.

Recurrence of disease should not be recorded as an adverse event or serious adverse event, since recurrence of disease will be captured as an efficacy endpoint. However in situations in which there is no confirmation, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of NSCLC recurrence. If the symptoms are later confirmed to be due to recurrence of disease, then symptoms reported as adverse events should be retracted. Data for disease recurrence will be captured as efficacy assessment data only.

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.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that 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 suffered an adverse event.
- Hospitalization due solely to disease recurrence of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.12 Adverse Events Associated with an Overdose

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious 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).

5.4 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 study. 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 treatment:

- Serious adverse events (see Section 5.4.2 for further details)
- Non-serious adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.2 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 based on 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

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 Responsible (listed above and/or on the Roche Medical Emergency List), 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 Responsible contact information will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events That Occur Prior to Study Treatment Initiation

After informed consent has been obtained, but prior to initiation of study treatment, only serious adverse caused by a protocol-mandated intervention should be reported. The Clinical Trial Adverse Event/Special Situations 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 emailing the form with use of the fax number or email address provided to investigators.

5.4.2.2 Events That Occur After Study Treatment Initiation

After initiation of study treatment, during both the enrollment phase (cisplatin-based chemotherapy) and randomization phase (atezolizumab or BSC), all serious adverse events and adverse events of special interest will be recorded during the study and for 90 days after the last dose of study treatment (last study assessment for patients in Arm B) or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study and for 30 days after the last dose of study treatment (last study assessment for patients randomized to Arm B) or until the initiation of another anti-cancer therapy, whichever occurs first. 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 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 Clinical Trial Adverse Event/Special Situations 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 emailing the form with use of the fax number or email 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 6 months after the last dose of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed). A Clinical Trial Pregnancy Reporting Form should be completed and submitted by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy), either by

faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment 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 addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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 cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed). A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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 cisplatin-based chemotherapy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. 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.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (because the Sponsor considers abortions to be medically significant events), 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study treatment 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 treatment or study-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.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious 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

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

The Sponsor should be notified if the investigator becomes aware of any adverse event that occurs after the end of the adverse event reporting period (defined as 90 days for serious adverse events and adverse events of special or 30 days for all other adverse events). Investigators are instructed to report all serious adverse events and adverse events of special interest considered to be related to study treatment regardless of the time after study. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study. These events should be

reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Clinical Trial Adverse Event/Special Situations Form with use of the fax number or email address provided to investigators.

During survival follow-up, deaths attributed to disease recurrence of NSCLC or confirmation of new primary NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious 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.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events with use of 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.

An external iDMC will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Efficacy analyses will be performed on randomized patients within one or more populations, including PD-L1 subpopulations of patients with Stage II-IIIA NSCLC, all randomized patients with Stage II-IIIA NSCLC, and the ITT population, with patients

grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study treatment.

Safety analyses will be performed on all randomized patients who received any amount of study treatment, with patients allocated by whether any amount of atezolizumab treatment was received.

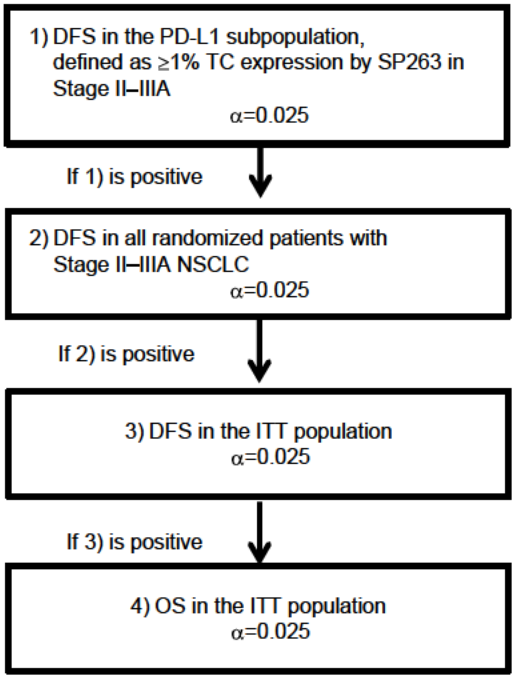
6.1 DETERMINATION OF SAMPLE SIZE

Approximately 1280 patients are expected to be accrued during the enrollment phase. With an approximate 21% dropout rate during adjuvant cisplatin-based chemotherapy, approximately 1005 patients will enter the randomization phase, including approximately 882 patients in the Stage II-IIIA population, and within Stage II-IIIA NSCLC patients, approximately 474 patients in the PD-L1 subpopulation (≥1% TC expression) defined by the SP263 IHC assay.

Emerging data from atezolizumab first-line NSCLC Phase III Study GO29431 (IMpower110; Herbst et al. 2019; Spigel et al. 2019) have observed clinical benefit with atezolizumab monotherapy in PD-L1 TC-defined subgroups. The TC-based assay SP263 appeared to capture a broader patient population with similar efficacy as compared to SP142. These findings are consistent with results observed in other PD-L1/PD-1 studies. With these data external to Study GO29431 and evolving biomarker landscape, the primary analysis of DFS in the PD-L1 subgroups (TC2/3 or IC2/3, TC1/2/3 or IC1/2/3) defined by SP142 will be replaced with DFS in the PD-L1 subgroup (≥1% TC expression) defined by SP263 (see Figure 2).

The overall type I error rate will be controlled for the one-sided test at 0.025.
The overview of the alpha control is shown in Figure 2.

Figure 2 Overview of the Alpha Control (One-Sided)



DFS = disease-free survival; ITT = intent to treat; OS = overall survival; TC = tumor cells.

The estimates of the number of events required to demonstrate efficacy with regard to DFS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the PD-L1 subpopulation defined by SP263 TC ≥1% within the Stage II-IIIA population, the randomized Stage II–IIIA population, and the ITT population.
- For Stage II–IIIA:

  89.8% power to detect an HR of 0.65, corresponding to an improvement in median DFS from 34 months to 52 months in the PD-L1 subpopulation defined by SP263 TC ≥1% within the Stage II–IIIA population

  90.7% power to detect an HR of 0.73, corresponding to an improvement in median DFS from 34 months to 46.6 months in the all-randomized Stage II–IIIA population
- For Stage IB–IIIA:

  76.4% power to detect an HR of 0.78, corresponding to an improvement in median DFS from 38 months to 48.7 months in the ITT population

- One DFS interim analysis to be performed when approximately 80% of the total DFS events in the primary efficacy analysis populations required for the primary analysis have occurred. The stopping boundaries for DFS interim and final analyses will be determined based on the Hwang-Shih-DeCani alpha spending function with the gamma parameter of –0.9 (Hwang et al. 1990; refer to Section 6.8.1 for details of the planned DFS interim analysis).
- Dropout rate of 5% per 24 months

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the ITT population (i.e., Stage IB-IIIA)
- 77% power to detect an HR of 0.78, corresponding to an improvement in median OS from 66 months to 84.6 months in the ITT population
- Four interim OS analyses to be performed, one at the time of the DFS interim analysis, the second one at the time of DFS final analysis, and the other two when approximately 73% and 88% of the total OS events required for the final analysis have occurred, respectively. The stopping boundaries for OS interim and final analyses will be determined based on the alpha spending function with the cumulative one-sided alpha of 0.001, 0.012, 0.022, 0.024, and 0.025 in the order of analyses (DeMets and Lan 1994; refer to Section 6.8.2 for details of the planned OS interim analyses).
- Dropout rate of 5% per 36 months

With these assumptions, the DFS final analysis will be conducted when approximately 237 DFS events in the PD-L1 subpopulation (defined by SP263 TC≥1%) within the Stage II–IIIA population have been observed. This is expected to occur approximately 68 months after the first patient is randomized. This number of events corresponds to a minimum detectable difference in HR of approximately 0.758 in the PD-L1 subpopulation within the Stage II–IIIA population.

Given the sample size of 1005, the final OS analysis will be conducted when approximately 564 OS events in the all randomized Stage IB–IIIA population have occurred, which is expected at approximately 121 months after the first patient is randomized.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study treatment administration, reasons for discontinuation from study treatment, and reasons for study termination will be summarized for patients who are enrolled but not randomized and for randomized patients in the PD-L1 subpopulation (defined by SP263 TC≥1%) within the Stage II–IIIA population, the Stage II–IIIA population, and the ITT population by treatment arm (depending on the results of the primary endpoint analyses). Major protocol deviations, including major deviations of

inclusion/exclusion criteria, will be reported and summarized by treatment arm for the ITT population.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, baseline disease characteristics (e.g., ECOG Performance Status), and cisplatin-based regimen, will be summarized by treatment arm. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of atezolizumab or BSC in the randomized phase, unless otherwise noted.

6.4 EFFICACY ANALYSES

To manage the small strata size with the consideration of prognostic significance, stratified analyses for DFS in the PD-L1 subpopulation defined by SP263 TC $\geq$ 1%, in all randomized patients with Stage II–IIIA NSCLC, and stratified analyses for DFS in all randomized patients with Stage II–IIIA NSCLC will use the following stratification factors at randomization: Stage (II vs. IIIA), sex (female vs. male), and histology (squamous vs. non-squamous); stratified analyses for DFS in the ITT population will use the following stratification factors at randomization: Stage ([IB and II combined] vs. IIIA), sex (female vs. male), histology (squamous vs. non-squamous), and SP142 PD-L1 tumor expression status by SP142 IHC assay ([TC2/3 and any IC, TC0/1 and IC2/3 combined] vs. [TC0/1 and IC0/1]). Stratified analyses of DFS in other PD-L1 subpopulations (e.g., SP263 TC$\geq$50% in all randomized patients with Stage II–IIIA NSCLC) will use the same set of stratification factors used for the stratified analyses of DFS in the PD-L1 subpopulation defined by SP263 TC $\geq$ 1% in all randomized patients with Stage II–IIIA NSCLC. The set of stratification factors used in the stratified analyses of DFS for a specific analysis population (e.g., the ITT population) will be applied to all other efficacy endpoints where stratified analyses are planned for the same analysis population.

An IRF may conduct a BICR of response endpoints.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is duration of DFS as assessed by the investigator. DFS is defined as the time from the date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC or death due to any cause, whichever occurs first. Data for patients who are not reported as experiencing disease recurrence, a new primary NSCLC, or death will be censored at the date of the last tumor assessment. If no post-baseline data are available, DFS will be censored at the date of randomization.

To control the overall level of significance at a one-sided error of 0.025, comparisons with respect to DFS between the treatment and control arm for the PD-L1 subpopulation

defined by SP263 TC≥1% within the Stage II–IIIA population, all-randomized Stage II–IIIA population, and the ITT population, will be conducted hierarchically as described in Figure 2.

The null and alternative hypotheses regarding DFS in each population can be phrased in terms of the DFS survival functions $S_A(t)$ in the atezolizumab arm (Arm A) and $S_B(t)$ in the control arm (Arm B), respectively:

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) > S_B(t)$$

The HR will be estimated with use of a stratified Cox regression model, including two-sided 95% CIs. The stratification factors used for the analysis are described in Section 6.4. The unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology will be used to construct the two-sided 95% CI for the median DFS for each treatment arm (Brookmeyer and Crowley 1982).

Analyses at landmark timepoints (Section 6.7.1) and subgroup analyses (Section 6.7.1) will be performed for the DFS endpoint described above.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Overall Survival Analysis

OS is defined as the time from the date of randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at 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.

The methodology (as described in Section 6.4.1) used for DFS will be applied for OS. An overview of the OS testing schema is shown in Figure 2.

6.4.2.2 Disease-Free Survival 3-Year and 5-Year Landmark Analysis

The DFS rate at 3 years and at 5 years will be analyzed for the PD-L1 subpopulation (defined by SP263 TC≥1% in all randomized patients with Stage II–IIIA NSCLC, the all-randomized Stage II–IIIA population, and the ITT population. These DFS rates will be estimated by the Kaplan-Meier methodology for each treatment arm, with two-sided 95% CIs calculated using Greenwood's formula.

6.4.2.3 Disease-Free Survival Analysis in Additional PD-L1 Subpopulation Defined by the Anti–PD-L1 (SP263) IHC Assay

DFS in the PD-L1 subpopulation, defined by SP263 TC ≥ 50% in all randomized patients with Stage II–IIIA NSCLC, will be analyzed by using the same methodology in Section 6.4.1.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population, defined as all randomized patients who received any amount of the study drug, with patients allocated according to whether or not any amount of atezolizumab was received.

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

Verbatim description of adverse events will be mapped to thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events that occur 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 (Grades 3, 4, or 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.

Summaries of treatment-related serious adverse events, adverse events of special interest, and all listings of adverse events will include all events that occur during or after the first study drug treatment. Safety summaries of all other adverse events will include treatment-emergent adverse events until patients receive another anti-cancer therapy.

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

Serum levels and incidences of ATA against atezolizumab will be summarized to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy. ATA results will be summarized and listed by patient and cycle.

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.

6.6 PHARMACOKINETIC ANALYSES

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 standard deviations as appropriate.

Additional PK and pharmacodynamic analysis will be conducted based on the availability of data.

6.7 EXPLORATORY ANALYSES

6.7.1 Exploratory Analyses of Disease-Free Survival and Overall Survival

Unless otherwise indicated, the exploratory efficacy endpoints will be analyzed in the PD-L1 subpopulation defined by SP263 TC≥1% within the Stage II–IIIA patients, all randomized Stage II–IIIA patients, and/or the ITT population (depending on the results of the primary endpoint analyses).

DFS and OS Rate at Landmark Timepoints. In addition to DFS 3-year and 5-year survival rates as secondary endpoints, the DFS and OS rate at various other timepoints (every 1 year from randomization) will be estimated with use of Kaplan-Meier methodology for each treatment arm, along with two-sided 95% CIs calculated with use of Greenwood's formula for exploratory purposes.

Subgroup Analysis. The effects of demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., tumor stage, PD-L1 expression level, chemotherapy regimen before randomization, histology, smoking history, and ECOG Performance Status) on duration of DFS and OS will be examined. Summaries of DFS and OS, including un-stratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median survival time will be produced separately for each level of the categorical variables.

Sensitivity Analyses. The impact of loss to follow-up on DFS will be assessed depending on the number of patients who are lost to follow-up. If more than 5% of patients are lost to follow-up for DFS in either treatment arm, a sensitivity analysis ("worse-case" analysis) will be performed in which patients who are lost to follow-up will be considered to have recurrent disease at the date of the last tumor assessment.

To evaluate the impact of missed visits, sensitivity analyses with a different censoring rule will be performed for the primary endpoint of DFS. Data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last date with adequate radiologic assessment prior to the missed visits.

DFS Analyses in Other PD-L1 Subpopulations. DFS in other PD-L1 subpopulations will be analyzed by using the same methodology in Section 6.4.1. These PD-L1 subpopulations include TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by PD-L1 SP142 IHC in both the Stage II–IIIA and the ITT populations; the PD-L1 subpopulations defined by 22C3 TPS≥1% and TPS≥50% in both the Stage II–IIIA and the ITT populations; and the PD-L1 subpopulations defined by SP263 TC≥ 1% and TC≥ 50% in the ITT population.

6.7.2 Exploratory Analyses of Biomarkers

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

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analysis for Disease-Free Survival

An external iDMC will evaluate safety data on an ongoing basis and will also review the interim analysis of DFS data. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center (iDCC). Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. A detailed plan will be included in the iDMC charter.

There will be one planned interim analysis for DFS in the study. To ensure the study continues to meet the highest standards of integrity, the interim analysis of DFS 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.

This DFS interim analysis will be conducted when approximately 80% of the information has been observed in the PD-L1 subpopulation defined by SP263 TC $\geq$ 1% within the Stage II–IIIA population (i.e., at the date when approximately 190 DFS events occur in the PD-L1 subpopulation within the Stage II–IIIA population). This is expected to occur approximately 56 months after the first patient is randomized; however, the exact timing of this analysis will depend on the actual number and the timing of DFS events.

The final DFS analysis will be conducted at the date when approximately 237 DFS events occur in the PD-L1 subpopulation within the Stage II–IIIA population. This is expected to occur approximately 68 months after the first patient is randomized; however, the exact timing of this analysis will depend on the actual number and timing of DFS events.

To control type I error for DFS at one-sided alpha of 0.025, the stopping boundaries for DFS interim and final analysis are to be computed with use of the Hwang-Shih-DeCani alpha spending function with the gamma parameter of –0.9 as shown in Table 26.

Table 26 Analysis Timing and Stopping Boundaries for Disease-Free Survival

Type of Analysis	Planned Information Fraction	Stopping Boundary (one-sided p-value)		
		Stage II–IIIA NSCLC PD-L1 subpopulation with SP263 TC ≥1%	Stage II–IIIA NSCLC All Randomized	Stage IB–IIIA NSCLC All Randomized
DFS interim analysis	80%	HR≤0.738 (p≤0.0181)	HR≤0.803 (p≤0.0181)	HR≤0.810 (p≤0.0181)
DFS final analysis	100%	HR≤0.758 (p≤0.0167)	HR≤0.820 (p≤0.0167)	HR≤0.825 (p≤0.0167)

HR = hazard ratio; NSCLC = non–small cell lung cancer; DFS = disease-free survival.

6.8.2 Planned Interim Analyses for Overall Survival

Four interim efficacy analyses of OS are planned. The first OS interim analysis will be conducted at the time of the DFS interim analysis (if DFS is positive as per Figure 2). It is projected that approximately 254 OS events in the ITT population (i.e., approximately 45% of the information) will have been observed at the DFS interim analysis, but the exact timing of this analysis may depend on the actual number and timing of DFS events.

The second interim OS analysis will be conducted at the time of the final DFS analysis. It is projected that approximately 333 OS events in the ITT population (i.e., approximately 59% of the information) will have been observed at the final DFS analysis, but the exact timing of this analysis may depend on the actual number and timing of DFS events.

The third interim OS analysis will be conducted at the date when approximately 73% of the information has been observed in the ITT population (i.e., at the date when approximately 412 OS events occur for the ITT population). This is expected to occur approximately 83 months after the first patient is randomized, but the exact timing of this analysis may depend on the actual number of OS events.

The fourth interim OS analysis will be conducted at the date when approximately 88% of the information has been observed in ITT population (i.e., at the date when approximately 497 OS events occur for the ITT population. This is expected to occur approximately 102 months after the first patient is randomized, but the exact timing of this analysis may depend on the actual number and timing of OS events.

The final OS analysis will be conducted at the date of when approximately 564 OS events have occurred in the ITT population. This is expected to occur approximately 121 months after the first patient is randomized, but the exact timing of this analysis may depend on the actual number and timing of OS events.

The stopping boundaries for the interim and final OS analyses are shown in Table 27. The p-value will be used to claim crossing of the boundaries.

Table 27 Stopping Boundaries for Overall Survival: Stage IB–IIIA NSCLC

Type of Analysis	Analysis Timing (Months from FPI)	Planned Information Fraction (Number of Events)	Stopping Boundary in HR (p-value) Stage IB–IIIA NSCLC
			All Randomized One-sided $\alpha = 0.025$
OS first interim analysis	56	45% (254)	HR ≤ 0.678 (p ≤ 0.0010)
OS second interim analysis	68	59% (333)	HR ≤ 0.780 (p ≤ 0.0119)
OS third interim analysis	83	73% (412)	HR ≤ 0.813 (p ≤ 0.0181)
OS fourth interim analysis	102	88% (497)	HR ≤ 0.809 (p ≤ 0.0093)
OS final analysis	121	100% (564)	HR ≤ 0.811 (p ≤ 0.0063)

FPI = first patient in; HR = hazard ratio; NSCLC = non–small cell lung cancer; OS = overall survival.

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 through 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, with use of 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 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, patient-reported outcomes, 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 study.

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 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

All primary imaging data used for tumor assessments will be collected by the Sponsor. An IRF may conduct a BICR of response endpoints if requested by health authorities.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer. Study data may be used for secondary purposes.

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 (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) *and applicable local, regional, and national laws*.

8.2 INFORMED CONSENT

Informed consent for participation must be obtained before performing any study specific screening tests or evaluations. This study will use the paper consent process and the patient will provide a wet ink signature prior to participation at all sites. Consent must be obtained per the consent process used at the investigational site. Records of Informed Consent for both enrolled patients and those who are not subsequently enrolled will be maintained at the study site. Copies of the study specific patient signed Informed Consent Forms will also be maintained at the site.

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 collection of optional samples and the use of remaining mandatory samples (whole blood and tissue) for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. 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 allow the collection of optional samples and to use any remaining specimens for exploratory research. Patients who decline to participate will not provide a separate signature.

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 with use of 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 the 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 (HIPAA) of 1996. 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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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 U.S. 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 the last patient has completed the study.

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. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

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 by Roche and managed by a contract research organization. Approximately 300 sites globally will participate in the study and approximately 1280 patients will be enrolled. Randomization will occur through an IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified

laboratory tests, and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A central imaging IRF will be used to perform BICR if requested by health authorities. BICR membership and procedures will be detailed in a BICR charter. An IRF may collect, store, and review imaging data.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or and other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. 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 Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical studies 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 study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies 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 studies 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 for Enrollment Phase (Cisplatin-Based Chemotherapy Administration)

Study Procedure	Screening	Day 1 of Cycles 1–4 (±3 days) [a]	Day 8 of Cycles 1–4 (±1 day)	Chemotherapy Discontinuation (<30 days after last treatment) [b]
Informed consent [c]	x [c]			
Biomarker samples [d]	x	x		
Demographic information	x			
Medical history	x			
Concurrent medications	x	x		
Serum pregnancy test (women of childbearing potential ONLY) [e]	x [c]			
Physical examination and ECOG Performance Status	x [c]	x		
Weight, blood pressure	x [c]	x		x
Height	x [c]			
12-lead ECG [f]	x [c]			
Serum chemistries [g]	x [c]	x [h]		x
HIV, HBV, HCV serology [i]	x			
CBC [j]	x [c]	x [h]	x	x
INR, aPTT [k]	x [c]			
Chest X-ray	x [c]			
Tumor assessment [l]	x [c]			x
Archival/screening FFPE tumor tissue specimen or 15 unstained slides [m]	x			
Pathology report [n]	x [m]			

Appendix 1: Schedule of Assessments for Enrollment Phase (Cisplatin-Based Chemotherapy Administration) (Cont.)

Study Procedure	Screening	Day 1 of Cycles 1–4 (±3 days) [a]	Day 8 of Cycles 1–4 (±1 day)	Chemotherapy Discontinuation (<30 days after last treatment) [b]
Toxicity assessment for chemotherapy-related serious adverse events [o]		x		x
Adverse events		x	x	x

CRCL=creatinine clearance; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed paraffin embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; IV=intravenous; MRI=magnetic resonance imaging; PD-L1=programmed death–ligand 1; RCR=Roche Clinical Repository.

[a] Patients will receive their first dose of chemotherapy the day of enrollment, if possible. If this is not possible, the first dose should occur no later than 5 days after enrollment. Screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. 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 4.6.2.

[b] This visit could be used as the screening visit for randomized phase if it is within the screening window. The visit at which the decision is made to discontinue treatment (e.g., after completion of four cycles or when disease recurrence or unacceptable toxicity is determined or confirmed) may be considered as the treatment discontinuation visit.

[c] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments, rather than repeating such tests. Screening evaluations that should be completed no earlier than 14 days prior to enrollment include: CBC with differential and platelet count, serum chemistries, physical examination, height, weight, medical history, concurrent medications, ECG, INR, aPTT, pathology report, serum pregnancy test, and toxicity assessment for chemotherapy-related serious adverse events. Chest X-ray and tumor assessment should be completed no earlier than 28 days prior to enrollment. Screening blood pressure must be done within 28 days of enrollment and must be <150/90 mmHg. Complete and limited physical examinations are defined in Section 4.5.3.

[d] Plasma and serum for biomarkers will be collected only from enrolled patients prior to pre-dose on Day 1 of Cycle 1 cisplatin-based chemotherapy administration. Whole blood will be collected at screening.

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

[f] ECG should be obtained within 14 days before enrollment if clinically indicated or if pre-operative test results showed abnormalities. If pre-operative ECG was normal and there is no indication of a change in cardiac condition a repeat ECG within 14 days is not mandatory. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[g] To include, at a minimum, sodium, potassium, chloride, BUN or urea, creatinine, AST (SGOT) and/or ALT (SGPT), total bilirubin, alkaline phosphatase.

[h] Tests should be obtained within 24 hours prior to day of treatment with results known prior to day of treatment. Laboratory samples that are drawn within 48 hours prior to treatment that are normal will be acceptable. CBC for Day 8 is only required for chemotherapy regimens with Day 8 administration.

[i] See Section 4.5.6 for serology tests. 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 DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for hepatitis B core antibody. HCV RNA must be collected on or before Cycle 1, Day 1 in patients who test positive for anti-HCV.

[j] To include ANC, platelet count, hemoglobin.

[k] More frequent testing is indicated if there is any suspicion of elevated values (i.e., patient is on low dose anticoagulation for a venous access device).

[l] CT scans (with oral and/or IV contrast unless contraindicated) of the chest and abdomen and a CT and/or MRI scan of the brain to rule out CNS metastasis, especially if patient has Stage IIIA disease. Bone scans and CT scans of the neck should also be performed if clinically indicated.

[m] A representative FFPE tumor specimen in paraffin block (preferred) or of 15 (or more) unstained, freshly cut, serial sections (on slides) from an FFPE resected tumor specimen is required for participation in this study. This specimen must be accompanied by the associated pathology report. Retrieval of archival tumor sample can occur outside the 28-day screening period.

[n] Copies of the pathology report must be submitted.

[o] For patients who experience an ongoing study agent-related serious adverse event upon active treatment completion, or at discontinuation from the study, should be contacted by the investigator or his/her designee until the event is resolved or determined to be irreversible

Appendix 2
Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care)

Study Procedure	Both Arms	Arm A (Atezolizumab)		Arm B (Best Supportive Care)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
	Days -28 to -1	Day 1 (±3 days)[b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥3)	Day 1 (±3 Days)	≤30 Days after 1 Year of Observation	Follow-Up
Review of eligibility criteria	x						
Pregnancy test (women of childbearing potential ONLY) [c]	x [c]	x [d]	x [d]				
ECOG Performance Status	x	x	x	x			
Complete physical examination [e]	x		x			x	
Limited physical examination [e]		x		x			
Weight	x	x	x	x		x	
Vital signs [f]	x	x	x	x		x	
12-lead ECG	x	x [g]	x [g]				
Hematology [h]	x	x [h]	x	x [h]		x	
Serum chemistry [i]	x	x [i]	x	x [i]		x	
Coagulation panel (aPTT, INR)	x		x				
Urinalysis [j]	x	x [k]		x [k]			

Appendix 2: Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care) (Cont.)

Study Procedure	Both Arms	Arm A (Atezolizumab)		Arm B (Best Supportive Care)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
	Days –28 to –1	Day 1 (±3 days)[b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥3)	Day 1 (±3 Days)	≤30 Days after 1 Year of Observation	Follow-Up
TSH, free T3, free T4	x	x (every four cycles)	x				
Serum sample for ATA assessment (atezolizumab patients only) [l]		x	x				
Serum sample for PK sampling (atezolizumab patients only) [l]		x	x				
Blood samples for biomarkers [m]		x [m]	x	x [m]		x	x
Study drug infusion [n]		x					
Fresh biopsy specimen (mandatory for both arms) [o]	At the time of radiographic confirmation of disease recurrence or new primary NSCLC [o]						

Appendix 2: Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care) (Cont.)

Study Procedure	Both Arms	Arm A (Atezolizumab)		Arm B (Best Supportive Care)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
	Days –28 to –1	Day 1 (±3 days)[b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥3)	Day 1 (±3 Days)	≤30 Days after 1 Year of Observation	Follow-Up
Tumor assessments [p]	x	All patients in the randomized phase will undergo scheduled tumor assessments at baseline and every 4 months starting at Cycle 1, Day 1 in the first year and every 6 months in the second year by CT following randomization. Patients who have not experienced recurrence of disease will undergo tumor assessments every 6 months during Years 3–5 by CT *or* X-ray post-randomization until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. *After the final DFS analysis is completed, tumor assessments will no longer be required as a part of the study and patients are to be followed according to local standard of care. If recurrence or a new primary NSCLC or new primary non-NSCLC malignancy is diagnosed as a part of local standard of care, the assessment confirming presence of disease is to be recorded in the EDC system.*						
Concomitant medications [q]	x	x	x	x	x	x	
Adverse events [r]	x	x	x	x	x	x	
Medical contact [s]					x		
Survival and anti-cancer therapy follow-up [t]							x

ATA = anti-therapeutic antibody; BSC = best supportive care; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; *EDC = electronic data capture;* MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; RCR = Roche Clinical Repository; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Patients will be asked to return to the clinic not more than 30 days after the decision to discontinue treatment for a treatment or observation discontinuation visit.

[b] Cycle 1, Day 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. 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 4.6.2.

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

[d] If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

[e] Complete and limited physical examinations are defined in Section 4.5.3.

[f] Vital signs include heart rate, respiratory rate, blood pressures, and temperature and will be performed as standard of care for patients randomized to the BSC arm. For patients randomized to the atezolizumab treatment arm, vital signs should be recorded as described in Table 10.

[g] ECG recordings will be obtained when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[h] Blood samples collected to monitor safety will be collected in patients randomized to both arms. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Refer to Section 4.5.6 for a list of laboratory test results obtained within 14 days prior to the first dose of atezolizumab treatment.

[i] Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the site), calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Refer to Section 4.5.6 for a list of laboratory results obtained within 14 days prior to first dose of atezolizumab treatment.

[j] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[k] Perform if clinically indicated.

[l] For patients assigned to atezolizumab treatment arm only. See Appendix 3 for details of the ATA and PK collection schedule. Blood samples should be processed to obtain serum. A post-treatment ATA and PK sample should be collected 120 days (± 30 days) after the last dose of atezolizumab received during the treatment period unless the patient withdraws consent or the study closes.

[m] See Appendix 3 for details of the biomarker sampling schedule.

[n] Patients randomized to atezolizumab arm will receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 5 days after randomization. The initial dose of atezolizumab treatment will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Atezolizumab treatment may be continued for a maximum of 16 cycles in the absence of meeting discontinuation criteria specified in Section 4.3.4.2.

[o] A mandatory biopsy is required, if clinically feasible, within 40 days of disease recurrence or prior to the start of the next anti-cancer therapy, whichever is sooner (see Section 4.5.8.1). *After the DFS final analysis is complete, tumor samples will no longer be collected.*

[p] Results must be reviewed by the investigator before dosing at the next cycle (in atezolizumab treatment arm only). Tumor assessments should continue *for at least 5 years* regardless of whether patients start new anti-cancer therapy in the absence of disease recurrence unless the patient withdraws consent for tumor assessments. If there is a recurrence, it is also strongly encouraged that patients be fully restaged, including a CT scan of the chest and abdomen, imaging (preferably MRI, but CT is acceptable) of the brain, and a radionuclide bone scan or positron emission tomography (PET) scan. Additional scans may be necessary as per investigator judgment if recurrence of primary lung cancer is suspected on treatment.

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

[r] Once randomized into the study, during both the enrollment phase (cisplatin-based chemotherapy) and randomization phase (atezolizumab or BSC), all serious adverse events and adverse events of special interest will be recorded during the study and for 90 days after the last dose of study treatment (last study assessment for patients in Arm B) or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study and for 30 days after the last dose of study treatment (last study assessment for patients randomized to Arm B) or until the initiation of another anti-cancer therapy, whichever occurs first.

[s] This medical contact can be either via telephone call or formal clinic visit. If the contact is via a formal clinic visit, additional assessments may be done as clinically indicated per local standard of care and at the discretion of the investigator.

[t] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every *6* months or more often until death, loss to follow-up, or study termination by Roche. All patients (irrespective of which arm they are randomized to) will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the atezolizumab study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. This also applies to patients randomized to BSC arm. Patients assigned to either study arm who complete either the initial treatment or the initial observation period (16 cycles) will discontinue atezolizumab treatment or BSC and will continue follow-up tumor assessments (per the tumor assessment schedule above–see footnote p). No patients are allowed to cross over.

Appendix 3
Anti-Therapeutic Antibody, Biomarker, and Pharmacokinetic Sampling Schedule

Enrollment Phase Sampling		
Study Visit	Time	Sample (All Enrolled Patients)
Screening	NA	Biomarker [a]
Cycle 1, Day 1	Pre-dose with cisplatin-based chemotherapy	Biomarker [b]

Randomized Phase (Post-Randomization) Sampling			
		Sample	
Study Visit	Time	Patients Randomized to BSC Arm	Patients Randomized to Atezolizumab Arm
	Pre-dose	Biomarker [b]	ATA Atezolizumab pharmacokinetics Biomarker [b]
Cycle 1, Day 1	30 min (± 10 min) after end of atezolizumab infusion		Atezolizumab pharmacokinetics
Cycles 2, 3, 4, and 5, Day 1	Pre-dose	Biomarker (Cycle 3, Day 1, and Cycle 5, Day 1) [b]	ATA (Cycles 2, 3, and 4) Atezolizumab pharmacokinetics (Cycles 2, 3, and 4) Biomarker (Cycles 2, 3, and 5) [b]
Cycles 7 and 15, Day 1	Pre-dose	Biomarker [b]	
Cycles 8 and 16, Day 1	Pre-dose		ATA Atezolizumab pharmacokinetics Biomarker [b]
At the time of first radiographic confirmation of disease recurrence or confirmation of a new primary NSCLC	At visit		Biomarker [b]

Appendix 3: Anti-Therapeutic Antibody, Biomarker, and Pharmacokinetic Sampling Schedule (Cont.)

Randomized Phase (Post-Randomization) Sampling			
		Sample	
Study Visit	Time	Patients Randomized to BSC Arm	Patients Randomized to Atezolizumab Arm
At time of fresh biopsy (e.g., at the time of first radiographic confirmation of disease recurrence or confirmation of a new primary NSCLC)		Biomarker [b]	Biomarker [b]
Treatment discontinuation visit	At visit	Biomarker [b]	ATA Atezolizumab pharmacokinetics Biomarker [b]
Follow-up (after completion of 16 cycles of atezolizumab or BSC)	At tumor assessment visit	Biomarker [b]	Biomarker [b]
120 days (±30 days) after last dose of atezolizumab in treatment stage	At visit		ATA Atezolizumab pharmacokinetics Biomarker [b]
Any time point during the study (RCR consent required)		Optional RCR whole blood (DNA extraction) [c]	Optional RCR whole blood (DNA extraction) [c]

ATA = anti–therapeutic antibody; NA = not applicable; NSCLC = non–small cell lung cancer; RCR = Roche Clinical Repository.

[a] Whole blood for biomarkers.

[b] Plasma and serum. Note: Except for Day 1 of Cycle 1 in the enrollment phase and Day 1 of Cycle 1 in the randomization phase, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Study assessments may be delayed or moved forward 3 days to accommodate holidays, vacations, and unforeseen delays. For biomarker samples, if the visit schedule can accommodate the ±3 day collection window, one set of samples can be noted as satisfying two visits (e.g., treatment discontinuation and the time of fresh biopsy collection). *After the DFS final analysis is complete, samples will no longer be collected.*

[c] The optional RCR whole blood sample (for DNA extraction) requires an additional informed consent and the sample can be collected at any time during the course of the study.

Appendix 4
Anti–PD-L1 (SP142) 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 GO29527, 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 36μg 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 5
Anti–PD-L1 (SP263) Immunohistochemistry

OVERVIEW

The Ventana PD-L1 (SP263) CDx Assay will be used to determine PD-L1 immunohistochemical (IHC) status. The assay uses an anti–PD-L1 rabbit monoclonal primary antibody (Ventana PD-L1 (SP263) antibody) to recognize the programmed death-ligand 1 (PD-L1) also known as B7 homolog 1 (B7-H1) or CD274. The Ventana PD-L1 (SP263) CDx Assay is currently being developed by Ventana Medical Systems as a companion diagnostic to atezolizumab. For Study GO29527, the Ventana PD-L1 (SP263) Assay will be used for investigational purposes only.

Ventana PD-L1 (SP263) CDx Assay is intended for the qualitative immunohistochemical assessment of the programmed death ligand 1 (PD-L1) protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung carcinoma (NSCLC) tissue stained with a BenchMark ULTRA IHC/ISH automated staining instrument. It is indicated as an aid in identifying patients eligible for treatment with PD-L1 or PD-1 targeted therapy.

This assay is for investigational use only. The performance characteristics of this product have not been established.

DEVICE DESCRIPTION

The VENTANA PD-L1 (SP263) 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 on Ventana Medical Systems automated BenchMark ULTRA platforms. One 5-mL dispenser of anti-PD-L1 (SP263) rabbit monoclonal primary antibody contains approximately 8.05 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

NSCLC neoplastic cells labeled with the Ventana PD-L1 (SP263) Assay are evaluated for percent positivity of the tumor cells with membrane staining at any intensity of the diaminobenzidine (DAB) signal. The immunohistochemical staining in NSCLC is membranous and/or cytoplasmic, and may be expressed homogeneously or heterogeneously throughout the neoplasm.

Appendix 6
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anticancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dysautonomia	Opsoclonus myoclonus syndrome
Addison disease	Epidermolysis bullosa acquisita	Ord thyroiditis
Ankylosing spondylitis	Gestational pemphigoid	Pemphigus
Antiphospholipid antibody syndrome	Giant cell arteritis	Pernicious anemia
Aplastic anemia	Goodpasture syndrome	Polyarteritis nodosa
Autoimmune hemolytic anemia	*Granulomatosis with polyangiitis*	Polyarthritis
Autoimmune hepatitis	Graves disease	Polyglandular autoimmune syndrome
Autoimmune hypoparathyroidism	Guillain-Barré syndrome	Primary biliary cholangitis
Autoimmune hypophysitis	Hashimoto disease	Psoriasis
Autoimmune myelitis	IgA nephropathy	Reiter syndrome
Autoimmune myocarditis	Inflammatory bowel disease	Rheumatoid arthritis
Autoimmune oophoritis	Interstitial cystitis	Sarcoidosis
Autoimmune orchitis	Kawasaki disease	Scleroderma
Autoimmune thrombocytopenic purpura	Lambert-Eaton myasthenia syndrome	Sjögren syndrome
Behçet disease	Lupus erythematosus	Stiff-Person syndrome
Bullous pemphigoid	Lyme disease - chronic	Takayasu arteritis
Chronic fatigue syndrome	Meniere syndrome	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Mooren ulcer	Vitiligo
Chung-Strauss syndrome	Morphea	Vogt-Koyanagi-Harada disease
Crohn disease	Multiple sclerosis	
Dermatomyositis	Myasthenia gravis	
Diabetes mellitus type 1	Neuromyotonia	
	Optic neuritis	

Appendix 7
Anaphylaxis Precautions

Equipment Needed

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

Procedures

1. In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:
2. Stop the study drug infusion.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.

Appendix 8
Cockcroft and Gault Formula

Creatinine Clearance

The standard Cockcroft and Gault (1976) formula or the measured glomerular filtration rate, using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA), must be used to calculate creatinine clearance (CRCL) for screening and/or dosing. The same method used at baseline should be used throughout the study.

$$\text{CRCL (Female)} = \frac{(140 - \text{age in years}) \times \text{body weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{CRCL (Male)} = \frac{(140 - \text{age in years}) \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Appendix 9
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Although toxicities observed with atezolizumab have been mild and self-limiting, they 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.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. Management guidelines for patients who experience adverse events associated with atezolizumab are provided in Table A9-1. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A9-1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab

GENERAL GUIDANCE

Early Recognition and Close Monitoring:

Patients and family caregivers should receive timely and up-to-date information prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related. Irrespective of severity grade, patients presenting with adverse events should be monitored closely and referred promptly to specialists for evaluation. Initiate treatment as per institutional guidelines and supportive care measures as deemed necessary.

Monitoring and evaluation of high-risk cardiac patients:

In high-risk cardiac patients (including those with abnormal baseline cardiac troponin levels, when available), TTE monitoring should be considered, as clinically indicated, and based on local clinical practice. All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, a TTE for evaluation of left ventricular ejection fraction and global longitudinal strain, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Adverse Event Management Guidance–Use of Corticosteroids and/or Immunosuppressants:

For Grade 1 events, atezolizumab therapy should be continued with close monitoring of the affected organ function (including but not limited to TSH, liver function tests, blood glucose, creatinine, urine protein, amylase, and lipase), with exceptions specified below. For Grade ≥ 2 events, initiate treatment with high-dose corticosteroids (1–2 mg/kg/day oral prednisone/IV methylprednisolone or equivalent) as clinically indicated (see the table below). If symptoms do not improve within 48 hours of high-dose corticosteroid use, other immunosuppressants may be considered. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. For toxicities not described below, refer to the current standard clinical practice/management guidelines of immune checkpoint inhibitor-related toxicities including but not limited to those provided by a professional society (e.g., NCCN, ESMO, SITC, and ASCO).

Action to be Taken with Atezolizumab:

For Grade 1 events, atezolizumab therapy should be continued. Consider withholding atezolizumab for most Grade 2 toxicities unless specified below. Withhold for all Grade 3 toxicities. Permanently discontinue for Grade 4 toxicities, with the exception of endocrinopathies that are controlled by hormone-replacement therapy. Atezolizumab can be withheld for up to 12 weeks after event onset. If atezolizumab is withheld for > 12 weeks, the patient should be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment.

For events, symptoms, and/or laboratory values that resolve to Grade 1 or better, resume atezolizumab. For events that do not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event, with exceptions listed below. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.

Appendix 9: Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management [guidance in addition to the general recommendations provided above]
Pulmonary event	Grade 1	• For pneumonitis, consider withholding *and resuming on radiographic evidence of improvement*.	• Re-evaluate on serial imaging.
	Grade 2	• Withhold.	• Consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with high-dose oral corticosteroids, followed by taper.
	Grade 2 recurrent/not improving after 48–72 hours of corticosteroids **or** Grades 3–4	• Permanently discontinue. • In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.	• Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with high-dose IV corticosteroids, followed by taper when event resolves to Grade 1 or better. • If event does not improve, consider adding an immunosuppressive agent.
Hepatic event	Guidelines for patients **<u>without</u>** hepatocellular carcinoma		
	Grade 2	**Events of > 5 days' duration:** • Withhold.	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Initiate treatment with high-dose oral corticosteroids.
	Grades 3–4	• Permanently discontinue.	• Consider liver biopsy to establish etiology of hepatic injury. • Initiate treatment with high-dose oral corticosteroids, followed by taper when event resolves to Grade 1 or better. • If event does not improve, consider adding an immunosuppressive agent.

	Guidelines for patients **with** hepatocellular carcinoma		
	AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN **or** AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to > 5 × ULN to ≤ 10 × ULN **or** AST/ALT is > 3 × ULN to ≤ 5 × ULN at baseline and increases to > 8 × ULN to ≤ 10 × ULN	• Withhold. • If event resolves to baseline or to Grade 1 or better, resume. • If event does not resolve to baseline or to Grade 1 or better while withholding, permanently discontinue and contact the Medical Monitor.	• Monitor LFTs more frequently until return to baseline values. • For events of > 5 days' duration, consider initiating treatment with high-dose oral corticosteroids.
	AST or ALT increases to > 10 × ULN or total bilirubin increases to > 3 × ULN	• Permanently discontinue.	• Consider liver biopsy to establish etiology of hepatic injury. • Initiate treatment with high-dose oral corticosteroids, followed by taper when event resolves to baseline. • If event does not improve, consider adding an immunosuppressive agent.

Diarrhea or colitis	Grade 2	• Withhold.	• Initiate symptomatic treatment. • Endoscopy is recommended. This also applies to Grade 1 events if symptoms persist for > 7 days. • If strong clinical suspicion for immune-mediated colitis, initiate empiric IV *corticosteroids* while waiting for definitive diagnosis. • For recurrent events or events that persist > 5 days, initiate treatment with high-dose oral corticosteroids. • If event does not improve, consider adding an immunosuppressive agent.
	Grade 3	• Withhold.	• Order confirmatory biopsy. • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper. • If event does not improve, consider adding an immunosuppressive agent.
	Grade 4	• Permanently discontinue.	
Hypothyroidism	Grade 2	• Consider withholding. • Resume when symptoms are controlled and thyroid function is improving.	• Initiate treatment with thyroid replacement hormone.
	Grades 3–4	• Withhold. • Resume when symptoms are controlled and thyroid function is improving. • Permanently discontinue and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.	• Initiate treatment with thyroid replacement hormone. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status).

Hyperthyroidism	Grade 1 with TSH < 0.1 mU/L **or** Grade 2	• Consider withholding. • Resume when symptoms are controlled and thyroid function is improving.	• Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed.
	Grades 3–4	• Withhold. • Resume when symptoms are controlled and thyroid function is improving. • Permanently discontinue and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism.	
Symptomatic adrenal insufficiency	Grades 2–4	• Withhold. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding, permanently discontinue and contact the Medical Monitor.	• Perform appropriate imaging. • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.
Hyperglycemia	Grades 3–4 or patient has Type 1 diabetes	• Withhold. • Resume when symptoms resolve and glucose levels are stable.	• Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis.

Hypophysitis (pan-hypopituitarism)	Grades 2–3	• Withhold.	• Perform brain MRI (pituitary protocol). • Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper. • Initiate hormone replacement if clinically indicated.
	Recurrent hypophysitis or Grade 4	• Permanently discontinue.	
Ocular event	Grade 1	• Continue.	• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
	Persistent Grade 1 despite treatment **or** Grade 2	• Withhold.	
	Grades 3–4	• Permanently discontinue.	• Initiate treatment with high-dose oral corticosteroids, followed by taper when event resolves to Grade 1 or better.
Myocarditis or pericardial disorders	Grades 2–4	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	• Consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with higher-dose IV corticosteroids equivalent to *1 g/day* IV methylprednisolone *for 3–5 days* and convert to high-dose oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better. • If event does not improve within *24* hours after initiating corticosteroids, consider adding an immunosuppressive agent.

Amylase and/or lipase elevation	Grade 2 with amylase and/or lipase > 1.5–2.0 × ULN	• Continue.	• For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone, followed by taper.
	Grade 2 asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN **or** Grades 3–4	• Withhold. • For recurrent events, permanently discontinue.	• If no improvement, consider treatment with high-dose oral corticosteroids, followed by taper.
Pancreatitis	Grades 2–3	• Withhold. • For recurrent events, permanently discontinue.	• Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper.
	Grade 4	• Permanently discontinue.	• Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better. • If event does not improve, consider adding an immunosuppressive agent.
Dermatologic event	Grade 1	• Continue.	• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2		• Consider biopsy, if indicated. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if the event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.

	Grade 3	• Withhold.	• If indicated, order a biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing to high-dose oral corticosteroids if event does not improve within 48–72 hours, followed by taper.
	Grade 4	• Permanently discontinue.	
Stevens-Johnson syndrome or toxic epidermal necrolysis	Any grade suspected event	• Withhold.	• Confirm diagnosis by referring the patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment/management guidelines of dermatologic events above.
	Any grade confirmed event	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	
Neuropathy, including facial paresis	Grade 2	• Withhold. **For facial paresis:** • If event resolves fully, resume. • If event does not resolve fully while withholding, permanently discontinue.	• Investigate etiology. **For facial paresis:** • *Initial observation OR initiate high-dose oral corticosteroids (if progressing from mild). Initiate treatment with gabapentin, pregabalin, or duloxetine, for pain.*
	Grades 3–4	• Permanently discontinue.	• *Proceed as per Guillain-Barré syndrome management.*
Myasthenia gravis and Guillain-Barré syndrome	Any grade	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	• Consider initiation of high-dose oral or IV corticosteroids, followed by taper. • *Consider IVIG or plasmapheresis in patients with rapid progression with development of bulbar and/or respiratory symptoms.* • *In life-threatening cases, consider higher-dose IV methylprednisolone 1 g/day for 3–5 days and other immunosuppressive agents.*

Myelitis	Grade 1	• Continue unless symptoms worsen or do not improve.	• Investigate etiology.
	Grade 2	• Permanently discontinue.	• Investigate etiology and rule out infection. • Initiate treatment with high-dose oral corticosteroids, followed by taper.
	Grades 3–4	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	• *Initiate non-opioid treatment (e.g., pregabalin, gabapentin, duloxetine) for pain.* • *Hospitalize patient.* • *Initiate treatment with IV corticosteroids equivalent to 1 g/day methylprednisolone.* • *If event does not improve or there is worsening of symptoms within 3 days, consider IVIG or plasmapheresis and manage as per institutional guidelines.*
Meningoencephalitis	Any grade	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	• Initiate treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better. • If event does not improve, consider adding an immunosuppressive agent.
Renal event	Grade 2	• Withhold.	• Initiate treatment with high-dose oral corticosteroids, followed by taper.
	Grades 3−4	• Permanently discontinue.	• Consider renal biopsy. • Initiate treatment with high-dose oral corticosteroids, followed by taper when the event resolves to Grade 1 or better. • If event does not improve, consider adding an immunosuppressive agent.

Myositis	Patients with possible myositis should be monitored for signs of myocarditis and myasthenia gravis.		
	Grade 2	• Withhold.	• Consider treatment with high-dose IV corticosteroids and convert to oral corticosteroids upon improvement, followed by taper. • If the event does not improve, consider adding an immunosuppressive agent.
	Grade 3	• Withhold.	• Initiate treatment with high-dose IV corticosteroids, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to oral corticosteroids upon improvement, followed by taper when event resolves to Grade 1 or better. • If event does not improve within 24–48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • *Consider IVIG or plasmapheresis.*
	Recurrent Grade 3 **or** Grade 4	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	
Suspected HLH [a]	Not applicable	• Permanently discontinue. • Atezolizumab should not be resumed after permanent discontinuation.	• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy, followed by taper when the event resolves to Grade 1 or better. • If the event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines. [b]

IRR and CRS	Grade 1 [c] fever [d] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose.	• Administer symptomatic treatment, [e] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS.
	Grade 2 [c] fever [d] with hypotension not requiring vasopressors **and/or** hypoxia requiring low-flow oxygen [f] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose.	• Administer symptomatic treatment. [e] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs and/or CRS.

			• If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.
	Grade 3 [c] fever [d] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** hypoxia requiring high-flow oxygen [f] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue. [g]	• Administer symptomatic treatment. [e] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
	Grade 4 [c] fever [d] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** hypoxia requiring oxygen by positive pressure	• Permanently discontinue. [g]	• Administer symptomatic treatment. [e] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.

	(e.g., CPAP, BiPAP, intubation and mechanical ventilation)		• Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [h] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

ASCO=American Society of Clinical Oncology; ASTCT=American Society for Transplantation and Cellular Therapy; BAL=bronchoscopic alveolar lavage; BiPAP=bi-level positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; ECMO=extracorporeal membrane oxygenation; eCRF=electronic Case Report Form; ESMO=European Society for Medical Oncology; HLH=hemophagocytic lymphohistiocytosis; ICU=intensive care unit; IRR=infusion-related reaction; IVIG=intravenous immunoglobulin; LFT=liver function test; MAS=macrophage activation syndrome; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network; NCI=National Cancer Institute; SITC=Society for Immunotherapy of Cancer; *TTE =transthoracic echocardiogram;* VAD=ventricular assist device; ULN=upper limit of normal.

[a] Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014).

[b] Refer to La Rosée (2015); Schram and Berliner (2015); La Rosée et al. (2019).

[c] Grading system for these management guidelines is based on ASTCT Consensus Grading Scale for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[d] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[e] Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[f] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[g] For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

[h] Refer to Riegler et al. (2019).

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Appendix 10
Investigational, Non-Investigational, and Auxiliary Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A10-1 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No [a]
Vinorelbine	NIMP *(background therapy)*	Authorized	*No* [b]
Docetaxel	NIMP *(background therapy)*	Authorized	*No* [b]
Gemcitabine	NIMP *(background therapy)*	Authorized	*No* [b]
Pemetrexed	NIMP *(background therapy)*	Authorized	*No* [b]
Cisplatin	*NIMP (background therapy)*	*Authorized*	*No* [b]

IMP = investigational medicinal product; NIMP = non-investigational medicinal product; U.K. = United Kingdom.

[a] Atezolizumab holds a Marketing Authorization in the U.K. but is not fully approved for the way in which it is used within this study.

[b] *Vinorelbine, docetaxel, gemcitabine, pemetrexed and cisplatin are not approved for the adjuvant treatment indication but are recommended in the clinical treatment guidelines.*

Table A10-2 Investigational and Authorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No [a]
Vinorelbine	AxMP *(background therapy)*	Authorized	*No* [b]
Docetaxel	AxMP *(background therapy)*	Authorized	*No* [b]
Gemcitabine	AxMP *(background therapy)*	Authorized	*No* [b]
Pemetrexed	AxMP *(background therapy)*	Authorized	*No* [b]
Cisplatin	*AxMP (background therapy)*	*Authorized*	*No* [b]

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

[a] Atezolizumab holds a Marketing Authorization in the EEA but is not fully approved for the way in which it is used within this study.

[b] *Vinorelbine, docetaxel, gemcitabine, pemetrexed and cisplatin are not approved for adjuvant treatment indication but are recommended in the clinical treatment guidelines.*

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