Official Title: A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study of Tiragolumab in Combination with Atezolizumab Plus Pemetrexed and Carboplatin/Cisplatin Versus Pembrolizumab Plus Pemetrexed and Carboplatin/Cisplatin in Patients with Previously Untreated Advanced Non-Squamous Non-Small-Cell Lung Cancer

NCT Number: NCT04619797

Document Date: Protocol Amendment Version 9: 15-Jul-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE II/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN VERSUS PEMBROLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER**
PROTOCOL NUMBER:	BO42592
VERSION NUMBER:	9
TEST COMPOUNDS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267) Pembrolizumab, Pemetrexed, Carboplatin/Cisplatin
STUDY PHASE	Phase II/III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 129258 EudraCT Number: 2020-002851-39 EU Trial Number: 2022-502031-20-00 PS ID Number: RD006584 CIV ID Number: CIV-22-11-041371 NCT Number: NCT04619797
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.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
9	See electronic date stamp on the final page of this document.
8	04 Dec 2023
7	4 April 2023
6	13 October 2022
5	12 August 2022
4	18 January 2022
3	8 July 2021
2	24 February 2021
1	26 June 2020

PROTOCOL AMENDMENT, VERSION 9: RATIONALE

Protocol BO42592 Version 9 has been amended based on the primary analysis of progression-free survival (PFS) and the first interim analysis of overall survival (OS) showing reduced efficacy in both primary endpoints for the combination of tiragolumab plus atezolizumab and chemotherapy compared to the comparator arm. The Sponsor issued an Urgent Safety Measure Dear Investigator Letter (USM DIL), dated 4 July 2024, communicating the benefit-risk profile does not support the use of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin as a first-line therapy for patients with advanced non-squamous non–small-cell lung cancer (NSCLC). Consequently, patients who are currently receiving study treatment on the investigational arm of tiragolumab in combination with atezolizumab and chemotherapy should discontinue from the study and seek other treatment options outside of the study for their non-squamous NSCLC. Changes to the protocol along with a rationale for each change are summarized below:

- [redacted]

- Treatment beyond 24 months is no longer permitted in either treatment arm due to the benefit/risk profile no longer supporting the use of tiragolumab plus atezolizumab and chemotherapy; and to align with the approved treatment duration of pembrolizumab plus chemotherapy (Section 3.1.1).

- Treatment beyond disease progression is no longer permitted, to align with the current label indication for patients on the comparator arm receiving pembrolizumab plus chemotherapy; [redacted] (Sections 3.1.1, 3.3, 4.5.1, 4.5.6, 4.6.1, and Appendix 1).

- The requirement for tumor assessments per protocol defined schedule following unblinding at study level has been removed to reduce administrative burden to patients. Investigators must continue to report tumor assessment results based on the frequency as per their local practices (Sections 3.1.1, 3.2.1, 4.5.6, 9.5, and Appendix 1).

- Patient-Reported Outcomes (PRO) assessments have been modified to remove the requirement for PRO questionnaires for all remaining patients at the time of unblinding at study level in order to reduce burden to patients (Sections 3.1.1, 3.2.1, and 4.5.9, and Appendix 1).

- The pharmacokinetic, immunogenicity, and biomarker sample collection schedule has been changed so that samples are no longer collected at any timepoint after

unblinding at study level because the Sponsor has decided no additional sample collection is needed (Sections 3.1.1 and 3.2.1, Appendix 1 and Appendix 2).

- No further subsequent efficacy analyses, [redacted], will be done based on the primary analysis of PFS and the first interim analysis of OS showing reduced efficacy in both primary endpoints for tiragolumab plus atezolizumab and chemotherapy compared to the comparator arm (Section 6).

Substantive new information (relative to Protocol Amendment Version 8) appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE II/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN VERSUS PEMBROLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED NON-SQUAMOUS NON–SMALL-CELL LUNG CANCER**
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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.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE II/III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TIRAGOLUMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN VERSUS PEMBROLIZUMAB PLUS PEMETREXED AND CARBOPLATIN/CISPLATIN IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED NON-SQUAMOUS NON–SMALL-CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 129258 EudraCT Number: 2020-002851-39 EU Trial Number: 2022-502031-20-00 PS ID Number: RD006584 CIV ID Number: CIV-22-11-041371 NCT Number: NCT04619797

STUDY RATIONALE

The purpose of this study is to assess the efficacy, safety, and pharmacokinetics of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin in treatment Arm A compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin in treatment Arm B in patients with previously untreated, locally advanced unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC). For patients whose tumors lack a targetable oncogenic aberration, current standard of care 1L regimens typically consist of an immune checkpoint inhibitor, including PD-L1/PD-1 blocking antibodies, with or without platinum-based doublet chemotherapy and bevacizumab. The majority of patients with advanced non-squamous NSCLC on currently available treatment options ultimately experience disease progression and succumb to this disease. Therefore, a high unmet medical need persists for advanced non-squamous NSCLC.

OBJECTIVES AND ENDPOINTS

Phase II Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (Arm A) compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin (Arm B)	• Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR, on two consecutive occasions $\geq$ 4 weeks apart), as determined by the investigator according to RECIST v1.1 • PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first

Phase II Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of Arm A compared with Arm B	• OS, defined as the time from randomization to death from any cause • DOR for patients with confirmed objective response, defined as the time from the first occurrence of a confirmed objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • TTCD in patient-reported physical functioning and GHS/QoL, as measured by the EORTC QLQ-C30, and in patient-reported lung cancer symptoms for cough, dyspnea (a multi-item subscale), and chest pain, as measured through the use of the EORTC QLQ-LC13
Phase III Primary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Arm A compared with Arm B	• PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause
Phase III Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Arm A compared with Arm B	• PFS, defined as the time from randomization to the first occurrence of disease progression as determined by an IRF according to RECIST v1.1, or death from any cause, whichever occurs first • The investigator-assessed PFS and OS in patients with PD-L1 expression at TCs $\geq$ 50% and TC $\geq$ 1% cut-off, as determined by central testing with investigational Ventana PD-L1 (SP263) assay • PFS at 6 months and 12 months, defined as the proportion of patients who have not experienced disease progression as determined by the investigator according to RECIST v1.1 or death from any cause at 6 months and at 12 months, respectively • OS rate at 12 months and 24 months, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months, respectively • Confirmed ORR • DOR • TTCD in patient-reported physical functioning and GHS/QoL, as measured by the EORTC QLQ-C30, and in patient-reported lung cancer symptoms for cough, dyspnea (a multi-item subscale), and chest pain, as measured through the use of the EORTC QLQ-LC13

Safety Objective	Corresponding Endpoints
• To evaluate the safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (Arm A) compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin (Arm B)	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 – [redacted] • Frequency of patients' response of the degree they are troubled with treatment symptoms, as assessed through use of the single-item EORTC Item List 46
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the pharmacokinetics of tiragolumab and atezolizumab	• Serum concentrations of tiragolumab and atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoints**
• To evaluate the immune response to tiragolumab and atezolizumab	• Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study • Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CR = confirmed response; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS/QoL = global health status/quality of life; IRF = independent review facility; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1; TC = tumor cell; TTCD = Time to confirmed deterioration.

OVERALL DESIGN AND STUDY POPULATION

This is a randomized, Phase II/III, global, multicenter, double-blind study designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC.

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

Phase:	Phase II/III	Population Type:	• Adult patients
Control Method:	• Active comparator • Placebo • Standard of care	• Population Diagnosis or Condition:	• Untreated locally advanced unresectable or metastatic non-squamous NSCLC • ECOG PS 0 or 1 • No *EGFR* or *ALK* genomic aberrations • Measurable disease per RECIST v1.1
Interventional Model:	Parallel group	Population Age:	≥ 18 years
Test Compound{s}:	Tiragolumab Atezolizumab	Site Distribution:	Multi-site
Active Comparator:	Pembrolizumab	Study Intervention Assignment Method:	Randomization and Stratification
Number of Arms:	2	Number of Participants to Be Enrolled:	Phase II: Approximately [redacted] Phase III: Approximately [redacted]

ALK = anaplastic lymphoma kinase; ECOG = Easter Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non–small-cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

STUDY TREATMENT

The investigational medicinal products for this study are tiragolumab, placebo, atezolizumab, and pembrolizumab. Depending on local classification, pemetrexed, carboplatin, and cisplatin are non-investigational medicinal products.

TEST PRODUCT (INVESTIGATIONAL DRUG)

Patients randomized to atezolizumab will receive 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle during the induction and maintenance phase. The atezolizumab dose is fixed and is not dependent on body weight. Following the administration of atezolizumab and an observation period, patients will receive 600 mg tiragolumab administered by IV infusion on Day 1 of each 21-day cycle. The tiragolumab dose is fixed and is not dependent on body weight.

Administration of atezolizumab and tiragolumab 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.

COMPARATOR

Patients randomized to pembrolizumab will receive 200 mg pembrolizumab administered by IV infusion on Day 1 of each 21-day cycle during the induction and maintenance phase. The pembrolizumab dose is fixed and is not dependent on body weight. Following the administration of pembrolizumab and an observation period, patients will receive 600 mg tiragolumab placebo administered by IV infusion on Day 1 of each 21-day cycle. The tiragolumab placebo dose is fixed and is not dependent on body weight.

Administration of pembrolizumab and tiragolumab 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.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Pemetrexed should be administered by IV infusion on Day 1 of each 21-day cycle during the induction and maintenance phase. Infusion should be over 10 minutes at a dose of 500 mg/m^2.

Patients should receive anti-emetics and IV hydration for platinum-pemetrexed treatments according to the local standard of care and manufacturer's instruction. However, due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In the event of pemetrexed-related skin rash, topical steroid use is recommended as front-line treatment whenever clinically feasible.

Carboplatin should be administered by IV infusion on Day 1 of each 21-day cycle during the induction phase only. Infusion should be over 30–60 minutes to achieve an initial target area under the concentration–time curve of 5 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

Cisplatin should be administered by IV infusion on Day 1 of each 21-day cycle during the induction phase only. Infusion should be over 60–120 minutes at a dose of 75 mg/m^2 per standard of care at the institution. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin.

DURATION OF PARTICIPATION

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years if Phase III expansion is not ungated or approximately 7 years if Phase III expansion is ungated.

COMMITTEES

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first-line
2L	second-line
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
ASTCT	American Society for Transplantation and Cellular Therapy
CD	cluster of differentiation
CDx	Companion Diagnostic
CE-IVD	Conformite Europeenne-In Vitro Diagnostic
CHO	Chinese hamster ovary
COVID-19	coronavirus disease 2019
CR	complete response
CRS	cytokine-release syndrome
CrCl	creatinine clearance
CT	computed tomography
CTLA4	cytotoxic T-lymphocyte associated protein 4
DLT	dose-limiting toxicity
DOR	duration of response
EBUS	endobronchial ultrasound
EBUS-TBNA	endobronchial ultrasound-transbronchial needle aspiration
[redacted]	[redacted]
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EAE	experimental autoimmune encephalitis
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GHS	global health status
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality-of-life
IC	immune cells
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IL46	Item List 46
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
ITIM	immunoreceptor tyrosine-based inhibition motif
ITT	intent-to-treat
LDH	lactate dehydrogenase
IxRS	interactive voice or Web-based response system
mAb	monoclonal antibody
MAS	macrophage activation syndrome
MN	mobile nursing
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NK	natural killer
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PA	primary analysis
PD	pharmacodynamic
PE	polyethylene

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	polyolefin
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
PVR	poliovirus receptor
Q3W	every 3 weeks
QoL	quality of life
RBR	Research Biosample Repository
ROS1	*c-ROS* oncogene 1
RECIST	Response Evaluation Criteria in Solid Tumors
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy for Cancer
SmPC	Summary of Product Characteristics
TC	tumor cells
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TPS	tumor proportion score
TTCD	time to confirmed deterioration
ULN	upper limit of normal
USM DIL	*Urgent Safety Measure Dear Investigator Letter*
USPI	U.S. Package Insert
VAS	visual analog scale
[redacted]	
WES	whole-exome sequencing
WGS	whole-genome sequencing
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide. In the United States, it was estimated that there were 228,820 new cases of lung cancer in 2019 (116,300 cases in men and 112,520 cases in women) and 135,720 lung cancer deaths (Siegel et al. 2020). Similar data from Europe estimated that in 2018, there were 387,900 lung cancer deaths (267,300 deaths in men and 120,600 deaths in women; Ferlay et al. 2018).

Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Howlader et al. 2015). NSCLC can be divided into two subcategories: squamous and non-squamous. Squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). Non-squamous NSCLC includes several histological subtypes, the most common of which is adenocarcinoma, which accounts for more than half of all NSCLC. The remaining cases of NSCLC are represented by other non-squamous NSCLC histologies, including large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

There are recognized differences in disease characteristics between adenocarcinoma and squamous NSCLC. Squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways.

The standard of care first-line (1L) treatment for advanced non-squamous NSCLC is largely driven by results of molecular profiling. Preferred 1L treatment for patients with tumors harboring an oncogenic driver mutation utilizes an approved targeted therapy, if available. For patients whose tumors lack a targetable oncogenic aberration, current standard of care 1L regimens typically consist of an immune checkpoint inhibitor, including PD-L1/PD-1 blocking antibodies, with or without platinum-based doublet chemotherapy and bevacizumab.

In the randomized Phase III Study IMpower150 (GO29436), overall survival (OS) and progression-free survival (PFS) were significantly prolonged with atezolizumab, bevacizumab, paclitaxel, and carboplatin relative to bevacizumab, paclitaxel, and carboplatin in patients with advanced non-squamous NSCLC without an activating epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) gene rearrangement. The hazard ratio (HR) for OS was 0.78 ($p < 0.02$) with a median OS of 19.2 months for atezolizumab, bevacizumab, paclitaxel, and carboplatin compared with 14.7 months for bevacizumab, paclitaxel, and carboplatin. The HR for PFS was 0.62 ($p < 0.001$) with a median PFS of 8.3 months for atezolizumab, bevacizumab, paclitaxel, and carboplatin compared with 6.8 months for bevacizumab, paclitaxel, and carboplatin. The unconfirmed objective response rate (ORR) was 63% for atezolizumab,

bevacizumab, paclitaxel, and carboplatin compared with 48% for bevacizumab, paclitaxel, and carboplatin (Socinski et al. 2018).

Additionally, in the Phase III Study KEYNOTE-189, OS and PFS were significantly improved with Keytruda® (pembrolizumab), pemetrexed, and carboplatin or cisplatin relative to pemetrexed and carboplatin or cisplatin in patients with advanced non-squamous NSCLC. The HR for OS was 0.56 ($p < 0.00001$) with a median OS of 22.0 months for pembrolizumab, pemetrexed, and carboplatin or cisplatin compared with 10.7 months for pemetrexed and carboplatin or cisplatin. The HR for PFS was 0.52 (95% CI: 0.45 to 0.70; $p < 0.001$) with a median PFS of 8.8 months for pembrolizumab, pemetrexed, and carboplatin or cisplatin compared with 4.9 months for pemetrexed and carboplatin or cisplatin. The confirmed ORR was 47.5% (95% CI: 42.6 to 52.5) for the pembrolizumab, pemetrexed, and carboplatin or cisplatin compared with 18.9% (95% CI: 13.8 to 25.0) (Gandhi et al. 2018; Gadgeel et al. 2019).

Results from these studies have led to the approval of pembrolizumab in combination with chemotherapy as 1L therapy for patients with advanced non-squamous NSCLC without an activating *EGFR* mutation or *ALK* gene rearrangement, irrespective of PD-L1 expression (Keytruda U.S. Package Insert [USPI] 2020; Keytruda Summary of Product Characteristics [SmPC] 2019) in the United States, the European Union, and other countries. Atezolizumab in combination with chemotherapy plus bevacizumab is also approved in the European Union for patients with *EGFR* or *ALK* genomic aberrations that have progressed on targeted therapies (Tecentriq® SmPC 2019).

Similarly, in the Phase III Study IMpower132, the coprimary endpoint of PFS was significantly improved with atezolizumab plus pemetrexed and carboplatin or cisplatin compared with pemetrexed plus carboplatin or cisplatin in chemotherapy-naïve patients with Stage IV non-squamous NSCLC. The HR for PFS was 0.60 (95% CI: 0.49 to 0.72; $p < 0.0001$) with a median PFS of 7.6 months for atezolizumab plus pemetrexed and carboplatin or cisplatin compared with 5.2 months for pemetrexed plus carboplatin or cisplatin (Papadimitrakopoulou et al. 2018). Confirmed ORR was 47% for atezolizumab plus pemetrexed and carboplatin or cisplatin compared with 32% for pemetrexed plus carboplatin or cisplatin. The interim analysis of the coprimary endpoint of OS showed a numerical and clinically meaningful but not statistically significant improvement in OS.

Clinical trial data indicate that the benefit of anti–PD-L1/PD-1 monotherapy compared with chemotherapy in NSCLC is largely driven by patients whose tumors express high levels of PD-L1 (Reck et al. 2016; Mok et al. 2019; Spigel et al. 2019). Consequently, current treatment guidelines limit the use of anti–PD-L1/PD-1 monotherapy in patients with high PD-L1 expression. However, multiple Phase III studies, including KEYNOTE-189, KEYNOTE-407, IMpower150, and IMpower130 have demonstrated that, when co-administered with chemotherapy, the efficacy benefit of PD-L1/PD-1 inhibitors extends across all PD-L1 subgroups (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019).

Despite these therapeutic advances, the majority of patients with advanced non-squamous NSCLC progress on currently available treatment options ultimately experience disease progression and succumb to this disease. Therefore, a high unmet medical need persists for advanced non-squamous NSCLC.

1.2 BACKGROUND ON BLOCKADE OF THE TIGIT PATHWAY AS A POTENTIAL ANTI-CANCER THERAPY

The inhibitory immunoreceptor T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibition motif (ITIM) domains (TIGIT) has been shown to limit the effector function of tumor-associated lymphocytes. TIGIT is an Ig super family member expressed on subsets of activated T cells and natural killer (NK) cells, and found highly expressed in tumor tissue and immune cells in many human cancers, including NSCLC. In multiple tumor types, TIGIT is coordinately expressed with PD-1 (Yu et al. 2009; Johnston et al. 2014; Manieri et al. 2017). Genetic ablation or antibody blockade of TIGIT has been shown to enhance NK-cell killing, cluster of differentiation (CD) 4 positive (CD4+) and CD8+ T-cell activation, and effector function in vitro and in vivo in nonclinical models (Stanietsky et al. 2009; Yu et al. 2009; Joller et al. 2011; Johnston et al. 2014). In the nonclinical tumor models, TIGIT interacted with high affinity to CD155 (also known as poliovirus receptor [PVR]), which also has an activating counter-receptor of CD226. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target tumor cells (TC; Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017). These studies identify TIGIT as an important immune checkpoint inhibitor that functionally limits chronically activated CD8+ T cells and tumor-infiltrating lymphocytes.

Therefore, TIGIT is a potential target of therapeutic intervention aimed at restoring the immune response against the tumor. Therapeutic blockade of TIGIT represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses and to enhance NK−cell-mediated anti-tumor immunity, which may result in improved and meaningful anti-tumor activity.

1.2.1 Combined Inhibition of TIGIT and PD-L1/PD-1 Pathways

Because TIGIT and PD-1 are coordinately expressed by tumor-infiltrating CD8+ T cells and NK cells in lung cancer (Johnston et al. 2014), inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab. Indeed, co-inhibition of both TIGIT and PD-L1/PD-1 has demonstrated promising activity. In nonclinical models, combination of anti-TIGIT and anti−PD-L1/anti−PD-1 therapies demonstrated superior efficacy over the respective single-agent treatments. In one such nonclinical model, tumor-infiltrating T cells demonstrated increased interferon (IFN)-γ expression only when both TIGIT and PD-1 are blocked concurrently, and not when each individual pathway is blocked by the respective single-agent treatment (Johnston et al. 2014).

The combined inhibition of the TIGIT and PD-L1/PD-1 pathways by tiragolumab and atezolizumab, respectively, has demonstrated promising clinical activity in the Phase I Study GO30103 and the Phase II Study CITYSCAPE (Study GO40290).
Study GO30103 is a first-in-human, combined Phase Ia/Ib, open-label, dose-escalation, multicenter study. The study evaluated the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of the biologic activity of tiragolumab administered as a single agent (Phase Ia) or in combination with atezolizumab (Phase Ib) to patients with locally advanced or metastatic malignancies.

Tiragolumab in combination with atezolizumab was further evaluated in patients with PD−L1-selected advanced NSCLC (tumor proportion score [TPS] ≥ 1%) in the Phase II, global, randomized, double-blind, placebo-controlled Study CITYSCAPE. As of the clinical cutoff date of 2 December 2019, the confirmed ORR in the intent-to-treat (ITT) population was higher in the tiragolumab and atezolizumab combination arm (37%) than in the placebo and atezolizumab combination arm (21%). Investigator-assessed PFS was also improved with a stratified HR of 0.58 (95% CI: 0.38 to 0.89) with a median PFS not estimable and 3.9 months in the tiragolumab and atezolizumab combination arm compared with the placebo and atezolizumab combination arm, respectively. Responses to tiragolumab and atezolizumab in combination were observed in patients with both squamous and non-squamous histologies (Rodríguez-Abreu et al. 2020).

As of the clinical cutoff date of 2 December 2019 in the CITYSCAPE study, there were 135 safety-evaluable patients. The safety profile was comparable between the tiragolumab and atezolizumab arm and the placebo and atezolizumab arm for all grades of adverse events (99% vs. 96%), Grade ≥ 3 adverse events (48% vs. 44%), Grade 5 adverse events (4.5% vs. 7.4%), serious adverse events (37% vs. 35%), and adverse events leading to study treatment withdrawal (10.4% vs. 8.8%). Study treatment-related adverse events occurred at a higher frequency in the tiragolumab and atezolizumab arm (82%) compared with the placebo and atezolizumab arm (72%).

Using a comprehensive medical concepts strategy, immune-mediated adverse events were reported with a higher frequency in the tiragolumab and atezolizumab arm (69%) compared with the placebo and atezolizumab arm (47%). The difference (≥ 10% difference between arms) was predominately attributed to events of immune-mediated rash (Preferred Terms of rash, rash maculopapular, dermatitis,

erythema, eczema, pruritic rash, folliculitis, and skin ulcer; 40% vs. 15%) and infusion-related reactions (Preferred Term of infusion-related reaction; 30% vs. 10%).

1.2.2 Combined Inhibition of TIGIT and PD-L1/PD-1 Pathways in Combination with Chemotherapy

Several Phase III studies, including KEYNOTE-189, KEYNOTE-407, IMpower150, and IMpower130 have documented that, when co-administered with chemotherapy, the efficacy benefit of PD-L1/PD-1 inhibitors extends across all PD-L1 subgroups (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019).

These data are consistent with the known effects of chemotherapy on the tumor microenvironment that may potentiate the effects of immunotherapies. In addition to direct cytotoxicity, which increases release of tumor antigens and enhances immunogenicity, chemotherapy has been shown to increase expression of PD-L1 (Zhang et al. 2008) and increase levels of CD155 (PVR), the ligand for TIGIT (Yoshida et al. 2019). [redacted]

1.3 BACKGROUND ON TIRAGOLUMAB

Tiragolumab (formerly MTIG7192A) is a fully human IgG1/γ monoclonal antibody (mAb) derived in open monoclonal technology rats that binds to TIGIT and prevents its interaction with PVR. The recombinant antibody is produced in Chinese hamster ovary (CHO) cells and consists of two heavy chains (456 amino acid residues each) and 2 light

chains (220 amino acid residues each). There are two *N*-linked glycosylation sites (Asn306) in the Fc domain. The predicted molecular weight of tiragolumab is 148,409 Da (peptide chains only, without a heavy chain C-terminal lysine residue).

Tiragolumab is being investigated in clinical studies as a potential therapy against various tumor types.

The current nonclinical and clinical data for tiragolumab are summarized in Section 1.2.1. Refer to the Tiragolumab Investigator's Brochure for additional details.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with metastatic cancer, including NSCLC. PD-L1/PD-1 inhibitors in combination with chemotherapy have demonstrated significant improvement in survival compared with standard chemotherapy, which has led to the recent approvals of these agents for the treatment of NSCLC and validates the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in NSCLC.

Despite the robust activity observed with anti–PD-L1/PD-1 agents, durable clinical benefit appears limited to a minority of patients. It is hypothesized that many of these patients with advanced NSCLC may have intrinsic or acquired resistance to checkpoint inhibition. Thus, another strategy to increase response to checkpoint inhibitors among patients has focused on treatment with novel immunotherapy combinations that may overcome such resistance.

TIGIT is an inhibitory immunoreceptor that can limit the effector function of tumor-associated lymphocytes. Unlike other inhibitory co-receptors, TIGIT is often coordinately expressed with PD-1 on tumor-infiltrating T cells in multiple tumors, including NSCLC. In nonclinical models, combined blockade of the TIGIT and PD-L1/PD-1 pathways has shown superior efficacy compared with blockade of each pathway alone (Johnston et al. 2014). Thus, the combined inhibition of the TIGIT and PD-L1/PD-1 pathways is a unique and attractive strategy to potentiate the activity of a PD-L1 antibody, such as atezolizumab, due to the complementary mechanisms of action of anti-TIGIT and anti–PD-L1.

In the Phase Ib Study GO30103, PRs occurred in patients with metastatic cancers, including NSCLC, [redacted] following treatment with an anti-TIGIT antibody, tiragolumab, in combination with an anti–PD-L1 antibody, atezolizumab. Data from the randomized Phase II Study CITYSCAPE indicate that combination therapy with tiragolumab plus atezolizumab may confer increased efficacy benefit in patients with untreated, PD-L1–positive, metastatic NSCLC relative to atezolizumab therapy alone.

Tiragolumab in combination with atezolizumab was well-tolerated in both the Phase Ib Study GO30103 and the Phase II CITYSCAPE study (Section 1.2.1 and Tiragolumab Investigator's Brochure). Adverse events with potentially immune-mediated causes have been observed with a higher frequency for tiragolumab in combination with atezolizumab in the CITYSCAPE study. However, the imbalance was mostly attributed to rash and infusion-related reactions (IRRs; both Grade 1–2). Grade 3–4 immune-mediated adverse events were similar between the tiragolumab and atezolizumab combined treatment arm compared with atezolizumab treatment alone. To date, immune-mediated adverse events have been manageable with standard medical practice supplemented with corticosteroids, immunosuppressive agents, and/or hormone replacement therapy.

The clinical benefit of chemotherapy treatment combined with PD-L1/PD-1 inhibitors has been documented by improved OS and PFS in patients throughout all PD-L1 subgroups (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019). The expectation that tiragolumab will enhance atezolizumab efficacy in the context of chemotherapy in NSCLC is supported by nonclinical evidence that the TIGIT pathway is associated with immune dysfunction and chemoresistance. Thus, TIGIT blockade may restore T-cell function and improve outcomes in patients treated with chemotherapy (see Section 1.2.2). [redacted]

The current study is designed to evaluate the efficacy of tiragolumab combined with atezolizumab plus chemotherapy compared with placebo and the current standard of care regimen of pembrolizumab plus chemotherapy in patients with locally advanced unresectable or metastatic non-squamous NSCLC with no *EGFR* mutations or *ALK* rearrangements. The combination of tiragolumab with atezolizumab plus chemotherapy in the experimental arm can represent a potentially valuable treatment option and can offer a reasonable benefit–risk balance for patients in this study.

In summary, the combination of tiragolumab with atezolizumab plus chemotherapy in this study may benefit patients beyond treatment with pembrolizumab plus chemotherapy. The toxicities of tiragolumab in combination with atezolizumab appear to be similar to atezolizumab alone. The immune-mediated adverse events, although reported at a higher frequency for the tiragolumab and atezolizumab arm in the Phase II Study CITYSCAPE, were generally mild, transient, monitorable, and manageable in nature. The toxicities of the combination of tiragolumab and atezolizumab plus chemotherapy are also expected to be similar to pembrolizumab plus chemotherapy. Therefore, the overall benefit–risk ratio is considered to be appropriate for the study population.

1.5 COVID-19 CONSIDERATIONS

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

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Wykes and Lewin 2018; Schorer et al. 2020). 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 COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and 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 severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection while receiving atezolizumab and/or tiragolumab. At this time, there is insufficient evidence for causal association between atezolizumab or tiragolumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with immune checkpoint inhibitors and clinical and radiologic features for COVID-19–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 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 SARS-CoV-2 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network® (NCCN®) COVID-19 Vaccination Advisory Committee, SARS-CoV-2 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 SARS-CoV-2 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this

study and receiving study 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 study treatment to receive SARS-CoV-2 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. The SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering SARS-CoV-2 vaccines. When administered, SARS-CoV-2 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the SARS-CoV-2 vaccine is considered a concomitant medication and should be documented as such.

2. OBJECTIVES AND ENDPOINTS

This Phase II/III study will evaluate the efficacy, safety, and pharmacokinetics of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin in treatment Arm A compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin in treatment Arm B in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

The details of the design of this Phase II/III study are described in Section 3.2.1.

[redacted]

2.1.1 Phase II Efficacy Objectives

2.1.1.1 Phase II Primary Efficacy Objectives

The primary efficacy objective for the Phase II part of this study (see Section 3.2.1) is to evaluate the efficacy of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (Arm A) compared with placebo in combination with

pembrolizumab plus pemetrexed and carboplatin/cisplatin (Arm B) on the basis of the following endpoints:

- Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR, on 2 consecutive occasions ≥4 weeks apart), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- Progression-free survival, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first

2.1.1.2 Phase II Secondary Efficacy Objectives

The secondary efficacy objective for the Phase II part of this study is to evaluate the efficacy of Arm A compared with Arm B on the basis of the following endpoints:

- Overall survival, defined as the time from randomization to death from any cause
- Duration of response (DOR) for patients with confirmed objective response, defined as the time from the first occurrence of a confirmed objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
- Time to confirmed deterioration (TTCD) in patient-reported physical functioning and global health status/quality of life (GHS/QoL), as measured by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, and in patient-reported lung cancer symptoms for cough, dyspnea (a multi-item subscale), and chest pain, as measured through the use of the EORTC QLQ-LC13

2.1.2 Phase III Efficacy Objectives

2.1.2.1 Phase III Primary Efficacy Objectives

The primary efficacy objective for the expanded Phase III study (see Section 3.2.1) is to evaluate the efficacy of Arm A compared with Arm B on the basis of the following endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first
- OS, defined as the time from randomization to death from any cause

2.1.2.2 Phase III Secondary Efficacy Objectives

The secondary efficacy objective of the expanded Phase III study is to evaluate the efficacy of Arm A compared with Arm B on the basis of the following endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression as determined by an independent review facility (IRF) according to RECIST v1.1, or death from any cause, whichever occurs first
- The investigator-assessed PFS and OS in patients with PD-L1 expression at TC ≥50% and TC ≥1% cut-off, as determined by central testing with investigational Ventana PD-L1 (SP263) assay

- PFS at 6 months and 12 months, defined as the proportion of patients who have not experienced disease progression as determined by the investigator according to RECIST v1.1 or death from any cause at 6 months and at 12 months, respectively
- OS rate at 12 months and 24 months, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months, respectively
- Confirmed ORR
- DOR
- TTCD in patient-reported physical functioning and GHS/QoL, as measured by the EORTC QLQ-C30, and in patient-reported lung cancer symptoms for cough, dyspnea (a multi-item subscale), and chest pain, as measured through the use of the EORTC QLQ-LC13

[redacted]

- [redacted]

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (Arm A) compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin (Arm B) on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0 (NCI CTCAE v5.0)
  - [redacted]
- [redacted]

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of tiragolumab and atezolizumab on the basis of the following endpoint:

- Serum concentrations of tiragolumab and atezolizumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to tiragolumab and atezolizumab on the basis of the following endpoints:

- Prevalence of anti-drug antibodies (ADAs) to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study
- Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study

[redacted]

3. STUDY DESIGN

3.1 *DISCONTINUATION OF EXPERIMENTAL TREATMENT AND UNBLINDING AT STUDY LEVEL*

On 4 July 2024, an update on this randomized Phase II/III, global, multicenter, double-blind study designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin compared with placebo in combination with pembrolizumab plus pemetrexed and

carboplatin/cisplatin in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC was released. The study did not meet the primary endpoints of PFS at primary analysis and OS at first interim analysis. On the same day, the Sponsor issued an Urgent Safety Measure Dear Investigator Letter (USM DIL) communicating the following actions or updates to study conduct to be implemented immediately, ahead of health authorities' approval:

- *Investigators are instructed to obtain the treatment assignment for their patients*
- *Patients who are currently receiving study treatment should be informed of the actual treatment they are receiving*
- *Patients who are currently receiving study treatment on the investigational arm of tiragolumab plus atezolizumab and chemotherapy should discontinue from the study and seek other treatment options outside of the study for their non-squamous NSCLC*
- *Patients who are currently receiving study treatment on the comparator arm of pembrolizumab and chemotherapy may continue receiving active treatment per the protocol or discontinue from the study and seek treatment options outside of the study for their non-squamous NSCLC*

3.1.1 ***Implications of Unblinding at Study Level on Study Design and Assessments***

[redacted]

Patients who are currently receiving study treatment(s) on the comparator arm of pembrolizumab and chemotherapy should discontinue from the study and seek treatment options outside of the study. If they stay on study, these patients may continue receiving active treatment(s) per protocol until disease progression, unacceptable toxicity, or up to 24 months, whichever occurs first. Placebo administration must be discontinued.

After unblinding at study level, treatment beyond 24 months is no longer permitted in either treatment arm. Patients who are continuing treatment beyond 24 months must discontinue from the study and seek other treatment options outside of the study.

After unblinding at study level, treatment beyond disease progression is no longer permitted in either treatment arm. Patients who are continuing treatment beyond disease progression must discontinue from the study and seek other treatment options outside of the study.

After unblinding at study level, investigators must continue to report tumor assessments based on the frequency as per local practices (Appendix 1).

After unblinding at study level, pharmacokinetic, immunogenicity, biomarker, and PRO assessments are no longer required (Appendix 1 and Appendix 2).

3.2 DESCRIPTION OF THE STUDY *PRIOR TO UNBLINDING AT STUDY LEVEL*

3.2.1 Overview of Study Design

This is a randomized, Phase II/III, global, multicenter, double-blind study designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC.

[redacted]

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

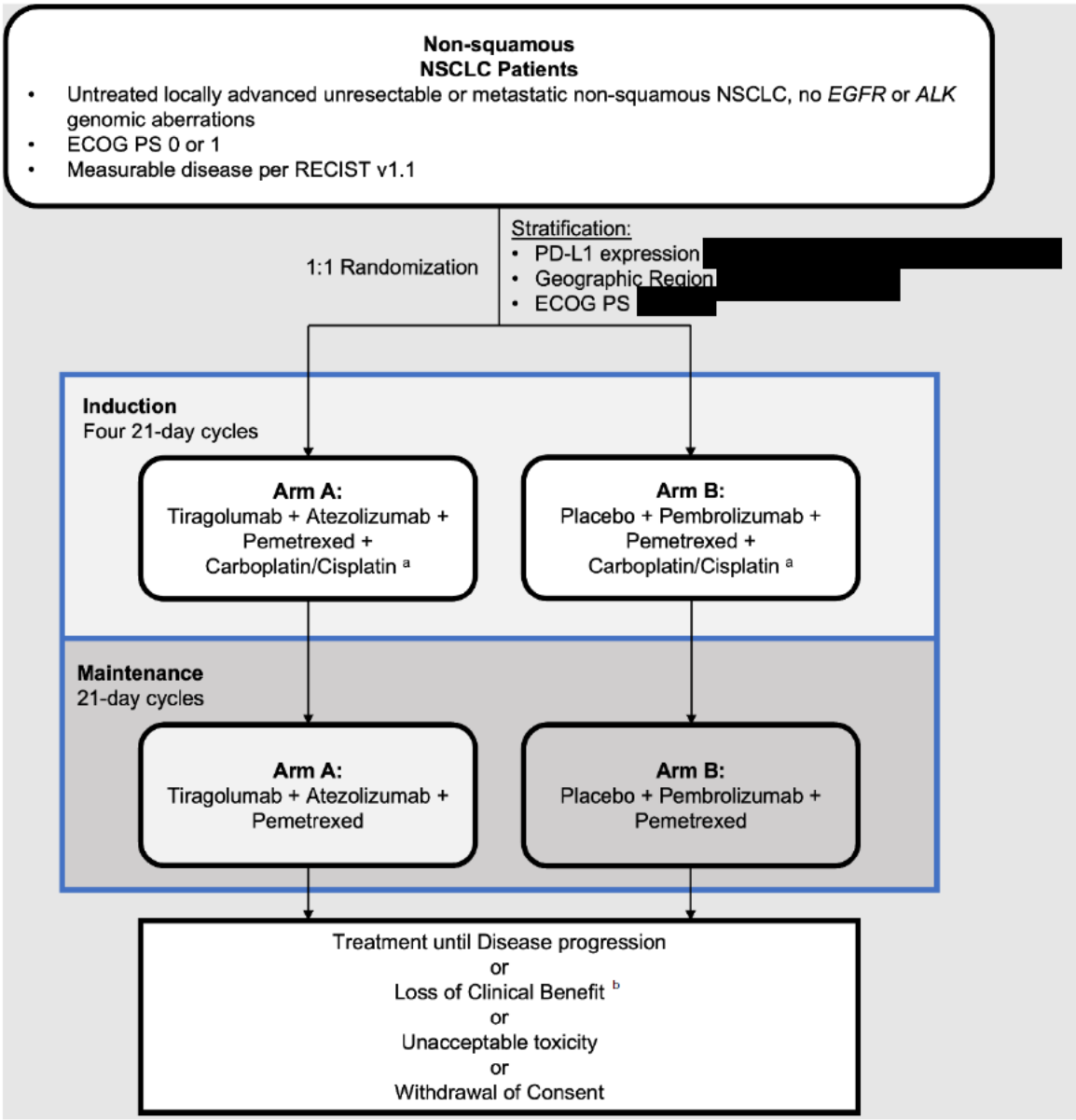
Previously untreated male and female patients age ≥ 18 years with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 who have locally advanced unresectable or metastatic non-squamous NSCLC, with no *EGFR* or *ALK* genomic aberrations, are eligible.

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities (Appendix 1). [redacted]

[redacted]

Patients whose tumors have a known *EGFR* or *ALK* rearrangement will be excluded from the study. Patients with tumors with unknown *EGFR* or *ALK* mutational status will be required to be tested prior to enrollment (see Section 4.1.1).

Figure 1 Study Schema



ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; ECOG PS=Eastern Cooperative Oncology Group Performance Status; iDMC=independent data monitoring committee; NSCLC=non–small-cell lung cancer; RECIST (v1.1)=Response Evaluation Criteria in Solid Tumors, Version 1.1; TC=tumor cells; TPS=tumor proportion score.

[a] Safety and tolerability data will be assessed by an independent Data Monitoring Committee

[b] [redacted]

Approximately [redacted] patients will be enrolled in the Phase II part of the study.

[redacted]

[redacted]

During both the Phase II part and Phase III expansion of the study, eligible patients will be randomized 1:1 to receive tiragolumab in combination with atezolizumab plus pemetrexed and cisplatin/carboplatin (Arm A) or placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (Arm B). The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the baseline characteristics of the following stratification factors:

- PD-L1 expression [redacted]
- Geographic region [redacted]
- ECOG Performance Status [redacted]

[redacted]

[redacted]

[redacted]

Induction treatment with tiragolumab in combination with atezolizumab plus pemetrexed and cisplatin/carboplatin (Arm A) or placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin (Arm B) will be administered on a 21-day cycle for four cycles.

Following the induction phase, patients will continue maintenance therapy with either tiragolumab in combination with atezolizumab and pemetrexed (Arm A) or placebo in combination with pembrolizumab and pemetrexed (Arm B).

A safety review of unblinded data will be performed by an iDMC (see Section 3.2.2) [redacted]

Patients will undergo tumor assessment at baseline and every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1, regardless of treatment dose delays.
After completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. [redacted]

Patients randomized during the Phase II part of the study will be asked to complete PRO questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, and EORTC IL46) during treatment until study treatment discontinuation, and at the study treatment discontinuation visit.

If Phase III expansion is ungated, patients randomized after the gating decision will be asked to complete PRO questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13, EORTC IL46, and EQ-5D-5L) during treatment, at the study treatment discontinuation visit, and during survival follow-up as specified in Section 4.5.9.1.

Safety assessments at study visits will include the incidence, nature, and severity of adverse events, protocol-mandated vital signs, laboratory abnormalities, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

During the study, serum samples will be collected to monitor tiragolumab and atezolizumab pharmacokinetics and to detect the presence of antibodies to tiragolumab and atezolizumab. [redacted]

After unblinding at study level:

- *tumor assessments will no longer be required per protocol defined schedule, and investigators must continue to report tumor assessment results based on the frequency as per local practices*
- *submission of primary imaging data used for tumor assessments to the IRF will be halted*
- *PRO questionnaires for all remaining patients will no longer be required*
- *pharmacokinetic, immunogenicity, and biomarker samples will no longer be collected at any timepoint*

3.2.2 Independent Data Monitoring Committee

An iDMC will be formed to evaluate safety at regular intervals during the study and to conduct the interim efficacy analysis. [redacted]

[redacted]

[redacted]

[redacted]

3.3 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date of the last patient last visit. The end of this study is expected to occur when remaining patients after unblinding at study level have completed up to two years of treatment followed by the required safety reporting period.

In addition, the Sponsor may decide to terminate the study at any time. [redacted]

3.4 DURATION OF PARTICIPATION

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately [redacted]

3.5 RATIONALE FOR STUDY DESIGN

This Phase II/III study design is based on the hypothesis that tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin may improve ORR and prolong PFS and/or OS compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin.

3.5.1 Rationale for Testing Tiragolumab and Atezolizumab in Combination with Pemetrexed and Carboplatin/Cisplatin in Patients with Non-Squamous NSCLC Across all PD-L1 Subgroups

Details on the rationale for tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin are described in Section 1.4.

Several Phase III studies (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; West et al. 2019) have demonstrated the benefit of immunotherapy combined with chemotherapy for patients with non-squamous NSCLC, regardless of PD-L1. In the Phase III Study IMpower132, PFS was significantly improved, and OS was numerically but not statistically improved with atezolizumab plus pemetrexed and carboplatin or cisplatin therapy (Papadimitrakopoulou et al. 2018). These data, together with the nonclinical data, and the results from the CITYSCAPE study, provide the rationale for further evaluation of the efficacy of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin as a 1L treatment for patients with locally advanced unresectable or metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic aberrations.

3.5.2 Rationale for Control Arm

The current NCCN and European Society of Medical Oncology (ESMO) treatment guidelines for 1L non-squamous NSCLC include pembrolizumab in combination with pemetrexed plus platinum-doublet chemotherapy (regardless of PD-L1 status) or pembrolizumab as a single agent for patients with high PD-L1 expression (TPS $\geq$ 50%; ESMO 2019; NCCN 2019). In this study, patients in the control arm will receive 4 cycles of placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin followed by placebo in combination with pembrolizumab plus pemetrexed until disease progression per RECIST v1.1. This control arm treatment is an approved option for the 1L treatment of non-squamous NSCLC (see Section 1.1).

[redacted]

[redacted]

3.5.4 Rationale for Dose and Schedule of Atezolizumab, Pembrolizumab, and Tiragolumab

[redacted]

3.5.4.2 Rationale for Dose and Schedule of Pembrolizumab

Pembrolizumab will be administered in a blinded fashion to all patients in the control arm at the approved fixed dose of 200 mg IV Q3W on Day 1 of each 21-day cycle. Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy is an approved 1L treatment option for patients with metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations.

Please refer to the pembrolizumab local prescribing information for a list of approved indications and a complete summary of safety information.

[redacted]

3.5.5 Rationale for Exclusion of Patients with an *EGFR* Mutation or *ALK* Rearrangements

Patients with tumors harboring an *EGFR* mutation or *ALK* rearrangements will not be eligible for this study. Genotype-directed therapy, rather than immunotherapy, remains the standard of care in the 1L treatment setting for these patients. For patients with NSCLC (of mainly non-squamous histology) with an *EGFR* mutation, randomized Phase III studies of the *EGFR* inhibitors gefitinib, erlotinib, and afatinib showed

significant improvement in PFS and ORR compared with platinum-doublet chemotherapy (Fukuoka et al. 2011; Rosell et al. 2012; Yang et al. 2012). More recently, osimertinib, a third-generation *EGFR* inhibitor, demonstrated significant improvement in PFS compared with gefitinib and erlotinib (Soria et al. 2018). For patients with metastatic NSCLC with *ALK* rearrangements, crizotinib and alectinib have demonstrated increased efficacy (Shaw et al. 2013; Peters et al. 2017).

When patients with metastatic NSCLC with *EGFR* mutations are treated with immunotherapy alone, there appeared to be no increased OS benefit. In Study GO28915 (OAK), patients with metastatic NSCLC with *EGFR* mutation-positive disease had similar OS benefit with atezolizumab or with docetaxel. The HR was 1.24 with a median OS of 10.5 months with atezolizumab compared with 16.2 months with docetaxel. Patients with *EGFR* wild type (WT) disease had an improved median OS of 15.3 months with atezolizumab compared with 9.5 months with docetaxel (HR = 0.69; Rittmeyer et al. 2017). Similarly, in the Phase III Study CheckMate-057 of nivolumab compared with docetaxel in the 2L treatment of NSCLC, patients with NSCLC with *EGFR* mutation-positive disease had a similar OS benefit with nivolumab or docetaxel (HR = 1.18), in contrast to patients with *EGFR* WT disease who had improved OS with nivolumab relative to docetaxel (HR = 0.66; Borghaei et al. 2015). Patients with NSCLC with *EGFR* mutation-positive disease were also excluded from the Phase III Studies KEYNOTE- 024 and KEYNOTE-042 of pembrolizumab vs. chemotherapy in the 1L setting (Reck et al. 2016; Mok et al. 2019). [redacted]
Therefore, on the basis of the data above, patients with known *EGFR* mutations or *ALK* rearrangements will be excluded from the study.

3.5.6 Rationale for Confirmed Objective Response Rate and Progression-Free Survival as Phase II Co-Primary Endpoints

Investigator-assessed confirmed ORR and PFS are the co-primary endpoints for the Phase II part of this study [redacted]

Confirmed ORR is a common primary endpoint in proof-of-concept Phase II studies given its usefulness as an early indicator of clinical activity (FDA 2007; EMA 2012). Although confirmed ORR can reflect tumor growth and can be assessed earlier and with a smaller sample size compared with survival studies, confirmed ORR may not always correlate with survival.

Progression-free survival as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit, depends upon the magnitude of the effect and the benefit–risk of the new treatment compared with available therapies (FDA 2007; EMA 2012).

3.5.7 Rationale for Progression-Free Survival and Overall Survival as Phase III Co-Primary Endpoints

Investigator-assessed PFS and OS are the co-primary endpoints for the expanded Phase III study.

The rationale for PFS as a co-primary endpoint is described above in Section 3.5.6.

To ensure the validity of investigator-assessed PFS as the primary endpoint, a number of measures have been implemented: a substantial target magnitude of benefit and study assessments that will allow a robust evaluation of benefit–risk (conventional RECIST v1.1 criteria to define radiographic disease progression with fixed assessment intervals that are identical in both treatment arms, and a robust definition of PFS and prospectively-defined methods to assess, quantify, and analyze PFS, including sensitivity analyses). To support the primary analysis of investigator-assessed PFS, the analysis of PFS as assessed by the IRF will be performed.

Overall survival is a co-primary endpoint for the Phase III part of this study. Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic lung cancer.

3.5.8 Rationale for Allowing Patients to Continue Study Treatment beyond Disease Progression per RECIST v1.1

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression and/or tumor immune infiltration, this study will allow patients randomized to receive either tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin or placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin to continue to receive study treatment with tiragolumab/placebo and atezolizumab/pembrolizumab after apparent radiographic progression, provided the benefit–risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see Section 3.2.1).

3.5.9 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts HRQoL (Sarna et al. 2004). This is especially true for studies that have PFS as a primary endpoint, to inform how delays in radiographic progression might be associated with delays in clinical progression of symptoms and their interference on functioning, including maintenance of low disease burden.

In addition, many of the most frequent adverse events attributed to study drugs (e.g., fatigue, rash, nausea) are symptoms directly reportable by patients; therefore, patients' reporting of their experience with these symptoms will complement the evaluation of treatment tolerability (King-Kallimanis et al. 2019).

This study includes use of validated patient-reported measures of symptom severity, and symptom impact on functioning, including HRQoL: the EORTC QLQ-C30, EORTC QLQ-LC13, and EORTC IL46 (see Appendix 5–Appendix 7). Data generated from these instruments will inform of patients' experience with disease burden and treatment tolerability as part of the totality of evidence generated to inform the benefit–risk profile of atezolizumab and tiragolumab.

[redacted]

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

When immunotherapy is co-administered with chemotherapy, the efficacy benefit of PD-L1/PD-1 inhibitors extends across all PD-L1 subgroups as shown in several Phase III studies, including KEYNOTE-189, KEYNOTE-407, IMpower150, and IMpower130 (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; Gadgeel et al. 2019; West et al. 2019). In the Phase II Study CITYSCAPE, which included patients with advanced NSCLC with PD-L1 expression of TPS $\geq$1%, tiragolumab in combination with atezolizumab demonstrated an improvement in the co-primary endpoints of ORR and PFS in the ITT population compared with atezolizumab alone, with improvement driven by patients who had PD-L1 expression of TPS $\geq$50% (Rodríguez-Abreu et al. 2020). [redacted]

[redacted]

[redacted]

[redacted]

3.5.11 Rationale for Biomarker Assessments

[redacted]

[redacted]

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.5.13 Rationale for the Collection of Tumor Specimens at Radiographic Progression

If clinically feasible, it is recommended that a tumor biopsy be performed at the time of radiographic progression in order to better understand the biological changes that drive the increase in size of the radiographically progressing lesion. [redacted]

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations will be enrolled in this study.

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 judgment
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Histologically or cytologically documented locally advanced unresectable or metastatic non-squamous NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy
  - [redacted]
  - [redacted]
- No prior systemic treatment for metastatic non-squamous NSCLC
  - [redacted]
- Known tumor PD-L1 status [redacted]
  - [redacted]
  - [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- Measurable disease, as defined by RECIST v1.1
  - [redacted]
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1):
  - [redacted]

  - [redacted]
  - [redacted]
- For patients not receiving therapeutic anticoagulation: INR and aPTT [redacted]
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HbsAg) test at screening
- Positive hepatitis B surface antibody (HbsAb) test at screening, or negative HbsAb at screening accompanied by either of the following:
  - [redacted]
  - [redacted]
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening
  - [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, [redacted]
  - [redacted]
  - [redacted] has not reached a postmenopausal state (≥12 continuous months of [redacted]
  - [redacted]

[redacted]

- [redacted]

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

4.1.2 Exclusion Criteria

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

- NSCLC known to have a mutation in the *EGFR* gene or an *ALK* fusion oncogene are excluded from the study
- Patients with non-squamous NSCLC who have an unknown *EGFR* or *ALK* status will be required to be tested at prescreening or screening
  - [redacted]

[redacted]

- Pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC
- Symptomatic, untreated, or actively progressing CNS metastases
  - [redacted]
  - [redacted]
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for [redacted] prior to randomization
- History of leptomeningeal disease
- Uncontrolled tumor-related pain
  - [redacted]
  - [redacted]
  - [redacted]

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
  - [redacted]
- Uncontrolled or symptomatic hypercalcemia [redacted]
- Active or history of autoimmune disease or immune deficiency, including, [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis [redacted]
  - [redacted]
- Known active tuberculosis
- [redacted]
- [redacted]
  - [redacted]

- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- 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
  - [redacted]
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than NSCLC within 5 years prior to randomization, 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 breast 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, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics [redacted] prior to initiation of study treatment
  - [redacted]
- 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 [redacted] prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or [redacted] after the final dose of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Any anti-cancer therapy, including hormonal therapy, [redacted] prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4, anti-TIGIT, 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 drug-elimination half-lives (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–tumor necrosis factor (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:
  - [redacted]
  - [redacted]
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies, fusion proteins, or platinum-containing compounds
- Known hypersensitivity to CHO cell products or to any component of the tiragolumab or atezolizumab or pembrolizumab formulation
- Known allergy or hypersensitivity or other contraindication to any component of the chemotherapy regimen the patient may receive during the study
- Hearing impairment (cisplatin only)
- Grade $\geq$2 peripheral neuropathy as defined by NCI CTCAE v5.0 (cisplatin only)
- Pregnant or breastfeeding, or intending to become pregnant during the study, for [redacted] after the final dose of tiragolumab or placebo, [redacted] after the final dose of atezolizumab or pembrolizumab, or 6 months after the final dose of pemetrexed, carboplatin or cisplatin
  - [redacted]
- Known targetable *c-ROS* oncogene 1 (*ROS1*) or *BRAF*^{V600E} genomic aberration
  - [redacted]

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a Phase II/III, randomized, double-blind, placebo-controlled study. [redacted]

Patients will be randomized to one of two treatment arms: Arm A (tiragolumab in combination with atezolizumab plus pemetrexed and cisplatin/carboplatin), and Arm B (placebo in combination with pembrolizumab plus pemetrexed and cisplatin/carboplatin). Randomization will occur in a 1:1 ratio through the use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- PD-L1 expression [redacted]
- Geographic region [redacted]
- ECOG Performance Status [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are tiragolumab, placebo, atezolizumab, and pembrolizumab. Pemetrexed, carboplatin, and cisplatin are considered non-IMPs. Appendix 13 identifies all IMPs, auxiliary medicinal products, and non-IMPs for this study.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Atezolizumab/Pembrolizumab

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

[redacted]

[redacted] For detailed instructions on the preparation of the following atezolizumab formulation, see the pharmacy manual.

- [redacted]
- [redacted]

Pembrolizumab will be supplied by the Sponsor as a sterile liquid in single-use 4-mL glass vials. Each vial contained approximately 4 mL (100 mg) of pembrolizumab. Pembrolizumab formulation will be prepared by an unblinded pharmacist and will be packaged in a PVC, PE, or PO infusion bag. For detailed instructions on the preparation of the following pembrolizumab formulation, see the pharmacy manual.

- 8 mL (200 mg) pembrolizumab
- 192 mL of 0.9% sodium chloride injection, USP

4.3.1.2 Tiragolumab/Placebo

Tiragolumab and placebo will be supplied by the Sponsor [redacted] For information on the tiragolumab/placebo formulation, see the pharmacy manual or the Tiragolumab Investigator's Brochure.

4.3.1.3 Pemetrexed, Cisplatin, and Carboplatin

Pemetrexed, carboplatin, and cisplatin will be used in the commercially available formulations.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

On Day 1 of each 21-day cycle, all eligible patients will be administered infusion of study treatments in the following order:

Induction (Cycles 1–4): atezolizumab/pembrolizumab → tiragolumab/placebo → pemetrexed → carboplatin or cisplatin

Maintenance (Cycles 5+): atezolizumab/pembrolizumab → tiragolumab/placebo → pemetrexed

Administration of study treatments 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 3. Guidelines for medical management of IRRs are provided in Appendix 11.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental

overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.6.12.

4.3.2.1 Atezolizumab/Pembrolizumab

Patients will receive fixed-dose 20 mL (1200 mg) atezolizumab in Arm A or 8 mL (200 mg) pembrolizumab in Arm B on Day 1 of each 21-day cycle.

Atezolizumab/pembrolizumab infusions will be administered per the instructions outlined in Table 2 below.

For Cycle 1, premedication for atezolizumab/pembrolizumab is not permitted.

No dose modifications for atezolizumab/pembrolizumab are allowed. Guidelines for treatment interruption or discontinuation are provided in Appendix 10. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.1.8, the Atezolizumab Investigator's Brochure, and the pembrolizumab local prescribing information.

4.3.2.2 Tiragolumab/Placebo

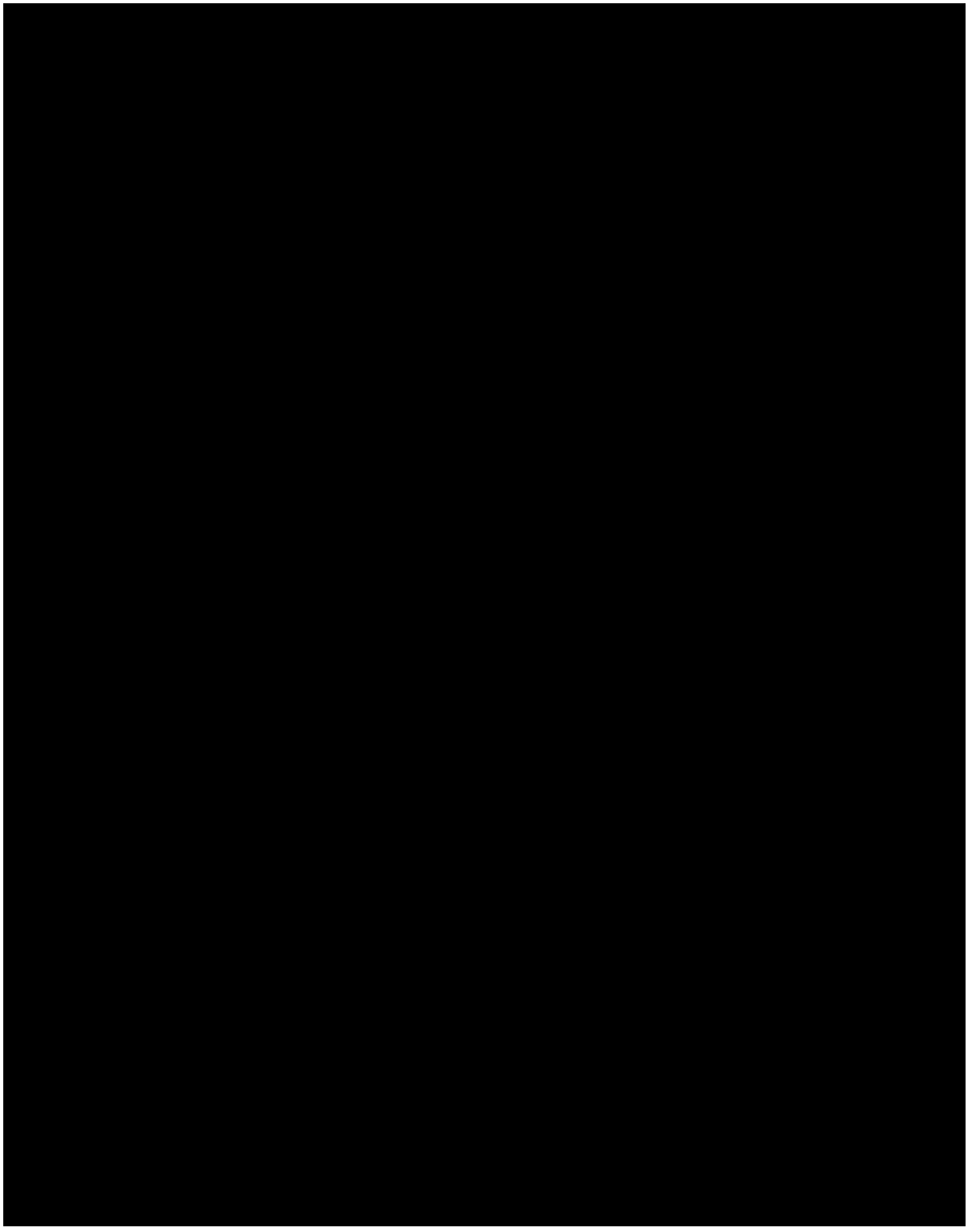
Patients will receive fixed-dose 10 mL (600 mg) tiragolumab in Arm A or 10 mL placebo in Arm B on Day 1 of each 21-day cycle.

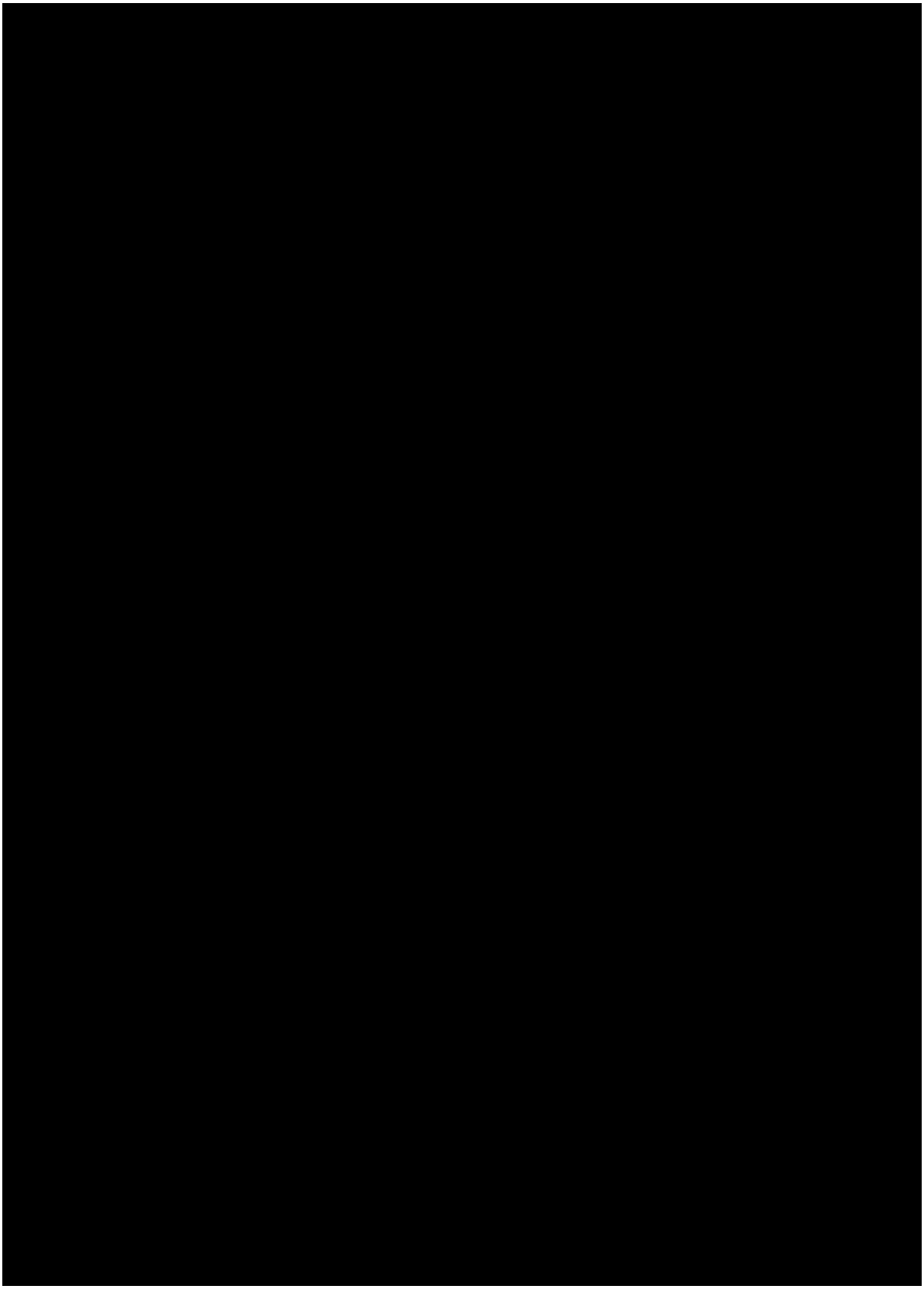
Tiragolumab/placebo infusions will be administered per the instructions outlined in Table 2 below.

[redacted]

[redacted]

[redacted]





Guidelines for the medical management of IRRs are provided in Appendix 11.

4.3.2.3 Pemetrexed, Cisplatin, and Carboplatin

Table 3 lists the doses and suggested infusion times for treatment administration for pemetrexed, carboplatin or cisplatin.

Table 3 Treatment Regimen for Pemetrexed, Carboplatin or Cisplatin

Study Drug	Dose and Route	Induction Period (4 Cycles)	Maintenance (Until PD)
Pemetrexed	500 mg/m^2 IV	Over approximately 10 minutes on Day 1 Q3W	Over approximately 10 minutes on Day 1 Q3W
Carboplatin	AUC 5 IV	Over approximately 30–60 minutes on Day 1 Q3W	Not applicable
Cisplatin	75 mg/m^2 IV	Over 1–2 hours on Day 1 Q3W	Not applicable

AUC = area under the concentration–time curve; Q3W = every 3 weeks.

Patients should receive anti-emetics and IV hydration for platinum-pemetrexed treatments according to the local standard of care and manufacturer's instruction.

[redacted]

Table 4 lists the suggested premedication for pemetrexed.

Table 4 Premedication for Pemetrexed

Premedication	Dose and Route	Timing
Dexamethasone	4 mg PO	Twice daily the day before, the day of, and the day after pemetrexed administration
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 Cycle 1, Day 1 and continuing until 3 weeks after discontinuation of pemetrexed

IM = intramuscular; PO = by mouth, orally; Q9W = every 9 weeks.

[redacted]

Guidelines for dose modification and treatment interruption or discontinuation for carboplatin or cisplatin and pemetrexed are provided in Section 5.1.8.1 and Section 5.1.8.2.

For further details on the preparation, storage, and administration instructions for pemetrexed, cisplatin, and carboplatin, refer to the pharmacy manual or the local prescribing information.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

Investigational medicinal products 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 accountability log.

Refer to the pharmacy manual, and/or the Tiragolumab Investigator’s Brochure, Atezolizumab Investigator’s Brochure, or local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Tiragolumab and Atezolizumab

Patients may be eligible to receive study drug as part of an extension study, as described in Section 3.3 or the Sponsor may offer continued access to Roche IMPs (tiragolumab and atezolizumab) after completing the study. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

https://www.roche.com/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 [redacted] prior to initiation of study drug to the study 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:

- [redacted]

- [redacted]

[redacted]

In general, investigators should manage a patient's care with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 4.4.2 and Section 4.4.3) as clinically indicated, per local standard practice. 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 β2-adrenergic agonists; see Appendix 11).

4.4.2 Cautionary Therapy

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-αinhibitors may attenuate potential beneficial immunologic effects of treatment with tiragolumab and/or atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-αinhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-αinhibitors 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 tiragolumab and/or atezolizumab therapy (see Appendix 11 for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended [redacted]

4.4.2.3 Other Cautionary Therapy

For information regarding medications that should be used with caution in combination with pemetrexed, cisplatin, and carboplatin, please refer to the local prescribing information.

4.4.3 Prohibited Therapy

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]

For information regarding medication that are contraindicated with pemetrexed, cisplatin, and carboplatin, please refer to the local prescribing information.

4.5 STUDY ASSESSMENTS

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

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

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

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

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.

[redacted]

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).

[redacted]

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, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and lung cancer mutational status (e.g., *EGFR* and *ALK*), reproductive status, smoking history, and use of alcohol and drugs of abuse, 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 [redacted] 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 should be performed at screening and will 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 postbaseline 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, and systolic and diastolic blood pressure while the patient is in a seated position, 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 details on vital signs on study treatment days, see in Table 2.

4.5.5 Performance Status

Performance status will be measured with use of the ECOG Performance Status at baseline, and will be assessed at regular intervals throughout the study (Appendix 1). For further details, see Appendix 9.

4.5.6 Tumor and Response Evaluations

Screening and subsequent tumor assessments must include CT scans of the abdomen and chest (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standard). A CT scan with contrast of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. Magnetic resonance imaging (MRI) scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with iodine-based contrast allergy or impaired renal clearance).

A CT (with contrast) or MRI scan with contrast (if CT contrast is contraindicated) of the head must be done at screening to evaluate CNS metastasis in all patients. If CT with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline.

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

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

[redacted]

All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation.

Patients will undergo tumor assessments at baseline and at every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1, regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessment will be required every 9 weeks (±7 days) regardless of treatment delays, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments every 6 weeks (±2 weeks) after initial documentation of progression, or more frequently if clinically indicated, regardless of time in study, until treatment is discontinued. At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected.

After unblinding at study level, tumor assessments will no longer be required per protocol defined schedule, and investigators must continue to report tumor assessment results based on the frequency as per local practices.

Response will be assessed by the investigator on the imaging modalities detailed above, with use of RECIST v1.1 (see Appendix 4). The investigator's assessment of overall tumor response at all timepoints should only be based on RECIST v1.1.

[redacted]

[redacted]

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), RBC count, hemoglobin, hematocrit, platelet count, and differential count
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (as clinically indicated), sodium, magnesium, potassium, calcium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase (LDH)
- Coagulation: INR and aPTT
- Thyroid function testing: TSH, T3 [redacted] and T4
- HIV serology
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Pregnancy test

  - All women of childbearing potential will have a serum pregnancy test during screening within [redacted] prior to the initiation of study drug. During the study, urine pregnancy tests will be performed on Day 1 of every cycle, and after study treatment is discontinued (see Appendix 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood)

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

- [redacted]
- Serum samples for assessment of ADAs to tiragolumab and to atezolizumab through use of validated tests (serum samples will be collected for both treatment arms but ADA assessment will only be performed on Arm A samples)
- Serum sample for C-reactive protein
- [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

[redacted]

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

[redacted]

[redacted]

Analysis of PD-L1 expression will be performed using the VENTANA PD-L1 (SP263) CDx Assay, which may be considered investigational per local regulations.

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.

4.5.8 Electrocardiograms

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

[redacted]

4.5.9 Clinical Outcome Assessments

Patient-reported outcome instruments will be completed to document the treatment benefit and more fully characterize the clinical profile of tiragolumab and atezolizumab plus pemetrexed with cisplatin/carboplatin. Patient-reported outcome data will be collected with use of the following instruments: the EORTC QLQ-C30, EORTC QLQ-LC13, and EORTC IL46 (a single item for trouble with side-effects).

[redacted]

After unblinding at study level, PRO questionnaires will no longer be required for patients.

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.9.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ C30 is a validated, reliable self reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; see Appendix 5).

All EORTC QLQ-C30 scales and single-item measures will be linearly transformed so that each score will range from 0–100. The EORTC QLQ-C30 module takes approximately 15 minutes to complete.

EORTC QLQ-LC13

The EORTC QLQ-LC13 (see Appendix 6) is comprised of 13 lung cancer-specific items and includes 11 disease-specific scales/items (dyspnea, coughing, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder, pain in other parts, pain medication; Bergman et al. 1994).
All EORTC QLQ-LC13 scales and single-item measures will be linearly transformed so that each score will range from 0–100. The EORTC QLQ-LC13 takes approximately 7 minutes to complete.

EORTC IL46

The EORTC IL46 (see Appendix 7), is a validated single-item question that assesses overall side effect impact. Each item is scored on a 4-point scale (1=Not at all, 2=A Little, 3=Quite a Bit, and 4=Very Much). It will be reported as raw score.
The EORTC IL46 takes approximately 1 minute to complete.

[redacted]

4.5.10 Blood Samples for Whole-Genome Sequencing or Whole-Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants 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, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. The DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

See Section 4.5.12.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at progression after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator).

[redacted]

Samples may be used for exploratory biomarker research as described in Section 4.5.12. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. See Section 4.5.12.3 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 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. Research Biosample Repository samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's 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 4.5.12.2) will not be applicable at that site.

4.5.12.3 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 tiragolumab, atezolizumab, non-squamous NSCLC, or drug safety:

- [redacted]
- [redacted]

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, whole-metagenomic sequencing for comprehensive analysis of the microbiome, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

Research Biosample Repository samples are to 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).

4.5.12.4 Confidentiality

Research Biosample Repository 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 samples, 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.

4.5.12.5 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.

4.5.12.6 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 RBR samples after closure of the site, the investigator must inform the Sponsor by e-mailing the study number and patient number to the following e-mail 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.

4.5.12.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice (GCP) 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 study treatment, 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
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of non–protocol-specified anti-cancer therapy
- Radiographic disease progression per RECIST v1.1

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

[redacted]

[redacted]

4.6.2 Patient Discontinuation from the 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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- 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 a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. [redacted]

[redacted]

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 GCP
- 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 tiragolumab alone and in combination with atezolizumab in Phase I and II studies, the clinical safety profiles of atezolizumab in combination with pemetrexed and carboplatin/cisplatin, and the clinical safety profiles of pembrolizumab in combination with pemetrexed and carboplatin/cisplatin. The anticipated important safety risks for tiragolumab, atezolizumab, pembrolizumab, pemetrexed, carboplatin, and cisplatin are outlined below. Please refer to the Tiragolumab Investigator's Brochure, the Atezolizumab Investigator's Brochure, and the pembrolizumab, pemetrexed, carboplatin, and cisplatin local prescribing information for a complete summary of safety information for each respective drug.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. An iDMC has also been incorporated into the study design to periodically review safety data (see iDMC Charter for detailed monitoring plan). Administration of study treatment 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 adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 10 and Appendix 11.

[redacted]

[redacted]

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 ESMO).

Severe COVID-19 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 COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Tiragolumab

[redacted] Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events). On the basis of experience with other therapeutic mAbs, other potential risks of tiragolumab include hypersensitivity and injection-site reactions.

See Appendix 11 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

5.1.1.1 Infusion-Related Reactions

Because tiragolumab is a therapeutic mAb and targets immune cells, IRRs associated with hypersensitivity reactions, and/or target-mediated cytokine release may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over[redacted] minutes followed by a [redacted]-minute observation period. Subsequent

infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

See Section 4.3.2 for detailed guidance on administration of tiragolumab in this study. See Appendix 3 for guidance on anaphylaxis precautions, and Appendix 11 for guidance on management of IRRs.

[redacted]

5.1.1.3 Lymphopenia

[redacted]

Patients with a lymphocyte count $<$500 cells/mL will be excluded from this study (see Section 4.1.2), and CBCs will be monitored regularly during the study (see Appendix 1).

5.1.1.4 Immune-Mediated Adverse Events

Nonclinical models have suggested a role of TIGIT signaling interruption in autoimmunity. In a knockout model (TIGIT-/-), loss of TIGIT signaling resulted in hyperproliferative T-cell responses and exacerbation of experimental autoimmune encephalitis (EAE). TIGIT-/- and wild-type B6 mice were immunized with myelin oligodendrocyte glycoprotein peptide in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT-/- mice developed severe EAE (Joller et al. 2011).

Clinical experience with therapeutic agents intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ systems and include, but are not limited to colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2).

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 11.

5.1.1.5 Embryofetal Toxicity

Embryofetal toxicity is a potential risk with tiragolumab. Administration of tiragolumab is expected to have adverse effects on pregnancy based on the expression of TIGIT on decidual NK and CD8+T cells (Powell et al. 2017; van der Zwan et al. 2018; Vento-Tormo et al. 2018), and the expected role of these cells in the recognition and response to foreign fetal, placental, and viral antigens at the maternal-fetal interface as well as maintenance of maternal-fetal tolerance. No reproductive or teratogenicity studies in animals have been conducted with tiragolumab. There are no clinical studies of tiragolumab in pregnant women. Tiragolumab should not be administered to pregnant women.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of embryofetal toxicity.

5.1.2 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). See Appendix 11 of the protocol and refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.3 Risks Associated with Combined Use of Tiragolumab and Atezolizumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab and atezolizumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to

monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section 5.1) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (other than autoimmune thyroid disease managed with thyroid-hormone replacement or vitiligo; see Section 4.1.2). Patients previously treated with approved or experimental cancer immune therapies will also be excluded from participation in this study. [redacted]

5.1.4 Risks Associated with Pembrolizumab

Pembrolizumab has been associated with immune-mediated risks such as pneumonitis, colitis, hepatitis, nephritis, endocrinopathies (adrenal insufficiency, hypophysitis, Type 1 diabetes mellitus, diabetic ketoacidosis, hypoparathyroidism, hypothyroidism, and hyperthyroidism), skin adverse reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), and other immune-mediated adverse reactions (uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, myelitis, cholangitis sclerosing, gastritis, and cystitis noninfective). Infusion-related reactions are identified risks with pembrolizumab. Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis.

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

5.1.5 Risks Associated with Pemetrexed

Pemetrexed is known to cause gastrointestinal toxicities (nausea, vomiting, diarrhea, or constipation), renal toxicities, neuropathy, myelosuppression, infection, fatigue, stomatitis, alopecia, and rash.

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

5.1.6 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 carboplatin prescribing information.

5.1.7 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.

5.1.8 Management of Patients Who Experience Adverse Events

5.1.8.1 Dose Modifications

[redacted]

5.1.8.2 Treatment Interruption

Study treatment may be temporarily suspended as appropriate for management of toxicity. On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to but independent of atezolizumab, may exacerbate the frequency or severity of atezolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguished from one another in the clinical setting, immune-mediated adverse events should generally be attributed to both study drugs, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to both tiragolumab and atezolizumab. Attribution of adverse events should be performed per investigator judgment.

[redacted]

[redacted]

Atezolizumab/pembrolizumab and/or tiragolumab/placebo may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of study treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

After both tiragolumab/placebo and atezolizumab/pembrolizumab have been permanently discontinued, the patient will be monitored for safety and efficacy as specified in Section 5.1.8 and Appendix 1.

5.1.8.3 Management Guidelines for Adverse Events Associated with Tiragolumab, Atezolizumab, and Pembrolizumab

See Appendix 11 for details on the management of tiragolumab, atezolizumab, and pembrolizumab-related adverse events. See Appendix 3 for precautions for anaphylaxis.

5.1.8.4 Chemotherapy Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

See Appendix 10 for details on chemotherapy dose modifications, treatment delays, or treatment discontinuation and management of specific adverse events.

5.1.9 Potential Overlapping Toxicities

Based on nonclinical and/or clinical studies with tiragolumab or atezolizumab as a single agent, clinical data from studies with tiragolumab and atezolizumab as a combination therapy, and data from molecules with similar mechanisms of action, there is a potential for overlapping toxicity in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these 2 molecules is to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses. The following adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab: immune-mediated pulmonary, hepatic, gastrointestinal, renal, endocrine, ocular, pancreatic, dermatologic, neurologic adverse events, as well as immune-mediated myocarditis, meningoencephalitis and myositis.

Based on the clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section 5.1) in order to reduce the potential risks to participating patients.

The risk of overlapping toxicities between tiragolumab/atezolizumab/pembrolizumab and pemetrexed and cisplatin/carboplatin is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with pemetrexed and cisplatin/carboplatin (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of tiragolumab and/or atezolizumab/pembrolizumab.

Toxicities should initially be managed according to the recommendations in Section 5.1.8.3 and Appendix 10 with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. [redacted]

[redacted]

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 GCP, 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 Sections 5.3.6.9 and 5.3.6.10 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 drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death
- Requires or prolongs inpatient hospitalization (see Section 5.3.6.11)

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; 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:

- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

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 5.3.5).

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until [redacted] days after the final dose of study treatment [redacted] and serious adverse events will continue to be reported until [redacted] days after the final dose of study treatment [redacted]

[redacted] In addition, adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted]

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: https://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 American Society for Transplantation and Cellular Therapy (ASTCT) Cytokine-Release Syndrome Consensus Grading Scale

The ASTCT CRS consensus grading scale (see Table 6) should be used in addition to NCI CTCAE when reporting severity of CRS (see Section 5.3.6.1 for details on CRS reporting).

Table 6 ASTCT CRS Consensus Grading

Grade	Symptoms
1	• Fever [a] with or without constitutional symptoms • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by

3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor with or without vasopressin – Hypoxia requiring high-flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring multiple vasopressors (excluding vasopressin) – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)
5	• Death due to CRS in which another cause is not the principal factor leading to this outcome

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome.

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

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

5.3.5 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 the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7).

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, 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 the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug 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 the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

If a patient requires a fresh biopsy for central PD-L1 SP263 testing, adverse event(s) experienced by that patient during and after the biopsy procedure must be evaluated by the investigator for relatedness to the biopsy.

[redacted]

[redacted] the investigator will be informed and the investigator will evaluate whether the patient's adverse event(s) are considered to be related to the central PD-L1 SP263 test result.

5.3.6 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.

5.3.6.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

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 on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine-release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF or Cytokine-Release Syndrome eCRF, as appropriate.

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 or Cytokine-Release Syndrome eCRF.

[redacted]

Guidelines for medical management of IRRs and CRS are provided in Appendix 11 (Table 9).

5.3.6.2 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 1 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.

5.3.6.3 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 3 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.

5.3.6.4 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.

5.3.6.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
  - Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating 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 5.3.6.4 for details on recording persistent adverse events).

5.3.6.6 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.6.4 for details on recording persistent adverse events).

5.3.6.7 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 5.3.6.2) 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 5.2.3).

5.3.6.8 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 of non-squamous NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An iDMC 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.

5.3.6.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.6.10 Lack of Efficacy or Worsening of Lung Cancer

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

5.3.6.11 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:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or performance of an efficacy measurement for the study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not experienced an adverse event.
- Hospitalization due solely to progression 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

5.3.6.12 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, 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 tiragolumab/placebo and atezolizumab/pembrolizumab 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 tiragolumab (or matching placebo) and atezolizumab 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 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.6.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. 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 drug:

- 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)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Medical Monitors and Emergency Medical Contacts

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 investigators.

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

5.4.2.1 Events that Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting 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 e-mailing the form using the fax number or e-mail address provided to investigators.

5.4.2.2 Events that Occur after Study Drug Initiation

After initiation of study drug, serious adverse events will be reported until [redacted] days after the final dose of study drug [redacted] In addition, adverse events of special interest will continue to be reported until 90 days after the final dose of study [redacted] 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 Serious Adverse Event/Adverse Event of Special Interest Reporting 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 e-mailing the form using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within [redacted] after the final dose of tiragolumab/placebo, [redacted] after the final dose of atezolizumab/pembrolizumab, or 6 months after pemetrexed and 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 e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within [redacted] after the final dose of tiragolumab/placebo, or within 6 months after the final dose of chemotherapy treatment (i.e., pemetrexed and carboplatin/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 e-mailing the form using the fax number or e-mail 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 drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.
An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (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 drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

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, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (as defined in Section 5.3.1), 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 drug, 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 e-mailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

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

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

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 through use of the reference safety information in the documents listed below:

Drug	Document
Tiragolumab	Tiragolumab Investigator's Brochure
Atezolizumab	Atezolizumab Investigator's Brochure
Pembrolizumab	Pembrolizumab EU SmPC

SmPC = Summary of Product Characteristics.

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

This is a Phase II/III, global, multicenter, randomized, double-blinded, placebo-controlled study, designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin (Arm A) compared with placebo in combination with pembrolizumab plus pemetrexed and carboplatin/cisplatin (Arm B) in patients with previously untreated, locally advanced unresectable or metastatic non-squamous NSCLC.

The analysis set for the efficacy analyses will consist of all randomized patients, with patients grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study treatment. Safety analyses will be performed on all randomized patients who receive any amount of study treatment and will be grouped by the actual treatment received, regardless of the initial treatment assignment at randomization. Specifically, a patient will be included in Arm A in the safety analyses if the patient receives any amount of tiragolumab or atezolizumab.

At the primary analysis of PFS and the first interim analysis of OS, reduced efficacy was shown in both primary endpoints for the combination of tiragolumab plus atezolizumab and chemotherapy compared to the comparator arm. Therefore, there will be no further subsequent efficacy analyses, [redacted]

6.1 DETERMINATION OF SAMPLE SIZE

This is a Phase II/III study. The Phase II part of the study has co-primary endpoints of confirmed ORR and PFS. There is no formal hypothesis testing in the Phase II part of the study, and the reported p-values will be descriptive. [redacted] the study may be expanded to a Phase III study with co-primary endpoints of PFS and OS, to test the hypothesis that Arm A prolongs the duration of PFS and/or OS relative to Arm B. In the case of no expansion, no formal hypothesis testing will be conducted for this study. The overall type I error control of the study is detailed in Section 6.1.2.1.

6.1.1 Phase II

Approximately [redacted] patients in total will be randomized in a 1:1 ratio into the Phase II part of this study. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.2 Phase III

Approximately [redacted] patients in total may be randomized in a 1:1 ratio into the expanded Phase III study. [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.1.2.2 Co-Primary Endpoint: Progression-Free Survival

The primary analysis of the co-primary endpoint of PFS will occur [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for study drug discontinuation, and reasons for discontinuation from the study will be summarized by treatment arm.
Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of any component of study treatment.

6.4 EFFICACY ANALYSES

Efficacy analyses will be conducted in all randomized patients with patients grouped according to their randomized treatments. [redacted]

[redacted]

6.4.1 Phase II

6.4.1.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are confirmed ORR and PFS as assessed by the investigator according to RECIST v1.1.

Confirmed ORR is defined as the proportion of patients who have achieved an objective response, characterized by a CR or PR, on two consecutive occasions ≥ 4 weeks apart. Objective response will be evaluated by treatment arm and patients without postbaseline overall response assessments will be counted as non-responders.

The analysis population for ORR will be all randomized patients with measurable disease at baseline. An estimate of the difference between the ORR in the treatment arms will be computed along with its 95% CI. The Mantel-Haenszel test will be used to compare the ORR between the treatment arms, stratified by the protocol-defined stratification factors. The p-value will be for descriptive purpose only; no formal hypothesis testing will be conducted.

Progression-free survival is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Patients who have not experienced disease progression or who have not died at the time of analysis will be censored at the time of the last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

Progression-free survival will be compared between treatment arms with use of the stratified log-rank test. The p-value will be for descriptive purpose only; no formal hypothesis testing will be conducted. The HR and its 95% CI for PFS will be estimated with use of a stratified Cox proportional-hazards model.

Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curve will be constructed to provide a visual description of the difference between treatment arms.

6.4.1.2 Secondary Efficacy Endpoints

Overall Survival

Overall survival is defined as the time from randomization to death from any cause. Data for patients who are alive at the time of the data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization.

A stratified Cox proportional-hazards model will be used to estimate the OS HR and its 95% CI. Kaplan-Meier methodology will be used to estimate the OS curve and median OS for each treatment arm.

Duration of Response

Duration of response is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first. The analysis of DOR will include only patients who achieved an objective response to study treatment. Duration of response will be estimated with use of the Kaplan-Meier methodology.

Patient-Reported Outcomes

Time to confirmed deterioration for cough, dyspnea, and chest pain symptoms with use of the EORTC QLQ-LC13, GHS/QoL, and physical functioning with use of the EORTC QLQ-C30 [redacted] Confirmed clinically meaningful deterioration in symptoms is defined as a score increase of ≥10-point (Osoba et al. 1998) from baseline in a symptom score that must be held for at least two consecutive assessments or an initial increase ≥10-point from baseline followed by death from any cause within 3 weeks. Confirmed clinically meaningful deterioration for GHS/QoL and physical functioning is defined as a score decrease of ≥10-point from baseline in GHS/QoL or physical functioning scale score that must be held for at least two consecutive assessments or an initial ≥10-point decrease from baseline followed by death from any cause within 3 weeks.

[redacted]

Time to confirmed deterioration with use of the EORTC scale will be analyzed with use of the same methods as for PFS. [redacted]

Completion rates will be summarized at each timepoint by treatment arm.

6.4.2 Phase III

6.4.2.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS, as assessed by the investigator according to RECIST v1.1, and OS.

[redacted]

The weights w_f, w_2, w_3 are determined prior to the interim efficacy analysis (see Section 6.10) and are based on the projected number of events at the time of the analyses. If Δ_f, Δ_2, Δ_3 are the total number events expected at the time of the interim efficacy analysis during the Phase II part of the study, cumulative number of events for the Phase II cohort at the analyses specified for the Phase III, and cumulative number of events in the phase III expansion cohort at the analyses specified for the Phase III, respectively, the weights can be expressed as follows.

$$W_f = \sqrt{\frac{\Delta_f}{\Delta_2 + \Delta_3}}$$

$$w_2 = \sqrt{\frac{\Delta_2 - \Delta_f}{\Delta_2 + \Delta_3}}$$

$$w_3 = \sqrt{\frac{\Delta_3}{\Delta_2 + \Delta_3}}$$

Two-sided p value based on $z_{P2/3}$ will be compared to two-sided type I error, 0.004, allocated for PFS testing for the PFS primary analysis (see Section 6.1.2). Based on the assumptions listed in Section 6.1.2, the values to be used for the PFS primary analysis are summarized in the Table 11 below.

[redacted]

[redacted]

[redacted]

The HR and 95% CI for PFS and OS will be estimated using a stratified Cox proportional hazards model. [redacted]

[redacted]

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

[redacted]

6.4.2.2 Secondary Efficacy Endpoints

Progression Free Survival assessed by Independent Review Facility

Independent review facility-PFS, defined as the time from randomization to the first occurrence of disease progression as determined by an IRF according to RECIST v1.1, or death from any cause, whichever occurs first. Independent review facility-PFS will be analyzed using the same methods described for the PFS analysis in all randomized patients (see Section 6.4.2.1).

Progression-Free Survival and Overall Survival for the SP263 PD-L1 Subpopulation

Treatment effects measured by investigator-assessed PFS and OS in patients with PD-L1 expression at TPS/TC $<1\%$, $1-49\%$, and $\geq 50\%$ cut-off determined using the VENTANA SP263 IHC assay will be analyzed. These will be analyzed using the same methods described for the PFS and OS analysis in all randomized patients (see Section 6.4.2.1), with the exception that the stratification factors used for the stratified analyses will be geographic region ([redacted]) and ECOG Performance Status [redacted]

Progression-Free Survival Rate at Specific Timepoints

The PFS rate at 6 months and 12 months will be estimated using Kaplan-Meier methodology for each treatment arm and the 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between the two treatment arms will be estimated using the normal approximation method.

Overall Survival Rate at Specific Timepoints

The OS rate at 12 months and 24 months will be estimated using Kaplan-Meier methodology for each treatment arm and the 95% CIs calculated using the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method.

Confirmed Objective Response Rate

Confirmed ORR is defined and analyzed using the same methods as for the Phase II (see Section 6.4.1).

Duration of Response

The DOR is defined and analyzed using the same methods as for the Phase II (see Section 6.4.1).

Patient Reported Outcomes

Time to confirmed deterioration is defined and analyzed using the same methods as for the Phase II (see Section 6.4.1).

6.5 SAFETY ANALYSES

Safety analyses will include all treated patients, defined as randomized patients who received any amount of study treatment.

Safety analyses will be performed by treatment arm and will be based on actual treatment received, regardless of the initial treatment assignment at randomization. Specifically, a patient will be included in Arm A in the safety analyses if the patient receives any amount of tiragolumab or atezolizumab.

Drug exposure will be summarized, including duration, dosage, and dose intensity. Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms. Severity for all adverse events will be graded by the investigator according to the NCI CTCAE v5.0, [redacted] ll adverse events will be summarized by treatment arm and NCI CTCAE grade. [redacted] In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data, including ADA results, will be summarized by treatment arm. Deaths and causes of deaths will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Samples will be collected for PK analyses and to compare exposure in this study with that attained in previous studies. Serum concentrations of tiragolumab and atezolizumab will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and cycle, when appropriate and as data allow. Individual and median serum tiragolumab and atezolizumab concentrations will be plotted by treatment arm and day. Tiragolumab and atezolizumab concentration data may be pooled with data from other studies with use of an established population PK model to derive PK parameters such as clearance, volume of distribution, and AUC, as warranted by the data. Potential correlations of relevant PK parameters with safety, efficacy, or biomarker outcomes may be explored.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ADA assessments, with patients grouped according to treatment received.

The numbers and proportions of treatment-emergent ADA-positive patients and ADA-negative patients for both tiragolumab and atezolizumab will be summarized.

[redacted]

[redacted]

6.10.3 Safety Monitoring

The iDMC will convene to review the interim safety analyses results for [redacted] See Section 3.2.2 for additional details regarding the iDMC. More details on the interim safety analyses will also be provided in the iDMC charter.

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.

Electronic Case Report Forms 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.

Patient-reported outcome 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. Electronic Case Report Forms 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. Electronic Case Report Forms 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 that must be kept with the study records. Acknowledgement of receipt of the data 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, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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 IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time

required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

Roche will retain study data for 25 years after the final study results have been reported 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 GCP 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 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) while a patient is participating in the study, the patient or a legally authorized representative must re-consent 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 Sponsor 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.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, 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 provided upon request (see Section 9.6).

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 3.3).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP 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 [redacted] sites globally will participate to enroll approximately [redacted] patients in the Phase II part of the study. [redacted]

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. 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 throughout the study and to review efficacy data at the PFS interim analysis, as specified in Section 3.2.2. [redacted]

All primary imaging data used for tumor assessments will be collected by the Sponsor and a centralized, blinded independent review by an IRF may be conducted.

After unblinding at study level, submission of primary imaging data used for tumor assessments to the IRF will be halted.

9.6 DISSEMINATION 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, 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

Procedure	Screening [a]	Treatment Cycle (21-Day Cycles) [b]		Treatment Discontinuation Visit [d]	Long Term and Survival Follow Up [e]
	[redacted]	Induction (Cycles 1–4) [c]	Maintenance (Cycles 5+)	[redacted] after	Approximately Every 3 Months
		Day 1 (±3 Days)	Day 1 (±3 Days)	Last Dose of Study Treatment	(±30 Days)
Informed consent(s) [f] • Optional Prescreening ICF for PD-L1 testing • Main ICF for study participation	x				
[redacted]	x				
EGFR or *ALK* mutational status [h]	x				
Demographic data	x				
Medical history, cancer history, and baseline conditions [i]	x				
Vital signs [j]	x	x [dd]	x [dd]	x [dd]	
Weight	x	x	x	x	
Height	x				
Complete physical examination [k]	x				
Limited physical examination [l]		x	x	x	
ECOG Performance Status [m]	x	x	x	x	
ECG [n]	x	As clinically indicated			
Hematology [o]	x	x [dd]	x [dd]	x [dd]	

Appendix 1: Schedule of Activities (cont.)

Procedure	Screening [a]	Treatment Cycle (21-Day Cycles) [b]		Treatment Discontinuation Visit [d]	Long Term and Survival Follow Up [e]
	[redacted]	Induction (Cycles 1–4) [c]	Maintenance (Cycles 5+)	[redacted] after Last Dose of Study Treatment	Approximately Every 3 Months (±30 Days)
		Day 1 (±3 Days)	Day 1 (±3 Days)		
Serum chemistry [p]	x	x [dd]	x [dd]	x [dd]	
Coagulation test (INR and aPTT)	x			x [dd]	
TSH, free T3, free T4 [q]	x	x [dd, q]	[redacted]	x [dd]	
HIV, [redacted] [r]	x				
Urinalysis [s]	x	As clinically indicated			
Pregnancy test (women of child-bearing potential only) [t]	x	x [dd]	x [dd]	x [dd]	
Induction treatment administration [c] Arm A: tiragolumab + atezolizumab + pemetrexed + carboplatin		x			
Arm A: tiragolumab + atezolizumab + pemetrexed + cisplatin		x			
Arm B: placebo + pembrolizumab + pemetrexed + carboplatin		x			

Appendix 1: Schedule of Activities (cont.)

Procedure	Screening [a]	Treatment Cycle (21-Day Cycles) [b]		Treatment Discontinuation Visit [d]	Long Term and Survival Follow Up [e]
	[redacted]	Induction (Cycles 1–4) [c]	Maintenance (Cycles 5+)	[redacted] after Last Dose of Study Treatment	Approximately Every 3 Months (±30 Days)
		Day 1 (±3 Days)	Day 1 (±3 Days)		
Arm B: placebo + pembrolizumab + pemetrexed + cisplatin		x			
Maintenance treatment administration Arm A: tiragolumab + atezolizumab + pemetrexed			x		
Arm B: pembrolizumab + pemetrexed			x		
Tumor response assessment [u, v]	x		x [v]		
Serum sample for C-reactive protein [w]		x			
Serum sample for PK and ADA assessments		See Appendix 2			
Blood samples for PD biomarkers		See Appendix 2			
[redacted] [x]		x	x	x	
Optional blood and stool sample for RBR [y]		See Appendix 2			
For patients randomized during the Phase II part of the study: Patient-reported outcomes (PRO) (EORTC QLQ-LC13, EORTC QLQ-C30, and EORTC IL46) [z]		[redacted]			

Appendix 1: Schedule of Activities (cont.)

Procedure	Screening [a]	Treatment Cycle (21-Day Cycles) [b]		Treatment Discontinuation Visit [d]	Long Term and Survival Follow Up [e]
	[redacted]	Induction (Cycles 1–4) [c]	Maintenance (Cycles 5+)	[redacted] after	Approximately Every 3 Months (±30 Days)
		Day 1 (±3 Days)	Day 1 (±3 Days)	Last Dose of Study Treatment	
For patients randomized during the Phase III part of the study: Patient-reported outcomes (PRO) (EORTC QLQ-LC13, EORTC QLQ-C30, EORTC IL46, and EQ-5D-5L) [aa]		[redacted]			
Adverse events [bb]		x [dd]	x [dd]	x [dd]	x
Cancer-related procedures (medical, surgical, and radiation)		x	x	x	
Concomitant medications [cc]	x	x [dd]	x [dd]	x [dd]	
Survival and anti-cancer therapy follow-up					x

ADA = anti-drug antibody; ALK = anaplastic lymphoma kinase; CT = computed tomography; [redacted] ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EGFR = epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; ICF = Informed Consent Form; [redacted] PD = pharmacodynamic; MRI = magnetic resonance imaging; PK = pharmacokinetic; PRO = Patient-Reported Outcome; Lung Cancer Module; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors.

Notes: All assessments should be performed within +3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 1: Schedule of Activities (cont.)

[a] Screening tests and evaluations will be performed [redacted] prior to Day 1 of Cycle 1, unless otherwise specified. Results of standard of care tests or examinations performed prior to obtaining informed consent and [redacted] prior to Day 1 may be used; such tests do not need to be repeated for screening. [redacted]

[b] [redacted]

[c] [redacted]

[d] Patients will be asked to return to the clinic for a treatment discontinuation visit [redacted] after the final dose of study treatment drug. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[e] [redacted]

[f] Informed consent must be documented before any study-specific screening procedure is performed, and [redacted] before initiation of study treatment.

[g] [redacted]

[h] For patients who have unknown *EGFR* or *ALK* status will be required to be tested at prescreening/screening. Epidermal growth factor receptor and/or *ALK* status may be assessed locally or at a central laboratory. Epidermal growth factor receptor status assessed locally must be performed on tissue or cytology with use of a validated health authority approved test that detects mutations in exons 18–21. [redacted]

[i] Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline.

[j] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. New or worsened clinically significant abnormalities should be recorded as adverse events in the Adverse Event eCRF.

[k] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[l] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. New or worsened clinically significant abnormalities should be recorded as adverse events in the Adverse Event eCRF. [redacted]

[m] Status will be measured with use of the ECOG Performance [redacted]

[n] Single lead ECG is required at screening, at the treatment discontinuation visit, and when clinically indicated. Electrocardiograms for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[o] Hematology includes WBC count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), RBC count, hemoglobin, hematocrit, platelet count, and differential count. [redacted]

[p] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (as clinically indicated), sodium, magnesium, potassium, chloride, calcium, phosphate, glucose, BUN or urea, creatinine, total protein, albumin, total bilirubin, ALP, ALT, AST, and LDH. [redacted]

[q] Thyroid stimulating hormone and free T3 [redacted] and free T4 will be collected at screening, on Day 1 of Cycle 1, and every fourth cycle thereafter (e.g., Cycles 1, 5, 9, 13, and so forth), and at treatment discontinuation. [redacted]

[r] [redacted] HIV [redacted] HIV-positive patients will be excluded from the study. [redacted]

[s] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and will be obtained when clinically indicated. [redacted]

[t] All women of childbearing potential will have a serum pregnancy test during screening within [redacted] prior to initiation of study drug. Urine pregnancy tests will be performed [redacted] before Day 1 of every cycle and at the study treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Screening and subsequent tumor assessments must include CT scans (with oral or IV contrast unless contraindicated). A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. Magnetic resonance imaging scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). A CT (with contrast if not contraindicated) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. At subsequent (post-screening) tumor assessments, patients with a history of irradiated brain metastases at screening are not required to undergo brain scans unless clinically indicated (e.g., in patients with neurological symptoms). If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan. Further investigations, such as bone scans and CT scans of the neck, should also be performed if clinically indicated.

[v] Patients will undergo tumor assessments at baseline and at every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays, until radiographic disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments every 6 weeks (±2 weeks) after initial documentation of progression, or more frequently if clinically indicated, regardless of time in study, until treatment is discontinued. At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected. The investigator's assessment of overall tumor response at all timepoints should only be based on RECIST v1.1 (see Appendix 4). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle. [redacted] *After unblinding at study level, tumor assessments will no longer be required per protocol defined schedule, and investigators must continue to report tumor assessment results based on the frequency as per local practices.*

[w] Only collected on Day 1 of Cycle 1 prior to the first dose of study treatment.

x [redacted]

y 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 [redacted]
See Section 4.5.9.1 for additional information. *After unblinding at study level, PRO questionnaires will no longer be required for patients.*

aa [redacted] The PRO instruments will be self-administered by the participant via paper or may be collected remotely via telephone on non-visiting dates (e.g., during follow-up or in exceptional circumstances). *After unblinding at study level, PRO questionnaires will no longer be required for patients.*

[bb] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until [redacted] days after the final dose of study treatment [redacted] All serious adverse events will continue to be reported until [redacted] days after the final dose of study treatment [redacted] In addition, adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted] 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 study drug treatment (see Section 5.6). Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until a final outcome can be reported.

[cc] 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 used [redacted] prior to the initiation of study treatment should be documented. At subsequent visits, changes to current medications or medications used since the last documentation will be recorded.

[dd] For patients in either arm at participating sites who have provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed by a trained nursing professional at the patient's home or another suitable location.

Appendix 2
Schedule of Pha[redacted]unogenicity, and

After unblinding at study level, the pharmacokinetic, immunogenicity, and biomarker sample collection schedule will change so that samples are no longer collected at any timepoints during study treatment period, and at treatment discontinuation visit.

Visit	Timepoint	Sample Type [a]
Day 1 of Cycle 1 [b]	Prior to the first infusion	Tiragolumab PK (serum) [c] Atezolizumab PK (serum) Tiragolumab ADA (serum) Atezolizumab ADA (serum) [redacted]
	30 (±10) minutes after end of tiragolumab infusion	Tiragolumab PK (serum)
	30 (±10) minutes after end of atezolizumab infusion	Atezolizumab PK (serum)
Day 1 of Cycles 2, 3, 4 (all samples)	Prior to the first infusion	Tiragolumab PK (serum) Atezolizumab PK (serum) Tiragolumab ADA (serum) Atezolizumab ADA (serum) [redacted]
Day 1 of Cycle 3	Between Cycle 2, Day 15 and predose on Cycle 3, Day 1	Stool sample for RBR (optional) [e]
Day 1 of Cycles 8, 12, and 16 (all samples)	Prior to the first infusion	Tiragolumab PK (serum) Atezolizumab PK (serum) Tiragolumab ADA (serum) Atezolizumab ADA (serum) [redacted]
Treatment Discontinuation Visit	NA	Tiragolumab PK (serum) Atezolizumab PK (serum) Tiragolumab ADA (serum) Atezolizumab ADA (serum) [redacted]
At time of fresh biopsy (if applicable) [f]	NA	[redacted]

Any timepoint during the study (RBR consent required)[g]	NA	[redacted]

ADA=anti-drug antibody; NA=not applicable; PK=pharmacokinetic; [redacted]

[a] Fluid biomarker sample collection will be optional in China.

[b] Serum samples collected for the assessment of pharmacokinetics, ADAs, or biomarkers at baseline and on Day 1 of Cycle 1 prior to the first dose of study treatment may be used for auto-antibody testing if an immune-mediated adverse event develops in a patient that would warrant such an assessment.

[c] Pharmacokinetic and ADA serum samples will be collected in both treatment arms but only tiragolumab and atezolizumab PK and tiragolumab and atezolizumab ADAs will be assessed via respective validated bioanalytical assays. Pembrolizumab PK and ADAs will not be assessed.

[redacted]

[f] If biomarker samples have been collected or will be collected at a visit within 7 days of the biopsy procedure date, an additional biomarker sample collection is not required.

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

Appendix 3
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous 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. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 4
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 the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions and 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. 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").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 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 lungs, peritoneal spread, and abdominal

[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.

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, positron emission tomography (PET) 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 loco-regional 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 not usually more than 4 weeks prior to 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 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 because 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

Computed tomography 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. Magnetic resonance imaging 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 (with or without MRI 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 (with or without MRI IV contrast) 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 because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, AND 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 20×30 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, given that 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 is 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 is 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 During 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 the 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 the 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 "unequivocal 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 following criteria used to determine objective tumor response for target lesions are provided:

- 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 at prior timepoints (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 a CR or a 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
  - 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
- 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 preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

there is definitely a new lesion, progression should be declared as of 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.

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.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/or measurement is performed 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 treatment. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

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.

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Appendix 5
European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30

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ENGLISH

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): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	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

Appendix 6
European Organisation for Research and Treatment of Cancer
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

Appendix 7
European Organisation for Research and Treatment of Cancer Item List 46 (EORTC IL46)

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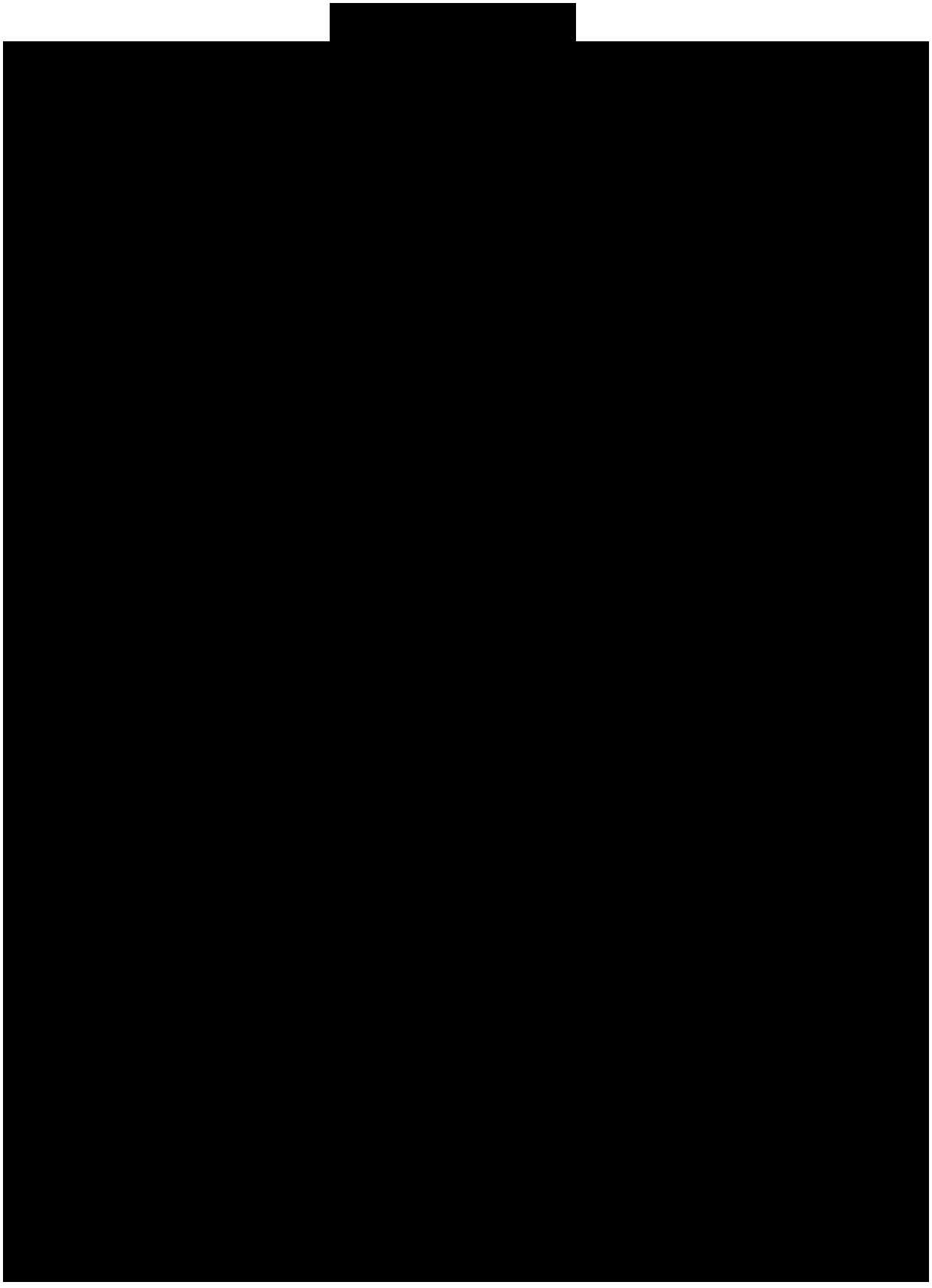
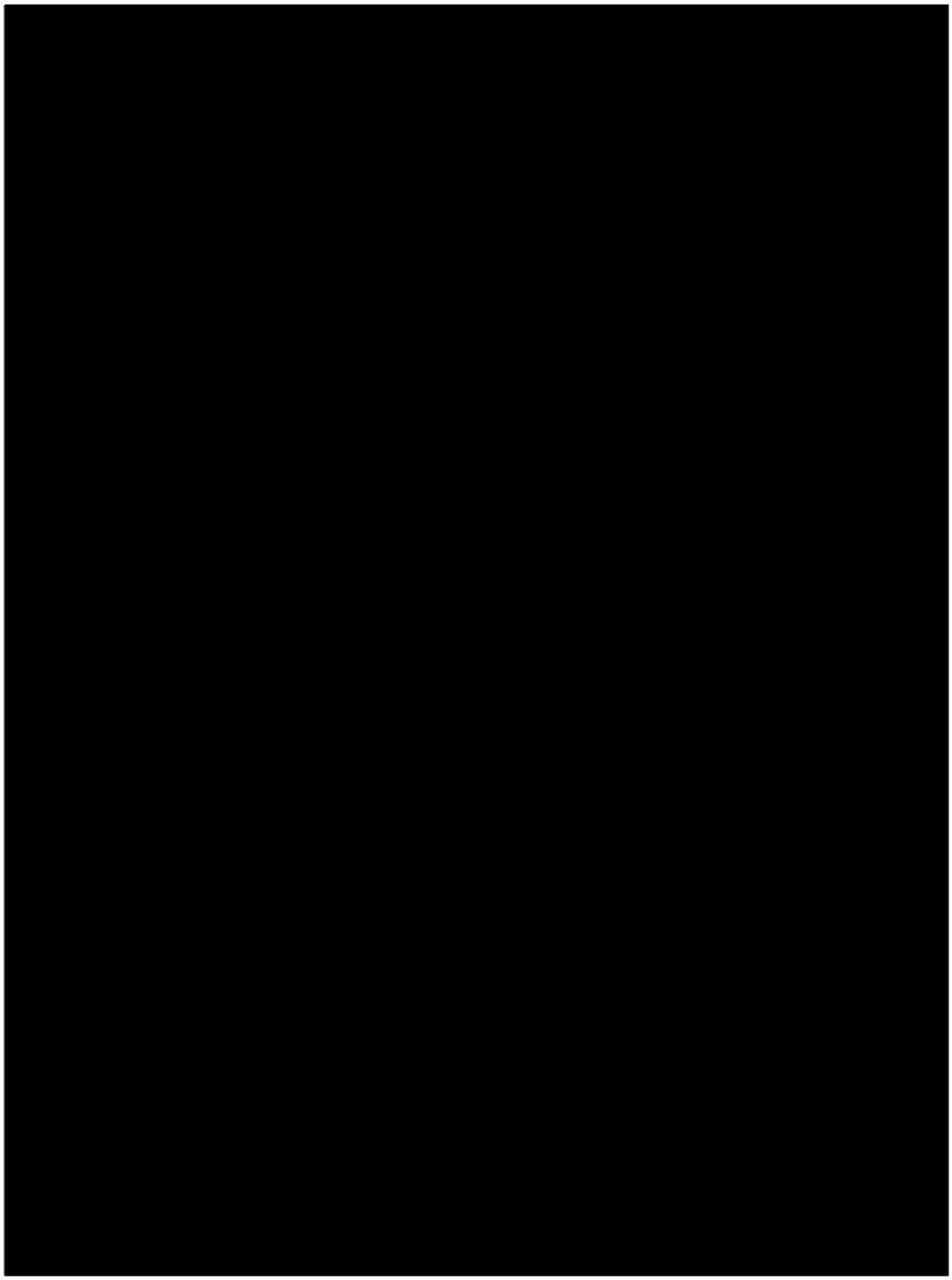
ENGLISH

EORTC IL46

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
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4





Appendix 9
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 10
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS FOR TIRAGOLUMAB/PLACEBO AND/OR ATEZOLIZUMAB/PEMBROLIZUMAB

[redacted]

TREATMENT INTERRUPTION FOR TIRAGOLUMAB/PLACEBO AND/OR ATEZOLIZUMAB/PEMBROLIZUMAB

See risks associated with tiragolumab/placebo or atezolizumab/pembrolizumab and guidelines for management of associated adverse events.

Tiragolumab/Placebo

Study treatment may be temporarily suspended as appropriate for management of toxicity. On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to but independent of atezolizumab/pembrolizumab, may exacerbate the frequency or severity of atezolizumab- and pembrolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab/pembrolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, immune-mediated adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to immune-mediated adverse events should be applied to both tiragolumab/placebo and atezolizumab/pembrolizumab.

[redacted]

[redacted]

Atezolizumab/Pembrolizumab

Atezolizumab/pembrolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. [redacted] The decision to rechallenge patients with tiragolumab and atezolizumab/pembrolizumab should be based on the investigator's benefit–risk assessment and documented by the investigator.

[redacted]

DOSE MODIFICATIONS FOR CHEMOTHERAPY

Dose modifications for pemetrexed and cisplatin/carboplatin are permitted for toxicity according to the prescribing information and local standard of care.

Dose modification guidelines are provided below. Once reduced, the dose cannot be increased back to 100%.

Treatment with pemetrexed or cisplatin/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 63 days due to toxicities.

HEMATOLOGIC TOXICITY

At the start of each cycle, the ANC should be ≥1500/μL and the platelet count should be ≥100,000/μL. Treatment could be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN® guidelines (Smith et al. 2015; NCCN® 2019.
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 1).

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

Table 1 Chemotherapy Dose Modification for Hematologic Toxicities

Toxicity [a]	Dose
ANC $<$ 500/μL and platelets $\geq$ 50,000/μL	75% of previous dose
Platelets $<$ 25,000/μL, regardless of ANC	75% of previous dose
Platelets $<$ 50,000/μL with Grade $\geq$ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<$ 1000/μL plus fever of $\geq$ 38.5°C	75% of previous dose

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 is 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 investigator's institution's guidelines.

NON-HEMATOLOGIC TOXICITY

For a non-hematologic toxicity (see Table 2), treatment should be delayed for up to 63 days until resolution to less than or equal to the patient's baseline value (or Grade $\leq$ 1 if the patient did not have that toxicity at baseline). Dose reductions at the start of the subsequent cycle should be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle. Table 2 provides recommended dose modifications for non-hematologic toxicities.

Table 2 Dose Modifications for Treatment Discontinuation for Non-Hematologic Toxicities

Toxicity		Adjusted 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 investigator, 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 may be controlled with adequate anti-emetics. For Grade 3 or 4 neurotoxicity chemotherapy should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on investigator's clinical judgment).

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Appendix 11
Risks Associated with Tiragolumab and/or Atezolizumab/Pembrolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab/Pembrolizumab

Toxicities associated or possibly associated with tiragolumab and/or atezolizumab/pembrolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology when clinically indicated.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of tiragolumab and/or atezolizumab/pembrolizumab 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.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events 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.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- The investigator should consider the benefit–risk balance for a given patient prior to further administration of tiragolumab/placebo and atezolizumab/pembrolizumab.
  [redacted]

DOSE MODIFICATIONS

Please see Appendix 10.

TREATMENT INTERRUPTION

Please see Appendix 10.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[redacted]	• [redacted]

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

[redacted]

a

b

c

d

HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug(s).

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
[redacted]	• [redacted] •
[redacted]	[redacted]

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3–5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
[redacted]	• [redacted]

GI=gastrointestinal.

a [redacted]

b

c

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic

resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 4 Management Guidelines for Endocrine Events (cont).

Event	Management
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

Table 4 Management Guidelines for Endocrine Events (cont.)

[redacted]

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
[redacted]	• [redacted]
[redacted]	•

Table 5 Management Guidelines for Ocular Events (cont.)

Event	Management
[redacted]	• [redacted]

a [redacted]

b

c

IMMUNE-MEDICATED CARDIAC EVENTS

[redacted] Management guidelines for cardiac events are provided in Table 6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., troponin, B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on immune-mediated pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of

gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

[redacted]

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on immune-mediated myocarditis above).

[redacted]

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
[redacted]	• [redacted]

INFUSION-RELATED REACTIONS

[redacted]

Infusion-related reactions are known to occur with the administration of monoclonal antibodies and have been reported with tiragolumab and atezolizumab/pembrolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of tiragolumab or atezolizumab/pembrolizumab administration and are generally mild to moderate in severity.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7.

[redacted]

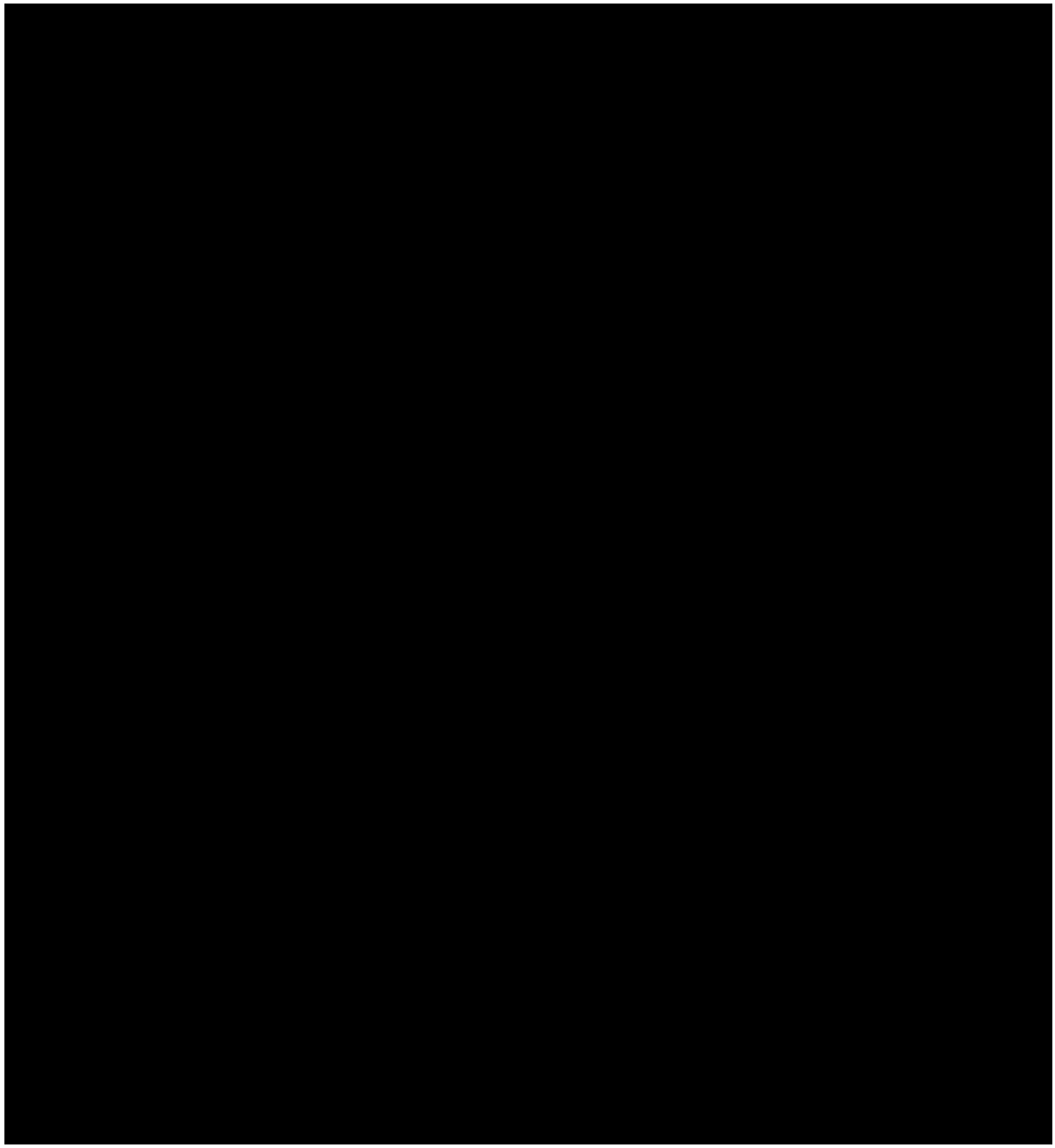
Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

IRR = infusion-related reaction.

[a] [redacted]

[redacted]



Appendix 11: Risks Associated with Tiragolumab or Atezolizumab/Pembrolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab/Pembrolizumab (cont.)

Appendix 11: Risks Associated with Tiragolumab or Atezolizumab/Pembrolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab/Pembrolizumab (cont.)

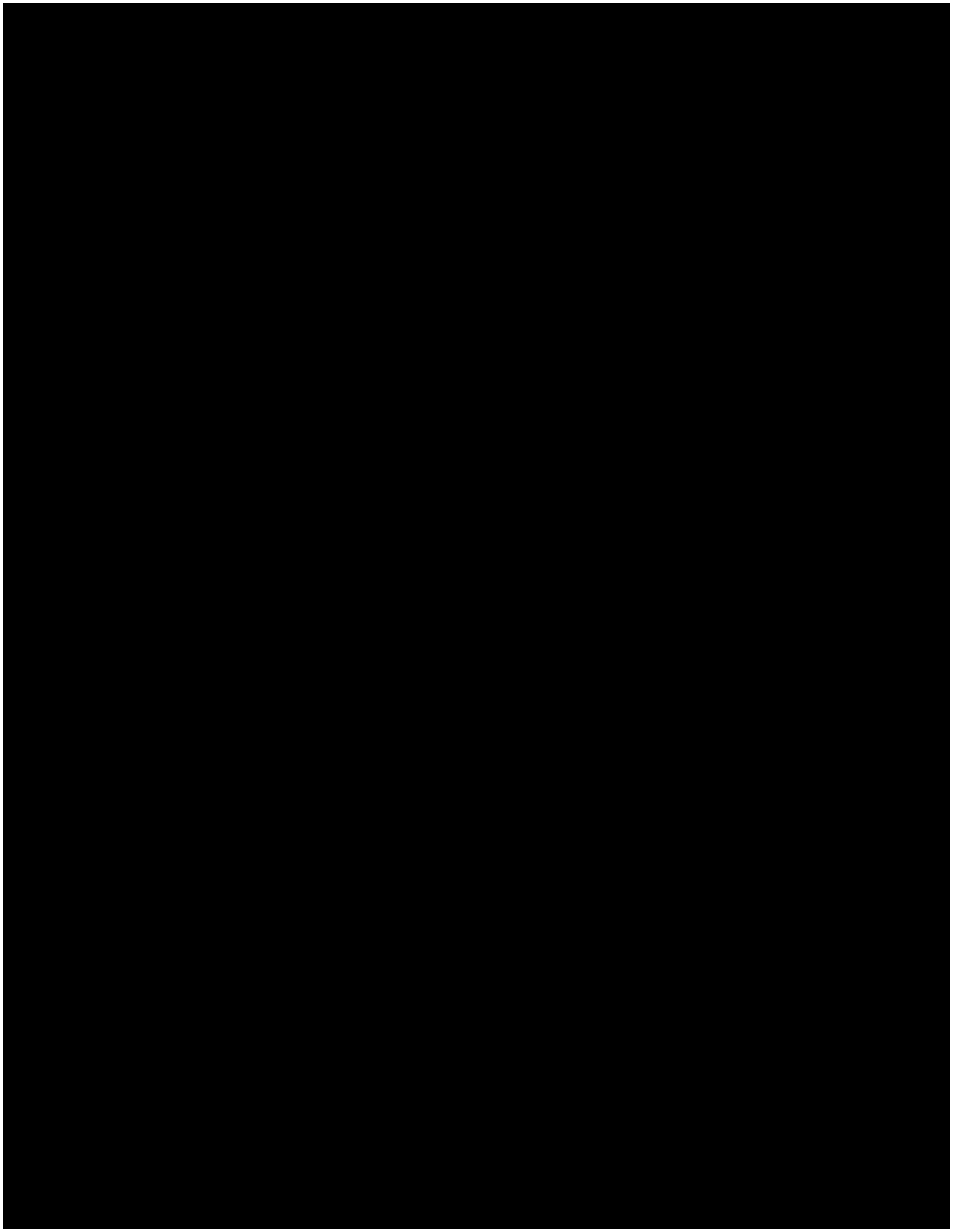


Table 8 Management Guidelines for Cytokine-Release Syndrome (cont.)

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 9.

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	[redacted]
[redacted]	
[redacted]	

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of tiragolumab, atezolizumab, or pembrolizumab were mild in severity and self-limited, with or without pruritus. [redacted] anagement guidelines for dermatologic events are provided in Table 10.

Table 10 Management Guidelines for Dermatologic Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	[redacted]

Table 10 Management Guidelines for Dermatological Events (cont).

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Myasthenia may be associated with myositis (see section on immune-mediated myositis) and patients should be managed accordingly. Management guidelines for neurologic disorders are provided in Table 11, with specific guidelines for myelitis provided in Table 12.

Table 11 Management Guidelines for Neurologic Disorders

Event	Management
[redacted]	[redacted]
[redacted]	

Table 11 Management Guidelines for Neurologic Disorders (cont).

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

[redacted]

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

[redacted]

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[redacted]	• [redacted]

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Renal Events

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

Table 14 Management Guidelines for Renal Events (cont.)

a	[redacted]
b	
c	

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. [redacted]

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Immune-Mediated Myositis

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

Table 15 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]

Table 15 Management Guidelines for Immune-Mediated Myositis (cont.)

[redacted]

a [redacted]

b [redacted]

c [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

[redacted]

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Appendix 12
Preexisting 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

Appendix 13
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 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
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Tiragolumab (RO7092284) placebo	IMP (placebo)	Unauthorized	Not applicable
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No
Pembrolizumab	IMP (comparator)	Authorized	Yes
Pemetrexed	AxMP (background therapy)	Authorized	Not applicable
Carboplatin	AxMP (background therapy)	Authorized	Not applicable
Cisplatin	AxMP (background therapy)	Authorized	Not applicable

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

Appendix 13: Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 2 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area and United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in {EEA/and/UK}	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Tiragolumab (RO7092284) placebo	IMP (placebo)	Unauthorized	Not applicable
Pembrolizumab	Non-Roche IMP (comparator)	Authorized	Yes
Carboplatin	Non-Roche NIMP (background treatment)	Authorized	Not applicable
Cisplatin	Non-Roche NIMP (background treatment)	Authorized	Not applicable
Pemetrexed	Non-Roche NIMP (background treatment)	Authorized	Not applicable

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product.

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