Official Title: A Phase III, Double-Blinded, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Neoadjuvant Treatment with Atezolizumab or Placebo in Combination with Platinum-Based Chemotherapy in Patients with Resectable Stage II, IIIa, Or Select IIIb Non-Small Cell Lung Cancer

NCT Number: NCT03456063

Document Date: Protocol Amendment Version 11: 05-Apr-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, DOUBLE-BLINDED, MULTICENTER, RANDOMIZED STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT TREATMENT WITH ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO40241
STUDY NAME:	IMpower030
VERSION NUMBER:	11
TEST COMPOUND:	Atezolizumab (RO5541267)
STUDY PHASE:	III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 117296 EU CT Number: 2023-504209-35-00 NCT Number: NCT03456063 EudraCT Number: 2017-002857-12
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol		Associated Country and/or Region-Specific Protocols		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
11	See electronic date stamp on the final page of this document	—	—	—
10	27 February 2023	—	—	—
9	28 February 2022	—	—	—
8	12 August 2021	—	—	—
7	24 February 2021	—	—	—
6	12 June 2020	—	—	—
5	12 December 2019	—	—	—
4	13 December 2018	VHP	4	8 March 2019
3	14 June 2018	—	—	—
1	3 November 2017	VHP	2	12 February 2018

PROTOCOL AMENDMENT, VERSION 11*:*
RATIONALE

Protocol GO40241 has been amended primarily to update the Statistical Analysis Plan as well as the risks and management guidelines for atezolizumab, to align with the latest Atezolizumab Investigator's Brochure, Version 20. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- Due to an unexpected slowing down of the event-free survival (EFS) event rate, the pre-planned second interim Independent Review Facility (IRF)-EFS analysis is converted to be the final IRF-EFS analysis. With this change, the newly proposed final analysis timing will occur with longer follow-up than the original final analysis.
  - The end of the study definition has been clarified as the date when the last patient, last visit (LPLV) occurs, regardless of the timing of the final analysis (Section 3.2).
  - After the final analysis is conducted, the Sponsor may continue to conduct tumor assessments and survival follow-up if requested by the health authorities (Section 4.5.5 and Appendix 1).
  - With this conversion, the final analysis timing and event numbers have been updated (Sections 6.1, 6.4 and 6.9).
- Language to describe investigational medicinal products, non-investigational medicinal products, and auxiliary medicinal products has been revised to align with CTR requirements (Section 4.3, and Appendix 12).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator’s Brochure, Version 20 (Appendix 9 and 10).
- 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 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, DOUBLE-BLINDED, MULTICENTER, RANDOMIZED STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT TREATMENT WITH ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO40241
STUDY NAME:	IMpower030
VERSION NUMBER:	*11*
TEST COMPOUND:	Atezolizumab (RO5541267)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLINDED, MULTICENTER, RANDOMIZED STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT TREATMENT WITH ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON–SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 117296 EU CT Number: 2023-504209-35-00 NCT Number: NCT03456063 EudraCT Number: 2017-002857-12

STUDY RATIONALE

This study will evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy, when compared with placebo with platinum-based chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" in the neoadjuvant treatment phase refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab or placebo with platinum-based chemotherapy).

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• IRF assessed EFS, defined as the time from randomization to the first documented disease progression per RECIST v1.1 that precludes surgery, local or distant disease recurrence (including occurrence of new primary NSCLC), or death from any cause, whichever occurs first

EFS = event-free survival; IRF = Independent Review Facility; NSCLC = non–small-cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

OBJECTIVES AND ENDPOINTS (CONT.)

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy	• IRF assessed pCR, defined as the absence of any viable primary tumor cells at the time of surgical resection in the primary tumor and all sampled lymph nodes as assessed by central pathology laboratory • IRF assessed MPR, defined as ≤10% residual viable tumor cells at the time of surgical resection in the primary tumor as assessed by central pathology laboratory • MPR and pCR at the time of surgical resection, as assessed by the investigator site pathology laboratory • Objective response, defined as a complete response or partial response, as determined by the investigator according to RECIST v1.1 (confirmation not required)
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• OS, defined as the time from randomization to death from any cause during the course of the study • Investigator assessed EFS • DFS, defined as the time from the first date of no disease to local or distant recurrence (including occurrence of new primary NSCLC) or death due to any cause, whichever occurs first, as determined by the investigator during the adjuvant treatment and observation follow-up • 2-year and 3-year OS, IRF assessed EFS and investigator assessed EFS during the study
• To evaluate PROs of HRQoL associated with atezolizumab in combination with platinum-based chemotherapy as neoadjuvant treatment followed by adjuvant atezolizumab	• Change from baseline in HRQoL scores as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30 at each assessment timepoint during the study through the completion of adjuvant treatment and observation follow-up assessments

DFS = disease-free survival; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; IRF = Independent Review Facility; MPR = major pathological response; NSCLC = non–small-cell lung cancer; OS = overall survival; pCR = pathological complete response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumors.

OBJECTIVES AND ENDPOINTS (CONT.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• Occurrence and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to NCI CTCAE v5.0 • Incidence and length of surgical delays, incidence of operative and post-operative complications, and/or reasons for surgical cancellations
Pharmacokinetic Objectives	**Corresponding Endpoint**
• To characterize the PK profile of atezolizumab when given in combination with platinum-based chemotherapy • To characterize the PK profile of atezolizumab alone	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Incidence of ADAs against atezolizumab during the study

ADA = anti-drug antibody; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic.

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

OVERALL DESIGN AND STUDY POPULATION

This is a global Phase III multicenter, double-blinded, randomized study designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy versus placebo plus platinum-based chemotherapy followed by adjuvant/post-operative atezolizumab or best supportive care (BSC) in patients with histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) non–small-cell lung cancer (NSCLC).

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

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC
Interventional Model:	Parallel group	**Population Age:**	Age ≥ 18 years at time of signing Informed Consent Form
Test Compound:	Atezolizumab (RO5541267)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 450

NSCLC = non–small-cell lung cancer.

STUDY TREATMENT

INVESTIGATIONAL MEDICINAL PRODUCTS

Test Product (Investigational Drug) (Patients in Arm A only)

- Atezolizumab (1200 mg IV) on Day 1 of each 21–day cycle (every 3 weeks) for 4 cycles during the neoadjuvant treatment phase
- Atezolizumab (1200 mg IV) every 3 weeks for 16 cycles during the post-operative adjuvant phase
- Nab-paclitaxel (100 mg/m^2 IV) on Days 1, 8, and 15 of each 21day cycle for 4 cycles during the neoadjuvant treatment phase

Comparator (Patients in Arm B only)

- Placebo (IV) on Day 1 of each 21–day cycle for 4 cycles during the neoadjuvant treatment phase
- Nab-paclitaxel (100 mg/m^2 IV) on Days 1, 8, and 15 of each 21–day cycle for 4 cycles during the neoadjuvant treatment phase

AUTHORIZED AUXILLIARY MEDICINAL PRODUCTS / **NON-INVESTIGATIONAL MEDICINAL PRODUCTS**

- Carboplatin (IV, initial target AUC of 6 mg/mL/min) on Day 1 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase
- Cisplatin (75 mg/m^2 IV) on Day 1 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase
- Pemetrexed (500 mg/m^2 IV) on Day 1 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase
- Gemcitabine (1250 mg/m^2 IV) on Days 1 and 8 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase

DURATION OF PARTICIPATION

Participation will continue until withdrawal or death due to any cause.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also called anti-therapeutic antibody
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
BSC	best supportive care
COPD	chronic obstructive pulmonary disease
COVID−19	coronavirus disease 2019
CRCL	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DL_{CO}	diffusion capacity of the lung for carbon monoxide
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-level version
FDA	Food and Drug Administration
[redacted]	
GGO	ground-glass opacity
GHS	global health status
[redacted]	
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee

Abbreviation	Definition
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRF	Independent Review Facility
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
MAS	macrophage activation syndrome
MPR	major pathological response
NCCN	National Cancer Comprehensive Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PET	positron emission tomography
[redacted]	
PK	pharmacokinetic
PORT	post-operative radiotherapy
[redacted]	
PRO	patient-reported outcome
QLQ-C30	quality of life questionnaire for cancer
QLQ-LC13	quality-of-life questionnaire for lung cancer
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy for Cancer
TC	tumor cell
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
[redacted]	

Abbreviation	Definition
VAS	Visual Analogue Scale
[redacted]	
WES	whole exome sequencing
WGS	whole genome sequencing
WT	wild type (excluding known EGFR/ALK mutations)

1. BACKGROUND

1.1 BACKGROUND ON NON–SMALL-CELL LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide. It is the most common cancer in both men and women and accounts for 12%–14% of all new cancer cases in the United States. In 2017, there were an estimated 222,500 new cases of lung cancer, resulting in 155,870 deaths (Siegel et al. 2017). In comparison, in Europe in 2012, there were approximately 313,000 new cases of lung cancer and 268,000 lung cancer deaths (Ferlay et al. 2013).

Non–small-cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Howlader et al. 2015). Non–small-cell lung cancer can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status, and a history of unintentional weight loss. More than half of patients with NSCLC are diagnosed with metastatic disease, 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). Radiation therapy 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 (Pezzi et al. 2017). However, the role of post-operative radiotherapy (PORT) for patients with N2 nodal involvement after neoadjuvant chemotherapy and surgery has been the subject of debate for many years. The role of PORT in the treatment of N2 tumors was evaluated by the randomized Phase III LungART trial (NCT00410683).

1.2 TREATMENT OPTIONS FOR RESECTABLE STAGE II, IIIA, OR SELECT IIIB (T3N2) NSCLC

The development of platinum-based chemotherapy has led to its use as adjuvant or neoadjuvant therapy together with surgery to improve survival outcome when compared with surgery alone. Adjuvant platinum-based chemotherapy is now the standard of care for fully resected (Stage II, IIIA, or select IIIB [T3N2]) NSCLC, and neoadjuvant platinum-based chemotherapy is a widely accepted alternative therapy as well.

Chemotherapy regimens used in the adjuvant and neoadjuvant settings involve platinum-based doublets, which are similar to those used in the metastatic settings. Agents that have been partnered with either cisplatin or carboplatin for the treatment of NSCLC include taxanes (paclitaxel, nab-paclitaxel, docetaxel), vinorelbine, gemcitabine, and pemetrexed. Combinations of these drugs with platinum analogues are superior to single agent therapy and have been shown to prolong survival, despite notably increased toxicity with platinum analogues (Azzoli et al. 2009).

1.2.1 Adjuvant Treatment for the Surgically Resected Stage II, IIIA, or Select IIIB (T3N2) NSCLC Population

1.2.1.1 Adjuvant Systemic Treatment

Adjuvant chemotherapy is the standard of care for fully resected (Stage II, IIIA, or select IIIB [T3N2]) NSCLC. The Lung Adjuvant Cisplatin Evaluation reported on the results of a pooled analysis of data from five large Phase III trials comparing cisplatin-based adjuvant chemotherapy with no chemotherapy in patients with resected Stage I–III (7th edition TNM staging) NSCLC (Pignon et al. 2008). The analysis was designed to identify treatment options associated with a higher degree of benefit or groups of patients benefiting more from adjuvant treatment. With a median follow-up time of 5.2 years, the hazard ratio (HR) for overall survival (OS) was 0.89 (95% CI: 0.82, 0.96; $p = 0.005$), corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. The survival benefit varied with stage, with the strongest effect seen in Stages II and III and a potential deleterious effect in Stage IA. The effect of chemotherapy on OS did not vary significantly (test for interaction with $p = 0.11$) 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 (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.

In the Phase III Cancer and Leukemia Group B 9633 study of adjuvant paclitaxel and carboplatin in Stage IB NSCLC, survival advantage was not observed with paclitaxel and carboplatin in the intent-to-treat (ITT) Stage IB population (Strauss et al. 2008). However, exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for patients who had tumors ≥ 4 cm in diameter (HR = 0.69; 95% CI: 0.48, 0.99).

In addition, with the successful development of cancer immunotherapy in advanced NSCLC, several adjuvant studies of anti–PD-1/PD-L1 inhibitors (atezolizumab, nivolumab, pembrolizumab, and durvalumab) are currently being conducted in resectable early-stage NSCLC.

1.2.1.2 Adjuvant Post-Operative Radiotherapy

Post-operative radiotherapy is no longer recommended after surgery as a treatment option for patients with early-stage resectable disease—specifically in patients with Stage I and II disease–because it has been shown to have a deleterious effect on

long-term survival (PORT Meta-Analysis Trialists Group 1998). On the other hand, PORT may help improve locoregional recurrence rates and/or survival in carefully selected patients, such as those with pathologically confirmed N2 disease or positive surgical margins (Decker and Wilson 2008). In a meta-analysis, patients with resected Stage III (N2+) disease had an observed 24% reduction in the overall risk of local recurrence with PORT, with no clear evidence of a detrimental effect on OS (PORT Meta-Analysis Trialists Group 1998). The LungART study was a randomized trial evaluating modern conformal mediastinal PORT after complete surgical resection with histologically proven N2 nodal involvement. The long-awaited trial results showed a non-significant improvement in disease-free survival (DFS; median 30.5 months vs. 22.8 months; HR=0.85 [95% CI 0.67–1.07], p=0.16), and while there was no significant detriment, it was overall a negative trial. Based on the results of the LungART study, PORT cannot be recommended as standard of care for completely resected N2 positive NSCLC and should only be considered on a case-by-case basis (Le Pechoux et al. 2020).

1.2.2 Neoadjuvant Treatment for the Surgically Resectable Stage II, IIIA, or Select IIIB (T3N2) NSCLC Population

Neoadjuvant chemotherapy is another approach to Stage II, IIIA, or select IIIB (T3N2) NSCLC, with survival benefits comparable to those achieved with adjuvant chemotherapy. A meta-analysis reported an indirect comparison of neoadjuvant and adjuvant chemotherapy and concluded that there were no differences in both OS and disease-free survival (DFS) between neoadjuvant and adjuvant chemotherapy (Lim et al. 2009). The data included 32 randomized trials (10 neoadjuvant and 22 adjuvant) involving more than 10,000 participants. For OS, the HR of adjuvant chemotherapy compared with neoadjuvant chemotherapy was 0.99 (95% CI: 0.81, 1.21), and for DFS the hazard ratio was 0.96 (95% CI: 0.77, 1.20).

A review of 15 neoadjuvant trials showed absolute survival improvement of 5% for 5-year OS and 13% reduction in the relative risk of death (OS HR=0.87; 95% CI: 0.78, 0.96) with neoadjuvant chemotherapy compared with surgery alone (NSCLC Meta-Analysis Collaborative Group 2014). There were no notable differences in survival between different chemotherapy regimens or scheduling, platinum agents, age, sex, performance status, histology, and whether or not PORT was given. Time to distant recurrence was also significantly longer for patients who received neoadjuvant treatment versus surgery alone (HR=0.69; 95% CI: 0.58, 0.82).

It is important to note that many studies were closed early because of positive outcomes in published adjuvant trials. Nevertheless, as a result of these reports, neoadjuvant platinum-based chemotherapy is considered an acceptable alternative to adjuvant chemotherapy for patients with resectable Stage II, IIIA, or select IIIB NSCLC.

There have been emerging data from prospective Phase II neoadjuvant trials with combination of chemotherapy and checkpoint inhibitors in early-stage NSCLC.

In the Phase II trial (AAAQ3153, NCT02716038) of neoadjuvant atezolizumab + carboplatin + nab-paclitaxel in patients with Stage IB-IIIA (7th edition of AJCC) resectable NSCLC, Shu and colleagues reported that of the 30 patients enrolled, 33% of patients achieved a pathological complete response (pCR) and 57% of patients achieved a major pathological response (MPR). In a post-hoc analysis of DFS, patients who achieved a MPR had a median DFS of 34.5 months versus 14.3 months in patients who did not have a MPR (Shu et al. 2020). The results from the NADIM trial showed that among the 46 patients with Stage IIIA N2+ NSCLC who were enrolled and treated with neoadjuvant nivolumab plus paclitaxel and carboplatin, the MPR rate was 83% including 63% pCR for patients who underwent surgery (41 patients) (Provencio et al. 2020). Compared with historic controls, a favorable 24 month PFS of 88% in patients with MPR and 24 month OS of 100% in patients with MPR was observed. Overall, these survival results are encouraging and exceed historic data for chemotherapy alone for resectable early-stage NSCLC patients.

In the Phase III CheckMate 816 trial, 358 patients were randomized to receive three cycles of neoadjuvant nivolumab plus chemotherapy or chemotherapy alone. A statistically significant improvement in the primary endpoint of pCR was observed (odds ratio [OR] = 13.94 [99% CI: 3.49, 55.75]; $p < 0.0001$) with 24% of patients in the nivolumab plus chemotherapy arm achieving pCR compared with 2.2% of patients in the chemotherapy alone arm (Forde et al. 2021). The pCR benefit was consistent across disease stages, histologies, and PD-L1 expression levels. Likewise, significant improvement in MPR was also observed with 36.9% of patients in the nivolumab plus chemotherapy arm achieving MPR versus 8.9% in the chemotherapy alone arm (OR = 5.70 [95% CI: 3.16, 10.26]). Importantly, nivolumab plus chemotherapy was tolerable, and the addition of nivolumab to chemotherapy did not increase post-surgical complications (Spicer et al. 2021). Numerically, a greater percentage of patients treated with nivolumab plus chemotherapy had definitive surgery and a complete resection, and fewer patients underwent pneumonectomy.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the treatment of advanced disease

and in the adjuvant setting, as well as in combination with chemotherapy, targeted therapy, and other cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, melanoma*, and alveolar soft part sarcoma.*

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

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and its expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy to restore tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard of care therapies. Objective responses have been observed with atezolizumab monotherapy across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. In particular, responses were seen in Cohorts C, D, and F of the Phase Ib Study GP28328 in patients receiving atezolizumab in combination with carboplatin, paclitaxel, nab-paclitaxel, and pemetrexed (see Atezolizumab Investigator's Brochure for detailed efficacy results). Furthermore, an OS benefit was observed in second-line NSCLC with atezolizumab monotherapy in the Phase III OAK trial (Rittmeyer et al. 2017).

Chemotherapy may enhance immunotherapy by cytotoxic killing of tumor cells and exposing the immune system to higher levels of tumor antigens (Merritt et al. 2003;

Apetoh et al. 2007). Atezolizumab may invigorate tumor-specific immunity and cytotoxicity through the inhibition of the PD-L1 pathway. Thus, deeper and more durable responses may be achieved in multiple malignancies when atezolizumab is combined with chemotherapy, compared with atezolizumab administered as monotherapy. Taking this approach, the combination of atezolizumab with platinum-based chemotherapy given preoperatively may enhance the immune response, increase cancer cell killing, eradicate micro-metastases prior to surgery, and reduce the risk of disease recurrence.

The combination of atezolizumab and platinum-based chemotherapy has been generally well tolerated and is currently being investigated as part of several studies including Studies GP28328, GO29437 (IMpower131), GO29438 (IMpower132), GO29537 (IMpower130), WO29522 (IMpassion130), WO39392 (IMpassion031), and YO29233. Safety profiles of combination therapy with atezolizumab have been consistent across different platinum-based chemotherapy regimens. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like symptoms, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). Adverse events that were most frequently reported with combination therapy were generalized symptoms such as fatigue, nausea, and vomiting, as well as those specific to cytotoxic chemotherapy such as hematologic toxicities and peripheral neuropathy (Liu et al. 2017; unpublished preliminary data from Study YO29233; also see Atezolizumab Investigator's Brochure for additional detailed safety results). To date, these events have been manageable with treatment and/or interruption of atezolizumab treatment. The benefit–risk ratio for atezolizumab in combination with platinum-based chemotherapy in the neoadjuvant setting is expected to be acceptable.

Given the evidence of clinical activity of atezolizumab in previously treated NSCLC as well as the need to improve upon survival and decrease recurrence rates for patients with resectable early-stage NSCLC, the Sponsor is conducting Study GO40241 (IMpower030). Patients with resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC will receive up to four cycles of neoadjuvant therapy with atezolizumab or placebo in combination with platinum-based chemotherapy, followed by surgical resection and then adjuvant treatment with atezolizumab or best supportive care (BSC).

Covid-19 Benefit-Risk Assessment

In the setting of the coronavirus 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 (Merad and Martin 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 judgement when evaluating and managing patients with pulmonary symptoms.

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

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 for 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). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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 COVID-19 vaccines. When administered, COVID-19 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 4.4.1).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy, when compared with placebo with platinum-based chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below in Table 1.

In this protocol, "study treatment" in the neoadjuvant treatment phase refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab or placebo with platinum-based chemotherapy).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• IRF assessed EFS, defined as the time from randomization to the first documented disease progression per RECIST v1.1 that precludes surgery, local or distant disease recurrence (including occurrence of new primary NSCLC), or death from any cause, whichever occurs first

EFS = event-free survival; IRF = Independent Review Facility; NSCLC = non–small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy	• IRF assessed pCR, defined as the absence of any viable primary tumor cells at the time of surgical resection in the primary tumor and all sampled lymph nodes as assessed by central pathology laboratory • IRF assessed MPR, defined as ≤ 10% residual viable tumor cells at the time of surgical resection in the primary tumor as assessed by central pathology laboratory • MPR and pCR at the time of surgical resection, as assessed by the investigator site pathology laboratory • Objective response, defined as a complete response or partial response, as determined by the investigator according to RECIST v1.1 (confirmation not required)
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• OS, defined as the time from randomization to death from any cause during the course of the study • Investigator assessed EFS • DFS, defined as the time from the first date of no disease to local or distant recurrence (including occurrence of new primary NSCLC) or death due to any cause, whichever occurs first, as determined by the investigator during the adjuvant treatment and observation follow-up • 2-year and 3-year OS, IRF assessed EFS and investigator assessed EFS during the study
• To evaluate PROs of HRQoL associated with atezolizumab in combination with platinum-based chemotherapy as neoadjuvant treatment followed by adjuvant atezolizumab	• Change from baseline in HRQoL scores as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30 at each assessment timepoint during the study through the completion of adjuvant treatment and observation follow-up assessments

DFS = disease-free survival; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; IRF = Independent Review Facility; MPR= major pathological response; NSCLC = non–small cell lung cancer; OS = overall survival; pCR= pathological complete response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab • To evaluate evolution of treatment/disease-related symptoms over time from the patients' perspective	• Subgroup analysis • Additional pathological response assessments • IRF assessed EFS by PD-L1 expression using the VENTANA® PD-L1 (SP263) Assay (TC ≥ 1% and ≥ 50%) • Additional PRO endpoints (e.g., time to confirmed symptom deterioration, clinical deterioration) documenting treatment and disease burden using EORTC QLQ-C30 and EORTC QLQ-LC13
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• Occurrence and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to NCI CTCAE v5.0 • Incidence and length of surgical delays, incidence of operative and post-operative complications, and/or reasons for surgical cancellations
Pharmacokinetic Objectives	**Corresponding Endpoint**
• To characterize the PK profile of atezolizumab when given in combination with platinum-based chemotherapy • To characterize the PK profile of atezolizumab alone	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Incidence of ADAs against atezolizumab during the study
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints

ADA = anti-drug antibody; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; IRF = Independent Review Facility; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-LC13 = Quality-of-Life Questionnaire for Lung Cancer 13; TC = tumor cell.

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Biomarker Objectives	Corresponding Endpoint
• To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with recurrence or progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology • To evaluate biomarkers at the time of apparent disease progression or recurrence of primary disease, and to distinguish any immunomodulatory activity of atezolizumab (e.g., tumor-immune infiltration) in patients with confirmed progression or recurrence of disease in patients assigned to atezolizumab	• Relationship between biomarkers (e.g., PD-L1, ctDNA, TMB, and others) in tumor tissue and/or blood (listed in Section 4.5.6) and efficacy, disease status, resistance, or other biomarker endpoints
Exploratory Health Status Objective	**Corresponding Endpoint**
• To evaluate health status utility scores of patients treated with atezolizumab	• Utility scores based on EQ-5D-5L (including VAS)

ctDNA = circulating tumor DNA; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-level version; TMB = tumor mutational burden; VAS = Visual Analogue Scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a global Phase III multicenter, double-blinded, randomized study designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy versus placebo plus platinum-based chemotherapy followed by adjuvant/post-operative atezolizumab or best supportive care in patients with histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC.

Patients must be eligible for R0 resection with curative intent at screening as well as meet all eligibility criteria specified in Section 4.1. Patients who do not initially meet all eligibility criteria may be re-screened.

After providing informed consent, patients will undergo screening procedures as outlined in Appendix 1. Eligible patients will be stratified by disease stage (II vs. IIIA N2− vs. IIIA/B N2+) and histology (non-squamous vs. squamous). Approximately 450 patients will be randomized in a 1:1 ratio to one of the following treatment arms:

- **Arm A**: Atezolizumab + platinum-based chemotherapy for 4 cycles, followed by surgical resection and then adjuvant/post-operative atezolizumab for 16 cycles
- **Arm B**: Placebo + platinum-based chemotherapy for 4 cycles, followed by surgical resection and then post-operative BSC and observation follow-up (Note: BSC is defined as symptomatic management and supportive measures for the patients' recovery from neoadjuvant therapy and surgery based on institutional standards and/or investigator judgement. This may include, but is not limited to, antibiotics, analgesics, fluids, physical therapy, counseling, diet, etc. Anti-cancer therapy is not allowed. For questions and clarifications regarding allowable BSC measures, please contact the Medical Monitor.)

Selection of the platinum-based neoadjuvant chemotherapy regimen will be at the discretion of the investigator (based on histology subtypes) and will be determined and documented at the time of randomization. The following platinum-based chemotherapy options are permitted for this study:

For Non-Squamous NSCLC

- Cisplatin + Pemetrexed
- Carboplatin + Pemetrexed
- Carboplatin + Nab-Paclitaxel

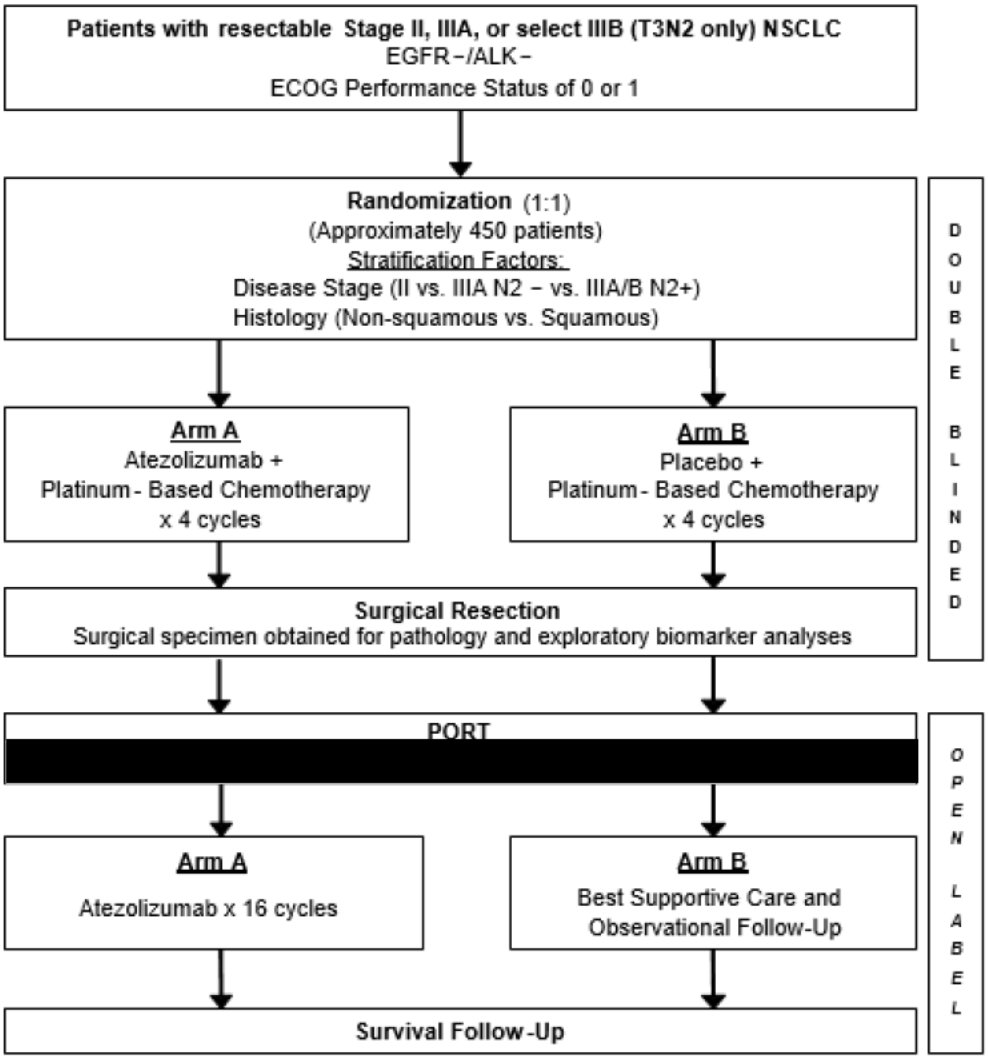
For Squamous NSCLC

- Cisplatin + Gemcitabine
- Carboplatin + Nab-Paclitaxel

Dosing and frequency of study treatment components are summarized in Section 4.3.2.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor; NSCLC = non–small cell lung cancer; PORT = post-operative radiation therapy.

Upon completion of neoadjuvant therapy, patients will undergo surgical resection of their tumor. Surgical specimens will be assessed for pathological response (MPR and pCR) by an independent central pathology laboratory as well as by the investigator site pathology laboratory. In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) will be performed.

Prior to surgery, the attending surgeon and medical oncologist will reassess the patient. The Pre-Surgery Visit should occur [redacted] days after the last dose of neoadjuvant treatment, [redacted]. The surgical procedure should be performed [redacted] days after

the Pre-Surgery Visit as best as possible per clinical judgement of both the attending surgeon and medical oncologist. Any anticipated delay beyond this time window should be discussed with the Medical Monitor. See Section 4.3.3 for guidance on surgical treatment plan.

Patients who are found to have disease progression at scheduled tumor assessments (after Cycle [redacted] and Cycle [redacted]) or at any time during neoadjuvant treatment and are still deemed resectable and non-metastatic will proceed to receive surgery if amenable and will remain eligible for all on-study treatment and evaluations.

The Medical Monitor must be consulted if investigator plans for a patient to proceed to surgery in the absence of disease progression and prior to completing all 4 cycles of neoadjuvant treatment.

Patients who discontinue neoadjuvant treatment early because of disease progression and do not proceed to surgery will be discontinued from further in-clinic study procedures, and will proceed to receive other treatment as determined by the investigator. These patients will still remain in the study for survival follow-up.
For patients who are responding to neoadjuvant therapy but cannot proceed to surgery (e.g., because of pulmonary embolism or myocardial infarction), the Medical Monitor must be informed. For these patients, if they are assigned to Arm A, atezolizumab monotherapy will be offered, with continued follow-up as per protocol. Patients randomized to Arm B will continue to be monitored and followed up as per protocol.

After surgery and local pathology response assessment, the adjuvant phase of this study will be open-label. The medical oncologist and/or attending surgeon will meet with the patient 14–21 days after surgery to assess their recovery and inform the patient of their post-surgery treatment plan for the study. [redacted] Patients randomized to Arm A will receive atezolizumab as post-operative adjuvant therapy and patients randomized to Arm B will receive BSC and observation follow-up visits. If PORT is not needed, Arm A patients receiving post-operative adjuvant atezolizumab should receive the first dose of atezolizumab (Cycle 5) within 60 days after surgery; initial dosing beyond 60 days should be discussed with the Medical Monitor. For Arm B patients that do not require PORT, observation follow-up visits should occur within 60 days after surgery. Patients will continue to receive adjuvant atezolizumab (Arm A) or undergo scheduled in-clinic observation follow-up visits (Arm B) until one of the following occurs: administration of 16 cycles of atezolizumab as adjuvant therapy (Arm A), completion of all scheduled observation follow-up assessment visits (Arm B), unacceptable toxicity (Arm A only), disease recurrence, death, or patient and/or physician decision to discontinue study treatment or observation follow-up visits.

All patients will undergo scheduled tumor assessment scans of the chest and abdomen by both computed tomography (CT) and positron emission tomography (PET) at screening and then by CT only after Cycles [redacted] and [redacted] of neoadjuvant treatment. [redacted]

If a disease follow-up assessment shows evidence of disease recurrence, it should be confirmed pathologically and/or by unequivocal radiographic evidence from the scan. If a scan shows equivocal findings (e.g., mediastinal nodes measuring <1.5 cm in the short axis, lung parenchymal lesions or visceral lesions measuring <1 cm in the longest diameter), a biopsy should be performed. If a biopsy is not feasible or safe, then confirmatory scans must be performed again within 4 to 8 weeks. If a biopsy for disease recurrence confirmation is performed, any leftover biopsy tissue is strongly encouraged to be submitted for exploratory biomarker research (optional consent required for exploratory research; see Section 4.5.7 for details). The biopsy should be performed prior to starting the next anti-cancer therapy. If the biopsy does not show evidence of disease recurrence (e.g., non-malignant infiltrates), then the patient may continue with scheduled study treatment, assessments, and/or follow-up. In the absence of disease recurrence, disease follow-up assessments should continue until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first (see Section 4.5.5 and Appendix 1 for details).

Patients may undergo an optional tumor biopsy sample upon disease progression per RECIST v1.1 during the neoadjuvant treatment phase for exploratory biomarker research (optional consent required; see Section 4.5.7 for details). These data may 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 may be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance and recurrence to atezolizumab compared with such mechanisms after treatment with neoadjuvant chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients will complete the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and lung cancer module (QLQ-LC13) to assess disease and/or treatment-related symptoms (e.g., dyspnea, pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, hemoptysis, functioning, and health-related quality of life [HRQoL]) at specified timepoints throughout the duration of the study (neoadjuvant, adjuvant/monitoring, and long-term survival follow-up) (see Appendix 4 and Appendix 5). Patients will also complete the European Quality of Life, 5-dimension, 5-level version (EQ-5D-5L) in its entirety, including the

Visual Analogue Scale (VAS) to document health status for pharmacoeconomic analyses (see Appendix 6).

Safety assessments will include the incidence, nature, and severity of adverse events, serious adverse events, adverse events of special interest, immune-mediated adverse events, and laboratory abnormalities, graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Patient samples, including archival and fresh tumor tissues as well as serum, plasma and whole blood, will be collected for future exploratory biomarker assessments.

All patients will undergo safety, tolerability, and exploratory assessments on Day 1 of each cycle in the blinded neoadjuvant treatment phase (both arms) and in the open-label adjuvant and observation follow-up phase (every cycle [i.e., every 3 weeks] for Arm A, and every 6 weeks for Arm B). After treatment or observation follow-up discontinuation, patient follow-up will be periodically performed for survival status, PROs, and any additional anti-cancer treatment.

3.1.2 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will evaluate safety data, review the interim analysis of Independent Review Facility (IRF) assessed EFS data, and assess study conduct during the study until the time of the analysis of the primary efficacy endpoints. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis. The first safety review will occur at approximately 6 months from the time of enrollment of the first patient or when approximately 22 patients have been randomized to the study, whichever occurs later. Subsequent safety review will occur approximately every 6 months during the study until the statistically significant IRF assessed EFS at the interim analysis by iDMC or final analysis of IRF assessed EFS by the Sponsor, whichever occurs first.

The iDMC will be responsible for evaluating IRF assessed EFS data at the time of the prespecified analysis. The efficacy analyses will be conducted in accordance with the methods that are specified in the Statistical Analysis Plan (SAP).

All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC).

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs). Details of the iDMC's conduct will be further described in the charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date of Sponsor decision to end the study, whichever is earlier.

The Sponsor may decide to terminate the study at any time.

The length of this study will be approximately 96 months from randomization of the first patient to the end of study as described above.

3.3 DURATION OF PARTICIPATION

Participation will continue until withdrawal or death due to any cause.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21–day cycle in both the neoadjuvant and adjuvant treatment phases, which is the approved dosage for atezolizumab [Tecentriq® U.S. Package Insert]). Antitumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic (PK), efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

3.4.2 Rationale for Patient Population

This study will enroll patients with resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC as determined at screening regardless of PD-L1 expression and without EGFR/ALK mutations.

For early-stage NSCLC, the 5-year survival rate is only 19%–43% (Goldstraw et al. 2007) with disease recurrence common in 30%–70% of patients who undergo surgical resection (Ponn et al. 2005). Despite improvements with the addition of adjuvant and neoadjuvant chemotherapy for resectable/resected early-stage NSCLC, disease recurrence remains common and improvement in OS remains marginal. Therefore, there is a need for more efficacious treatment regimens for patients with resectable early-stage NSCLC.

3.4.3 Rationale for Control Group

Platinum-based chemotherapy is the standard of care for adjuvant and neoadjuvant treatment of resected/resectable early-stage NSCLC. For this study, carboplatin and cisplatin are provided as platinum options for investigators to select from as described in Section 3.1, as there is no clear evidence in the difference of survival outcomes between these two agents in the neoadjuvant setting (NSCLC Meta-Analysis Collaborative Group 2014). The specified choices for platinum-based chemotherapy regimens are also based on evidence of activity and safety in combination with atezolizumab from completed and ongoing studies. Patients randomized to the control group (Arm B) will receive up to 4 cycles of placebo plus investigator-selected platinum-based chemotherapy allowed by the study in the neoadjuvant treatment phase. The addition of placebo during the blinded neoadjuvant treatment phase is intended to ensure more uniform treatment completion rates between both treatment arms that may otherwise be affected by knowledge of treatment arm assignment and to minimize potential bias.

3.4.4 Rationale for Primary Endpoint and Key Secondary Endpoints

The primary objective of this study is to evaluate the efficacy of neoadjuvant treatment with atezolizumab plus platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy followed by adjuvant/post-operative atezolizumab or best supportive care in resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC as measured by IRF assessed EFS. The key secondary endpoints are IRF assessed pathological response, including pCR and MPR, and OS.

As with OS, EFS is considered a measure for long-term clinical benefit. Thus, for this study, EFS will be used to evaluate if the totality of the treatment effect observed by combining neoadjuvant atezolizumab + platinum-based chemotherapy followed by adjuvant atezolizumab monotherapy will prolong EFS when compared with the current standard of neoadjuvant platinum-based chemotherapy alone followed by best supportive care.

The use of intermediate survival clinical endpoints that are similar to EFS (e.g., DFS and PFS) is supported for accelerated approval or regular approval of cancer drugs and biologics (FDA 2007). This is not without precedent in early-stage NSCLC, as demonstrated with the recent approval of durvalumab in Stage III unresectable NSCLC based on PFS results (Antonia et al. 2017; FDA 2018) and osimertinib for the adjuvant treatment of EGFR-mutation positive NSCLC based on DFS (Wu et al. 2020). While these survival endpoints are termed differently, the measured outcome is similar in principle with the intention to capture disease progression or recurrence events before or after definitive treatment.

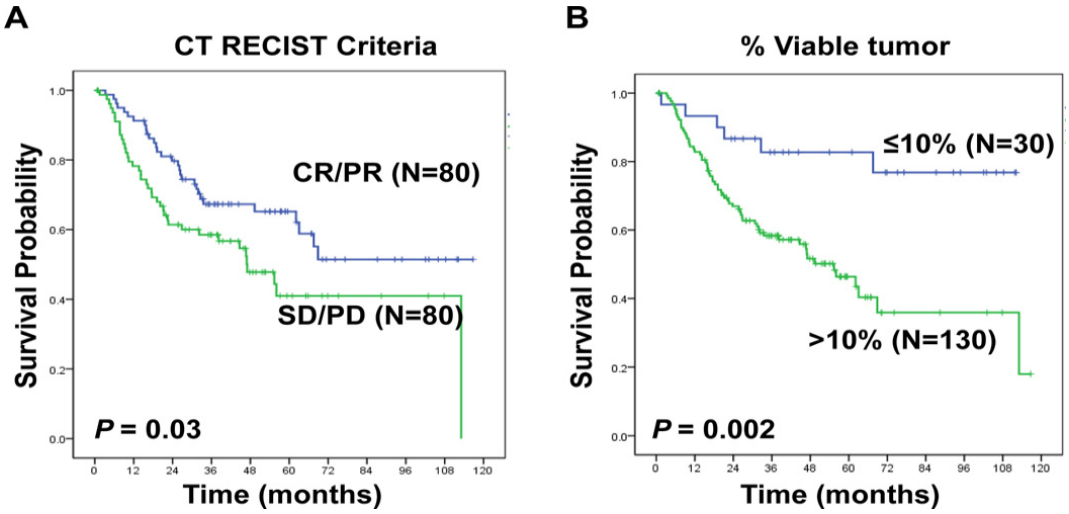
While OS is the gold standard in evaluating clinical benefit in adjuvant and neoadjuvant NSCLC trials, readout of OS often takes many years, especially in early-stage disease. Thus, adopting meaningful surrogate endpoints may expedite the evaluation of new

therapies and bring new treatments to NSCLC patients sooner. Pathological response after surgical resection of NSCLC has been proposed as a surrogate endpoint for OS (Hellmann et al. 2014). Hellmann et al. cited the U.S. Food and Drug Administration (FDA) definition of the surrogate endpoint in which the endpoint should be "reasonably likely to predict clinical benefit" (Hellmann et al. 2014). They advocate that using pathological response in the neoadjuvant setting demonstrates this criterion based on three findings: 1) pathological response strongly correlates to OS; 2) pathological response is reflective of neoadjuvant chemotherapy; and 3) the degree of pathological response correlates with the degree of OS benefit.

Pathological response as a surrogate endpoint is not without precedent. Trials for breast cancer have used pCR for evaluating the efficacy of neoadjuvant treatment. In NSCLC, other than pCR (defined as 0% viable tumor in all pathological assessed specimens), MPR, defined as $\leq$10% residual viable tumor tissue, is also considered as a surrogate endpoint for survival for patients with resectable NSCLC receiving treatment with neoadjuvant chemotherapy (Hellmann et al. 2014).

This is based on studies in which investigators, in acknowledgement of the rarity of pCR in NSCLC, considered other definitions of pathological response, including residual viable tumor as a surrogate survival endpoint. Junker et al. performed pathological analysis of 40 tumors from patients with Stage IIIA and IIIB disease who were given sequential neoadjuvant chemotherapy treatment, chemoradiotherapy, and surgical resection (Junker et al. 1997). Patients with $\leq$10% residual tumor in this group had a median survival of 36 months, while patients who had $>$10% residual viable tumor tissue had a median survival of 14 months. Two prospective trials reported an MPR rate of approximately 22% with neoadjuvant chemotherapy in NSCLC. The first study noted that of the 90 patients with Stage IIIA disease who received neoadjuvant chemotherapy (cisplatin+docetaxel), the median pathological response (amount of tumor necrosis and fibrosis) was 60%, with a median OS of 61 months compared with 22 months in patients with $<$60% pathological response (Betticher et al. 2006). Another study showed that of the 50 patients who received neoadjuvant chemotherapy (cisplatin+docetaxel) in combination with bevacizumab, patients with MPR had a significantly longer 3-year survival rate compared with patients who did not achieve MPR (61 months vs. 22 months) (Chaft et al. 2013). A retrospective study from the MD Anderson Cancer Center by William and colleagues (William et al. 2013) showed that in 160 patients who received neoadjuvant platinum-based chemotherapy, MPR was a stronger predictor of OS than clinical RECIST response (see Figure 2).

Figure 2 Overall Survival by Clinical Response and by Pathological Response



CT RECIST = computed tomography Response Evaluation Criteria in Solid Tumors; CR/PR = complete response/partial response; SD/PD = stable disease/progressive disease.
Source: William et al. 2013.

Since there are currently no reported data on pCR and MPR correlation to survival endpoints from confirmatory trials, having pCR and MPR as secondary endpoints provides an opportunity to evaluate efficacy according to a potential surrogate marker while maintaining an established clinical endpoint as part of the primary objectives, as outlined by the FDA and International Association for the Study of Lung Cancer (IASLC) neoadjuvant working group to support regulatory approval (Blumenthal et al. 2018). This approach will also help demonstrate the magnitude of benefit that pCR and MPR may have in relation to a survival-related clinical endpoint, as well as potentially accelerate the evaluation of new and meaningful therapies for patients with early-stage resectable NSCLC, where the survival benefit remains low with current standards of care.

There have been emerging data with regards to pathological response from prospective Phase II neoadjuvant NSCLC trials with the combination of chemotherapy and checkpoint inhibitors.

In the Phase II trial (AAAQ3153, NCT02716038) of neoadjuvant atezolizumab + carboplatin + nab-paclitaxel in patients with Stage IB-IIIA (7th edition of AJCC) resectable NSCLC, Shu and colleagues reported that of the 30 patients enrolled and treated with atezolizumab and chemotherapy, 33% of patients achieved a pCR and 57% of patients achieved a MPR. In a post-hoc analysis of DFS, patients who achieved a MPR had a median DFS of 34.5 months versus 14.3 months in patients who did not have a MPR (Shu et al. 2020).

Results from the NADIM trial showed that among the 46 patients with Stage IIIA N2 + NSCLC who were enrolled and treated with neoadjuvant nivolumab plus paclitaxel

and carboplatin, the MPR rate was 83% including 63% pCR among patients who underwent surgery (41 patients) (Provencio et al. 2020). Compared to historic controls, a favorable 24 month PFS of 88% in patients with MPR and a 24 month OS of 100% in patients with MPR was observed.

In the SAKK 16/14 trial (NCT02572843), 67 patients with resectable Stage III (N2+) NSCLC were treated with neoadjuvant cisplatin plus docetaxel sequentially with durvalumab, followed by 12 months of adjuvant durvalumab (Rothschild et al. 2020). Among the 55 patients who underwent surgery, MPR was observed in 60% of patients including 18.2% with a pCR. The primary endpoint of 12-month EFS was 73.4%, and at a median follow-up of 28.6 months, median EFS and OS was not reached.

Overall, these results are encouraging and exceed historic data for chemotherapy alone for resectable early-stage NSCLC patients, and are supportive of a potential correlation between pathological response and EFS outcomes.

3.4.5 Rationale for Biomarker Assessments

In this study, archival or baseline pretreatment tumor specimens as well as surgically resected specimens following the neoadjuvant phase will be collected from patients and tested for exploratory biomarkers. Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In addition, data from a Phase II study in patients with previously treated NSCLC (POPLAR) suggest that higher expression of genes related to PD-L1 and T-effector biology in tumor tissue is associated with improved efficacy of atezolizumab compared with docetaxel (Fehrenbacher et al. 2016). Similar observations have been reported for other PD-L1 or PD-1 inhibitors (Higgs et al. 2015; Muro et al. 2015; Seiwert et al. 2015). Furthermore, expression of PD-L1 on immune cells was reported to be associated with expression of a T-effector gene signature, therefore representing a pre-existing immunity (Fehrenbacher et al. 2016). In addition to the assessment of PD-L1, other exploratory biomarkers may be evaluated to identify potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type. This evaluation of biomarkers may help to identify which patients may potentially benefit most from atezolizumab, and may help guide future development of alternative diagnostic options.

Tumor tissue may also be collected from an optional biopsy at the time of first evidence of radiographic disease progression or recurrence if deemed clinically feasible by the investigator, to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as tumor mutational burden and

ctDNA may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that may predict which patients are more likely to benefit from atezolizumab.

Tumor tissue and blood samples may be analyzed through use of next-generation sequencing (NGS), including, but not limited to, whole exome sequencing (WES), to identify somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

3.4.6 Rationale for Patient-Reported Outcome Assessments

The long-term goals of lung cancer surgery include improved length and quality of life (Denton et al. 1995; Win et al. 2005). Although lung resection remains the most effective treatment for patients with operable NSCLC, these patients are at increased risk of complications from surgery and of functional impairment post-operatively (Win et al. 2005). Previous studies have shown that patients with resectable lung cancer present with mild to moderate fatigue, dyspnea, and cough symptoms and that patients' HRQoL scores tend to return to preoperative levels 6–9 months after surgery.

To comprehensively capture disease and treatment burden from the patients' perspective, patient-relevant endpoints of symptom severity and their impact on function and HRQoL will be collected using paper versions of the EORTC QLQ-C30 and QLQ-LC13 throughout the study. Both measures generate valid and reliable scores with accepted thresholds in patients with lung cancer for interpreting the clinical significance of score changes (Aaronson et al. 1993; Bergman et al. 1994; Sprangers et al. 1996; Fitzsimmons et al. 1999; Bezjak et al. 2006; Blackhall et al. 2014) (see Appendix 4 and Appendix 5). EORTC QLQ-C30 and QLQ-LC13 throughout the study will be analyzed according to the scoring manual (Fayers et al. 2001). This will enable documentation of the impact of neoadjuvant and adjuvant treatment with patient-relevant outcomes to further inform the benefit-risk assessment for atezolizumab. Change from the baseline global health status (GHS) /QoL scale score (Questions 29 and 30 of the EORTC QLQ-C30) during the neoadjuvant, post-surgery, and post-treatment phases will be assessed.

In addition, to minimize burden to patients and clinical research staff, only the EQ-5D-5L and select items of the EORTC QLQ-C30 to assess GHS (Questions 29 and 30), physical functioning (Questions 1–5), and role functioning (Questions 6 and 7) will be administered to patients during survival follow-up by phone.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgement
- Pathologically documented Stage II, IIIA, or select IIIB (T3N2 only) NSCLC of squamous or non-squamous histology

  Staging should be based on the 8th edition of the American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) NSCLC staging system.

  – T4 primary NSCLC will be allowed only on the basis of size (tumors >7 cm). Invasion of the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, and separate tumor nodules in a different ipsilateral lobe is not permitted.
  – Patients with mixed NSCLC histology (squamous and non-squamous) or NSCLC not otherwise specified are eligible.

  Patients may be screened based on clinical stage, but mandatory preoperative documentation of N2 nodal involvement by invasive mediastinal staging (e.g., CT-guided biopsy, endobronchial ultrasound [EBUS], mediastinoscopy) is required for PET-positive N2 nodes. Preoperative staging of levels 5/6 nodes is optional.

- Solid or subsolid appearance of NSCLC on CT scan with no appearance of purely ground-glass opacity (GGO)

  For subsolid lesions, the tumor size (i.e., clinical T stage) should be measured based on solid component only, exclusive of the GGO component.

- Evaluation by the operating attending surgeon and involved medical oncologist prior to study enrollment to verify study eligibility for R0 resection with curative intent (see Section 4.3.3)
- [redacted]

[redacted]

- Adequate cardiac function to be eligible for surgical resection with curative intent

  If clinically indicated, patients with underlying ischemic, valvular, or other significant heart diseases should be evaluated preoperatively by a cardiologist.

- Measurable disease as assessed by the investigator per RECIST v1.1
- Eligibility to receive a platinum-based chemotherapy regimen

  Please refer to the Warnings and Precautions section in the prescribing information of each individual chemotherapy treatment (i.e., carboplatin, cisplatin, pemetrexed, nab-paclitaxel, or gemcitabine) in the intended regimen for each patient to determine eligibility.

- Availability of a representative tumor specimen suitable for determination of PD-L1 status via central testing (results of PD-L1 testing are not required for patient to be randomized into the study)

  A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least a minimum of 3 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report before or within 4 weeks after randomization. Any additional slides beyond the required minimum of 3 slides are strongly encouraged for other exploratory biomarker research. If archival tumor tissue is unavailable, tumor tissue must be obtained from a biopsy performed at screening. Refer to Section 4.5.6 for additional information on tumor specimens collected at screening.

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

  ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support

  Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)

  Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion

  Hemoglobin ≥ 90 g/L (9.0 g/dL)

  Patients may be transfused to meet this criterion.

  AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN)

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

  Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN

  Creatinine clearance ≥ 45 mL/min (calculated using the Cockcroft-Gault formula)

For patients intended to receive cisplatin: creatinine clearance ≥ 60 mL/min

Serum albumin ≥ 25 g/L (2.5 g/dL)

For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or a positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab, 30 days after the last dose of nab-paclitaxel, or 6 months after the last dose of pemetrexed, gemcitabine, carboplatin, or cisplatin, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal 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). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, 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 trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period for 6 months after the last dose of nab-paclitaxel, pemetrexed, gemcitabine, carboplatin, or cisplatin, whichever is later, to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

Male patients should be advised regarding the conservation of sperm prior to treatment because of the possibility of irreversible infertility resulting from therapy with gemcitabine.

4.1.2 Exclusion Criteria

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

- Illness or condition that may interfere with a patient's capacity to understand, follow, and/or comply with study procedures
- NSCLC with histology of large cell neuroendocrine carcinoma or sarcomatoid carcinoma
- Mixed NSCLC and small-cell lung cancer histology
- Any prior therapy for lung cancer, including chemotherapy, or radiotherapy
- Major surgical procedure, other than for diagnosis, within 28 days prior to initiation of study treatment, or anticipation of need for non-protocol-mandated major surgical procedure during the study
- NSCLC with an activating mutation in the epidermal growth factor receptor (EGFR) or with an anaplastic lymphoma kinase (ALK) fusion oncogene

  For patients with non-squamous NSCLC histology: unknown EGFR and/or ALK status require test results at screening.

  For patients with squamous histology: unknown EGFR and/or ALK status do not require test results at screening. However, exclusion is applied if the status of either driver oncogene is known to be positive.

  For patients with mixed histology: unknown EGFR and/or ALK status require test results at screening if any components of non-squamous histology are observed

  ALK and/or EGFR may be assessed locally or at a central laboratory (for China, testing will only be performed at a central laboratory).

  If samples are submitted for central testing, additional tissue, cytology, and/or plasma samples are required (see Section 4.5.6 for details).
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus

erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 7 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover $<10\%$ of body surface area
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high-risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab

    Patients being treated with chemotherapy (i.e., carboplatin, cisplatin, pemetrexed, nab-paclitaxel, or gemcitabine) should not receive live vaccines.
- Current treatment with anti-viral therapy for HBV
- Treatment with investigational therapy within 42 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

    Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) may be eligible for the study after consulting with the Medical Monitor.

    Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the chemotherapy regimen the patient will be assigned to
- For patients intended to receive cisplatin, any significant hearing impairment per the investigator's clinical judgement

- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after last dose of atezolizumab, 30 days after the last dose of nab-paclitaxel, or 6 months after last dose of pemetrexed, gemcitabine, carboplatin, or cisplatin

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blinded, placebo-controlled study for the neoadjuvant treatment phase followed by an open-label post-operative adjuvant treatment/monitoring phase. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomized in a 1:1 ratio to one of two treatment arms for the neoadjuvant treatment phase: Arm A (atezolizumab + platinum-based chemotherapy) or Arm B (placebo + platinum-based chemotherapy).

Randomization will be stratified by the following factors:

- Stage (II vs. IIIA N2− vs. IIIA/B N2+)
- Histology (non-squamous vs. squamous)

A permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm within levels of the stratification factors.

Patients should receive their first dose of study treatment on the day of randomization if possible. If treatment on the day of randomization is not possible, the first dose should occur no later than 5 days after randomization.

4.2.2 Blinding

The Sponsor and its agents (with the exception of the IxRS service provider [the external independent statistical coordinating center responsible for verifying patient randomization and study treatment kit assignments], the iDCC, and the iDMC members); the study site personnel, including the investigator and local pathology assessors; and the patient will be blinded to treatment assignment during the neoadjuvant treatment phase and surgery. The central pathology assessor and central radiology reviewer will be blinded to treatment assignment through the duration of the study.

While PK and anti-drug antibody (ADA) samples must be collected from patients assigned to the comparator arm (Arm B) to maintain the blinding of treatment assignment during the neoadjuvant treatment phase, PK and ADA results for these

patients are generally not needed for the safe conduct or proper interpretation of the results of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to Arm B will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples may be analyzed for all patients. Post-baseline ADA samples from patients assigned to Arm B will not be analyzed for ADAs except by request.

4.2.3 Unblinding at the Patient Level

4.2.3.1 Unblinding after Pathological Response Assessment

The patient's treatment assignment will be unblinded following surgery after local pathological assessment is performed in order to inform further post-operative adjuvant treatment. The central pathologist will remain blinded.

4.2.3.2 Emergency Unblinding before Pathological Response Assessment

If necessary, study treatment assignment may be unblinded for any drug-related toxicity during the neoadjuvant treatment phase. Emergency unblinding should be a last resort performed only in cases where knowledge of treatment assignment will affect ongoing treatment of the toxicity. Unblinding should not result in the withdrawal of the patient from the study. Every effort should be made to retain unblinded patients and continue data collection as per protocol.

4.2.3.3 Non-Emergency Unblinding before Pathological Response Assessment

Prior to surgery and local pathology assessment, the patients' treatment allocation must remain blinded. However, if the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, they must contact the Sponsor. Non-emergency unblinding may be allowed for, but not limited to, the following reasons:

- To help inform the investigator of subsequent non-protocol treatment decisions for patients who are not responding to treatment and are ineligible to proceed to surgery
- To help inform the investigator of whether the patient may be considered for another clinical trial if they are unable to continue with study treatment and procedures
- The investigator wishes to continue atezolizumab monotherapy for patients who are responding to neoadjuvant atezolizumab and chemotherapy treatment but cannot proceed to surgery due to a medical comorbidity that occurred during the conduct of the trial (e.g., myocardial infarction, severe physical trauma)

The investigator and site will be required to send all requests for non-emergency unblinding, including supporting documentation and explanation for the request, to the Sponsor for approval. Each request will be evaluated by the Medical Monitor prior to

granting approval for non-emergency unblinding. Approval of such non-emergency unblinding will occur only during the Sponsor's business hours.

4.2.4 Unblinding at the Study Level

For regulatory reporting purposes, if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are atezolizumab, nab-paclitaxel, and placebo. Pemetrexed, Gemcitabine, Cisplatin, and Carboplatin are considered *authorized auxiliary medicinal products (AxMP) /* non-investigational medicinal products (NIMP). Appendix 12 identifies all IMPs *and AxMPs / NIMPs* for this study.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab and Placebo

Atezolizumab and placebo will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL of atezolizumab (1200 mg) or placebo solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

4.3.1.2 Nab-Paclitaxel

Nab-paclitaxel will be supplied to the sites by the Sponsor in its commercially available formulation.

For information on the formulation, packaging, and handling of nab-paclitaxel, please refer to the EU summary of product characteristics (SmPC).

4.3.1.3 Carboplatin, Cisplatin, Pemetrexed, and Gemcitabine

Carboplatin, cisplatin, pemetrexed, and gemcitabine will be used in the commercially available formulation where allowed by local regulations.

For information on the formulation, packaging, and handling of carboplatin, cisplatin, pemetrexed, and gemcitabine, please refer to the local prescribing information for each drug.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The permitted platinum-based chemotherapy treatment options are summarized in Section 3.1.1.

Each study treatment component will be administered at the doses and frequency specified in Table 2.

Table 2 Study Treatment Component Regimens

Study Treatment Component	Timing
Neoadjuvant Treatment Phase	
Atezolizumab (1200 mg IV) or placebo	Day 1 of each 21-day cycle for 4 cycles
Nab-paclitaxel (100 mg/m^2 IV)	Days 1, 8, and 15 of each 21-day cycle for 4 cycles
Pemetrexed (500 mg/m^2 IV)	Day 1 of each 21-day cycle for 4 cycles
Carboplatin (IV, initial target AUC of 6 mg/mL/min)	Day 1 of each 21-day cycle for 4 cycles
Cisplatin (75 mg/m^2 IV)	Day 1 of each 21-day cycle for 4 cycles
Gemcitabine (1250 mg/m^2 IV)	Days 1 and 8 of each 21-day cycle for 4 cycles
Post-Operative Adjuvant Phase (Patients in Arm A Only)	
Atezolizumab (1200 mg IV)	Every 3 weeks for 16 cycles

AUC = area under the concentration–time curve.

During the neoadjuvant treatment phase, eligible patients will be administered study treatment infusions in the following order on Day 1 of each cycle:

Atezolizumab/placebo → nab-paclitaxel → carboplatin
or
Atezolizumab/placebo → pemetrexed → carboplatin or cisplatin
or
Atezolizumab/placebo → gemcitabine → cisplatin

Patients should receive their first dose of study treatment on the day of randomization if possible. If treatment on the day of randomization is not possible, the first dose should occur no later than 5 days after randomization.

For Cycle 1, premedication for primary prophylaxis (antihistamines, anti-pyretics, and/or analgesics) of atezolizumab/placebo is not permitted. Patients should receive anti-emetics and IV hydration for the selected chemotherapy backbone regimen according to the local standard of care and manufacturer's instruction. However, because of the immunomodulatory effects of corticosteroids, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2.1). A list of premedication for pemetrexed is provided in Table 3. All medications must be recorded on the appropriate Concomitant Medications electronic Case Report Form (eCRF).

Table 3 Premedication for Pemetrexed

Premedication	Dose and Route	Timing
Folic acid	350–1000 μg PO	Once daily beginning at least 5–7 days before Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Vitamin B_{12}	1000 μg IM	Q9W beginning with the week preceding Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed
Dexamethasone (suggested)	4 mg PO	Twice daily the day before, the day of, and the day after pemetrexed administration

IM = intramuscular; PO = oral; Q9W = every 9 weeks.

After surgery and local pathological response assessment, treatment assignment will be open-label (Note: The central pathology assessor and central radiology reviewer will remain blinded). Patients assigned to Arm B will receive BSC, while those assigned to Arm A will receive adjuvant treatment with atezolizumab 1200 mg IV every 3 weeks for 16 cycles. Treatment with atezolizumab should begin within 14–60 days after surgery or [redacted] In case initiation of adjuvant atezolizumab treatment needs to be delayed beyond 60 days, please contact the Medical Monitor.

Cases of accidental overdose or medication error associated with atezolizumab (or matching placebo), along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 9 (for chemotherapy) and in Appendix 10 and the Atezolizumab Investigator's Brochure.

4.3.2.1 Atezolizumab or Placebo

Atezolizumab or placebo will be administered by IV infusion at a fixed dose of 1200 mg every 21 days in the neoadjuvant treatment phase for 4 cycles. For patients assigned to treatment Arm A, atezolizumab will be administered at the same dose and frequency in the adjuvant treatment phase for up to 16 cycles.

Administration of atezolizumab/placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. Atezolizumab infusions will be administered per the instructions outlined in Table 4.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 10 and the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed.

4.3.2.2 Nab-Paclitaxel + Carboplatin, Pemetrexed + Carboplatin or Cisplatin, Gemcitabine + Cisplatin

In this section, instructions for the chemotherapy components of the study treatment are provided. Sites should adhere to the information below and to the local prescribing information. In general, sites should also follow their institutional and local standard of care for determining dose adjustments in the event of patient weight changes.

Nab-Paclitaxel

Nab-paclitaxel injection must be diluted prior to infusion. Nab-paclitaxel should be diluted in 0.9% Sodium Chloride Injection to a final concentration of 5 mg/mL.
The infusion site should be closely monitored for possible infiltration during drug administration. Limiting the infusion of nab-paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions. Following administration, the IV line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

See the prescribing information for nab-paclitaxel for more information.

Pemetrexed

Institutions should follow their standard administration procedures for pemetrexed. Administration of pemetrexed should be administered by IV infusion over at least 10 minutes. The premedication doses administered should be in compliance with the prescribing information (see Table 3). All patients eligible for pemetrexed therapy should avoid taking nonsteroidal anti-inflammatory drugs with long elimination half-lives for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

Gemcitabine

Gemcitabine must be diluted prior to infusion. The recommended diluent for reconstitution of gemcitabine is 0.9% sodium chloride injection without preservatives. Gemcitabine should be administered by IV infusion over 30 minutes. The administration of gemcitabine should be done in accordance with local practice and the prescribing information.

Carboplatin

Carboplatin should be administered by IV infusion, immediately after the completion of nab-paclitaxel or pemetrexed administration, over 15–30 minutes to achieve an initial target area under the concentration–time curve (AUC) of 6 mg/mL/min (Calvert formula dosing) and with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 6 will be calculated using the Calvert formula (Calvert et al. 1989):

Calvert Formula

$$\text{Total Dose (mg)} = (\text{target AUC}) \times (\text{glomerular filtration rate [GFR]} + 25)$$

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

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

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

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

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

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

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

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is $6 \times (125 + 25) = 900$ mg.
For a target AUC = 5, the maximum dose is $5 \times (125 + 25) = 750$ mg.
For a target AUC = 4, the maximum dose is $4 \times (125 + 25) = 600$ mg.

Cisplatin

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

Refer to local clinical practice guidelines for further details.

4.3.3 Surgical Treatment Plan

An attending thoracic surgeon with experience in early-stage resectable NSCLC should evaluate patients at screening to determine surgical fitness and eligibility for surgical resection. Patients must be eligible for an R0 resection with curative intent at time of screening.

[redacted]

[redacted]

[redacted]

4.3.4 Post-Operative Radiotherapy

[redacted]

[redacted]

[redacted]

[redacted]

4.3.5 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before

any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.6 Continued Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide atezolizumab or any other study treatments or interventions to patients 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 consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment or observation follow-up discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for exacerbation of pre-existing medical conditions (e.g., chronic obstructive pulmonary disease, asthma)
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care (including pre-existing conditions) with supportive therapies (e.g., granulocyte colony-stimulating factor, blood transfusions) other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab/placebo infusions only, at the discretion of the investigator. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 10 and the Atezolizumab Investigator's Brochure for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator (see Section 4.4.3).

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, immunotherapy, radiotherapy and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression or recurrence is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 42 days prior to initiation of study treatment and during study treatment.

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the last dose of atezolizumab.

  Patients being treated with chemotherapy (i.e., carboplatin, cisplatin, pemetrexed, nab-paclitaxel, or gemcitabine) should not receive live vaccines.
- Systemic immunostimulatory agents (including, but not limited to, IFN and IL-2 are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. 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.

All treatment visits must occur ±3 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments should be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration should be performed prior to dosing, unless otherwise specified.

The following assessments may be performed ≤4 days before Day 1 of each cycle:

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

With the exception of tumor assessments (see Section 4.5.5 for details on time window), screening assessments performed ≤4 days before Day 1 of Cycle 1 are not required to be repeated on Day 1 of Cycle 1.

If a holiday, weekend, or other event precludes scheduled dosing, 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.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed

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

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.5 Tumor Response and Disease Follow-Up Evaluations

Screening assessments must include PET (whole body, or skull base to mid-thighs) with CT scans (with oral/IV contrast) of the chest and abdomen. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or a severe allergy), a non-contrast CT scan of the chest and abdomen may be performed along with the PET scan (whole body, or skull base to mid-thighs). A CT scan with contrast or MRI scan of the head must be done at screening to evaluate the presence of CNS metastasis in all patients to ensure eligibility (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Tumor assessments performed as standard of care prior to obtaining informed consent and within [redacted] days (for CT or MRI scan) or [redacted] days (for PET scan) prior to initiation of study treatment do not have to be repeated at screening.

All measurable and evaluable lesions should be assessed and documented at screening and reassessed at each subsequent tumor evaluation during the neoadjuvant treatment phase. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 3) during the neoadjuvant treatment phase. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

During the neoadjuvant treatment phase, patients will undergo tumor assessments at baseline and following the completion of Cycles [redacted] as per Appendix 1.
The investigator must review the scan results after Cycle 2 to determine if the patient is eligible to receive Cycle [redacted] of neoadjuvant treatment, or if the patient should proceed with surgery (those with disease progression but still amenable to curative surgery) or other standard of care treatment (those with disease progression not amenable to curative surgery). Similarly, the investigator must review tumor assessment scans after Cycle [redacted] to assess response and confirm disease resectability.

[redacted]

[redacted]

Disease recurrence after surgery should be confirmed pathologically and/or by unequivocal radiographic evidence. If a scan shows equivocal findings (e.g., mediastinal nodes measuring <1.5 cm in the short axis, lung parenchymal lesions or visceral lesions measuring <1 cm in the longest diameter), a biopsy should be performed. If a biopsy is not feasible or safe, then confirmatory scans should be performed again within 4 to 8 weeks. If the confirmatory scan confirms disease recurrence, then the event should be documented at the previous confirmatory scan date that showed the equivocal event.

If a biopsy for disease recurrence confirmation is performed, any leftover biopsy tissue is strongly encouraged to be submitted for exploratory biomarker research (optional consent required, see Section 4.5.7 for details). The biopsy should be performed prior to starting next anti-cancer therapy. If the biopsy does not show evidence of disease recurrence (e.g., non-malignant infiltrates), then the patient may continue with scheduled study treatment, assessments, and/or follow-up.

Tumor or disease follow-up assessments should continue in patients who discontinue treatment early for reasons other than disease progression or recurrence (e.g., because of toxicity). In the absence of disease progression or recurrence, tumor or disease follow-up assessments should continue in all patients, regardless of whether they start new anti-cancer therapy, until disease progression or recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

All scans will be submitted to an IRF for blinded independent review during the pre-surgery neoadjuvant treatment phase for RECIST v1.1 review as well as post-surgery disease assessment review.

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. Please refer to Appendix 1 for the specific tests required at screening and subsequent visits.

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, total HBcAb

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must be performed at screening to determine whether the patient has an HBV infection.
- HCV serology: HCV antibody and HCV RNA (only if HCV antibody test is positive)

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at every cycle during the neoadjuvant treatment phase for both treatment arms, and during every cycle in the adjuvant treatment phase for Arm A only. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal 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).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Archival or newly collected tumor tissue sample obtained at baseline suitable for PD-L1 testing (required) and for other exploratory research on biomarkers (strongly encouraged).

A representative FFPE tumor specimen in a paraffin block (preferred) or a minimum of 3 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report before or within 4 weeks after randomization. Any additional slides beyond the required minimum of 3 slides are strongly encouraged for other exploratory biomarker research.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples should be collected via resection, core-needle biopsy (at least 1–2 cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, and lavage samples are not acceptable.

If archival tumor tissue is unavailable, a pretreatment tumor biopsy is required.

Local PD-L1 testing: If no tissue specimen is available or if tissue sample was inadequate for PD-L1 central testing, documented known PD-L1 status as established by a health authority-approved PD-L1 assay is recommended.

- Resected tumor tissue and lymph node samples for evaluating pathological response evaluation and exploratory biomarker analysis

  The same slides from resected tumor tissue and lymph nodes used for local pathology assessment should be sent to the central pathology laboratory for central assessment. Slides may be returned to the local site afterwards.

  For exploratory biomarker analysis, if there is adequate remaining tumor and lymph node tissue, sites should submit a representative FFPE tumor specimen in a paraffin block (preferred) or a set of slides containing unstained, freshly cut, serial sections (10 slides for tumor bed or 3 slides for lymph node, if possible).

- Serum samples for atezolizumab PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of validated assays
- Blood, plasma, and serum samples for exploratory research on biomarkers

  Blood samples may be processed to obtain plasma, serum, peripheral blood mononuclear cells (PBMCs) and other derivatives (e.g., RNA, DNA, etc.).

  Exploratory biomarker research in tumor tissue and blood may include, but will not be limited to, analysis of proteins, genes or gene signatures associated with tumor immunobiology, PD-L1, markers associated with T-cell activation, or density, localization, and activation status of immune cells and their subsets, and may involve extraction of DNA, circulating tumor DNA, or RNA, analysis of somatic mutations, and use of NGS (including but not limited to WES).

  (Exception: For sites in China, samples for exploratory research on biomarkers will not be collected.)

The following samples will be sent to the study site's local laboratory or to one or several central laboratories or to the Sponsor or a designee for analysis:

- Baseline tissue samples for ALK and/or EGFR status, if not known, for patients with non-squamous NSCLC or mixed histology with non-squamous component observed (for sites in China, samples will require central laboratory testing)

Additional baseline samples are required for EGFR and ALK central testing (see the laboratory manual):

- For EGFR central testing, tissue, cytology, and/or plasma samples may be submitted. (Exception: For sites in China, cytology samples are not acceptable.)
- For ALK central testing, tissue or cytology samples may be submitted. (Exception: For sites in China, cytology samples are not acceptable.)

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Screening blood and tumor tissue samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the Clinical Study Report has been completed.
- Blood, plasma, serum, and fresh tumor tissue samples and their derivatives collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Optional Tumor Biopsies

Consenting patients will undergo the following optional tumor biopsies (if deemed clinically feasible by the investigator) for exploratory research on biomarkers:
an optional tumor biopsy at the time of radiographic disease progression and/or any time during treatment or survival follow-up (at the investigator's discretion). Biopsies at the time of disease progression or recurrence should be performed prior to the next anti-cancer therapy. Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response).

Samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. Refer to Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

An ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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

4.5.9 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through use of the following instruments: the EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L. Patients will complete paper questionnaire forms to capture PRO data during the neoadjuvant treatment and post-surgery phases of the study. Scheduled assessments are outlined in Appendix 1. The questionnaires will be translated as appropriate into the local language. Patients for whom the PRO questionnaires are not available in their native language may be exempt from completing PRO assessments. For patients who are unable to come to the clinic due to government restrictions or safety considerations, PROs may be completed via a telephone call; source documentation sufficient to pass an audit should be obtained which includes, among other information, that the questionnaires were administered via telephone because of government restrictions or safety considerations. During follow-up visits, PROs will be administered by site personnel to the patient via telephone in order to collect data without mandating that patients travel to the study site.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

During survival follow-up, patients will complete the global health status (Questions 29 and 30), physical functioning (Questions 1−5), and role functioning (Questions 6 and 7) scales of the EORTC QLQ-C30, and full EQ-5D-5L questionnaires via telephone at the scheduled survival follow-up calls at 3 and 6 months only. These assessments may be exempt if the study site is unable to administer these questionnaires in the patients' native language.

4.5.9.1 EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 4). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

4.5.9.2 EORTC QLQ-LC13

The EORTC QLQ-LC13 is a 13-item modular supplement to the EORTC quality of life questionnaire for use in lung cancer (see Appendix 5). This module incorporates one multiple-item scale to assess dyspnea and a series of single items assessing pain,

coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. The QLQ-LC13 module takes approximately 5 minutes to complete.

4.5.9.3 EQ-5D-5L

The EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 6). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analogue Scale (VAS) that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. The data will be used in this study for informing pharmacoeconomic evaluations and will not be included in the Clinical Study Report.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be used to achieve the following objectives:

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

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR 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 RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab or diseases:

- Blood sample for the RBR at Cycle [redacted] of Day [redacted], or as soon as possible after randomization, during the conduct of the clinical study
- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, PBMCs, proteins, peptides, etc.), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens will be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples 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.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or

patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent 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 RBR samples. 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 and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples 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 RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her samples 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 this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples 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 samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. 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 RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- 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

  Chemotherapy may be continued if atezolizumab/placebo is discontinued during the neoadjuvant treatment phase.

- Intolerable toxicity related to other components of the study treatment

  If any or all chemotherapeutic agents have been discontinued because of chemotherapy-related toxicities during the neoadjuvant treatment phase, atezolizumab/placebo should still be administered.

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Unequivocal radiographic disease progression per RECIST v1.1 during the neoadjuvant treatment phase
- Pathologically confirmed or unequivocal radiographic evidence of disease recurrence for Arm A patients receiving atezolizumab during the adjuvant treatment phase

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

Patients who discontinue neoadjuvant study treatment prior to receiving four cycles (e.g., because of treatment intolerability or lack of response) will be assessed by the treating medical oncologist and attending surgeon for surgical resection or non-surgical standard of care treatment measures (if not amenable for surgery). Patients who proceed with planned protocol-specified surgery remain eligible for all post-operative study treatment and procedures.

Patients will return to the clinic for a treatment or observation follow-up discontinuation visit no later than [redacted] days after the last dose of study treatment or last observation follow-up visit. The visit at which the response assessment shows disease progression or confirmed disease recurrence may be used as the treatment or observation follow-up discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or recurrence (e.g., toxicity) will continue to undergo scheduled tumor or disease follow-up as outlined in the schedule of activities (see Appendix 1). Patients who discontinue study treatment or observation follow-up for any reason will undergo PRO assessments at the treatment or observation follow-up discontinuation visit and at the scheduled survival follow-up calls at 3 and 6 months only (see Appendix 1).

After treatment or observation follow-up discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from Study

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

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

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. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.6.3 Study 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 Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with atezolizumab as monotherapy as well as atezolizumab administered in combination with nab-paclitaxel, pemetrexed, gemcitabine, carboplatin, and cisplatin in ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1–5.1.6).

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 of patients during the study. Guidelines for concomitant therapy, including therapy prohibited prior to study drug initiation and during the study, are outlined in Section 4.4. An iDMC has also been incorporated into the study design to periodically review safety data (see Section 3.1.2).

Administration of atezolizumab and the investigator-chosen chemotherapy regimen (nab-paclitaxel + carboplatin, pemetrexed + carboplatin/cisplatin, or gemcitabine + cisplatin) will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or

discontinuation, are provided in Appendix 9 and Appendix 10. Refer to Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology 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 judgement. 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: 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 10 and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Nab-Paclitaxel

In clinical studies and post-marketing experience, nab-paclitaxel has been associated with alopecia, myelosuppression (neutropenia, anemia, thrombocytopenia), peripheral neuropathy, cranial nerve palsies, severe hypersensitivity reactions, pneumonitis, gastrointestinal events (i.e., nausea, vomiting, diarrhea), myalgia, arthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, drug-induced lupus erythematous, infusion site reactions/extravasation, hepatic toxicity (drug-induced liver injury), acute renal failure, and hemolytic-uremic syndrome.

Patients will be monitored for nab-paclitaxel–related adverse events, including hematologic, gastrointestinal, and hepatic toxicities and peripheral neuropathy.

For more details regarding the safety profile of nab-paclitaxel, refer to the prescribing information for nab-paclitaxel.

5.1.3 Risks Associated with 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. Patients will be monitored for pemetrexed-related adverse events.

For more details regarding the safety profile of pemetrexed, refer to the prescribing information for pemetrexed.

5.1.4 Risks Associated with Gemcitabine

Gemcitabine infusion times that are longer than 60 minutes or gemcitabine administration that occurs more frequently than once a week have been shown to increase toxicity. Pulmonary toxicity has been reported with the use of gemcitabine. Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs. Hemolytic-uremic syndrome and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. 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. Due to the risk of cardiac and vascular disorders with gemcitabine, care should be exercised in patients with a history of cardiovascular events. Capillary leak syndrome and posterior reversible encephalopathy syndrome also has been reported in patients receiving treatment with gemcitabine as single agent or in combination with other chemotherapy agents. The administration of yellow fever vaccine and other live attenuated vaccines is not recommended during gemcitabine treatment due to reported risk of systemic and possibly fatal disease. Toxicity has been associated with concurrent radiotherapy (given together or $\leq$ 7 days apart). Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

Patients will be monitored for gemcitabine-related adverse events. For more details and precautions regarding the safety profile of gemcitabine, refer to the gemcitabine prescribing information.

5.1.5 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events.

For more details regarding the safety profile of carboplatin, refer to the prescribing information for carboplatin.

5.1.6 Risks Associated with 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, refer to the prescribing information for cisplatin.

5.1.7 Risks Associated with Atezolizumab Combined with Chemotherapy

Overlapping side effects between atezolizumab and chemotherapy are not expected nor have been observed based on completed and ongoing clinical studies to date. No new safety signals have been identified when atezolizumab was combined with carboplatin and nab-paclitaxel, and adverse events observed were consistent with the known profiles of each individual drug. Studies involving combinations of atezolizumab with cisplatin or carboplatin, pemetrexed, and gemcitabine are still ongoing with no new safety signals identified thus far.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- 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 treatment
- Is a significant medical event in the investigator's judgement (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported 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). Adverse events of special interest for this study are as follows:

- 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 treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, CRS, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

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 Section 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, surgery, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until [redacted] days after the last dose of study treatment or last observation follow-up visit or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the last dose of study treatment or last observation follow-up visit or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as 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

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgement?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme 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 meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgement

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgement should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgement

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgement should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

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 progression or recurrence of NSCLC should be recorded on the "Death Attributed to Disease Progression or Recurrence" eCRF. All other deaths that occur during the adverse event reporting period, 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). An independent monitoring committee will monitor the frequency of deaths from all causes.

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").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Pre-existing Medical Conditions

A pre-existing 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 pre-existing 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression or recurrence of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on radiographic evidence of disease progression (per RECIST v1.1) or evidence of radiographic disease recurrence after surgical resection of the primary tumor. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression or recurrence through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression or recurrence, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient 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:

- Planned hospitalization required by the protocol (e.g., planned surgical resection or for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study.

The patient has not experienced an adverse event.

- Hospitalization due solely to progression or 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 that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, 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). For any study drug, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with study treatment medications, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong

dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data (i.e., EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L) by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

Medical Monitor Contact Information for All Sites

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to all investigators.

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

5.4.2.1 Events That Occur Prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor 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 using 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, all adverse events will be reported until 30 days after the last dose of study treatment, or last observation follow-up visit, or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or last observation follow-up visit or until initiation of new systemic 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 electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor 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 using 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 serious adverse events that occur $>$90 days after the last dose of study treatment 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab, within 30 days after the last dose of nab-paclitaxel, or within 6 months after last dose of pemetrexed, gemcitabine, carboplatin, or cisplatin. A paper 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. 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 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

Atezolizumab is not expected to be genotoxic. In addition, the anticipated concentrations of atezolizumab in seminal fluid as well as the potential risk to the developing conceptus is low after seminal transfer of atezolizumab to a female partner.

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the neoadjuvant treatment phase, or within 30 days after the last dose of nab-paclitaxel, or 6 months after the last dose of carboplatin, cisplatin, gemcitabine, or pemetrexed. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form 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 study treatment. 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 with additional information on the pregnant partner and the course and outcome of the pregnancy as it 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 (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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 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 to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study treatment or last observation follow-up visit or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event 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 paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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 using the following reference documents:

- Atezolizumab Investigator's Brochure
- EU SmPC for nab-paclitaxel

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 iDMC will monitor the incidence of the above-listed anticipated 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

Independent Review Facility assessed EFS and OS analyses will be performed on stage IIB-IIIB-wild type (WT) patients and ITT-WT patients (i.e., the stage IIB-IIIB patients per AJCC v8 and all randomized patients without a known EGFR activating mutation or an ALK fusion oncogene, respectively). The secondary and exploratory efficacy endpoints, except IRF assessed pCR, IRF assessed MPR and OS (Section 6.4.2.1 and Section 6.4.2.2), will be analyzed in the stage IIB-IIIB-WT and/or the ITT-WT populations depending on the results of the primary endpoint analysis. Safety analyses will be performed on all randomized patients who received any amount of study treatment, with patients grouped according to whether any amount of atezolizumab was received, including cases where atezolizumab was received in error.

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately 450 patients will be randomized into this study. Patients who are randomized to the study and have confirmed EGFR/ALK mutations will be excluded from the efficacy analysis and all remaining randomized patients will be included in the ITT-WT population. It is assumed approximately [redacted] randomized patients will have a retrospectively identified EGFR activating mutation or an ALK fusion oncogene either by retesting tissue (for those originally tested by plasma) or by protocol deviation of exclusion criteria. Therefore, there will be approximately [redacted] patients in the ITT-WT population, and approximately [redacted] of the randomized patients are in the stage IIB-IIIB population (Wakelee et al. 2021), then approximately [redacted] patients are in the stage IIB-IIIB-WT population.

[redacted]

[redacted]

Assumptions for the Number of Events Required to Demonstrate Efficacy for IRF Assessed EFS in the Stage IIB-IIIB-WT Population:

- 1:1 randomization ratio

[redacted]

[redacted]

Assumptions for the Number of Events Required to Demonstrate Efficacy for IRF Assessed EFS in the ITT-WT Population:

- 1:1 randomization ratio

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and reasons for discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will be also tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics such as ECOG Performance Status, disease stage, and histology will be summarized by treatment arm. Descriptive statistics (mean, standard deviation, median, and range including minimum and maximum) 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 patients receiving the first dose of study treatment, unless otherwise noted.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

6.4.1.1 Independent Review Facility Assessed Event-Free Survival

The primary endpoint, IRF assessed EFS, is defined as the time from the date of randomization to any of the following events, whichever occurs first: disease progression per RECIST v1.1 that precludes surgery; local or distant disease recurrence (including occurrence of new primary NSCLC); or death due to any cause.

Patients who have not experienced disease progression that precludes surgery, local or distant disease recurrence (including occurrence of new primary NSCLC), or death at the time of analysis will be censored at the time of last tumor or disease follow-up assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization. Patients with missing baseline scan imaging will be censored at the date of randomization.

[redacted]

Kaplan-Meier methodology will be used to estimate the median EFS in each treatment arm, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median EFS in each arm. Treatment comparisons will be based on the stratified log-rank test. The HR for EFS will be estimated using a stratified Cox regression model. Stratification factors for analysis will include stage (II vs. IIIA N2− vs. IIIA/B N2+) and histology (non-squamous vs. squamous). The 95% CI for the HR will be provided. Results from unstratified analyses will also be provided.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- IRF assessed pCR and MPR
- OS
- Investigator assessed EFS
- Investigator assessed objective response according to RECIST v1.1
- Investigator assessed pCR and investigator assessed MPR at the time of surgical resection
- 2-year and 3-year OS, IRF assessed and investigator assessed EFS for each treatment arm
- Investigator assessed DFS during the adjuvant setting in patients completing surgical resection

- Change from baseline in HRQoL scores as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30, at each assessment timepoint during the study through the completion of adjuvant treatment and observation follow-up assessments

6.4.2.1 Independent Review Facility Assessed Pathological Complete Response Rate and Major Pathological Response Rate

Independent Review Facility assessed pCR rate is defined as the proportion of patients with an absence of invasive neoplastic cells at microscopic examination of the primary tumor and all sampled lymph node remnants after surgery, as determined by the central pathology laboratory. Patients not meeting these criteria, including patients who did not have surgical resection, will be considered as non-responders.

Independent Review Facility assessed MPR is defined as $\leq$10% residual viable tumor cells in the primary tumor at the time of surgical resection, assessed by the central pathology laboratory. It considers the averaged percentage of viable tumor cells on each slide that is prepared and available (Hellmann et al. 2014; Pataer et al. 2012). MPR rate is defined as the proportion of patients who have MPR.

The pCR and MPR rates between treatment arms will be compared using a Cochran-Mantel-Haenszel test stratified by stage (II vs. IIIA N2$-$ vs. IIIA/B N2$+$) and histology (non-squamous vs. squamous). An unstratified χ^2 test will also be provided as a sensitivity analysis. The difference in pCR and MPR rates will be provided with 95% CI, using the normal approximation to the binomial distribution. The Clopper-Pearson method will be used to construct the 95% CI for pCR and MPR rates for each treatment arm.

[redacted]

6.4.2.2 Overall Survival

OS is defined as the time from randomization to death from any cause. Patients who are not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization. OS will be analyzed using the same statistical methodology as EFS.

[redacted]

[redacted]

6.4.2.3 Investigator Assessed Event-Free Survival

Investigator assessed EFS is defined as the time from the date of randomization to any of the following events, whichever occurs first: progression of disease that precludes surgery per RECIST v1.1, as assessed by the investigator; local or distant disease recurrence (including occurrence of new primary NSCLC), as assessed by the investigator; or death due to any cause. Investigator assessed EFS will be assessed using the same statistical methodology as the primary endpoint, IRF assessed EFS.

6.4.2.4 Investigator Assessed Objective Response Rate

Objective response rate is defined as the proportion of patients with a best overall response of complete response or partial response as determined by the investigator per RECIST v1.1 (confirmation not required) during the neoadjuvant treatment phase. Patients not meeting these criteria, including patients without at least one post-baseline tumor assessment, will be considered non-responders. Investigator assessed ORR will be analyzed using the same statistical methodology as the secondary endpoints, IRF assessed pCR and MPR.

6.4.2.5 Investigator Assessed Pathological Complete Response Rate and Major Pathological Response Rate

The definition of investigator assessed pCR and MPR is the same as that of the IRF assessed pCR and MPR except that this will be assessed by the investigator site pathologist after surgical resection of the primary tumor. Investigator assessed pCR and MPR rates will be analyzed using the same statistical methodology as the central pathology laboratory assessed pCR and MPR rate.

6.4.2.6 2-Year and 3-Year Overall Survival, Independent Review Facility Assessed, and Investigator Assessed Event-Free Survival for Each Treatment Arm

The 2-year and 3-year OS rates are defined as the probability that a patient will be alive 2 years and 3 years after randomization, respectively. The 2-year and 3-year IRF assessed EFS and investigator assessed EFS rates are defined as the probability that a patient will be event-free 2 years and 3 years after randomization, respectively.
The Kaplan-Meier method will be used to estimate the 2-year and 3-year survival rate for each treatment arm. The 95% CI for the difference in survival rates between the two treatment arms will be estimated through use of the normal approximation method, and standard errors will be computed through use of the Greenwood method.

6.4.2.7 Disease-Free Survival

Disease-free survival is defined as the time from the first date of no disease (i.e., date of surgery) to local or distant recurrence (including occurrence of new primary NSCLC), or death due to any cause, whichever occurs first. DFS will be analyzed only for patients who underwent surgery and had no evidence of residual NSCLC disease. After surgery, patients who withdraw from the study without documented disease recurrence (including occurrence of new primary NSCLC) or death will be censored at the date of the last assessment when the patient is known to be free from disease recurrence. Patients without post-surgery assessments but known to be alive will be censored at the date of surgery. DFS will be analyzed using the same statistical methodology as the primary endpoint, IRF assessed EFS.

6.4.2.8 Patient-Reported Outcomes

The GHS/QoL scale responses will be scored according to the EORTC scoring manual guidelines (Fayers et al. 2001). The change from baseline in GHS/QoL scores at each assessment timepoint during the study through the completion of adjuvant treatment/observation follow-up assessments, as measured by the EORTC QLQ-C30 GHS/QoL scale, will be analyzed by treatment arm for all randomized patients. Details will be provided in the SAP.

6.4.3 Exploratory Endpoints

6.4.3.1 Independent Review Facility Assessed Event-Free Survival by PD-L1 Subpopulations

Independent Review Facility assessed EFS in the PD-L1 subpopulations, defined by SP263 TC $\geq$ 1% and TC $\geq$ 50%, will be assessed using the same statistical methodology as the primary endpoint IRF assessed EFS.

6.4.3.2 Subgroup Analysis

The effects of demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (e.g., tumor stage and histology), and biomarker status (e.g., SP263 TC $\geq$ 1% and TC $\geq$ 50%) on the primary efficacy endpoint, IRF assessed EFS, will be examined. Summaries of EFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median EFS, will be produced separately for each level of the categorical variables. Additional subgroup analyses of other secondary efficacy endpoints (e.g., investigator assessed EFS, pCR, MPR, and OS) may be conducted, if deemed necessary.

6.4.3.3 Biomarker Analysis

Exploratory biomarker analysis will be performed in an effort to understand the association of these markers with study treatment response, efficacy (including pathological response), and/or adverse events. The tumor biomarkers from tissue and blood samples include, but are not limited to, PD-L1, CD-8, tumor mutational burden, and circulating tumor DNA. Methods for assessment include, but are not limited to,

IHC and qRT-PCR. These results may be reported separately from the Clinical Study Report.

6.4.3.4 Patient-Reported Outcomes

The EORTC QLQ-C30 and QLQ-LC13 will be scored according to the EORTC scoring manual guidelines (Fayers et al. 2001). A change of ≥ 10 points on scales of the EORTC was established by Osoba et al. (1998) to be clinically meaningful.

The number and proportion of patients who improved, worsened, or remained stable on all of the scales of the EORTC QLQ-C30 and QLQ-LC13 will be summarized at each timepoint. A confirmed time to deterioration (TTD) analysis in patient-reported lung cancer symptoms of cough, fatigue, and pain and in GHS/QoL and Physical Functioning will be conducted and will be detailed in the SAP.

The EQ-5D-5L will be scored according to its manual, and results will be reported separately from the Clinical Study Report.

6.4.3.5 Additional Exploratory Pathological Response Assessments

To further elucidate the role of pathological response on clinical outcomes among subgroups, additional exploratory pathological response assessments will be performed. These include assessing pathological response in lymph nodes by central pathology assessment, as well as the potential role of digital pathology in the assessment of pathological response. Additional assessments include assessing pathological response by PD-L1 expression as well as the degree of pathological response by histology as there may be different cutoffs for predicting survival (Qu et al. 2019). Lastly, other exploratory assessments include rate of MPR (centrally and locally assessed), specifically in patients who have had surgery. These results may be reported separately from the Clinical Study Report.

6.5 SAFETY ANALYSES

Safety analysis will be performed on the safety population. The safety population will consist of all randomized patients who received at least one dose of study treatment. For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including cases where atezolizumab was received in error. The surgical safety population will consist of the safety population that has undergone protocol-mandated surgery.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, study treatment exposures, and impact to surgery. These summaries will be presented by treatment arm.

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

Impact to surgery, including incidence and length of surgical delays, incidence of operative and post-operative complications, and/or reason for surgical cancellations, will be summarized for each treatment arm using descriptive statistics.

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

The treatment-emergent adverse events leading to withdrawal of study treatment, leading to dose reduction or interruption, related to study drug, severe (i.e., Grade ≥ 3), fatal (i.e., Grade 5), serious, and of special interest will be also summarized.

All deaths and causes of death will be summarized.

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

6.6 PHARMACOKINETIC ANALYSES

Pharmacokinetic samples will be collected in this study as outlined in Appendix 2. Atezolizumab serum concentration data (minimum and maximum serum concentrations) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

6.7 IMMUNOGENICITY ANALYSES

Incidence of ADA against atezolizumab will be summarized. The analyses of pharmacokinetics, efficacy, and safety by ADA status may be conducted to explore the potential impact of immunogenicity.

6.8 HANDLING OF MISSING DATA

For MPR, ORR, and pCR, patients not meeting response criteria (including those without any post-baseline assessment) will be considered as non-responders.

For EFS, patients without disease progression, local or distant disease recurrence (including occurrence of new primary NSCLC), or death will be analyzed as censored observations on the date of the last tumor assessment or disease follow-up assessment. If no post-baseline tumor assessment or disease follow-up assessment is available, EFS will be censored at the date of randomization.

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

For DFS, data will be analyzed only for patients who underwent surgery. Patients who withdraw from the study without documented disease recurrence or death will be analyzed as censored observations on the date of the last assessment when the patient is known to be free from disease recurrence. If no post-surgery tumor assessment is available but the patient is known to be alive, DFS will be censored at the date of surgery.

For PRO data, the EORTC QLQ-C30 and QLQ-LC13 questionnaires will be scored according to the EORTC scoring manual guidelines (Fayers et al. 2001). Missing scores will not be imputed.

[redacted]







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, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms 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 and review 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 trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 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 IMPs, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

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.

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 applicable 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

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms")

before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. 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.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must be re-consented by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (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 9.7).

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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

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 or a designee 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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 125 sites [redacted] 450 patients. [redacted]

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety and efficacy throughout the study.

9.6 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. 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 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. 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 trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.7 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 Activities

Assessment			Neoadjuvant Treatment				Adjuvant Treatment/ Observation FU			
	[redacted]									
Informed consent [a, g]	x									
ALK and/or EGFR assessment (if status is unknown) [h]	x									
Baseline tumor tissue sample [i]	x									
Surgical tumor tissue and lymph node sample [j]					x					
Pathological response assessment					x					

Appendix 1: Schedule of Activities (cont.)

Assessment			Neoadjuvant Treatment				Adjuvant Treatment/ Observation FU			
Demographic data	x									
Medical history and baseline conditions	x									
Thoracic surgery evaluation	x			x						
Patient-reported outcomes [k]			[redacted]	x		x	[redacted]	x	x	[redacted]
Vital signs [l]	x		x				x		x	
Weight	x		x				x		x	
Height	x									

Appendix 1: Schedule of Activities (cont.)

Assessment			Neoadjuvant Treatment				Adjuvant Treatment/ Observation FU			
[redacted]										
Complete physical examination [m]	x									
Limited physical examination [n]			x				x	x		
[redacted]										
ECOG Performance Status	x								x	
ECG [p]	x		x				x	x		
Hematology [q]		x	x [r]				x		x	
Chemistry [s]		x	x [r]				x		x	
Pregnancy test [t]		x	x				x		x [t]	
Coagulation (INR, aPTT)		x							x	

Appendix 1: Schedule of Activities (cont.)

Assessment			Neoadjuvant Treatment				Adjuvant Treatment/ Observation FU			
TSH, free T3 (or total T3), free T4 [u]	x		x [r, u]				x [u]		x	
Viral serology [v]	x									
Urinalysis [w]	x		x [w]				x [w]	x [w]		
Blood, plasma, serum, sample for biomarkers	x [x]		x [x]	x [x]		x [x]	x [x]	x [x]	x [x]	x [x]
Serum samples for PK and ADA analyses			x [x]				x [x]		x [x]	
Blood for RBR (optional) [y]			x [y]							

Appendix 1: Schedule of Activities (cont.)

Assessment			Neoadjuvant Treatment				Adjuvant Treatment/ Observation FU			
Optional consent for exploratory research on disease recurrence biopsy							x [z]	x [z]	x [z]	
Optional tumor biopsy at the time of disease progression			x [z]						x [z]	
Optional tumor biopsy at other timepoints [aa]			Any time during study treatment, observation FU or survival FU (at investigator's discretion)							
Tumor response and disease FU assessments	x [bb]		x [cc]				x [dd]	x [dd]		x [dd]

Appendix 1: Schedule of Activities (cont.)

Assessment			Neoadjuvant Treatment				Adjuvant Treatment/ Observation FU			
Concomitant medications [ee]	x		x	x	x	x	x	x	x	
Adverse events [ff]	x		x	x		x	x	x	x	x
Study treatment administration [gg]			x				x			
Survival FU and anti-cancer treatment										x [hh]

ADA = anti-drug antibody; ALK = anaplastic lymphoma kinase ; BSC = best supportive care; CT = computed tomography (scan); ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EGFR = epidermal growth factor; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5 Dimension Questionnaire, 5-level version; FU = follow-up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDH = lactate dehydrogenase; MPR = major pathological response; MRI = magnetic resonance imaging; NSCLC = non-small-cell lung cancer; pCR = pathological complete response; PET = positron emission tomography; PK = pharmacokinetic; PORT = post-operative radiotherapy; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; QLQ-C30 = quality of life questionnaire for cancer; QLQ-LC13 = quality of life questionnaire for lung cancer; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Appendix 1: Schedule of Activities (cont.)

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within [redacted] days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[redacted]

[e] Patients randomized to Arm A will receive adjuvant treatment with atezolizumab Q3W for 16 cycles and will be scheduled for disease FU assessments. Patients randomized to Arm B on BSC will be required to come in for observation FU visit assessments Q6W for up to 8 visits and will be scheduled for disease FU assessments as well. [redacted]

[f] Patients who discontinue study treatment will return to the clinic for a treatment or observation FU discontinuation visit not more than [redacted] days after the last dose of study treatment or last observation FU visit (for Arm B patients). The visit at which response assessment shows disease progression or recurrence may be used as the treatment or observation FU discontinuation visit.

[g] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than [redacted] days before initiation of study treatment.

[h] For patients with non-squamous or mixed histology with observed non-squamous component that have unknown EGFR and/or ALK status, test results are required at screening. ALK and/or EGFR status may be assessed locally or at a central laboratory (in China, will be assessed centrally only). Additional tissue material and/or a plasma sample is required for central testing of EGFR and/or ALK. See laboratory manual for details.

[i] Archival or newly collected tumor tissue sample suitable for central PD-L1 testing is required (results of PD-L1 testing are not required for patient to be randomized into the study). Additional tissue material, if available, is strongly encouraged to be submitted for exploratory biomarker research. Samples and associated pathology report should be submitted before or within [redacted] weeks after randomization. Refer to Section 4.5.6 for tissue sample requirements.

[j] Tumor tissue and lymph node tissue obtained from surgical resection is required for pathological response analysis. Assessments on surgical specimen will be done for MPR, pCR, and exploratory biomarker analysis (if adequate tissue remains). Refer to Section 4.5.6 for tissue sample requirements.

Appendix 1: Schedule of Activities (cont.)

[k] PRO assessments EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires are required to be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory results or health record, before administration of study treatment, and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. During the neoadjuvant treatment phase, PRO assessments will be administered on Day 1 of each cycle only. For patients randomized to Arm A during the adjuvant treatment phase, PRO assessments will be administered on Day 1 of Cycle [redacted] and Day 1 of every other cycle thereafter. For patients who are unable to come to the clinic due to government restrictions or safety considerations, PROs may be completed via a telephone call; source documentation sufficient to pass an audit should be obtained which includes, among other information, that the questionnaires were administered via telephone because of government restrictions or safety considerations. During follow-up visits, PROs will be administered by site personnel to the patient via telephone in order to collect data without mandating that patients travel to the study site.

During survival FU, patients will complete the global health status (Questions 29 and 30), physical functioning (Questions 1−5) and role functioning (Questions 6 and 7) scales of the EORTC QLQ-C30, and full EQ-5D-5L questionnaires via telephone at the survival FU calls scheduled at [redacted] months only.

[l] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during the infusion and at 30 (±10) minutes after the infusion.

[m] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[n] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[redacted]

[p] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

Appendix 1: Schedule of Activities (cont.)

[q] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Hematology labs should also be performed prior to administration of Day [redacted] of gemcitabine infusion as well as Days [redacted] of nab-paclitaxel infusion.

[r] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle [redacted], they do not have to be repeated.

[s] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH. Chemistry panel labs should also be performed prior to administration of Day [redacted] of gemcitabine infusion as well as Days [redacted] of nab-paclitaxel infusion.

[t] All women of childbearing potential will have a serum pregnancy test at screening, within [redacted] days prior to initiation of study treatment. Urine pregnancy tests will be performed at every cycle in the neoadjuvant phase for both treatment arms, and during every cycle in the adjuvant treatment phase for Arm A. Urine pregnancy test will also be performed at the Treatment or Observation FU Discontinuation Visit for Arm A and for Arm B if the last dose of neoadjuvant treatment was administered within 6 months of treatment or observation FU discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day [redacted] of Cycles [redacted] for both treatment arms in the neoadjuvant phase, and Day [redacted] of Cycles [redacted] in the adjuvant phase only for patients assigned to Arm A.

[v] At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[w] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Urinalysis should be performed as clinically indicated during study treatment.

[x] See Appendix 2 for detailed schedule. During survival FU, biomarker plasma and serum samples will be collected only at the time of disease progression or recurrence (before administration of subsequent therapy if planned).

[y] A blood sample for the RBR will be collected on Cycle [redacted], Day [redacted]. However, if this sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study. Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[z] Patients will undergo an optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 during the neoadjuvant treatment phase or to submit tissue samples obtained from pathological confirmation of disease recurrence (for exploratory biomarker research) during the adjuvant treatment/monitoring phase. Biopsies should be performed prior to the next anti-cancer therapy. Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.6 for tissue sample requirements.

[aa] Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.7 for details.

Appendix 1: Schedule of Activities (cont.)

[bb] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within [redacted] days (for CT or MRI scan) or [redacted] days (for PET scan) prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include PET scan (whole body, or skull base to thighs) and CT scan (with oral or IV contrast) of the chest, abdomen, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or severe allergy), a non-contrast CT scan of the chest and abdomen may be performed along with the PET (whole body, or skull base to thighs). A CT scan with contrast or MRI scan of the head must be done at screening to rule out CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[cc] Patients will undergo tumor assessments after completion of Cycles [redacted] following treatment initiation per RECIST v1.1 during the neoadjuvant treatment phase. All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). The investigator must review the scan results after Cycle [redacted] to determine if the patient is eligible to continue receiving Cycle [redacted] of neoadjuvant treatment, or if the patient should proceed with surgery (those with disease progression but still amenable to curative surgery) or other standard of care treatment (those with disease progression not amenable to curative surgery). Similarly, the investigator must review tumor assessment scans after Cycle [redacted] to assess response and confirm disease resectability.

[dd] [redacted] If a disease FU assessment suggests potential disease recurrence, the event should be confirmed pathologically and/or by unequivocal radiographic evidence. If a scan shows equivocal findings (e.g., mediastinal nodes measuring < 1.5 cm in the short axis, lung parenchymal lesions or visceral lesions measuring < 1 cm in the longest diameter), a biopsy should be performed. The biopsy should be performed prior to starting the next anti-cancer therapy. If the biopsy does not show evidence of disease recurrence (e.g., non-malignant infiltrates), then the patient may continue with scheduled study treatment and/or FU. If a biopsy is not feasible or safe, then confirmatory scans should be performed again within 4–8 weeks.

[redacted]

All scans will be submitted to an IRF for blinded independent review during the pre-surgery neoadjuvant treatment phase for RECIST v1.1 review as well as post-surgery disease assessment review.

Appendix 1: Schedule of Activities (cont.)

[ee] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from [redacted] days prior to initiation of study treatment until the treatment or observation FU discontinuation visit.

[ff] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] days after the last dose of study treatment or last observation FU visit or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the last dose of study treatment or last observation FU visit or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). 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 FU, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[gg] The initial infusion of atezolizumab/placebo will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. For carboplatin, cisplatin, pemetrexed, gemcitabine, and nab-paclitaxel, study treatment will be administered according to the local prescribing information, including premedication with corticosteroids (see Section 4.3.2).

[hh] After treatment or observation FU discontinuation, information on survival FU and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from FU, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) in accordance with local regulations to obtain information about survival status only. *Additional survival* FU *visits may be collected after the final IRF-EFS/OS analysis if requested by health authorities.*

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Blood Samples

Visit	Timepoint	Sample Type
Screening (Day [redacted])	NA	• Blood for biomarkers [a] • Plasma for EGFR central testing [b]
Neoadjuvant Treatment		
Day 1 of Cycles [redacted]	Pre-dose	• Plasma and serum for biomarkers (Cycle [redacted]) • Serum for PK and ADA analyses (Cycle [redacted]) • Optional blood for RBR (Cycle [redacted]) [c]
	30 (±10) minutes after end of atezolizumab/placebo infusion	• Serum for PK analyses (Cycle [redacted])
Pre-Surgery Visit	NA	• Plasma and serum for biomarkers
Post-Surgery Visit	NA	• Blood for biomarkers [a] • Plasma and serum for biomarkers
Adjuvant Treatment (Arm A Only)		
Day [redacted] of Cycles [redacted]	Pre-dose	• Plasma and serum for biomarkers • Serum for PK and ADA analyses (Cycle [redacted] only)
	30 (±10) minutes after end of atezolizumab infusion	• Serum for PK analyses (Cycle [redacted])
Best Supportive Care and Observation FU (Arm B Only)		
Visits [redacted]	NA	• Plasma and serum for biomarkers
Arm A and Arm B		
Disease Progression/ Recurrence or Treatment/Observation FU Discontinuation Visit (≤30 days after last dose)	NA	• Plasma and serum for biomarkers • Serum for PK and ADA analyses [d]

ADA = anti-drug antibody; EGFR = epidermal growth factor receptor; FU = follow-up; NA = not applicable; NSCLC = non–small cell lung cancer; PK = pharmacokinetic; RBR = Research Biosample Repository.

Note: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] If this sample is not collected during the scheduled visit, it may be collected at any other visit during the conduct of the clinical study.

[b] Only to be performed if EGFR activating mutation status is unknown for patients with non-squamous or mixed histology with observed non-squamous component and if there is inadequate tissue for central EGFR testing.

[c] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. The whole blood sample for the RBR will be collected on Day [redacted] of Cycle [redacted]. However, if this sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[d] Serum draws for PK and ADA analyses at disease progression or treatment discontinuation will occur in both treatment arms during the double-blinded neoadjuvant treatment phase and only in Arm A during the open-label adjuvant treatment phase.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints in the neoadjuvant treatment phase. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

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

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

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

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

but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to <10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be 0 even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

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

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

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

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

NEW LESIONS

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

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

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

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

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

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

Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

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

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.
The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1 and Table 2.

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

REFERENCES

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

Appendix 4
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: EORTC QLQ-C30

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix 5
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13)

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ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

SPECIMEN

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Appendix 6
EuroQol 5-Dimension Questionnaire, Five-Level Version (EQ-5D-5L)

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Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking	❑
I have slight problems walking	❑
I have moderate problems walking	❑
I have severe problems walking	❑
I am unable to walk	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

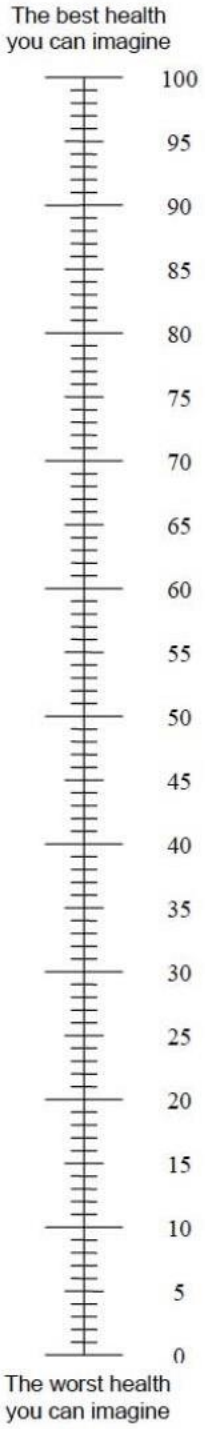
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 7
Pre-existing Autoimmune Diseases and Immune Deficiencies

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 listed in the table below 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-related hypothyroidism on a stable dose of thyroid replacement hormone may be 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 anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies (cont.)

• Churg-Strauss syndrome • Crohn disease	• Myasthenia gravis	

Appendix 8
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 9
Overall Guidelines for Management of Patients Who Experience Adverse Events

TREATMENT INTERRUPTION

With regard to chemotherapy toxicities, if one drug in a chemotherapy regimen is interrupted, the other chemotherapy agent must be held as well. In general, treatment could be held for up to 42 days after Day 1 of the last cycle to allow sufficient time for recovery from the toxicities listed below. If one drug in a chemotherapy regimen is permanently discontinued, the other chemotherapy may be continued as a single agent.

MANAGEMENT GUIDELINES

Guidelines for atezolizumab/placebo discontinuation for patients who experience adverse events in addition to or outside of the guidelines in this appendix are provided in Appendix 10 and the Atezolizumab Investigator's Brochure.

For adverse events associated with carboplatin, nab-paclitaxel, cisplatin, gemcitabine, and pemetrexed that are not listed in Tables 1–11 below, refer to guidelines in the applicable Summary of Medicinal Product Characteristics. For cases in which management guidelines are not covered in the protocol or prescribing information, patients should be managed as deemed appropriate by the investigator according to best medical judgement. When a treatment cycle is delayed or interrupted because of toxicity resulting from either component of the chemotherapy regimen, all study drugs (including atezolizumab or placebo) should generally be withheld and resumed together to remain synchronized. At the subsequent cycle, if chemotherapy still cannot be given due to prolonged AE and toxicities, then atezolizumab or placebo should be given for that cycle alone. If chemotherapy has been withheld for 42 days (delayed cycle + subsequent cycle), then it should permanently be discontinued.

Investigators should be vigilant and alert to early and overt signs of myelosuppression/infection/febrile neutropenia or other chemotherapy induced toxicities, 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.

NAB-PACLITAXEL: DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

Dose modifications of nab-paclitaxel are allowed as described in the following sections.

Nab-Paclitaxel: Hematologic Toxicity

In general, per common standard of care guidelines, ANC must be ≥ 1500 cells/μL and platelet count must be ≥ 100,000/μL on Day 1 of each cycle. When nab-paclitaxel is administered on Day 1, it should not be administered on Days 8 or 15 of the cycle unless

ANC≥500 cells/μL and platelet count ≥50,000/μL. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2006; NCCN 2017).

If the start of a cycle is delayed for low counts, postpone Day 1 and resume dosing when counts recover with applicable reductions according to criteria in Table 1.
If nab-paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels. When dosing resumes, the nab-paclitaxel doses should be permanently reduced as outlined in Table 1.

Table 1 Nab-Paclitaxel Permanent Dose Reductions Based on Nadir Absolute Neutrophil Count and Platelets

Hematologic Toxicity	Occurrence	Weekly Nab-Paclitaxel Dose (mg/m^2)
Neutropenic fever (nadir ANC <500 cells/μL with fever >38°C) or Delay of next scheduled dose by >7 days for nadir ANC <1500 cells/μL or Nadir ANC <500/μL for >7 days	First	75
	Second	50
	Third	Discontinue treatment
Nadir platelet count <50,000/μL	First	75
	Second	Discontinue treatment

ANC = absolute neutrophil count.

Nab-Paclitaxel: Gastrointestinal Toxicity

For Grade 3 or 4 gastrointestinal toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on gastrointestinal toxicities from the dose administered in the preceding cycle. Table 2 provides the relevant dose adjustments for gastrointestinal toxicities.

Table 2 Nab-Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity	Occurrence	Adjusted Nab-Paclitaxel Dose as % of Previous Dose
Grade 3 diarrhea or Grade 3 mucositis/stomatitis or Grade 3 or 4 nausea/vomiting	First	75%
	Second	50%
	Third	Discontinue treatment
Grade 4 oral mucositis/stomatitis	—	Discontinue treatment
Grade 4 diarrhea	—	Discontinue treatment

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs in spite of anti-emetics, the dose should be reduced by 25% for the next and subsequent courses.

If, on Day 1 of any treatment cycle, the patient has oral mucositis/stomatitis, the treatment should be withheld until the oral mucositis/stomatitis is cleared. If the oral mucositis/stomatitis has not cleared in 42 days, nab-paclitaxel should be discontinued. See Table 2 for additional details on dose reductions. Dose reductions listed are permanent.

Nab-Paclitaxel: Neurological Toxicity

Nab-paclitaxel should be withheld for Grade 3–4 peripheral neuropathy. Nab-paclitaxel may be resumed at reduced doses (see Table 3) when peripheral neuropathy recovers to Grade 1 or completely resolves.

Table 3 Nab-Paclitaxel Permanent Dose Reductions for Neurological Toxicity

Adverse Reaction	Occurrence	Weekly Nab-Paclitaxel Dose (mg/m^2)
Grade 3 or 4 sensory neuropathy	First	75
	Second	50
	Third	Discontinue treatment

Nab-Paclitaxel: Hepatic Toxicity

For patients who develop severe enzyme elevations during study treatment (ALT and/or AST $\geq 5\times$ ULN or total bilirubin $\geq 3\times$ ULN), study treatment should be interrupted, hepatic toxicity must resolve to baseline levels prior to dosing. If nab-paclitaxel is withheld because of hepatic toxicity, the accompanying chemotherapeutic agent (i.e., carboplatin) should also be withheld and administered when nab-paclitaxel is resumed. If nab-paclitaxel is withheld, hepatic values must recover to baseline levels within 3 weeks or the patient's nab-paclitaxel treatment will be discontinued.

For patients with mild hepatic impairment (total bilirubin >1 to $\leq 1.5\times$ ULN and ALT/AST $\leq 5\times$ ULN), no dose adjustments are required. Treat with the same doses as patients with normal hepatic function.

If moderate to severe hepatic elevations (total bilirubin >1.5–$5.0\times$ ULN or ALT and/or AST 5–$10\times$ ULN) occur at any time, the nab-paclitaxel dose should be permanently reduced to 80% of the starting dose (i.e., to 80 mg/m^2). Nab-paclitaxel will be discontinued for patients with total bilirubin $>5\times$ ULN or AST $>10\times$ ULN.

Nab-Paclitaxel: Pulmonary Events and Pneumonitis

Note: When atezolizumab is administered without nab-paclitaxel, refer to Appendix 10 or the Atezolizumab Investigator's Brochure for management of pulmonary events, including pneumonitis.

Atezolizumab

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

Mild to moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia or infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension:

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

Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest at every tumor assessment. See Table 4 for management guidelines for pulmonary events and pneumonitis.

Nab-Paclitaxel

Interstitial pneumonitis has been observed in < 1% of patients with nab-paclitaxel monotherapy and 4% with the use of nab-paclitaxel in combination with gemcitabine. Patients should be monitored closely for signs and symptoms of pneumonitis.

Nab-paclitaxel should be permanently discontinued upon ruling out infectious etiology and making a diagnosis of pneumonitis. Promptly initiate appropriate treatment and supportive measures.

Infections should be ruled out with routine microbiological and/or immunologic methods.

After ruling out an infectious etiology, IV high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide.

Table 4 details the management of pulmonary events/pneumonitis when atezolizumab/placebo and nab-paclitaxel are administered together, or when nab-paclitaxel is administered alone.

Table 4 Management Guidelines for Pneumonitis for Patients Treated with Nab-Paclitaxel

	Management Guidelines	
Severity	Atezolizumab/Placebo	Nab-Paclitaxel [a]
Grade 1	• Withhold atezolizumab/placebo with close monitoring. • Resume when event improves to Grade 0. Re-evaluate on serial imaging. • Consider pulmonary consultation.	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.

BAL = broncho-alveolar lavage.

Note: When atezolizumab is administered without nab-paclitaxel, refer to Appendix 10 and the Atezolizumab Investigator's Brochure for management of pulmonary events, including pneumonitis.

[a] Whether administered with or without atezolizumab/placebo.

Table 4 Management Guidelines for Pneumonitis for Patients Treated with Nab-Paclitaxel (cont.)

Grade 2	• Withhold atezolizumab/placebo. • Pulmonary and infectious disease consultation with consideration for bronchoscopy/BAL. • Start 60 mg prednisone or equivalent per day. • When improves to Grade 0 or Grade 1, then taper corticosteroids over ≥1 month. • Atezolizumab/placebo may be resumed if the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to the equivalent of oral prednisone 10 mg daily or less. • Treat as Grade 3 or 4 if recurrent episode of pneumonitis.	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.
Grade 3 or 4	• Permanently discontinue atezolizumab/placebo and contact the Medical Monitor. • Bronchoscopy/BAL is recommended. • Start 60 mg prednisone or equivalent per day. • Taper corticosteroids over ≥1 month after symptoms improve to Grade 0 or Grade 1. • If not improving after 48 hours or worsening, add additional immunosuppression (e.g., infliximab, cyclophosphamide, IVIg, or mycophenolate mofetil).	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.

BAL = broncho-alveolar lavage; Ig = immunoglobulin; IVIg = intravenous immunoglobulin.

Note: When atezolizumab is administered without nab-paclitaxel, refer to Appendix 10 and the Atezolizumab Investigator's Brochure for management of pulmonary events, including pneumonitis.

[a] Whether administered with or without atezolizumab/placebo.

Nab-Paclitaxel: Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, nab-paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. Nab-paclitaxel may be resumed at reduced doses (see Table 5) when toxicity recovers to Grade 1 or completely resolves. If recovery to Grade 1 toxicity does not occur within 42 days, nab-paclitaxel should be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

Table 5 Nab-Paclitaxel Permanent Dose Reductions for Non-Hematologic, Non-Gastrointestinal, Non-Neurologic, and Non-Hepatic Toxicity

Adverse Reaction	Occurrence	Weekly Nab-Paclitaxel Dose (mg/m^2)
Grade 3 or 4 non-hematologic, non-GI, non-neurologic, non-hepatic toxicity	First	75
	Second	50
	Third	Discontinue treatment

GI = gastrointestinal.

CARBOPLATIN DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

Treatment with carboplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment is delayed for more than 42 days due to toxicities.

Carboplatin: 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 42 days to allow sufficient time for recovery. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2006; NCCN 2017). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table 6).

Table 6 Carboplatin Dose Modification for Hematologic Toxicities

Toxicity [a]	Carboplatin Dose
ANC < 500 cells/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

ANC = absolute neutrophil count.

[a] Nadir prior cycle.

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

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 will then be resumed.

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

Carboplatin: Non-Hematologic Toxicity

For any non-hematologic toxicity listed in Table 7, treatment should be delayed for up to 42 days until resolution to less than or equal to the patient's baseline value (or Grade ≤ 1 if patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle will be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 7 provides the relevant dose adjustments for non-hematologic toxicities.

Table 7 Carboplatin Dose Modification on the Basis of Non-Hematologic Toxicities in the Preceding Cycle

Toxicity		Adjusted Carboplatin Dose as % of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%
Nausea/vomiting	Grade 3 or 4 [c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue
Other	Grade 3 or 4	75%

AUC = area under the concentration–time curve.

[a] If deemed appropriate by the treating physician, adjust carboplatin dose to the specified percentage of the previous AUC.

[b] Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization.

[c] Despite the use of anti-emetics.

Diarrhea should be controlled with adequate anti-diarrhea medication. Nausea and/or vomiting should be controlled with adequate anti-emetics. For a Grade 3 or 4 neurotoxicity, carboplatin should be resumed at 50% of the previous dose upon improvement, or discontinued immediately (based on investigator's clinical judgement).

CISPLATIN DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

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 42 days because of toxicities. Additionally, if the patient becomes intolerable to cisplatin because of the toxicities stated above, the investigator may consider switching to carboplatin.

Cisplatin: Hematologic Toxicity

At the start of each cycle, the ANC must be $\geq$1500/μL, and the platelet count must be $\geq$100,000/μL. Treatment should be delayed for up to 42 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 National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2006; NCCN 2017). 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.

Cisplatin: Non-Hematologic Toxicity

If a patient develops any non-hematologic toxicity listed in Table 8, cisplatin should be withheld for up to 42 days after Day 1 of the last cycle until resolution to less than or equal to the patient's baseline (or Grade $\leq$1 if patient did not have that toxicity at baseline). Treatment should be resumed according to the guidelines in Table 8.

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

Table 8 Cisplatin Dose Modifications for Non-Hematologic Toxicities (Excluding Neurotoxicity and Nephrotoxicity)

Toxicity	Adjusted Cisplatin Dose as % of previous Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication	75%
Grade 3 or 4 nausea/vomiting [a]	75%
Any other Grade 3 or 4 toxicity	75%

[a] Despite the use of anti-emetics.

Cisplatin: Nephrotoxicity

Creatinine clearance (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 judgement 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 42 days after Day 1 of the last cycle, the patient should be discontinued from cisplatin.

Cisplatin: Neurotoxicity

In the event of neurotoxicity, the recommended dose adjustment for cisplatin is documented in Table 9. 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 judgement).

Table 9 Cisplatin Dose Modifications or Treatment Discontinuation for Associated Neurotoxicity

Toxicity	Adjusted Cisplatin Dose as % of Previous Dose
Grade 0 or 1 neurotoxicity	100%
Grade 2 neurotoxicity	75%
Grade 3 or 4 neurotoxicity	50% 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 8 for dose modifications.

PEMETREXED DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC ADVERSE EVENTS

The dose modification guidelines are applicable for pemetrexed used in combination with either carboplatin or 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 42 days after Day 1 of the last cycle because of toxicities.

Pemetrexed: 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 42 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 2017). 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 10).

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

Table 10 Pemetrexed Dose Modifications for Hematologic Toxicities

Toxicity [a]	Adjusted Pemetrexed Dose as % of Previous Dose
ANC <500/μL and platelets ≥50,000/μL	75%
Platelets <50,000/μL, regardless of ANC	75%
Platelets <50,000/μL with Grade ≥2 bleeding, regardless of ANC	50%

ANC = absolute neutrophil count.

[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.

Pemetrexed: Non-Hematologic Toxicity

At the start of each cycle, the CRCL must be ≥45 mL/min. If a patient develops any non-hematologic toxicity listed in Table 11, pemetrexed should be withheld for up to 42 days after Day 1 of the last cycle until resolution to equal or less than 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. 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 judgement).

Table 11 Pemetrexed Dose Modifications for Non-Hematologic Toxicities

Toxicity	Adjusted Pemetrexed Dose as% of Previous Dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication.	75%
Neurotoxicity	
Grade 2	75%
Grade 3 or 4	50% or permanent discontinuation
Any other Grade 3 or 4 toxicities	75%

Pemetrexed: 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 5–7 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.

GEMCITABINE DOSE MODIFICATION AND MANAGEMENT OF SPECIFIC 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 42 days after Day 1 of the last cycle because of toxicities.

Hematologic Toxicities

At the start of each cycle, the ANC must be ≥1500 cells/μL and the platelet count must be ≥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 12 and Table 13). Patients receiving gemcitabine should be monitored prior to each dose with a full blood count, including differential and platelet counts. Growth factors may be used in accordance with ASCO and NCCN guidelines (Smith et al. 2006; NCCN 2017). 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 12).

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

Table 12 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

ANC = absolute neutrophil count.

[a] Nadir of prior cycle.

Table 13 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 judgement.

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 14 provides dose modification guidelines for non-hematologic toxicities.

Table 14 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.		

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Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab/Placebo

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 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 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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

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 **without** 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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	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	• 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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	AST/ALT is $>3\times$ ULN to $\leq 5\times$ ULN at baseline and increases to $>8\times$ ULN to $\leq 10\times$ ULN		
	AST or ALT increases to $>10\times$ ULN or total bilirubin increases to $>3\times$ 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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
Amylase and/or lipase elevation	Grade 2 with amylase and/or lipase $>1.5–2.0\times$ 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 $>2.0–5.0\times$ 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).

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	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.	• 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.*

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	Grade 2	• If event does not resolve fully while withholding, permanently discontinue.	
	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.*

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	Grades 3–4		• *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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
	Grade 2		• 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]

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
IRR and 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		• 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 low-flow oxygen [f] by nasal cannula or blow-by	• 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.

Table 1 Dose Modification and Management Guidelines for Patients Who Experience Adverse Events Associated with Atezolizumab (cont.)

Event	CTCAE Toxicity Grade or Condition	Action to be Taken with Atezolizumab	Adverse Event Management (guidance in addition to the general recommendations provided above)
IRR and CRS			• 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 (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	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. • 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 v5.0 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 $\geq 38°C$ 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 11
American Joint Committee on Cancer Non-Small Cell Lung Cancer Staging, 8th Edition

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a(mi)	**Minimally invasive adenocarcinoma**[b]
T1a	**Tumor ≤1 cm in greatest dimension**[a]
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension**[a]
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension**[a]
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features[c]: - **Involves main bronchus regardless of distance from the carina but without involvement of the carina** - Invades visceral pleura - **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm,** mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis**[e]
M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition are in bold.
[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.
[c]T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) lymph node.

Appendix 11: American Joint Committee on Cancer Non-Small Cell Lung Cancer Staging, 8th Edition (cont.)

		N categories			
		Overall stage			
Descriptor in 7th edition	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	**IIB** (IIA)	**IIIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

[a]Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
T, tumor; M, metastasis.

Appendix 12
Investigational, Non-Investigational, and *Auxiliary Medicinal Product Designations* (for Use in United Kingdom and European Economic Area)

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

Product Name	IMP/NIMP Designation	Marketing Authorization Status in the UK	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No
Nab-paclitaxel	IMP (test product) [a]	Authorized	No
Placebo	IMP (placebo)	Not Authorized	Not applicable
Pemetrexed	NIMP (background)	Authorized	*No* [b]
Gemcitabine	NIMP (background)	Authorized	*No* [b]
Cisplatin	NIMP (background)	Authorized	*No* [b]
Carboplatin	NIMP (background)	Authorized	*No* [b]

IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

[a] Nab-paclitaxel is considered to be an IMP test product as well as an IMP comparator.

[b] *Pemetrexed, Gemcitabine, Carboplatin and Cisplatin are not approved for the neoadjuvant treatment indication but are recommended as per the NCCN treatment guidelines*

Table 2 Investigational, Authorized Auxiliary, and Unauthorized 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
Nab-paclitaxel	IMP (test product) [a]	Authorized	No
Placebo	IMP (placebo)	Not Authorized	Not applicable
Pemetrexed	AxMP (background)	Authorized	*No* [b]
Gemcitabine	AxMP (background)	Authorized	*No* [b]
Cisplatin	AxMP (background)	Authorized	*No* [b]
Carboplatin	AxMP (background)	Authorized	*No* [b]

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

[a] Nab-paclitaxel is considered to be an IMP test product as well as an IMP comparator.

[b] *Pemetrexed, Gemcitabine, Carboplatin and Cisplatin are not approved for the neoadjuvant treatment indication but are recommended as per the NCCN treatment guidelines*

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