Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab Plus Carboplatin and Etoposide With or Without Tiragolumab (Anti-TIGIT Antibody) in Patients with Untreated Extensive-Stage Small Cell Lung Cancer

NCT Number: NCT04256421

Document Date: Protocol Amendment Version 7: 11-Dec-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS CARBOPLATIN AND ETOPOSIDE WITH OR WITHOUT TIRAGOLUMAB (ANTI-TIGIT ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO41767
VERSION NUMBER:	7
TEST COMPOUND:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
STUDY PHASE	III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 129,258 EU CT Number: 2022-502988-37-00 EUDRACT Number: 2019-003301-97 NCT Number: NCT04256421
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		Associated Country-Specific Protocols		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
7	See electronic date stamp on final page of this document.	—	—	—
6	20 December 2022	—	—	—
5	15 November 2021	—	—	—
4	9 June 2021	—	—	—
3	22 October 2020	—	—	—
2	12 May 2020	VHP	1	25 March 2020
1	24 September 2019	—	—	—

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol GO41767 has been amended primarily to follow-up ongoing patients in the study for limited information after the final overall survival (OS) analysis is conducted, to incorporate changes to update and align study drug risks and adverse event management guidelines for atezolizumab with the Atezolizumab Investigator's Brochure Version 20 (IB v20), and also to align with Clinical Trials Regulation (CTR) requirements. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

[redacted]

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

Updates to the adverse event management guidelines for atezolizumab to align with the Atezolizumab IB v20 and the CTR changes are summarized below:

- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.5).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1).

- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab IB v20 (Appendix 13 and 14).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS CARBOPLATIN AND ETOPOSIDE WITH OR WITHOUT TIRAGOLUMAB (ANTI-TIGIT ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE 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 *as instructed by your local study monitor.*

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB PLUS CARBOPLATIN AND ETOPOSIDE WITH OR WITHOUT TIRAGOLUMAB (ANTI-TIGIT ANTIBODY) IN PATIENTS WITH UNTREATED EXTENSIVE-STAGE SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 129,258 EU CT Number: 2022-502988-37-00 EUDRACT NUMBER:2019-003301-97 NCT Number: NCT04256421

STUDY RATIONALE

The purpose of this study is to evaluate the safety and efficacy of tiragolumab in combination with atezolizumab and carboplatin and etoposide (CE) compared with treatment with placebo in combination with atezolizumab and CE in patients who are chemotherapy-naive extensive-stage small cell lung cancer (ES-SCLC). The current standard first-line treatment for patients with ES-SCLC is the PD-L1 inhibitor atezolizumab given with platinum-based chemotherapy consisting of CE as induction therapy for 4 cycles, followed by atezolizumab maintenance therapy. Despite the improved efficacy observed with first-line atezolizumab plus CE, most patients with ES-SCLC experienced disease progression, and upon relapse, their prognosis is poor. Therefore, novel strategies are needed to deliver better long-term survival. The addition of complementary immunomodulatory agents to the current treatment backbone is an appealing strategy to further improve the prognosis of patients with advanced small cell lung cancer.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Corresponding Endpoint
To evaluate the efficacy of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE in patients with untreated ES-SCLC	• PFS after randomization, 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 in patients who are randomly assigned without presence or history of brain metastases at baseline (PAS) • OS after randomization, defined as the time from randomization to death from any cause in the PAS

Secondary Efficacy Objectives	Corresponding Endpoints
To evaluate the efficacy of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE	• PFS in the FAS • OS in the FAS • Confirmed ORR, defined as the proportion of patients with a confirmed objective response (i.e., CR or PR on two consecutive occasions ≥4 weeks apart), as determined by the investigator according to RECIST v1.1 in the PAS and the FAS who have measurable disease at baseline • DOR for patients with confirmed objective response, defined as the time from the first occurrence of a documented, confirmed objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first in the PAS and the FAS • PFS rates at 6 months and at 12 months in the PAS and the FAS • OS rates at 12 months and 24 months in the PAS and the FAS • TTCD in patient-reported physical functioning and GHS/QoL, as measured by the EORTC QLQ-C30 in the PAS and the FAS
Safety Objective	Corresponding Endpoints
To evaluate the safety of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE, Version 5.0 • [redacted]
PK Objective	Corresponding Endpoints
To characterize the PKs 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
Health Status Utility Objective	Corresponding Endpoints
To evaluate the impact of health status utility scores of patients treated with tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE	• Change in EQ-5D-5L index-based and Visual Analog Scale scores at specified timepoints during the study (including post-progression)

ADAs = anti-drug antibodies; [redacted]
CE = carboplatin and etoposide; CR = complete response; CRS = cytokine-release syndrome; DOR = duration of response; ES-SCLC = extensive-stage small cell lung cancer; EORTC = European Organisation for the Research and Treatment of Cancer; FAS = full analysis set; GHS = global health status; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = Overall survival; PAS = primary analysis set; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; QLQ-C30 = Quality of Life-Core 30 Questionnaire; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; TTCD = time to confirmed deterioration.

OVERALL DESIGN AND STUDY POPULATION

This is a randomized, Phase III, global, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of tiragolumab in combination with atezolizumab and CE compared with treatment with placebo in combination with atezolizumab and CE in patients who are chemotherapy-naive ES-SCLC.

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

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Active Comparator, Placebo	**Population Diagnosis or Condition:**	Extensive-stage small cell lung cancer
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Compounds:	tiragolumab	**Site Distribution:**	Multi-site
Active Comparator:	atezolizumab and carboplatin and etoposide	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 470 patients

STUDY TREATMENT

Eligible patients will be stratified by Eastern Cooperative Oncology Group Performance Status (0 vs. 1), LDH (≤ upper limit of normal [ULN] vs. > ULN), and presence or history of brain metastasis (yes vs. no) and randomly assigned in a 1:1 ratio to receive one of the following treatment regimens during the induction phase:

- Arm A: tiragolumab plus atezolizumab plus CE
- Arm B: placebo plus atezolizumab plus CE

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

Arm A: atezolizumab → tiragolumab → carboplatin → etoposide

Arm B: atezolizumab → placebo → carboplatin → etoposide

During the induction phase, study treatment should be administered in the following manner on Day 1:

Atezolizumab 1200 mg administered intravenously over 60 (± 15) minutes (for the first infusion and shortening to 30 [± 10] minutes for subsequent infusions), followed by tiragolumab/placebo 600 mg administered intravenously over [redacted] minutes (for the first infusion and shortening to [redacted] minutes for subsequent infusions), followed by carboplatin administered intravenously over 30–60 minutes to achieve an initial target area under the concentration–time curve (AUC) of [redacted] mg/mL/min (Calvert formula dosing), followed by etoposide (100 mg/m^2) administered intravenously over 60 minutes.

During the induction phase, etoposide (100 mg/m^2) will be also administered intravenously over 60 minutes on Days 2 and 3.

Cycles in which no chemotherapy is given do not count toward the total number of induction chemotherapy cycles.

After the induction phase, patients will begin maintenance therapy with atezolizumab plus tiragolumab/placebo.

The suggested infusion times for CE may be adapted in accordance with local standard of care.

Following the induction phase, patients will continue maintenance therapy with either atezolizumab plus tiragolumab (Arm A) or atezolizumab plus placebo (Arm B).

Treatment will be continued until radiographic disease progression according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment (tiragolumab plus atezolizumab or placebo plus atezolizumab) if they meet all criteria and provide written consent.

There will be no dose modifications for tiragolumab/placebo and/or atezolizumab in this study.

Dose modifications for carboplatin and etoposide 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 carboplatin or etoposide should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or 4 toxicity after two dose reductions or treatment is delayed for more than [redacted] 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 [redacted] days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology and National Comprehensive Cancer Network (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 below).

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

Chemotherapy Dose Modification for Hematologic Toxicities

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

[a] Nadir of prior cycle.

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 below), treatment should be delayed for up to [redacted] days until resolution to less than or equal to the patient's baseline value (or Grade ≤ 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. The table below provides recommended dose modifications for non-hematologic toxicities.

Dose Modifications or 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).

Suggested recommendations for dose modification of etoposide for renal impairment are provided in the table below.

Etoposide Dose Modification for Renal Impairment

Creatinine clearance (mL/min)	Etoposide Dose
> 50	100%
15–50	75% of dose

DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be up to approximately 72 months.

COMMITTEES

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
[redacted]	
AUC	area under the concentration–time curve
CD	cluster of differentiation
CE	carboplatin and etoposide
CHO	Chinese hamster ovary
CIT	cancer immunotherapy
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CR	complete response
CRCL	creatinine clearance
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
EAE	experimental autoimmune encephalitis
[redacted]	
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
ES-SCLC	extensive-stage small cell lung cancer
FACS	fluorescence-activated cell sorting
FAS	full analysis set
Fc	fragment crystallizable
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GFR	glomerular filtration rate
GHS	global health status
[redacted]	
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis

Abbreviation	Definition
HR	hazard ratio
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFN-γ	interferon-gamma
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
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
MAb	monoclonal antibody
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not estimable
NGS	next-generation sequencing
NK	natural killer (cell)
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	primary analysis set
PCI	prophylactic cranial irradiation
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
[redacted]	[redacted]
PVR	poliovirus receptor
QoL	quality of life
Q3W	every 3 weeks
QLQ-C30	Quality of Life–Core 30 Questionnaire
RBR	Research Biosample Repository

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small cell lung cancer
SITC	Society for Immunotherapy of Cancer
TC	tumor cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TNF	tumor necrosis factor
TPS	tumor proportion score
TTCD	time to confirmed deterioration
TTE	*transthoracic echocardiogram*
ULN	upper limit of normal
VALG	Veterans Administration Lung Study Group
VCA	viral capsid antigen
WES	whole exome sequencing
WGS	whole genome sequencing

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 will be 228,150 new cases of lung cancer in 2019 (116,440 in men and 111,710 in women) and 142,670 lung cancer deaths (Siegel et al. 2019). Similar data from Europe estimate that in 2018, there were 387,900 lung cancer deaths (267,300 in men and 120,600 in women) (Ferlay et al. 2019).

Non−small cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Howlader et al. 2014). Small cell lung cancer (SCLC) accounts for approximately 15% of all cases and is distinguished from NSCLC by its rapid growth rate and early development of metastatic disease (Govindan et al. 2006). Nearly all cases of SCLC are attributable to cigarette smoking (Pesch et al. 2012). Poor prognostic factors for survival in patients with SCLC include extensive-stage disease, poor performance status, weight loss, and markers associated with excessive bulk of disease, such as lactate dehydrogenase (LDH) (Yip and Harper 2000; Foster et al. 2009).

Patients with limited-stage SCLC can be treated with chemotherapy and radiation with the potential for long-term survival (Stinchcombe and Gore 2010), although a majority will relapse. The majority (approximately 70%) of patients with SCLC are diagnosed with extensive-stage small cell lung cancer (ES-SCLC), which has poor survival prospects (median overall survival [OS] approximately 10−12 months) (Socinski et al. 2009; Horn et al. 2018). Chemotherapy alone can palliate symptoms and prolong survival for patients with ES-SCLC; however, long-term survival is rare (Johnson and Janne 2004; Demedts et al. 2010).

1.1.1 First-Line Treatment for Extensive-Stage Small Cell Lung Cancer

The current standard first-line treatment for patients with ES-SCLC is the PD-L1 inhibitor atezolizumab given with platinum-based chemotherapy consisting of carboplatin and etoposide (CE) as induction therapy for 4 cycles, followed by atezolizumab maintenance therapy (National Comprehensive Cancer Network [NCCN] 2019). In the randomized Phase III Study GO30081 (IMpower133), a total of 201 patients were randomly assigned to the atezolizumab plus CE group, and 202 patients assigned to the placebo plus CE group. At a median follow-up of 13.9 months, the hazard ratio [HR] for death was 0.70 (95% CI: 0.54 to 0.91; p=0.007) with a median OS of 12.3 months in the atezolizumab plus CE group and 10.3 months in the placebo plus CE group. The HR for progression-free survival (PFS) was 0.77 (95% CI: 0.62 to 0.96; p=0.02) with a median PFS of 5.2 months and 4.3 months for atezolizumab plus CE and placebo plus CE, respectively. The safety profile of atezolizumab plus CE was consistent with the

previously reported safety profile of the individual agents, with no new findings observed (Horn et al. 2018).

Despite the improved efficacy observed with first-line atezolizumab plus CE, most patients with ES-SCLC experienced disease progression, and upon relapse, their prognosis is poor. Therefore, novel strategies are needed to deliver better long-term survival. The addition of complementary immunomodulatory agents to the current treatment backbone is an appealing strategy to further improve the prognosis of patients with advanced SCLC.

1.2 TIGIT PATHWAY IN CANCER AS POTENTIAL ANTI-CANCER THERAPY

T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel immune inhibitory receptor that is a member of the immunoglobulin superfamily (Yu et al. 2009; Manieri et al. 2017). T-cell immunoreceptor with Ig and ITIM domains is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with cluster of differentiation [CD] 155 (also known as poliovirus receptor [PVR]) (Yu et al. 2009). Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses in nonclinical models of autoimmune diseases and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). T-cell immunoreceptor with Ig and ITIM domains expression is observed in the tumor microenvironment in many human tumors, is coordinately expressed with other checkpoint immune-receptors such as PD-1, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (TCs) (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

T-cell immunoreceptor with Ig and ITIM domains is expressed in a wide variety of human tumors and is highly correlated with T-cell infiltration and PD-1 expression (Johnston et al. 2014). Fluorescence-activated cell sorting (FACS) analysis on fresh tumor samples showed that TIGIT and PD-1 are also co-expressed on NSCLC tumor-infiltrating T cells. T-cell immunoreceptor with Ig and ITIM domains expression ranges from 30%–80% and 50%–80% on tumor-infiltrating CD4+ and CD8+ T cells, respectively (Johnston et al. 2014). Similarly, TIGIT and PD-1 are expressed on CD8+ tumor-infiltrating lymphocytes in SCLC (Xu et al. 2019). The TIGIT ligand PVR is broadly expressed in SCLC cell lines and tumor samples (Yu et al. 2018a, 2018b; Xu et al. 2019). Poliovirus receptor is predominantly present on the membrane of tumor cells, and 79% of SCLC patients express PVR with a ≥50% tumor positivity score (Yu et al. 2018a).

[redacted]

[redacted] Together, these data support the hypothesis that anti-TIGIT treatment in combination with anti–PD-L1 treatment may reactivate anti-tumor immunity in SCLC, which may lead to clinical benefit for patients (see Section 1.3).

1.3 COMBINED INHIBITION OF THE TIGIT AND PD-L1/PD-1 PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

The inhibitory immunoreceptor TIGIT has been shown to limit the effector function of tumor-associated lymphocytes. Activation of TIGIT on T cells and NK cells limits proliferation, effector cytokine production, and killing of target TCs. Therefore, in the context of the tumor microenvironment, TIGIT acts to limit anti-tumor immune responses. Interference with the TIGIT/PVR interaction may enhance the magnitude and quality of tumor-specific T-cell responses through increased expansion of T cells as well as improved T-cell priming and/or effector function. Because TIGIT and PD-1 are coordinately expressed by tumor-infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathway may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor, such as atezolizumab (Johnston et al. 2014).

In nonclinical models, concomitant blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. In one such nonclinical model, tumor-infiltrating T cells demonstrate increased interferon-gamma (IFN-γ) expression (a hallmark of activation and anti-tumor activity of T cells) only when both TIGIT and PD-1 are blocked concurrently and not when each individual pathway is blocked by the respective single-agent treatments. Notably, co-inhibition of TIGIT and PD-L1 in this syngeneic tumor model was not associated with body weight loss or any other observable adverse responses (Johnston et al. 2014).

1.4 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa monoclonal antibody (MAb) that binds 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 two light chains (220 amino acid residues each). There are two N-linked glycosylation sites (Asn306) in the fragment crystallizable (Fc) domain. The predicted molecular weight of tiragolumab is 148,409 Da (peptide chains only, without heavy chain C-terminal lysine residue).

Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is used as a single agent or in combination with other cancer immunotherapies (CITs).

Tiragolumab is being investigated as a potential therapy against tumors in humans.

Please refer to the Tiragolumab Investigator's Brochure for additional details on the nonclinical and clinical studies for tiragolumab.

1.4.1 Summary of Nonclinical Data with Tiragolumab

The nonclinical strategy for tiragolumab was to demonstrate in vitro and in vivo pharmacology, to evaluate the pharmacokinetic (PK) profile, to demonstrate an acceptable safety profile, [redacted]. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with tiragolumab.

The completed nonclinical pharmacology studies demonstrate that tiragolumab binds TIGIT and prevents TIGIT/PVR interactions. [redacted]. In the CT26 syngeneic colon tumor model, co-inhibition of the TIGIT/PVR and PD-L1/PD-1 pathways improves anti-tumor activity when compared with inhibition of only one pathway with either monotherapy in the absence of body weight loss or any other observable adverse responses. Taken together, these data provide a rationale for evaluating the combination of anti-TIGIT with anti–PD-L1 in clinical studies (Johnston et al. 2014).

[redacted]. Overall, the nonclinical PK behavior observed for tiragolumab is consistent with that expected for a receptor-targeting human IgG1 MAb. [redacted] On the basis of the proposed mechanism of action of tiragolumab, possible safety risks to patients following TIGIT/PVR pathway inhibition include heightened immune responses and the potential to increase the frequency and/or the severity of immune-associated inflammatory lesions. These potential effects are considered to be monitorable and are expected to be manageable (see Section 5.1 for the safety plan).

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

Please refer to the Tiragolumab Investigator's Brochure for additional details on nonclinical studies.

1.4.2 Clinical Experience with Tiragolumab

Please refer to the Tiragolumab Investigator's Brochure for additional details on clinical studies conducted to date.

1.4.2.1 Ongoing Clinical Studies with Tiragolumab

Tiragolumab has been tested in a Phase I study (GO30103), a combined Phase Ia/Phase Ib multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of tiragolumab administered as a single agent by IV infusion every 21 days (Phase Ia) or in combination with atezolizumab at 1200 mg administered by IV infusion every 21 days (Phase Ib) to patients with locally advanced or metastatic malignancies (please see the Tiragolumab Investigator's Brochure for a full study description). [redacted] Refer to the Tiragolumab Investigator's Brochure for further details.

The combination of tiragolumab plus atezolizumab is being investigated further in Study GO40290 (CITYSCAPE), an ongoing Phase II, global, multicenter, randomized, blinded, placebo-controlled trial. This study was designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced, unresectable or metastatic PD-L1–selected (tumor proportion score [TPS] $\geq$ 1%) NSCLC (please see the Tiragolumab Investigator's Brochure for a full study description). The co-primary endpoints for the study are objective response rate (ORR) and PFS. Secondary endpoints include duration of response (DOR), OS, safety, pharmacokinetics, and immunogenicity.

Patients were eligible if they were $\geq$ 18 years old with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 and had previously untreated, locally advanced unresectable or metastatic PD-L1–selected NSCLC without a sensitizing epidermal growth factor receptor mutation or anaplastic lymphoma rearrangement.

For the purposes of PD-L1 selection, formalin-fixed tumor samples were assessed locally by the commercially available PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assays (Dako) or, when unavailable, patients were prospectively tested for PD-L1 expression by central testing using the same assay. Programmed death-ligand 1–selected tumors were defined as tumors with a TPS $\geq$ 1% by the PD-L1 IHC 22C3 pharmDx assay.

Eligible patients were stratified by the PD-L1 IHC 22C3 pharmDx assay result (TPS 1%–49% vs. TPS ≥50%), tumor histology (non-squamous vs. squamous), and patient's history of tobacco use (yes vs. no).

Patients for this study were enrolled at 39 sites in France, Spain, Serbia, South Korea, Taiwan, and the United States between August 2018 and March 2019. As of the primary analysis data cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS ≥1% (22C3) by local analysis were included in the intent-to-treat (ITT) population and were randomly assigned to tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). Of the enrolled patients, 43% of patients had a TPS of ≥50% versus 57% of patients with a TPS 1%–49%; 59.3% had non-squamous histology versus 40.7% of patients who had squamous histology; and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were generally well balanced between treatment groups as well, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab groups. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab group compared with the placebo plus atezolizumab group.

At the primary analysis, in the ITT population, 47.8% of patients in the tiragolumab plus atezolizumab group versus 27.9% of patients in the placebo plus atezolizumab group were still receiving study treatment. In the TPS ≥50% population, 65.5% of patients in the tiragolumab plus atezolizumab group versus 24.1% of patients in the placebo plus atezolizumab group were still receiving study treatment.

Available single agent and combination safety and preliminary efficacy data from Study GO30103 and combination safety data and efficacy data from Study GO40290 are summarized below.

1.4.2.2 Clinical Safety of Tiragolumab

[redacted]

Clinical Safety of Single-Agent Tiragolumab: Study GO30103

[redacted]

Clinical Safety of Tiragolumab plus Atezolizumab: Study GO30103

[redacted]

[redacted]

Clinical Safety of Tiragolumab plus Atezolizumab in Patients with Non–Small Cell Lung Cancer: Study GO40290

In the Phase II, randomized, double-blinded Study GO40290, as of 30 June 2019, a total of 135 patients had been enrolled. A total of 67 patients received tiragolumab (600 mg) in combination with atezolizumab (1200 mg) every 3 weeks (Q3W), and 68 patients received placebo in combination with atezolizumab Q3W. The safety profile was comparable between the tiragolumab plus atezolizumab arm and the placebo plus atezolizumab arm for all grades of adverse events (98.5% vs. 95.6%), Grade 3–5 adverse events (41.8% vs. 44.1%), Grade 5 adverse events (3.0% vs. 7.4%), serious adverse events (34.3% vs. 35.3%), and adverse events leading to study treatment withdrawal (7.5% vs. 10.3%). Study treatment–related adverse events occurred at a higher frequency in the tiragolumab plus atezolizumab arm (80.6%) compared with the placebo plus atezolizumab arm (72.1%).

Adverse events (MedDRA terms) that occurred at a higher frequency (≥5% difference between arms) in the tiragolumab plus atezolizumab arm were infusion-related reaction (IRR) (28.4% vs. 10.3%), fatigue (22.4% vs. 13.2%), pruritus (19.4% vs. 11.8%), rash (19.4% vs. 8.8%), arthralgia (16.4% vs. 8.8%), edema peripheral (10.4% vs. 4.4%), rash maculo-papular (9.0% vs. 2.9%), pleural effusion (9.0% vs. 2.9%), and back pain (9.0% vs. 2.9%). Adverse events that occurred at a higher frequency in the placebo plus atezolizumab arm included dyspnea (13.4% vs. 20.6%), productive cough (4.5% vs. 10.3%), ALT increased (4.5% vs. 10.3%), respiratory tract infection (3.0% vs. 8.8%), and hypercalcemia (0% vs. 5.9%). Grade ≥3 adverse events (≥2% difference between arms) that occurred at a higher frequency in the tiragolumab plus atezolizumab arm were pneumonia (9.0% vs. 4.4%), pleural effusion (6.0% vs.1.5%), lipase increased (6.0% vs. 2.9%), and hypokalemia (3.0% vs. 0%); Grade ≥3 adverse events that occurred at a higher frequency in the placebo plus atezolizumab arm were

pulmonary embolism (0% vs. 2.9%), amylase increased (0% vs. 2.9%), and asthenia (0% vs. 2.9%).

Grade 5 adverse events in Study GO40290 that occurred in the tiragolumab plus atezolizumab arm were Epstein-Barr virus (EBV) infection and pyrexia (reported for 1 patient each), and Grade 5 adverse events in the placebo plus atezolizumab arm were cardiorespiratory arrest, cerebrovascular accident, multiple-organ dysfunction syndrome, pneumonia, and pulmonary embolism (1 patient each).

[redacted]

Please refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the adverse events observed in patients treated with tiragolumab plus atezolizumab.

Clinical Safety of Tiragolumab plus Atezolizumab and Chemotherapy

The safety profiles resulting from combining PD-1/PD-L1 inhibitors and chemotherapy have generally been consistent with the known toxic effects of each agent as observed in multiple clinical trials of advanced solid tumors (Gandhi et al. 2018; Horn et al. 2018; Paz-Ares et al. 2018; Schmid et al. 2018). [redacted]

Please refer to the Tiragolumab Investigator's Brochure for further details and the current information on the safety of tiragolumab.

1.4.2.3 Clinical Activity of Tiragolumab Plus Atezolizumab

Clinical Activity of Single-Agent Tiragolumab: Study GO30103

[redacted]

[redacted]

Clinical Activity of Tiragolumab Plus Atezolizumab: Study GO30103

[redacted]

Clinical Activity of Tiragolumab Plus Atezolizumab in Patients with Non–Small Cell Lung Cancer: Study GO40290

As of the primary clinical cutoff date of 30 June 2019, a total of 135 patients with a PD-L1 TPS $\geq$1% were included in the ITT population and were randomly assigned to receive tiragolumab plus atezolizumab (n=67) or placebo plus atezolizumab (n=68). Of the enrolled patients, 43.0% of patients had a TPS $\geq$50% relative to 57.0% of patients with a TPS 1%–49%, 59.3% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers versus 89.6% who had smoked. These three stratification factors were well balanced between treatment groups. Demographics were also generally well balanced between treatment groups, with a median age of 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. There were more females (41.8% vs. 29.4%) and more White patients (62.7% vs. 58.8%) in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm.

In the ITT population, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%). In the subgroup of patients with TPS $\geq$50%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (n=29; 55.2% [95% CI: 35.4% to 75.0%]) than the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8% to 32.7%]). Of note, responders in the tiragolumab plus atezolizumab arm included patients with both squamous and non-squamous histology.

In the ITT population, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (stratified HR = 0.57 [95% CI: 0.37 to 0.90]; median PFS 5.4 vs. 3.6 months, respectively). In the subgroup of patients with TPS ≥ 50%, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified HR = 0.33 [95% CI: 0.15 to 0.72]; median PFS not estimable [NE] vs. 3.9 months, respectively).

1.4.2.4 Clinical Pharmacokinetics and Immunogenicity of Tiragolumab and Atezolizumab

Clinical Pharmacokinetics and Immunogenicity of Tiragolumab

[redacted]

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information.

Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

[redacted]

[redacted]

Please refer to the Atezolizumab Investigator's Brochure for details on the clinical pharmacokinetics of atezolizumab.

1.5 BACKGROUND ON ATEZOLIZUMAB

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

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and CIT.

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

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

1.6 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.6.1 Rationale for Testing Tiragolumab in Combination with Atezolizumab and Carboplatin and Etoposide in First-Line Extensive-Stage Small Cell Lung Cancer

The current standard first-line treatment for patients with ES-SCLC is atezolizumab plus CE. Despite the survival benefit observed with this regimen, median survival remains at approximately 1 year, leaving considerable room for improvement in outcomes. Tumor-cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens. Therefore, invigorating tumor-specific T-cell immunity by inhibiting PD-L1/PD-1 signaling and TIGIT/PVR may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007; Yu et al. 2018a, 2018b; Xu et al. 2019). Evaluating the safety and efficacy of these treatment combinations in patients with SCLC will enable future tests of this hypothesis.

In light of these observations, this study (Study GO41767) is designed to evaluate whether the anti-tumor effect of the combination of atezolizumab plus CE (IMpower133 regimen) can be enhanced by adding tiragolumab in treating patients with chemotherapy-naive ES-SCLC. This study will allow for the evaluation of efficacy of tiragolumab plus atezolizumab plus chemotherapy in the full analysis set (FAS) [redacted]

Patients with SCLC frequently present with symptoms of widespread metastatic disease and may experience fast clinical deterioration; therefore, there is a need for rapid treatment initiation for these patients. In addition, tissue sample collection for investigational [redacted] may be difficult in this patient population because the amount of tissue available in many cases is limited. Because the benefit of atezolizumab plus chemotherapy was observed in all-comer patients in IMpower133, this study will enroll patients with ES-SCLC whose disease is unselected for PD-L1 expression. [redacted]

This study will enroll patients with ES-SCLC who are chemotherapy-naive for their extensive-stage disease, and for whom the experimental arm can represent a valuable treatment option and a reasonable benefit–risk balance.

In summary, treatment with tiragolumab plus atezolizumab in combination with CE offers the potential for clinical benefit in patients with ES-SCLC.

1.6.2 Study Rationale

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with metastatic cancer, including SCLC. Recent approvals by the U.S. Food and Drug Administration (FDA) of atezolizumab plus chemotherapy in metastatic SCLC in the first-line setting validate the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in these patients. Furthermore, the safety profile of atezolizumab plus chemotherapy appears to be as tolerable as chemotherapy doublet combinations in the front-line setting.

Nevertheless, despite the robust activity observed with atezolizumab plus chemotherapy, durable clinical benefit appears limited to a minority of treated patients. It is hypothesized that many of these patients with metastatic SCLC may have intrinsic or acquired resistance to checkpoint inhibition. Thus, another strategy to increase the response to checkpoint inhibitors among patients has focused on treatment with novel immunotherapy combinations that may overcome such intrinsic or acquired resistance to PD-L1/PD-1 antibodies.

T-cell immunoreceptor with Ig and ITIM domains is an inhibitory immunoreceptor that can limit the effector function of tumor-associated lymphocytes. [redacted]. In preliminary data from the interim analysis of the Phase II Study GO40290, the ORR (confirmed and unconfirmed responses) was higher in the tiragolumab plus atezolizumab group than in the placebo plus atezolizumab group in both the ITT and TPS ≥ 50% populations. Consistent with the Phase Ib study, the combination of tiragolumab with atezolizumab was well tolerated in the Phase II study.

Therefore, the current study is designed to evaluate whether the anti-tumor effects of atezolizumab plus chemotherapy, as measured by OS, PFS, ORR, and DOR, can be improved with the addition of the anti-TIGIT antibody tiragolumab to atezolizumab and chemotherapy in patients with ES-SCLC.

1.6.3 Benefit–Risk Assessment

This study will enroll patients with ES-SCLC with no prior systemic treatment, and all patients will receive standard atezolizumab plus chemotherapy, either in the experimental arm or in the placebo arm. The standard of care of atezolizumab plus chemotherapy was well tolerated in the pivotal IMpower133 study, with a safety profile consistent with the known risks of individual treatment and comparable to the treatment of chemotherapy alone. The combination of tiragolumab plus atezolizumab with chemotherapy in the experimental arm can represent a potential valuable treatment option and can offer a reasonable benefit–risk balance for patients in this study.

The combination of tiragolumab plus atezolizumab was tolerated in both the Phase Ib (GO30103) and Phase II (GO40290) studies. In Study GO40290, tiragolumab plus atezolizumab demonstrated an overall safety profile similar to that of placebo plus atezolizumab in terms of any grade adverse events, Grade 3–4 adverse events, serious adverse events, and adverse events leading to study treatment discontinuation (see Section 1.4.2.2). While adverse events related to any study treatment and adverse events leading to dose interruption of any study treatment were higher in the tiragolumab plus atezolizumab arm, there was no increase in Grade 5 adverse events (see Section 1.4.2.2). Adverse events with potentially immune-mediated causes were

observed with a higher incidence in the tiragolumab plus atezolizumab arm in Study GO40290. However, the imbalance was mostly attributed to Grade 1–2 rash and IRRs (see Section 1.4.2). Grade 3–4 immune-mediated adverse events were similar between the treatment arms. To date, immune-mediated adverse events have been manageable with standard medical practice supplemented with corticosteroids, immunosuppressive agents, and/or hormone replacement therapy. There were no Grade 5 immune-mediated adverse events reported in the Phase Ib and Phase II studies.

In summary, the combination of tiragolumab with atezolizumab plus chemotherapy in this study may benefit patients beyond treatment with atezolizumab plus chemotherapy. [redacted]. Immune-mediated adverse events, although reported at a higher frequency for the tiragolumab plus atezolizumab arm in the Phase II study (GO40290), are 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 with the standard of care of atezolizumab plus chemotherapy. Therefore, the overall benefit–risk ratio is considered to be appropriate for the study population.

[redacted]

COVID-19 Benefit-Risk Assessment

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

A possible consequence of 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. In nonclinical models, PD-L1/PD-1 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; Wykes and Lewin 2018; Schorer et al. 2020). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by CIT.

Severe SARS-CoV-2 infection appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). [redacted]

[redacted] At this time, there is insufficient evidence for causal association between atezolizumab or tiragolumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

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

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

Per recommendations of the NCCN COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving CIT (SITC 2020). For patients enrolling in this study and receiving atezolizumab and/or tiragolumab/placebo treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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

Society for Immunotherapy of Cancer and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

2. OBJECTIVES AND ENDPOINTS

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE in patients with untreated ES-SCLC on the basis of the following co-primary endpoints:

- PFS after randomization, 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 in patients who are randomly assigned without presence or history of brain metastases at baseline (primary analysis set [PAS])
- OS after randomization, defined as the time from randomization to death from any cause in the PAS

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE on the basis of the following endpoints:

- PFS in the FAS
- OS in the FAS
- 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 in the PAS and the FAS who have measurable disease at baseline
- DOR for patients with confirmed objective response, defined as the time from the first occurrence of a documented, confirmed objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first in the PAS and the FAS
- PFS rates at 6 months and at 12 months in the PAS and the FAS
- OS rates at 12 months and 24 months in the PAS and the FAS
- 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 the Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 Questionnaire (QLQ-C30) in the PAS and the FAS

[redacted]

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE 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, Version 5.0 (NCI CTCAE v5.0)
- [redacted]

[redacted]

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

2.3 PHARMACOKINETIC OBJECTIVES

The 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

[redacted]

- [redacted]

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 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]

- [redacted]

[redacted]

- [redacted]

2.6 HEALTH STATUS UTILITY OBJECTIVE

The health status utility objective for this study is to evaluate the impact of health status utility scores of patients treated with tiragolumab plus atezolizumab and CE compared with placebo plus atezolizumab and CE on the basis of the following endpoint:

- Change in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and Visual Analog Scale scores at specified timepoints during the study (including post-progression)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a randomized, Phase III, global, multicenter, double-blinded, placebo-controlled study designed to evaluate the safety and efficacy of tiragolumab in combination with atezolizumab and CE compared with treatment with placebo in combination with

atezolizumab and CE in patients who are chemotherapy-naive ES-SCLC. Figure 1 illustrates the study design. The schedule of activities is provided in Appendix 1.

Figure 1 Study Schema

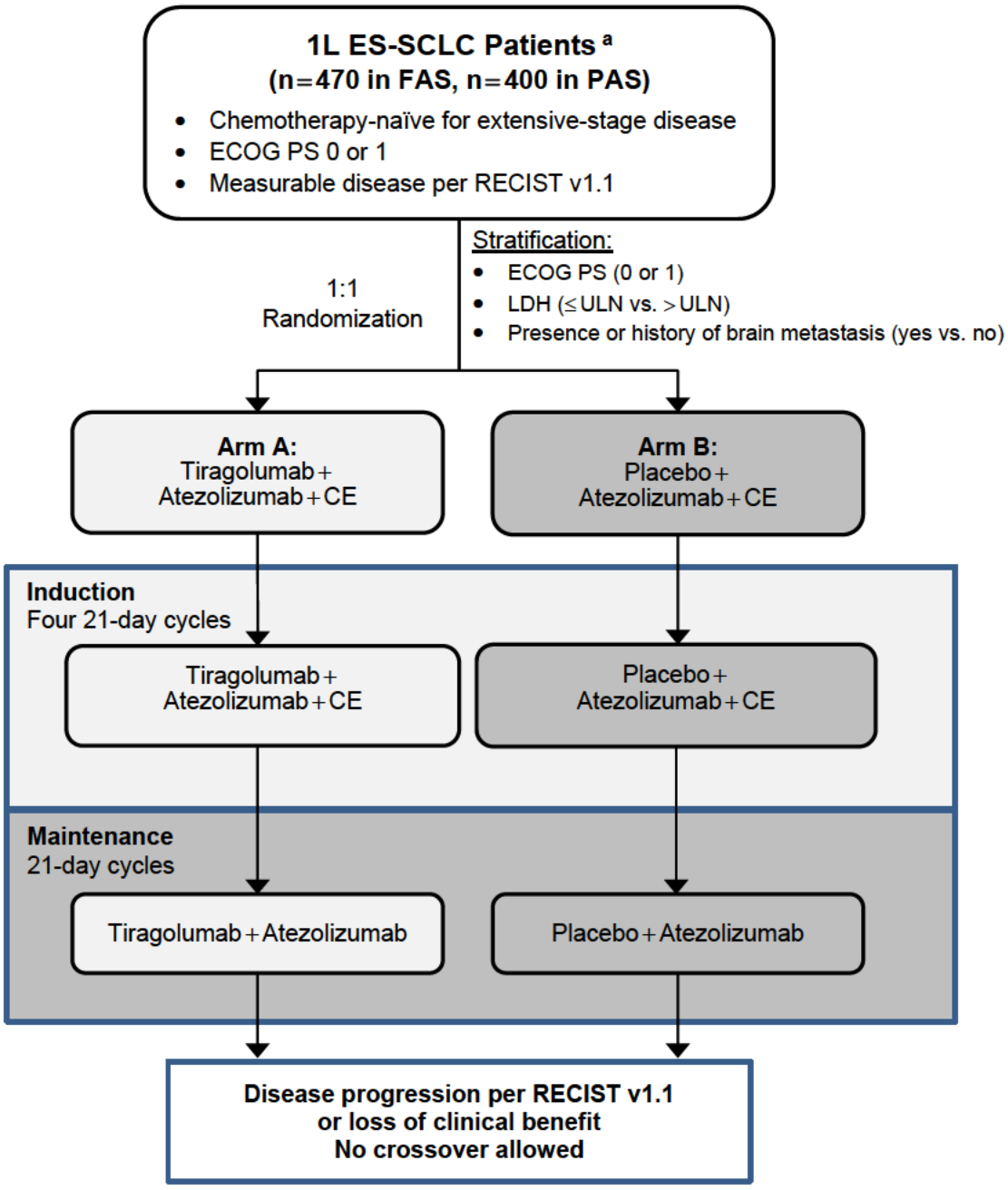

Figure 1 Study Schema (cont.)

1L = first-line; CE = carboplatin and etoposide; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ES-SCLC = extensive-stage small cell lung cancer; FAS = full analysis set; PAS = primary analysis set; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal.

[a] For the first 24 patients (approximately 12 per arm) who are randomly assigned, safety and tolerability data will be assessed by an independent Data Monitoring Committee.

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities (Appendix 1). Patients who do not initially meet all eligibility criteria for participation in this study may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 60 days after previously signing the consent form. For patients who are re-screened, all eligibility criteria must be re-evaluated and screening assessments should be repeated as applicable to meet the eligibility criteria outlined in Section 4.1. The investigator will record reasons for screening failure in the screening log (see Section 4.5.1).

Eligible patients will be stratified by ECOG Performance Status (0 vs. 1), LDH (≤ upper limit of normal [ULN] vs. > ULN), and presence or history of brain metastasis (yes vs. no) and randomly assigned in a 1:1 ratio to receive one of the following treatment regimens as shown in Table 1.

Table 1 Study GO41767 Treatment Arms

Treatment Arm	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tiragolumab + Atezolizumab + CE	Tiragolumab + Atezolizumab
B	Placebo + Atezolizumab + CE	Placebo + Atezolizumab

CE = carboplatin and etoposide.

Induction treatment will be administered on a 21-day cycle for 4 cycles.

Following the induction phase, patients will continue maintenance therapy with either atezolizumab plus tiragolumab (Arm A) or atezolizumab plus placebo (Arm B). During the maintenance phase, prophylactic cranial irradiation (PCI) is permitted (although not mandated) per local standard of care, and will be reported on the PCI electronic Case Report Form (eCRF). Consolidative thoracic radiation with curative intent or the intent to eliminate residual disease is not permitted. Palliative radiation for symptomatic management is allowed (please refer to Section 4.4.1 for further details).

Treatment will be continued until radiographic disease progression according to RECIST v1.1, or as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data,

biopsy results (if available), and clinical status. Patients who meet the criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment (tiragolumab plus atezolizumab or placebo plus atezolizumab) if they meet all of the criteria specified in Section 3.1.2 and provide written consent.

[redacted]

Patients will undergo tumor assessments 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 treatment dose delays. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 (see Section 3.1.2) will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days] thereafter, until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first), regardless of whether the patient starts a new anti-cancer therapy.

[redacted]

The investigator's assessment of overall tumor response at all timepoints should be based on RECIST v1.1. Assessments should be performed by the same evaluator, if

possible, to ensure internal consistency across visits. All primary imaging data used for tumor assessments will be collected by the Sponsor; centralized, blinded, independent review of response endpoints by an independent review facility (IRF) may be conducted.

In order not to confound the OS endpoint, crossover will not be allowed from the control arm (placebo plus atezolizumab plus CE) to the experimental arm (tiragolumab plus atezolizumab plus CE).

During the study, patients will be asked to complete PRO questionnaires at the beginning of the study, at treatment discontinuation, and during survival follow-up (see Section 4.5.10 and Appendix 1 for details on the surveys and schedule).

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

3.1.2 Treatment after Disease Progression

During the study, patients who meet criteria for radiographic disease progression per RECIST v1.1 may continue treatment at the investigator's discretion, provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic progression per RECIST v1.1

Investigator assessment of overall tumor response at all timepoints will be based on RECIST v1.1.

3.1.3 Independent Data Monitoring Committee

An iDMC will be used to evaluate safety during the study. [redacted]

The safety data will include disposition, demographic data, adverse events, serious adverse events, and relevant laboratory data.

[redacted]

Members of the iDMC will be external to the Sponsor and will follow a separate iDMC Charter that outlines their roles and responsibilities, as well as a detailed monitoring plan.

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

3.2 END OF STUDY AND LENGTH OF STUDY

[redacted]

- [redacted]
- [redacted].

Additionally, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in a post-trial access program or an extension study.

3.3 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be up to approximately [redacted] months.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Tiragolumab Dose and Schedule

Tiragolumab will be administered to all patients on the experimental arm at a fixed dose of 600 mg IV Q3W on Day 1 of each 21-day cycle. [redacted]

For further details, please refer to the Tiragolumab Investigator's Brochure.

3.4.2 Rationale for Control Arm

The current standard of care in the first-line treatment for ES-SCLC is atezolizumab plus CE (NCCN 2019). In this study, patients in the control arm will receive 4 cycles of placebo plus atezolizumab and CE followed by placebo plus atezolizumab until disease progression per RECIST v1.1. During the maintenance phase, PCI is permitted per local standard of care. This control arm treatment is recognized as the recommended standard of care for the first-line treatment of ES-SCLC (see Section 1.1.1).

3.4.3 Rationale for Evaluation of Patients Without Brain Metastases at Baseline (Primary Analysis Set for Statistical Analysis)

The brain is a common site of metastases for ES-SCLC patients with some studies showing as high as 18% of patients having brain metastases at diagnosis, and up to 80% are expected to have brain disease involvement during the first 2 years following diagnosis (Seute et al. 2004; Pacheco and Bunn 2019). In general, benefits from the immunotherapy and chemotherapy combination have been shown in patients with ES-SCLC. However, this benefit may be attenuated in those with brain metastasis at baseline as seen in the IMpower133 trial where this patient subgroup had an HR

of 1.07 compared to a HR of 0.68 for patients without brain metastases (Horn et al. 2018).

KEYNOTE-604 is another Phase III trial that suggests that patients with ES-SCLC with brain metastasis at diagnosis may achieve less or no overall survival benefit to first-line immunotherapy plus chemotherapy in comparison to those without. In fact, patients with brain metastases had an OS HR of 1.32 versus 0.75 for patients without brain metastases (Rudin et al. 2020). The CASPIAN study initially reported an OS HR of 0.69 in patients with brain metastasis; however, in the updated analysis, the HR became 0.79. The OS HR in those without brain metastasis in initial and updated reports was 0.74 and 0.76, respectively (Paz-Ares et al. 2018, 2020).

It is critical to understand the benefit of the study regimen in both of the patient subgroups, thus, the testing statistical testing hierarchy was implemented to test the PAS first, and then subsequently the FAS (see Section 6.1.1, Figure 2).

3.4.4 Rationale for Progression-Free Survival and Overall Survival as Co-Primary Endpoints

Investigator-assessed PFS and OS are the co-primary endpoints for this study.

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 (Guidance for Industry 2007; European Medicines Agency 2012).

Overall survival is a co-primary endpoint in this study. Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced/unresectable or metastatic lung cancer. In the randomized Phase III study in patients with advanced SCLC (IMpower133), an OS benefit in the atezolizumab plus chemotherapy arm was observed compared with the placebo plus chemotherapy arm (Horn et al. 2018).

3.4.5 Rationale for Tiragolumab and/or Atezolizumab Treatment Beyond Initial Radiographic Disease Progression

Patients with ES-SCLC experience rapid tumor growth and fast clinical deterioration and have an overall poor prognosis. First-line therapy with atezolizumab plus CE has demonstrated high response rates and significant clinical benefit. However, after disease progression, treatment options are limited and such options have shown limited efficacy and significant toxicity (see Section 1.1.1). Given that the greatest opportunity to achieve a clinically significant benefit from therapy is in the front-line setting and given the poor efficacy and high toxicity profile of second-line therapies, patients may be considered for treatment beyond radiographic disease progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient, only if they meet all of the criteria described in Section 3.1.2.

In addition, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression/tumor-immune infiltration, this study will allow patients to remain on treatment after apparent radiographic disease progression per RECIST v1.1, provided all criteria in Section 3.1.2 are met. Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 4.6.1).

3.4.6 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both increase survival and palliate symptoms because disease symptoms have negative impacts on health-related quality of life (Hyde and Hyde 1974; Hopwood and Stephens 1995; 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 tiragolumab and atezolizumab (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, [redacted] Data generated from these instruments will inform patients' experience with disease burden and treatment tolerability as part of the totality of evidence generated to inform the risk–benefit profile of tiragolumab and atezolizumab.

The EQ-5D-5L (see Appendix 8) is also included in this study to generate utility scores for use in economic models for reimbursement.

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients may be eligible if they are chemotherapy-naive for their ES-SCLC.

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible 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
- ECOG Performance Status of 0 or 1 (see Appendix 9)
- Histologically or cytologically confirmed ES-SCLC (per the modified Veterans Administration Lung Study Group [VALG] staging system) (Micke et al. 2002; see Appendix 3)
- No prior systemic treatment for ES-SCLC
- For patients who have received prior chemoradiotherapy for limited-stage SCLC: must have had treatment with curative intent and a treatment-free interval of at least 6 months between the last dose/cycle of chemotherapy, thoracic radiotherapy, or chemoradiotherapy and the diagnosis of ES-SCLC
- Measurable disease, as defined by RECIST v1.1

  [redacted]
- Submission of a pre-treatment tumor tissue sample (see Section 4.5.7 for information on tumor specimens)

  [redacted].

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

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 90 days after the final dose of tiragolumab or placebo, for 5 months after the final dose of atezolizumab, and for 6 months after the final dose of CE. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation

methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Women who would like to become pregnant after study treatment discontinuation should seek advice on oocyte cryopreservation prior to initiation of study treatment because of the possibility of irreversible infertility due to treatment with carboplatin and/or etoposide.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 90 days after the final dose of tiragolumab or placebo, and for 6 months after the final dose of carboplatin or etoposide. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period, for 90 days after the final dose of tiragolumab, and for 6 months after the final dose of carboplatin or etoposide to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

  Men who would like to father a child after study treatment initiation should seek advice on conservation of sperm prior to initiation of study treatment because of the possibility of irreversible infertility due to treatment with carboplatin and/or etoposide.

4.1.2 Exclusion Criteria

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

- Symptomatic or actively progressing CNS metastases

  Note: Asymptomatic patients with treated (i.e., local CNS-directed therapy) or untreated CNS lesions are eligible, provided that all of the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage from CNS disease.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

- The patient has no symptoms caused by CNS disease (i.e., no headache, nausea, vomiting, convulsion, paralysis, etc.).
- The patient has no ongoing requirement for anticonvulsants for CNS disease.
- The patient has no ongoing requirement for dexamethasone/corticosteroids for CNS disease (previously untreated patients must also not have any history of requiring or receiving dexamethasone/corticosteroids for CNS disease).
- For patients with previously treated CNS metastases, there is no evidence of interim CNS progression between the completion of CNS-directed therapy and randomization.
- For previously untreated patients, there is no evidence of brain edema related to CNS disease (e.g., vasogenic edema).
- For previously untreated patients, a brain magnetic resonance imaging (MRI) scan with contrast is required at screening and is the preferred modality for all subsequent scheduled follow-up tumor assessments.

  Note: Computed tomography (CT) scan with contrast may be acceptable for all subsequent scheduled follow-up tumor assessments if the following criteria are met.

  - Both brain MRI and CT scan with contrast must be performed at screening to assess untreated CNS disease.
  - The CT scan with contrast can be used to reliably evaluate lesions identified on the screening MRI with contrast.

  If CT scan with contrast cannot be used to reliably evaluate lesions identified on the screening MRI with contrast, then MRI scan with contrast must be used at all subsequent scheduled follow-up tumor assessments.

  The same modality must be used at every tumor assessment.

- 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 ≥ 1 week prior to randomization
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, total serum calcium > 12 mg/dL, or corrected calcium $>$ ULN)
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- Malignancies other than SCLC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death (e.g., expected

5-year OS >90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous-cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal breast carcinoma in situ treated surgically with curative intent)

- Active or history of autoimmune disease or immune deficiency, [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- Active tuberculosis
- Severe infection at the time of randomization, 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

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

    Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure other than for diagnosis [redacted] prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high-risk for treatment complications
- Patients with illnesses or conditions that interfere with their capacity to understand, follow, and/or comply with study procedures
- Treatment with investigational agent within 28 days prior to initiation of study treatment
- [redacted]
- Administration of a live, attenuated vaccine [redacted] before randomization or anticipation that such a live, attenuated vaccine will be required during the study

    Patients must not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, and for 5 months following the last dose of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-cytotoxic T lymphocyte–associated protein 4, anti-TIGIT, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug elimination half-lives (whichever is longer) prior to randomization
- Treatment with systemic immunosuppressive medications (including, but not limited to corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) [redacted] prior to randomization or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

    Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose systemic corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose mineralocorticoids for orthostatic hypotension or low-dose mineralocorticoids and corticosteroids for adrenal insufficiency are eligible for the study.

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to CHO cell products or to any component of the tiragolumab or atezolizumab formulations
- History of allergic reactions to carboplatin or etoposide
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the final dose of atezolizumab or tiragolumab or for 6 months after the final dose of carboplatin or etoposide

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind, placebo-controlled study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method. Patients will be randomly assigned to one of two treatment arms: A) tiragolumab + atezolizumab + CE or B) placebo + atezolizumab + CE. 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:

- ECOG Performance Status (0 vs. 1)
- LDH ($\leq$ ULN vs. $>$ ULN)
- Presence or history of brain metastasis (yes vs. no)

[redacted]

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study until the time of the final OS analysis. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to

patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for tiragolumab in these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing tiragolumab PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. Pharmacokinetic samples from patients assigned to the comparator arm will not be analyzed for tiragolumab PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline (Cycle 1, Day 1 pre-infusion) immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs to tiragolumab except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding may be permitted if an investigator is deciding whether a patient should withdraw from the study and initiate subsequent treatment with a proven therapy. However, unblinding will not be permitted if an investigator is deciding whether a patient should initiate subsequent treatment with an unproven therapy. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to tiragolumab/placebo. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are tiragolumab, placebo, and atezolizumab. Carboplatin and etoposide are considered non-IMPs. Appendix 12 identifies all IMPs, auxiliary medicinal products, and non-IMPs for this study.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Tiragolumab and Placebo

Tiragolumab and placebo will be supplied by the Sponsor as a sterile liquid in a single-use, 15-mL glass vial. The vial contains approximately 10 mL (600 mg) of tiragolumab or placebo solution.

For information on the formulation and handling of tiragolumab and placebo, see the pharmacy manual and the Tiragolumab Investigator's Brochure.

4.3.1.2 Atezolizumab

The atezolizumab drug product 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 solution.

For information on the formulation and handling of atezolizumab, refer to the Atezolizumab Pharmacy Manual and Investigator's Brochure.

4.3.1.3 Carboplatin and Etoposide

Carboplatin and etoposide will be used in the commercially available formulation.

For information on the formulation, packaging, and handling of CE, refer to the prescribing information for each drug.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1, Table 1.

The induction phase of the study will consist of 4 cycles of atezolizumab plus tiragolumab/placebo plus chemotherapy, with each cycle being 21 days in duration. On Day 1 of each cycle, all eligible patients will be administered study drug infusions in the following order:

Arm A: atezolizumab → tiragolumab → carboplatin → etoposide

Arm B: atezolizumab → placebo → carboplatin → etoposide

For Cycle 1, premedication administered for atezolizumab or tiragolumab/placebo is not permitted. Patients should receive anti-emetics and IV hydration for CE according to the local standard of care and manufacturer's instruction. However, because of the immunomodulatory effects of corticosteroids, premedication with corticosteroids should

be minimized to the extent that is clinically feasible (see Section 4.4.2). All medications must be recorded on the appropriate Concomitant Medications eCRF.

During the induction phase, study treatment should be administered in the following manner on Day 1:

1. Atezolizumab 1200 mg administered intravenously over 60 (±15) minutes (for the first infusion and shortening to 30 [±10] minutes for subsequent infusions) (see Table 2), followed by
2. Tiragolumab/placebo 600 mg administered intravenously over [redacted] minutes (for the first infusion and shortening to [redacted] minutes for subsequent infusions) (see Table 2), followed by
3. Carboplatin administered intravenously over 30–60 minutes to achieve an initial target area under the concentration–time curve (AUC) of [redacted] mg/mL/min (Calvert formula dosing), followed by
4. Etoposide (100 mg/m^2) administered intravenously over 60 minutes

During the induction phase, etoposide (100 mg/m^2) will be also administered intravenously over 60 minutes on Days 2 and 3.

Cycles in which no chemotherapy is given do not count toward the total number of induction chemotherapy cycles.

After the induction phase, patients will begin maintenance therapy with atezolizumab plus tiragolumab/placebo.

The suggested infusion times for CE may be adapted in accordance with local standard of care.

Any dose modification should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Administration of atezolizumab 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. For anaphylaxis precautions, see Appendix 10.

Guidelines for dose modification and treatment interruption or discontinuation for CE are provided in Sections 5.1.6 and 5.1.6.3.

4.3.2.1 Atezolizumab

All patients will receive 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle. The atezolizumab dose is fixed and is not dependent on body weight. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Appendix 13 and Appendix 14. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.1.6.2.

For further details on dose preparation, storage, and administration instructions for atezolizumab, please refer to the pharmacy manual and/or the Atezolizumab Investigator's Brochure.

4.3.2.2 Tiragolumab/Placebo

[redacted] (see Table 2), patients will receive 600 mg tiragolumab/placebo administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.4.1). The tiragolumab/placebo dose is fixed and is not dependent on body weight. Tiragolumab/placebo infusions will be administered per the instructions outlined in Table 2.

No dose modification for tiragolumab/placebo is allowed. Guidelines for treatment interruption or discontinuation are provided in Appendix 13 and Appendix 14. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.1.6.2.

For further details on dose preparation, storage, and administration instructions for tiragolumab/placebo, please refer to the pharmacy manual and/or the Tiragolumab Investigator's Brochure.

Table 2 Administration of First and Subsequent Atezolizumab and Tiragolumab/Placebo Infusions

	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is *permitted prior to* the atezolizumab *infusion*. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) *should be measured* within 60 minutes prior to the infusion. • *Atezolizumab should be infused* over 60 (±15) minutes. • If clinically indicated, vital signs *should be measured* every 15 (± 5) minutes during the infusion *and at 30 (±10) minutes after the infusion.*	• If the patient experienced an IRR during any previous infusion of atezolizumab, premedication with *antihistamines, anti-pyretic medications,* and/or *analgesics* may be administered for subsequent *doses* at the discretion of the investigator. • Vital signs *should be measured* within 60 minutes prior to the infusion.

Table 2 Administration of First and Subsequent Atezolizumab and Tiragolumab/Placebo Infusions (cont.)

	First Infusion	Subsequent Infusions
	• *Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.*	▲ *Atezolizumab should be* infused over 30 (± 10) minutes *if the previous infusion was tolerated without an IRR, or 60 (±15) minutes if the patient experienced an IRR with the previous infusion.* If the patient experienced an IRR with the previous infusion *or if clinically indicated,* vital signs *should be measured* during the infusion *and at 30 (±10) minutes after the infusion.*
Observation period after infusion of atezolizumab	• After the infusion of atezolizumab, the patient begins a 60-minute observation period. • Record the patient's vital signs at 30 (±10) minutes after the infusion of atezolizumab. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous infusion of atezolizumab well without an IRR, the observation period may be reduced to 30 minutes for subsequent infusions. • If the patient experienced an IRR in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, record the patient's vital signs at 30 (±10) minutes after the infusion.
Infusion of tiragolumab/ placebo	• No premedication is allowed for the first infusion of tiragolumab/placebo. • Record the patient's vital signs (pulse rate, respiratory rate, blood pressure, and temperature) within [redacted] minutes prior to starting the infusion. • Infuse tiragolumab/placebo over [redacted] minutes. • Record the patient's vital signs every [redacted] minutes during the infusion.	• If the patient experienced an IRR during any previous infusion of tiragolumab/placebo, [redacted] may be administered for subsequent infusions at the discretion of the investigator. • Record the patient's vital signs within [redacted] minutes prior to starting the infusion. • If the patient tolerated the first or a subsequent infusion of tiragolumab/placebo well without an IRR, the next infusion of tiragolumab/placebo may be infused over [redacted] minutes. • If no reaction occurs, continue subsequent infusions of tiragolumab/placebo over [redacted] minutes. • If the patient experienced an IRR with the previous infusion, the next infusion of tiragolumab/placebo should be administered over [redacted] minutes. • Continue to record vital signs within [redacted] minutes prior to starting infusion • Record vital signs during the infusion if clinically indicated.

Table 2 Administration of First and Subsequent Atezolizumab and Tiragolumab/Placebo Infusions (cont.)

	First Infusion	Subsequent Infusions
Observation period after infusion of tiragolumab/ placebo	• After the infusion of tiragolumab/placebo, the patient begins a [redacted]-minute observation period. • Record the patient's vital signs at [redacted] minutes after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous infusion of tiragolumab/placebo well without an IRR, the observation period may be reduced to [redacted] minutes for subsequent infusions. • If the patient experienced an IRR in the previous infusion, the observation period should be [redacted] minutes. • If clinically indicated, record the patient's vital signs at [redacted] minutes after the infusion of tiragolumab/placebo.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs are provided in Appendix 14.

4.3.2.3 Atezolizumab and Tiragolumab/Placebo

The following rules apply as long as neither atezolizumab nor tiragolumab/placebo has been permanently discontinued:

- Treatment cycles will normally begin with dosing of atezolizumab and tiragolumab/placebo on Day 1 of each 21-day cycle. [redacted]
- [redacted]

Carboplatin and/or etoposide may be administered as planned in the event that atezolizumab and/or tiragolumab/placebo dose(s) are delayed. If carboplatin and/or etoposide doses must be delayed, atezolizumab and/or tiragolumab may be administered as planned.

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.6.

4.3.2.4 Carboplatin + Etoposide

Carboplatin

During the induction phase, carboplatin will be administered after completion of tiragolumab/placebo by IV infusion over 30–60 minutes to achieve an initial target AUC of [redacted] mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate tiragolumab- and/or atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). Carboplatin infusion times may be adapted in accordance with local standard of care.

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

Calvert Formula

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

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

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

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

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

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

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

Maximum carboplatin dose (mg) = target AUC (mg × min/mL) × (GFR + 25 mL/min)

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

[redacted]

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.6.

Etoposide

During the induction phase, on Day 1 of each cycle, etoposide (100 mg/m^2) will be administered by IV infusion over 60 minutes following carboplatin administration. On Days 2 and 3 of each cycle, etoposide (100 mg/m^2) will be administered by IV infusion over 60 minutes. Premedication should be administered according to local standard of care. Because the effects of corticosteroids on T-cell proliferation have the potential to attenuate tiragolumab- and/or atezolizumab-mediated anti-tumor immune activity, premedication with corticosteroids should be minimized to the extent that is clinically feasible (see Section 4.4.2). Etoposide infusion times may be adapted in accordance with local standard of care.

Guidelines for treatment interruption or discontinuation are provided in Sections 4.6.1 and 5.1.6.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (tiragolumab and atezolizumab) 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 using 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, either by time monitoring (shipment arrival date and time) or temperature monitoring, 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 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 for information on IMP handling, including preparation, storage, and accountability.

4.3.4 Continued Access to Tiragolumab and/or Atezolizumab

Patients may be eligible to receive tiragolumab and/or atezolizumab as part of a post-trial access program, or an extension study, as described in Section 3.2. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://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 from 7 days prior to initiation of study treatment to the treatment 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]

[redacted]

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 10).

4.4.2 Cautionary Therapy for Tiragolumab- and/or Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

[redacted]

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 (refer to Appendix 14 for details).

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

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

- [redacted]

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.

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.

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.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

[redacted]

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

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

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

Patients who show apparent radiographic disease progression per RECIST v1.1 at a tumor response evaluation, and are eligible and willing to continue study treatment beyond disease progression, must sign an informed consent at that time to acknowledge the deferment of other treatment options in favor of continuing study treatment.

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

Small cell lung cancer history will include the VALG staging system and staging by the American Joint Committee on Cancer, Eighth Edition.

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

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified 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, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

See Table 2 for details on the measurements of vital signs during study treatment.

4.5.5 Performance Status

Performance status will be measured using the ECOG Performance Status at baseline and will be assessed at regular intervals throughout the study (see Appendix 1).

4.5.6 Tumor and Response Evaluations

Screening and subsequent tumor assessments must include CT scans (with IV contrast, unless contraindicated, and oral contrast as appropriate per institutional standards) of the chest and abdomen. 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 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 IV 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.

Patients with active or untreated symptomatic CNS metastases are not eligible for the study (see Section 4.1.2). Patients with untreated asymptomatic CNS metastasis at screening may be eligible. For untreated patients, brain MRI scan with contrast at screening is required, and need to meet all eligibility criteria as specified in Section 4.1.2.

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. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation.

[redacted] The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

For patients with previously untreated CNS metastases, a brain MRI scan with contrast is required at screening and is the preferred modality for all subsequent scheduled follow-up tumor assessments. [redacted] The same modality must be used at every tumor assessment.

[redacted]

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 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first (see Section 3.1.2). At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected.

[redacted]

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

Study treatment may be continued as long as patients are experiencing clinical benefit as assessed by the investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment if they meet all of the criteria specified in Section 3.1.2 and provide written consent.

Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. Patients who start a new anti-cancer therapy in the absence of radiographic disease progression per RECIST v1.1 will continue tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

To facilitate evaluation of post-progression tumor changes while treatment is ongoing, tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive study treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression),

and evaluation of any newly identified lesions (including measurements, if lesions are measurable; see Appendix 4) at all subsequent assessments.

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: [redacted]
- Chemistry panel (serum or plasma): [redacted]
- Coagulation: [redacted]
- Thyroid function testing: [redacted]
- EBV serology, [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- HIV serology
- [redacted]
- [redacted]
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. 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.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

- Urinalysis [redacted]

[redacted]

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

[redacted]

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

[redacted]

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

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

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

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

4.5.8 Optional Tumor Biopsies

[redacted]

4.5.9 Electrocardiograms

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

[redacted]

4.5.10 Clinical Outcome Assessments

Patient-reported outcome data will be collected to document the treatment benefit and more fully characterize the clinical profile of tiragolumab + atezolizumab.

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.11 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. DNA extracted from blood may be used to identify germline mutations and may be compared with DNA extracted from tissue to identify 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 or 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 (Section 4.5.11) 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).

Refer to Section 4.5.7 for details on 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 or 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) 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, SCLC, or drug safety:

- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives

thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

- Optional whole blood sample for DNA extraction collected at any time during study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, 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 emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.12.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data

confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results if available, and the patient's clinical status
- 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 may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non–protocol-specified anti-cancer therapy (see Section 4.4.3)
- Pregnancy
- Radiographic disease progression per RECIST v1.1 (unless treating beyond radiographic progression; see below)

However, to better accommodate standard clinical practice, which is guided by the fact that patients with ES-SCLC whose disease progresses after first-line treatment have limited treatment options and such options also have limited efficacy and significant toxicity, patients may be considered for treatment beyond radiographic progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient, only if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic progression per RECIST v1.1

Treatment should be discontinued if clinical deterioration due to disease progression occurs at any time. In addition, patients should be discontinued for unacceptable toxicity or for any other signs or symptoms of deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status.

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment (see Appendix 1). [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
- 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. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

[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 Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on anticipated mechanism of action, results from nonclinical studies, published data on similar molecules, clinical experience with tiragolumab alone and in combination with atezolizumab in Phase I and II studies, and the clinical safety profile of atezolizumab as a single agent. The anticipated important safety risks for tiragolumab and atezolizumab are outlined below (see Sections 5.1.1, 5.1.2, and 5.1.3). Refer to the Tiragolumab Investigator's Brochure and the Atezolizumab Investigator's Brochure for a complete summary of safety information for each respective study 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 the iDMC Charter for a 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 patients who experience anticipated adverse events, including criteria for treatment interruption or discontinuation, are provided in Appendix 13 and Appendix 14. Refer to

Sections 5.2–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

[redacted]

5.1.1 Risks Associated with Tiragolumab

[redacted]

Refer to Appendix 14 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 monoclonal antibody and targets tumor-infiltrating 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.

[redacted]

[redacted]

Please see Sections 4.3.2.1 and 4.3.2.2 for detailed guidance on administration of atezolizumab and tiragolumab/placebo in this study. Please see Appendix 10 for guidance on anaphylaxis precautions, and see Appendix 14 for guidance on management of IRRs and risks associated with tiragolumab.

[redacted]

5.1.1.3 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 therapeutics 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. [redacted] Refer to the Tiragolumab Investigator's Brochure for more details on these adverse events.

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 14.

5.1.1.4 Lymphopenia

[redacted]

Transient lymphocyte count decreases without clinical sequelae have been observed in patients treated with tiragolumab with or without atezolizumab.

[redacted]

5.1.1.5 Embryofetal Toxicity

[redacted]

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). Refer to Appendix 14 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.3 Risks Associated with Combination Use of Tiragolumab and Atezolizumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential for overlapping toxicities in patients treated with tiragolumab plus 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. [redacted]

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 [redacted], see Section 4.1.2). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. [redacted]

5.1.4 Risks Associated with Etoposide

The risk of overlapping toxicities between tiragolumab/atezolizumab and CE is thought to be minimal (see Section 5.1.7). Etoposide is known to cause bone marrow suppression including myelosuppression, anemia, thrombocytopenia, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), hepatotoxicity, and alopecia. Etoposide-based chemotherapy is considered to be moderately emetogenic. Etoposide carries a risk of secondary hematologic malignancy. Patients will be monitored for etoposide-related adverse events.

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

5.1.5 Risks Associated with Carboplatin

The risk of overlapping toxicities between tiragolumab/atezolizumab and CE is thought to be minimal (see Section 5.1.7). 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.

5.1.6 Management of Adverse Events

5.1.6.1 Dose Modification

General Notes Regarding Dose Modification

Reasons for dose modifications including dose delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.

The severity of adverse events will be graded according to the NCI CTCAE v5.0 grading system.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- When treatment is temporarily interrupted because of toxicity caused by tiragolumab/placebo, atezolizumab, carboplatin, or etoposide, the treatment cycles should be restarted such that the atezolizumab and tiragolumab/placebo infusions remain synchronized and aligned with the chemotherapy schedule.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one chemotherapy drug, the dose of the other chemotherapy drug does not require modification.

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

5.1.6.2 Tiragolumab and/or Atezolizumab Dose Modification, Treatment Interruption, or Treatment Discontinuation

Dose Modifications

There will be no dose modifications, including dose reductions, for tiragolumab/placebo or atezolizumab in this study.

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,

[redacted]

[redacted]

After both tiragolumab/placebo and atezolizumab have been permanently discontinued, the patient will be monitored for safety and efficacy as specified in Section 4.6 and Appendix 1.

Management Guidelines for Tiragolumab- and Atezolizumab-Specific Adverse Events

Refer to Appendix 14 for details on the management of tiragolumab- and atezolizumab-specific adverse events. See Appendix 10 for precautions for anaphylaxis.

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

Refer to Appendix 13 for details on chemotherapy dose modifications, treatment delays, or treatment discontinuation and management of specific adverse events.

5.1.7 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. [redacted]

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. Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2). Patients previously treated with approved or experimental CIT will also be excluded from participation in this study. [redacted]

The risk of overlapping toxicities between tiragolumab/atezolizumab and carboplatin/etoposide 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 CE (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of tiragolumab and/or atezolizumab.

Toxicities should initially be managed according to the recommendations in Sections 5.1.5 and 5.1.6 and Appendix 13, with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause.

For severe (Grade 3) or persistent Grade 1–2 diarrhea, an endoscopic evaluation should be considered. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology for adverse events listed above. If, in the opinion of the investigator, tiragolumab and/or atezolizumab is a potential inciting factor, the dose of tiragolumab and/or atezolizumab may be held for a [redacted] after event onset (see Appendix 13). 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 treatment and documented by the investigator. The Medical Monitor is available to advise as needed. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or TNF-α inhibitors. These cases should be discussed with the Medical Monitor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's 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). [redacted]

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
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- [redacted]
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- [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 5.3.4).

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until [redacted] days after the 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]. 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 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 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
5	Death related to adverse event [d]

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

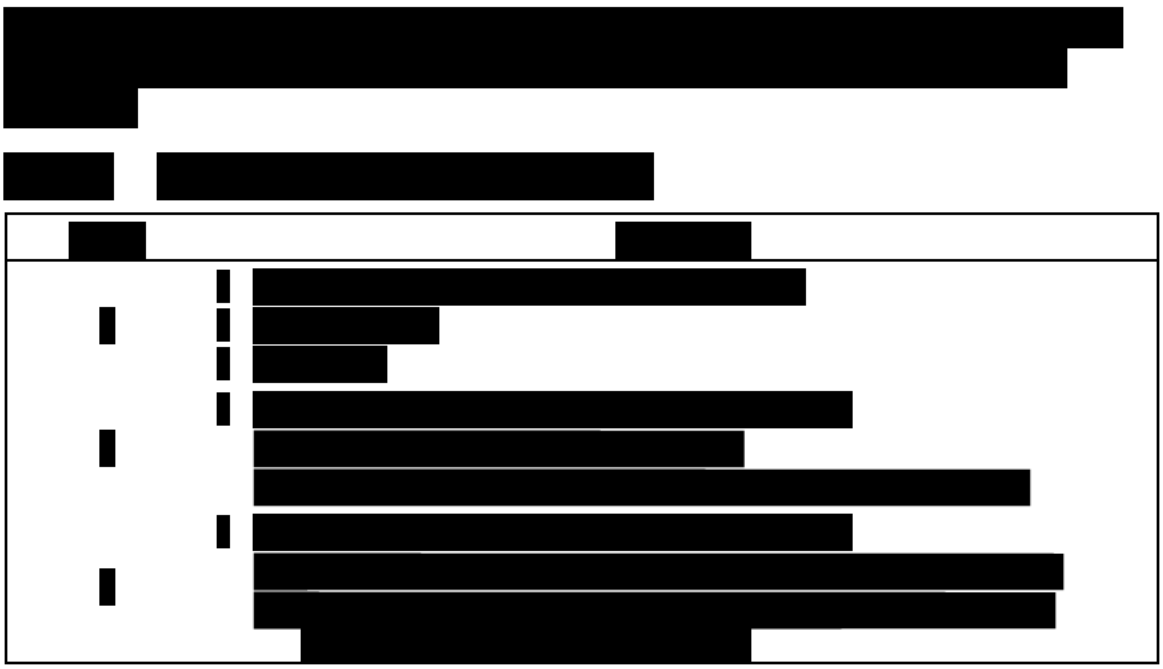
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

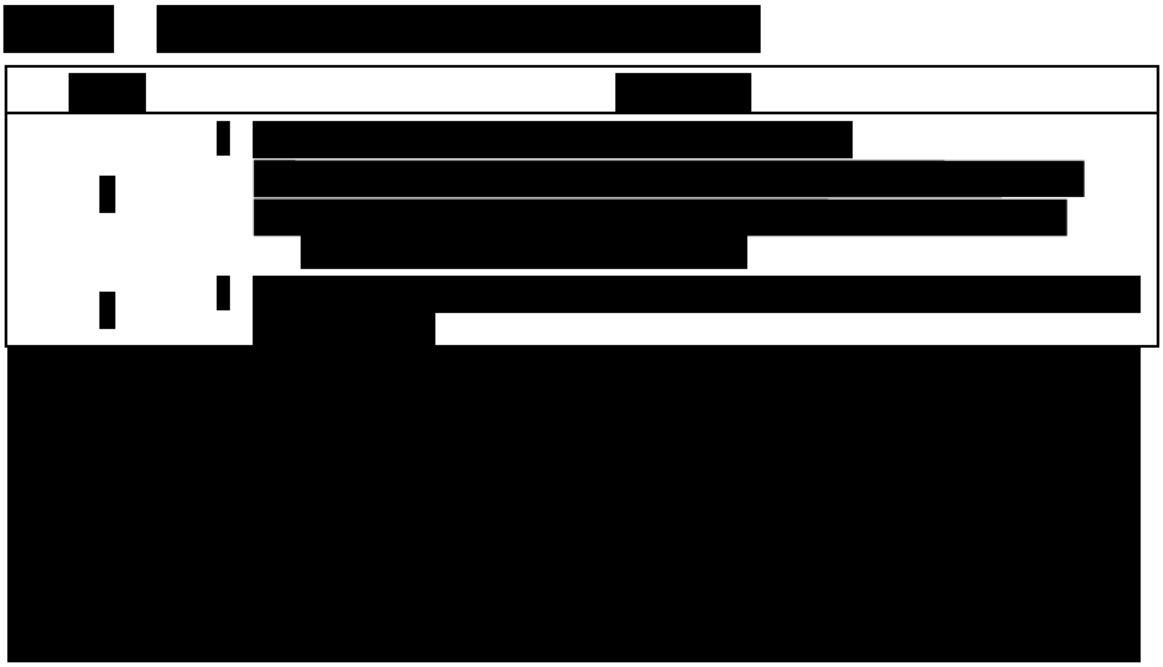
[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

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

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





5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

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

Table 5 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

[redacted]

[redacted]

[redacted]

5.3.5.2 Diagnosis Versus Signs and Symptoms

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

5.3.5.3 Adverse Events that are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

- [redacted]
- [redacted]

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of SCLC 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 treatment, 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.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Small Cell Lung Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. 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.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

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

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

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization 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

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For tiragolumab (or matching placebo) and atezolizumab,

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 two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from [redacted] PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms (via [redacted]) with investigator reports of adverse events. Sites are not expected to review the [redacted] PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

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

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 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week.

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 t*oll-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 Treatment Initiation

After informed consent has been obtained, but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events that Occur After Study Treatment Initiation

After initiation of study treatment, serious adverse events will be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest will be reported until 90 days after the final dose of study treatment, regardless of initiation of subsequent anti-cancer therapy. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study, within 90 days after the final dose of tiragolumab/placebo, or within 5 months after the final dose of atezolizumab, or within 6 months after the final dose of carboplatin or etoposide, whichever is later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study, within

6 months after the final dose of chemotherapy study treatment (i.e., CE), or within 90 days after the final dose of tiragolumab/placebo), whichever is later. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient

is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events (defined as [redacted] days after the final dose of study treatment [redacted]), and adverse events of special interest (defined as [redacted] days after the final dose of study treatment, [redacted], all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

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

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

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (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

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 safety data 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 randomized, Phase III, global, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of tiragolumab plus atezolizumab in combination with CE compared with treatment with placebo plus atezolizumab and CE in patients who have ES-SCLC and are chemotherapy-naive for their extensive-stage disease.

The analyses of PFS and OS will be performed in the PAS and the FAS. Patients will be grouped according to the treatment assigned at randomization, regardless of whether they receive any assigned study drug. Confirmed ORR will be analyzed in patients within the PAS and the FAS who have measurable disease at baseline. Duration of response will be assessed in patients who have a confirmed objective response in the PAS and the FAS. Time to confirmed deterioration analyses and change from baseline analysis on PROs will be performed in the PAS and the FAS.

Safety analyses will be conducted in all patients who are randomly assigned who received at least one dose of study treatment. Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the tiragolumab plus atezolizumab arm in the safety analyses if the patient receives any amount of tiragolumab, regardless of the initial treatment assignment at randomization.

Hypothesis tests will be two-sided unless otherwise indicated. Details of the analyses will be provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to test the hypothesis that tiragolumab in combination with atezolizumab in combination with CE prolongs the duration of PFS and/or OS relative to the control arm in the PAS. The PAS will include approximately 400 patients, assuming a 15% prevalence of presence or history of brain metastases at baseline. Approximately 470 patients in total will be randomly assigned in this study.

[redacted]

6.1.2 Co-Primary Endpoint: Progression-Free Survival in the Primary Analysis Set

[redacted]

[redacted]

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

[redacted]

6.1.3 Co-Primary Endpoint: Overall Survival in the Primary Analysis Set

The final analysis of the co-primary endpoint of OS will occur when approximately 288 deaths (72% of 400; see Section 6.10.2) have been observed in the PAS. This provides [redacted] power to detect a target HR of [redacted] for OS at a [redacted], based on the following assumptions:

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

It is projected that an observed HR of [redacted] or better for OS in the PAS will result in a statistically significant difference between the treatment arms. That is, an HR of [redacted] will be the minimally detectable difference for the analysis; this corresponds to an improvement of [redacted] in median OS from [redacted] in the placebo + atezolizumab + CE arm to [redacted] in the tiragolumab + atezolizumab + CE arm.

The timing of the interim analyses and the final analysis for OS in the PAS are summarized in Table 6 below, with the additional assumption on accrual.

The OS interim analysis is planned to be conducted by the Sponsor when approximately 202 deaths in the PAS have been observed. The stopping boundaries for the OS interim and final analyses are to be computed using the [redacted].

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study drug administration, reasons for discontinuation from the study drug, and reasons for study termination will be summarized by treatment arm. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

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

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

6.4 EFFICACY ANALYSES

6.4.1 Co-Primary Efficacy Endpoints

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

Progression-free survival is defined as the time between the date of randomization and the date of first documented disease progression (as assessed by investigators according to RECIST v1.1) or death, whichever occurs first. Patients who have not experienced disease progression and have not died by the data cutoff date 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.

Overall survival is defined as the time between the date of randomization and death from any cause.

Data for patients who are not reported as having died by the data cutoff date will be censored at the date when they were last known to be alive. Data for patients who do not have postbaseline information will be censored at the date of randomization.

Progression-free survival and OS will be compared between treatment arms with use of the stratified log-rank test. The HR for PFS and OS will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be those used for randomization from the IxRS (i.e., ECOG Performance Status and LDH). Stratification factor(s) may be removed from the stratified analyses if there is risk of overstratification. Analyses based on stratification factors recorded on the eCRF will also be provided if considerable discrepancy is observed between IxRS and eCRF records. Results from an unstratified analysis will also be provided.

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% CIs for the median PFS and median OS for each treatment arm (Brookmeyer and Crowley 1982).

The timing of the final PFS analysis is described in Section 6.1.2, and the analysis timing for OS is described in Section 6.1.3. To control the overall type I error rate at 0.05, the hypothesis test for PFS will be conducted at a two-sided α of 0.001. If PFS is not statistically significant, OS will be tested at a two-sided α of 0.049; if PFS is statistically significant, OS will be tested at a two-sided α level of 0.05 (see Section 6.1.1).

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Progression-Free Survival and Overall Survival in the Full Analysis Set

If the difference in OS in the PAS is statistically significant, PFS and OS will be tested in the FAS, following the same α-allocation ratio (1:49) and α-recycle strategy for the analysis of the co-primary efficacy endpoints as described in Section 6.4.1. Progression-free survival and OS in the FAS will be analyzed at the same time with the PAS, using the same methods as described in Section 6.4.1, except that all three stratification factors used for randomization from the IxRS (i.e., ECOG Performance Status, LDH, and presence or history of brain metastasis) will be included in the stratified analyses for the FAS. Stratification factor(s) may be removed from the stratified analyses if there is risk of overstratification.

6.4.2.2 Confirmed Objective Response Rate

A confirmed objective response is defined as either a CR or a PR on 2 consecutive occasions $\geq$4 weeks apart, as determined by the investigator using RECIST v1.1. Patients not meeting these criteria, including patients without any postbaseline tumor assessment, will be considered non-responders.

Confirmed ORR is defined as the proportion of patients who had a confirmed objective response. The analysis population for confirmed ORR will be the PAS and the FAS with measurable disease at baseline. An estimate of confirmed ORR and its 95% CI will be calculated using the Wilson score method for each treatment arm. Confidence intervals for the difference in confirmed ORRs between the two treatment arms will be determined using the Newcombe method.

6.4.2.3 Duration of Response

Duration of response will be assessed in patients who had a confirmed objective response as determined by the investigator using RECIST v1.1 in the PAS and the FAS. Duration of response is defined as the time interval from the date of the first occurrence of a confirmed objective response until the first date that progressive disease as determined by the investigator according to RECIST v1.1 or death is documented, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. Duration of response is based on a non-randomized subset of patients (specifically, patients who achieved a confirmed objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.4.2.4 Landmark Analysis on Progression-Free Survival and Overall Survival

The PFS rates at 6 months and at 1 year after randomization will be estimated using Kaplan-Meier methodology for each treatment arm, along with 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.

Similar analyses will be performed for the OS rates at 1 and 2 years after randomization.

6.4.2.5 Patient-Reported Outcomes

Time to confirmed deterioration in the PAS and the FAS for physical functioning and GHS/QoL using the EORTC QLQ-C30 is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration.

Confirmed clinically meaningful deterioration for physical functioning and GHS/QoL is defined as a clinically meaningful decrease from baseline in physical functioning or GHS score that must be held for at least two consecutive assessments or an initial clinically meaningful decrease above baseline followed by death.

A score change of $\geq$10-point change in GHS/QoL and functional subscale score is perceived by patients as clinically meaningful (Osoba et al. 1998).

For TTCD, data for patients will be censored at the last time when they completed an assessment if they have not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date. If no baseline or postbaseline assessment is performed, patients will be censored at the randomization date. Time to confirmed deterioration using the EORTC scale will be analyzed using the same methods as for PFS. Further details regarding the TTCD analysis for the EORTC measures will be described in the SAP.

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) and the mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of the EORTC QLQ-C30 and EORTC IL46, an item for trouble with side effects questionnaires according to the EORTC scoring manual guidelines.

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

6.5 SAFETY ANALYSES

Safety analyses will be conducted in all patients who are randomly assigned who received at least one dose of study treatment.

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

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] All 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 occurrence 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 and grade. Vital signs will also be summarized by treatment arm and visit. Deaths and causes of deaths will be summarized.

6.6 PHARMACOKINETIC ANALYSES

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

Plasma concentrations of CE will be collected in a subset of patients in this study as outlined in Appendix 2. The concentrations of CE will be summarized using descriptive statistics as described above.

Additional PK analyses will be conducted, as appropriate, based on the availability of data.

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 during both the treatment and follow-up periods for both tiragolumab and atezolizumab will be summarized by treatment arm.

The relationship between ADA status and safety, efficacy, and PK endpoints may be analyzed and reported via descriptive statistics.

[redacted]

[redacted]

[redacted]

[redacted]

6.10.2 Overall Survival

[redacted]. The final OS analysis will be conducted when approximately [redacted] OS events in the PAS have been observed. This is expected to occur approximately [redacted] after the first patient is randomly assigned. The exact timing of these analyses will depend on the actual number of OS events. [redacted]

Table 7 Analysis Timing and Stopping Boundary of Overall Survival in the Primary Analysis Set

A total of two analyses are planned for the co-primary endpoint of OS in the FAS, to be conducted at the same time as for the PAS. The same information fraction in the PAS, based on the actual number of events observed, will be applied to calculate the statistical boundary for the OS analyses in the FAS.

6.10.3 Safety Monitoring

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

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 *are* required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of 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 Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or* Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms, such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified

translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Informed Consent Form will also contain a separate signature page for patients who meet all of the criteria specified in Section 3.1.2, and decide to continue study treatment beyond radiographic disease progression per RECIST v1.1. This separate consent is to be signed after initial radiographic disease progression has occurred and patients have discussed other available treatment options and the potential risks of continuing study treatment.

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 other summary reports 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 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, 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 prior to study initiation. 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 study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 150 sites globally will participate in the study and approximately 470 patients will be randomly assigned during the study. Randomization will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will monitor and evaluate patient safety throughout the study, as detailed in Section 3.1.3. Tumor response and progression will be evaluated by the investigator. 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.

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	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase (Starting from Cycle 5)		Approx. Every 6 Months After Disease Progression or Loss of Clinical Benefit
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days After Last Dose of Study Treatment	
Informed consent	x				
Screening tumor tissue specimen for [redacted]	x [c]	x [c]			
Demographic data	x				
Medical history and baseline conditions	x				
SCLC cancer history	x				
Vital signs [d]	x	x	x	x	
Weight	x	x	x	x	
Height	x				
Complete physical examination	x				
Limited physical examination [e]		x [f]	x [f]	x	
ECOG Performance Status	x	x [f]	x [f]	x	
ECG	x	Perform when clinically indicated			
Hematology [g]	x [h]	x [f]	x [f]	x	
Serum chemistry [i]	x [h]	x [f]	x [f]	x	
Coagulation test [redacted]	x [h]			x	

Appendix 1: Schedule of Activities

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase (Starting from Cycle 5)		Approx. Every 6 Months After Disease Progression or Loss of Clinical Benefit
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days After Last Dose of Study Treatment	
Pregnancy test (women of childbearing-potential only)	x [j]	x [k]	x [k]	x [k]	x [k]
TSH, free T3, free T4 [l]	x	x [l,f]	x [l,f]	x	
[redacted]	x				
Urinalysis [n]	x [n]	Perform when clinically indicated			
Induction treatment administration Arm A: atezolizumab + tiragolumab + CE Arm B: atezolizumab + placebo + CE		x [o]			
Maintenance treatment administration Arm A: atezolizumab + tiragolumab Arm B: atezolizumab + placebo			x [p]		
PCI			x [p]		
Tumor response assessment	x [q]	x [r]	x [r]		x [s]
Informed consent to continue study treatment beyond radiographic disease progression per RECIST v1.1		At time of initial radiographic progression			
Serum sample for tiragolumab ADA assessment		Refer to Appendix 2, Table A2-1			
Serum sample for atezolizumab ADA assessment		Refer to Appendix 2, Table A2-1			

Appendix 1: Schedule of Activities

Procedure	Screening Days −28 to −1	All Treatment Cycles [a] Induction Phase (Cycles 1–4) Every 21 Days (±3 Days) [b]	All Treatment Cycles [a] Maintenance Phase (Starting from Cycle 5) Every 21 Days (±3 Days)	Treatment Discontinuation Visit ≤30 Days After Last Dose of Study Treatment	Survival Follow-Up Approx. Every 6 Months After Disease Progression or Loss of Clinical Benefit
Serum sample for tiragolumab PK sampling		Refer to Appendix 2, Table A2-1			
Serum sample for atezolizumab PK sampling		Refer to Appendix 2, Table A2-1			
Plasma sample for carboplatin and etoposide PK sampling		Refer to Appendix 2, Table A2-2			
[redacted]		[redacted]			
[redacted]		[redacted]			
[redacted]					
[redacted]					
[redacted]					
Adverse events	x	x	x	x [v]	x [v]
Cancer-related procedures (medical, surgical, and radiation)		x	x	x	x
Concomitant medications	x [w]	x [w]	x [w]	x [w]	
[redacted]		[redacted]			

Appendix 1: Schedule of Activities

Procedure	Screening	All Treatment Cycles [a]		Treatment Discontinuation Visit	Survival Follow-Up
		Induction Phase (Cycles 1–4)	Maintenance Phase (Starting from Cycle 5)		
	Days −28 to −1	Every 21 Days (±3 Days) [b]	Every 21 Days (±3 Days)	≤30 Days After Last Dose of Study Treatment	Approx. Every 6 Months After Disease Progression or Loss of Clinical Benefit
[redacted]		[redacted]			

ADA = anti-drug antibody; CE = carboplatin and etoposide; CT = computed tomography; [redacted] ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form [redacted] MRI = magnetic resonance imaging; *OS = overall survival*; PCI = prophylactic cranial irradiation; PD = pharmacodynamic; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality-of-Life Questionnaire Core 30; [redacted]; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small cell lung cancer.

[a] Assessments should be performed before study drug infusion unless otherwise noted.

[b] Cycle 1 must be performed within 5 days after the patient is randomly assigned. [redacted]

[c] [redacted]

[d] Vital signs include pulse rate, respiratory rate, blood pressures, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[e] Symptom-directed physical examinations; see Section 4.5.3 for details.

[f] [redacted]

[g] Hematology [redacted]

[h] At screening, the patient must have adequate hematologic and end-organ function defined by laboratory test results obtained within 14 days prior to Cycle 1, Day1. See Section 4.1.1 for details.

[i] Chemistry panel [redacted]

[j] Serum pregnancy test within 14 days prior to initiation of study treatment.

[k] During the study, urine pregnancy tests will be performed on Day 1 of every cycle. After study treatment discontinuation, a urine pregnancy test will be performed at either 6 months after the final dose of carboplatin or etoposide, at 90 days after the final dose of tiragolumab/placebo, or at 5 months after the final dose of atezolizumab, whichever is later. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

[l] Thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycles 1, 5, 9, and 13, and every fourth cycle thereafter. The Cycle 1 thyroid function testing does not need to performed if the previous test was performed within the screening window.

[m] [redacted]

[n] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Urinalysis is required at screening and will be obtained when clinically indicated.

[o] [redacted] For CE, study drug will be administered as described in Section 4.3.2. [redacted]

[p] [redacted] Additionally, during this phase, PCI is permitted as per local standard of care and will be reported on the Prophylactic Cranial Irradiation eCRF.

[q] Computed tomography scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) of the chest and abdomen. A CT with contrast of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. See Section 4.5.6 for details.

[r] Perform every 6 weeks (±7 days) for 48 weeks following Cycle 1, Day 1 and then every 9 weeks (±7 days) thereafter, after completion of the Week 48 tumor assessment, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. [redacted]

[s] If the patient discontinues study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration), tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [±7 days] for 48 weeks following Cycle 1, Day 1 and then every 9 weeks [±7 days] thereafter) until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first, even if the patient starts a new anti-cancer therapy after study treatment discontinuation. See Section 4.5.6 for details. [redacted]

[t] [redacted].

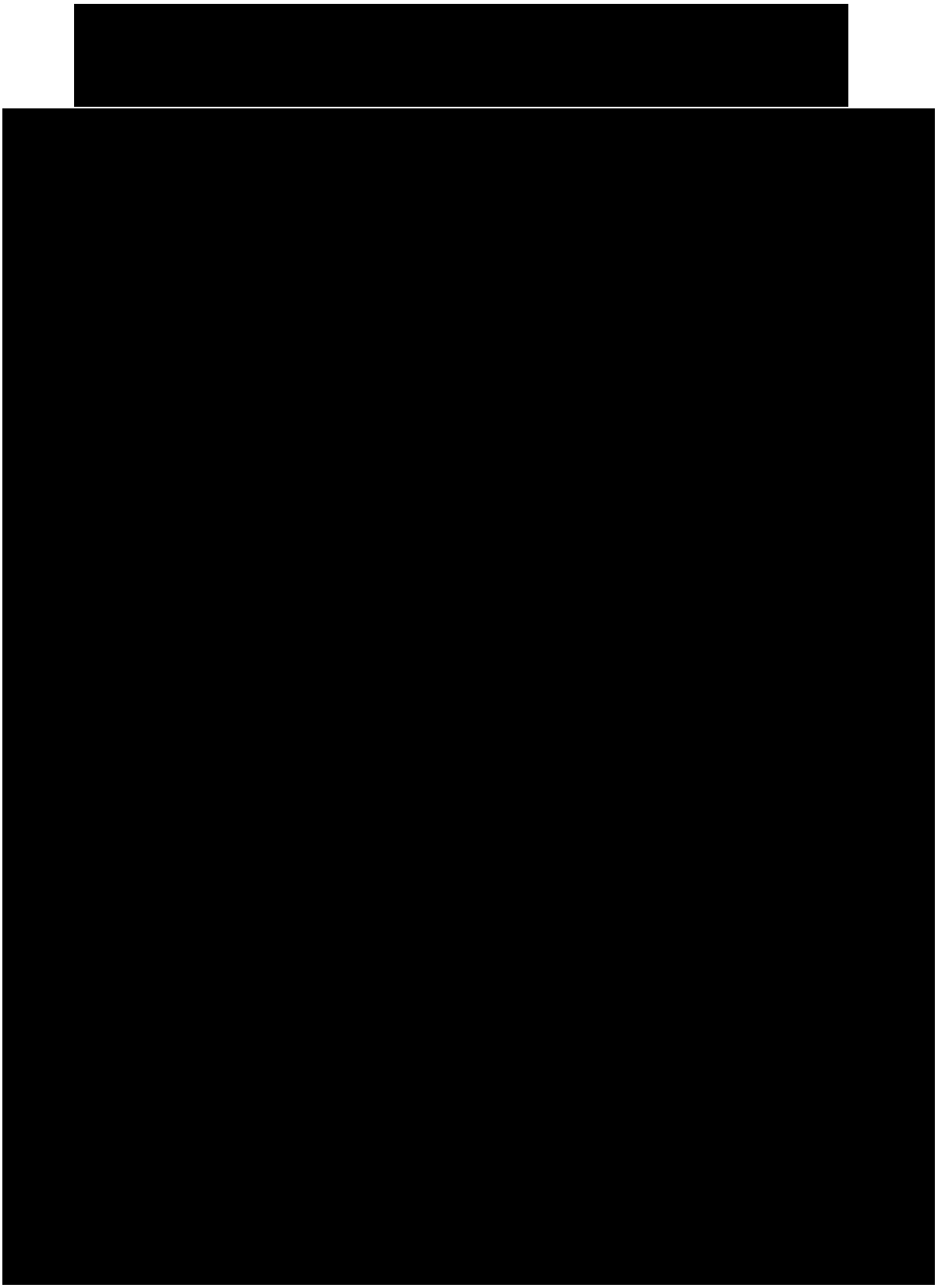
[u] [redacted]

[v] All serious adverse events regardless of relationship to study drug, will be reported until [redacted] days after the last dose of study drug [redacted]. In addition, adverse events of special interest will continue to be reported until [redacted] days after the final dose of study treatment, [redacted]. All other adverse events, regardless of relationship to study drug, will be reported until [redacted] days after the last dose of study drug [redacted] After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6). These events should be reported using the Adverse Event eCRF.

[w] From 7 days prior to initiation of study treatment until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[x] 

[y] After radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1) and study treatment has been discontinued, survival follow-up information will be collected by telephone, patient medical records, and/or clinic visits every 6 months or more frequently (± 30 days) until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from the study, study staff may use a public information source (e.g., county records), when permissible, to obtain information about survival status only.



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

Table A2-2 Schedule of Pharmacokinetic Samples for Chemotherapy in a Subset of Patients

Study Visit	Time	Sample type(s)
Cycle 1 and 3, Day 1	Predose (same day as treatment administration)	• Carboplatin PK (plasma) • Etoposide PK (plasma)
	5–10 minutes before end of carboplatin infusion	• Carboplatin PK (plasma)
	5–10 minutes before end of etoposide infusion	• Etoposide PK (plasma)
	1 hour (±15 minutes) after end of carboplatin infusion	• Carboplatin PK (plasma)
	1 hour (±15 minutes) after end of etoposide infusion	• Etoposide PK (plasma)

PK = pharmacokinetics.

Note: At select sites, a subset of approximately 40 patients (approximately 20 per arm) will undergo the above additional PK assessments for carboplatin and etoposide. The additional PK assessments should be taken only if the patient is receiving both carboplatin and etoposide at the cycle.

Appendix 3
Veterans Administration Lung Study Group (VALG) Staging System for SCLC

Stage	Characteristics
Limited SCLC	• Disease confined to one hemithorax, although local extensions may be present; • No extrathoracic metastases except for possible ipsilateral, supraclavicular nodes if they can be included in the same portal as the primary tumor; and • Primary tumor and regional nodes that can be adequately treated and totally encompassed in every portal
Extensive SCLC	• Inoperable patients who cannot be classified as having limited disease

SCLC = small cell lung cancer.

Source: Micke et al. 2002.

REFERENCE

Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? Lung Cancer 2002;37:271–6.

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 slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other 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 never more than 4 weeks before the beginning of the treatment.

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

CLINICAL LESIONS

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

CHEST X-RAY

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

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING 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 (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must

be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

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

CALCULATION OF SUM OF DIAMETERS

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

Measuring Lymph Nodes

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

Measuring Lesions That Become Too Small to Measure

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

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

assigned in this circumstance as well and "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

- CR: Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- 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 CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

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

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

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

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

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

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

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

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A4-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A4-1 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/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The

objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A4-1.

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.

REFERENCE

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

Appendix 5
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 <u>long</u> walk?	1	2	3	4
3.	Do you have any trouble taking a <u>short</u> 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

<u>Please go on to the next page</u>

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 8
EuroQol EQ-5D-5L

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Health Questionnaire

English version for the USA

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

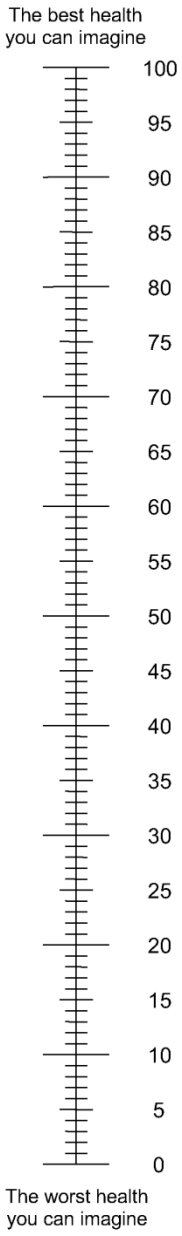
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



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
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, IV, 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 11
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 and tiragolumab 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 12
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 12-1 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
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No [a]
Tiragolumab placebo	IMP (placebo)	Unauthorized	Not applicable
Carboplatin	Non-Roche AxMP (background treatment)	Authorized	No [a]
Etoposide	Non-Roche AxMP (background treatment)	Authorized	No [a]

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

[a] Atezolizumab, carboplatin, and etoposide are approved for the treatment of small cell lung cancer, but not in combination with RO7092284.

Table 12-2 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA and UK	Used within Marketing Authorization
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No [a]
Tiragolumab placebo	IMP (placebo)	Unauthorized	Not applicable
Carboplatin	Non-Roche NIMP[b] (background treatment)	Authorized	No [a]
Etoposide	Non-Roche NIMP[b] (background treatment)	Authorized	No [a]

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

[a] Atezolizumab, carboplatin, and etoposide are approved for the treatment of small cell lung cancer, but not in combination with RO7092284.

[b] Carboplatin and etoposide are considered PeIMP in Italy.

Appendix 13
Overall Guidelines for Management of Patients Who Experience Adverse Events

DOSE MODIFICATIONS FOR TIRAGOLUMAB/PLACEBO AND/OR ATEZOLIZUMAB

[redacted]

TREATMENT INTERRUPTION FOR TIRAGOLUMAB/PLACEBO AND/OR ATEZOLIZUMAB

See Appendix 14 for risks associated with tiragolumab or atezolizumab and guidelines for management of associated adverse events.

Atezolizumab and tiragolumab/placebo treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. [redacted]

DOSE MODIFICATIONS FOR CHEMOTHERAPY

Dose modifications for carboplatin and etoposide 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 carboplatin or etoposide 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 [redacted] 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 [redacted] days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology and National Comprehensive Cancer Network (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 A13-1).

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

Table A13-1 Chemotherapy Dose Modification for Hematologic Toxicities

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

[a] Nadir of prior cycle.

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 A13-2), treatment should be delayed for up to [redacted] days until resolution to less than or equal to the patient's baseline value (or Grade ≤ 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 A13-2 provides recommended dose modifications for non-hematologic toxicities.

Table A13-2 Dose Modifications or 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).

Suggested recommendations for dose modification of etoposide for renal impairment are provided in Table A13-3.

Table A13-3 Etoposide Dose Modification for Renal Impairment

Creatinine clearance (mL/min)	Etoposide Dose
> 50	100%
15–50	75% of dose

Appendix 14
Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

Toxicities associated or possibly associated with tiragolumab and/or atezolizumab 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/placebo and/or atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

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]

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

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 A14-1.

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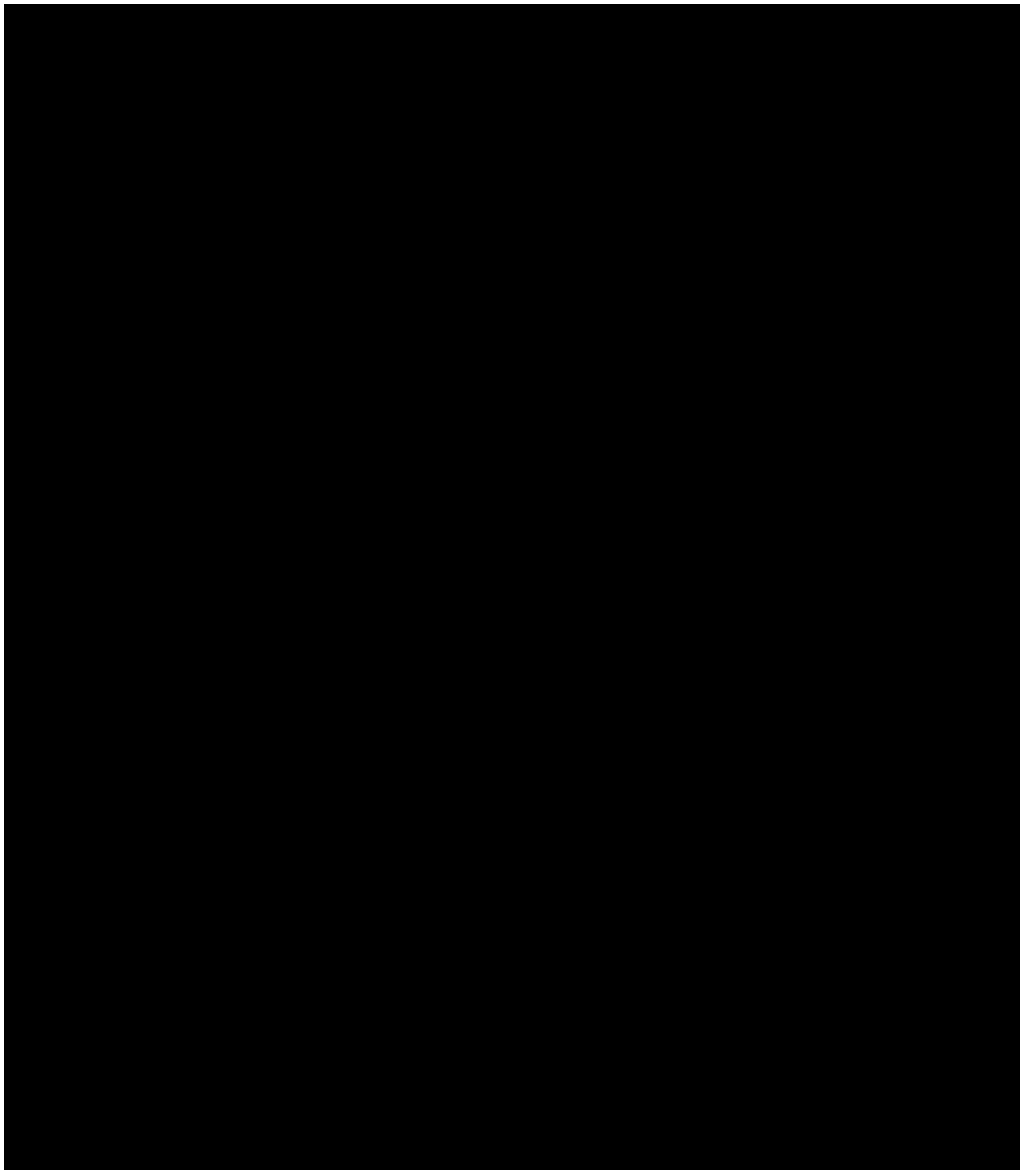


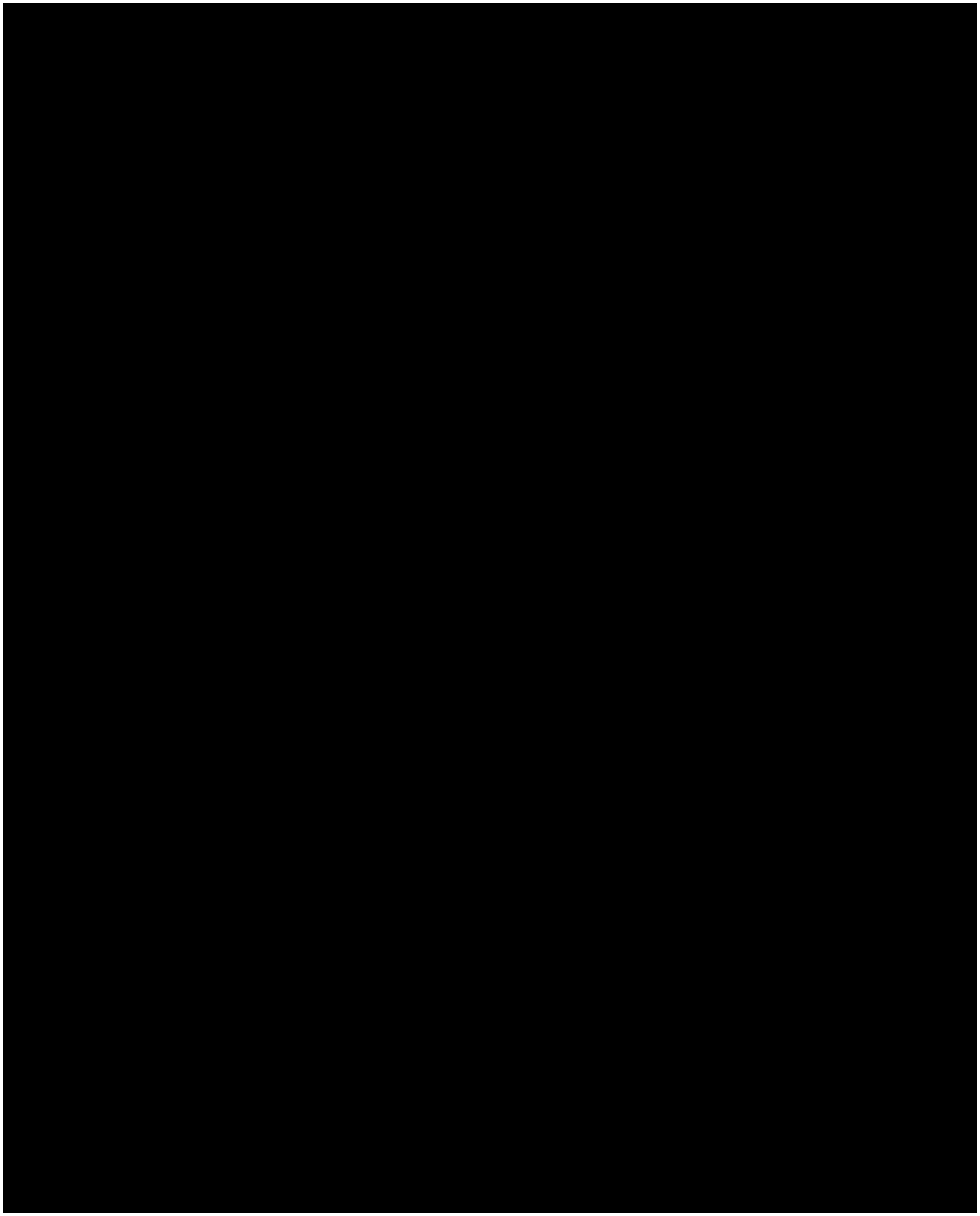
HEPATIC EVENTS

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 A14-2.

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.

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab



GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A14-3.

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 three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

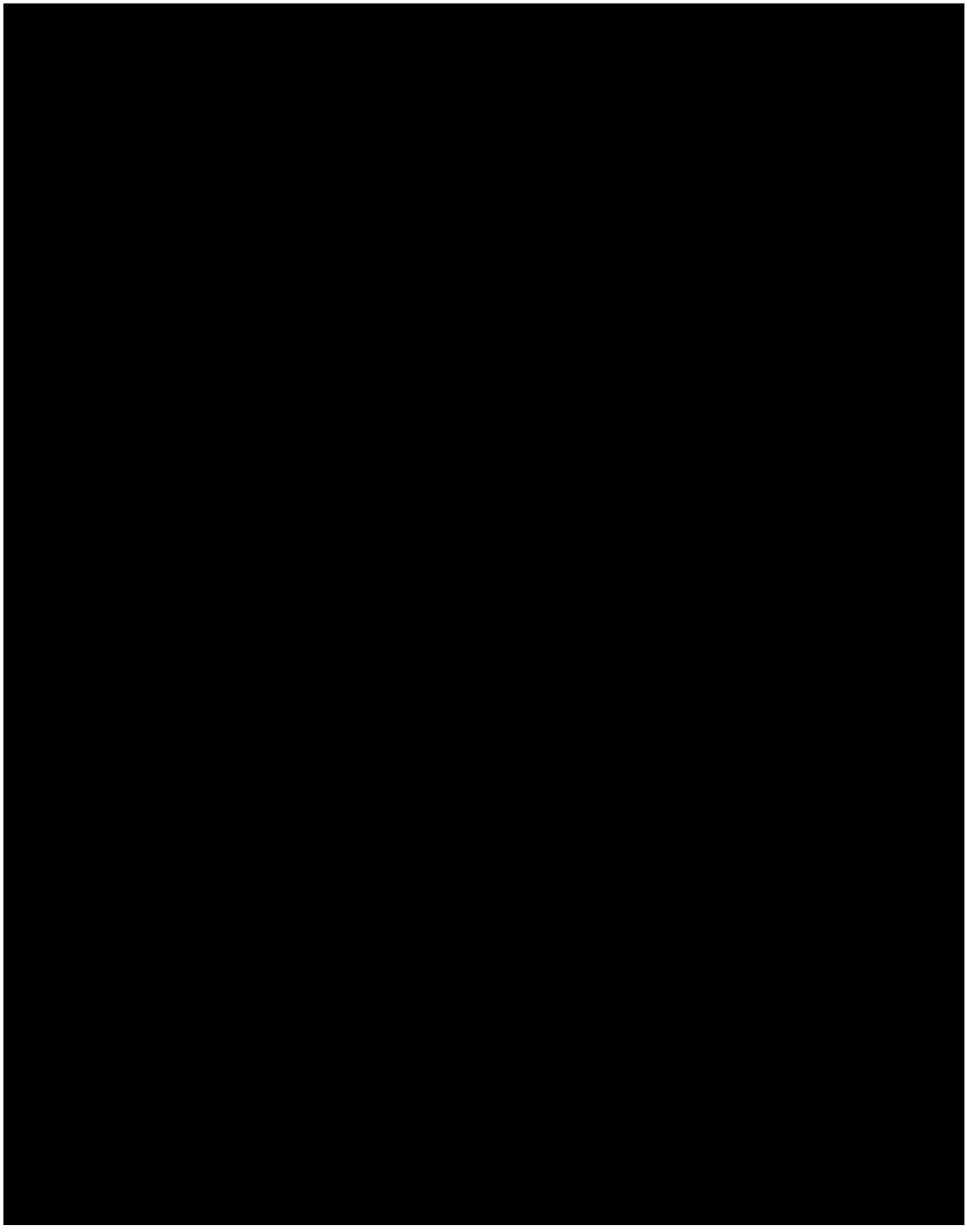
Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A14-4.

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. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone and free triiodothyronine and thyroxine 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.

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab



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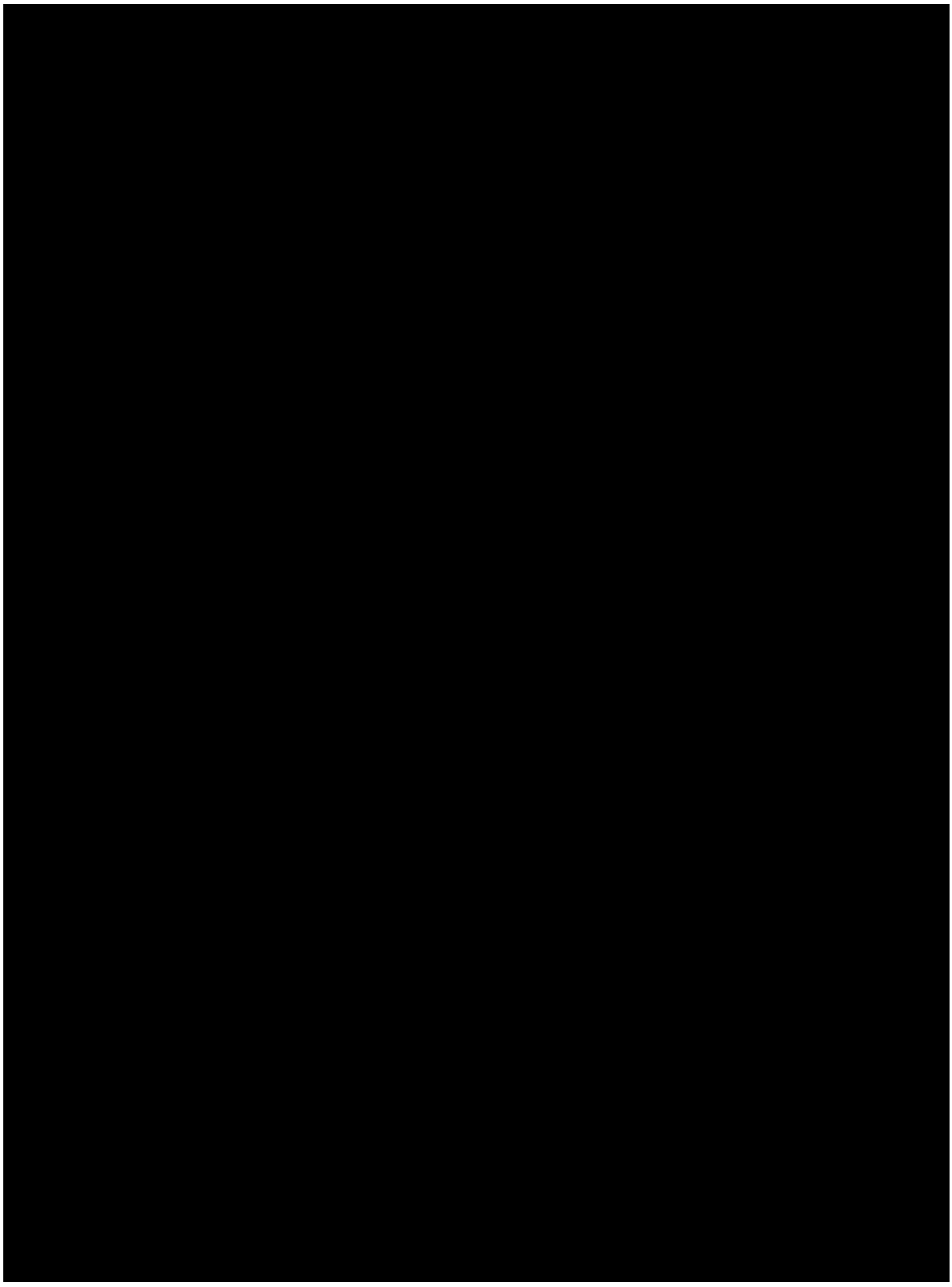

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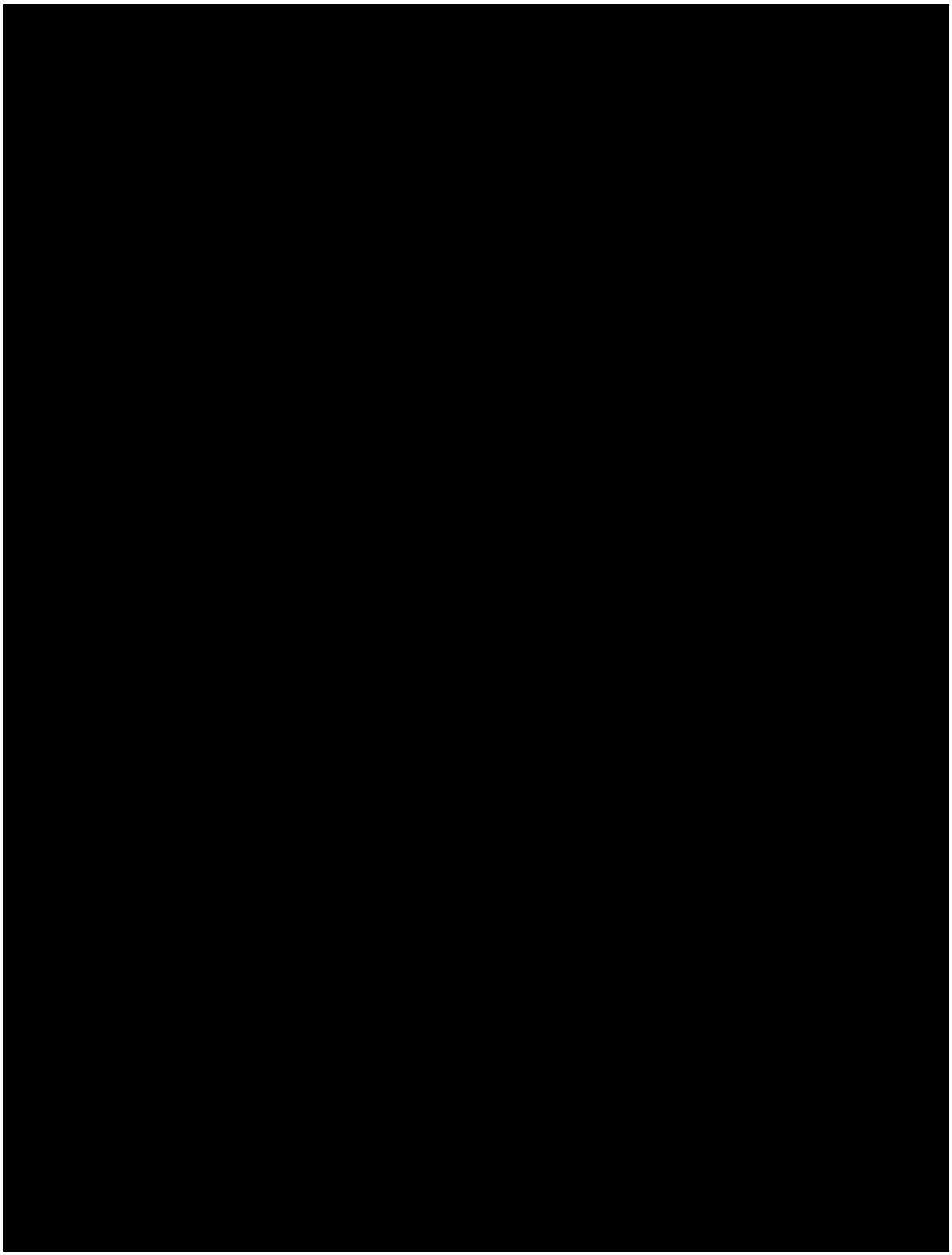
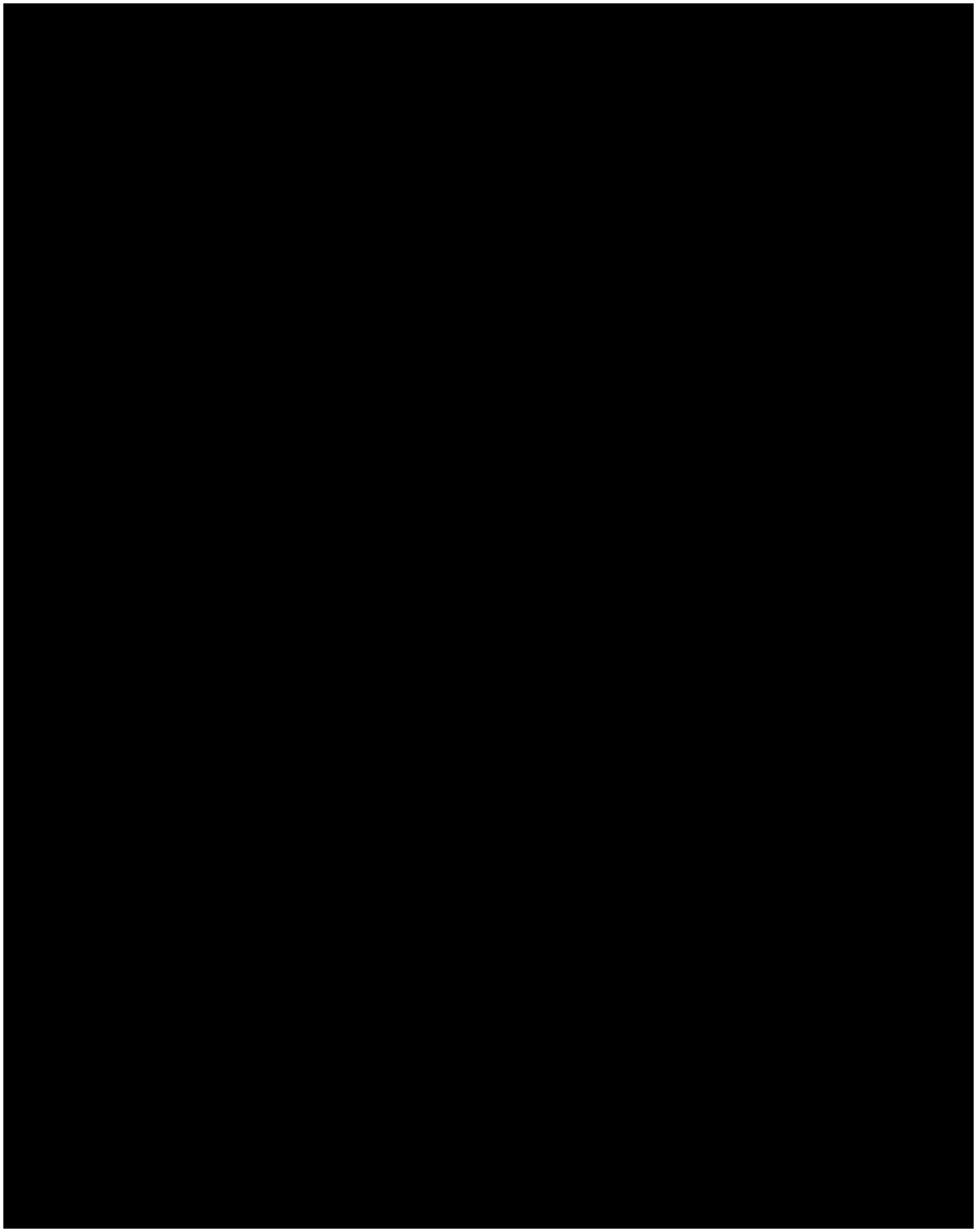


OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A14-5.



IMMUNE-MEDIATED CARDIAC EVENTS

[redacted]

[redacted]. Management guidelines for cardiac events are provided in Table A14-6.

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 A14-6.

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]

[redacted]

[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. 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 administration and are generally mild to moderate in severity.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table A14-7 . For subsequent cycles, IRRs should be managed according to institutional guidelines.

[redacted]

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

[redacted]

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

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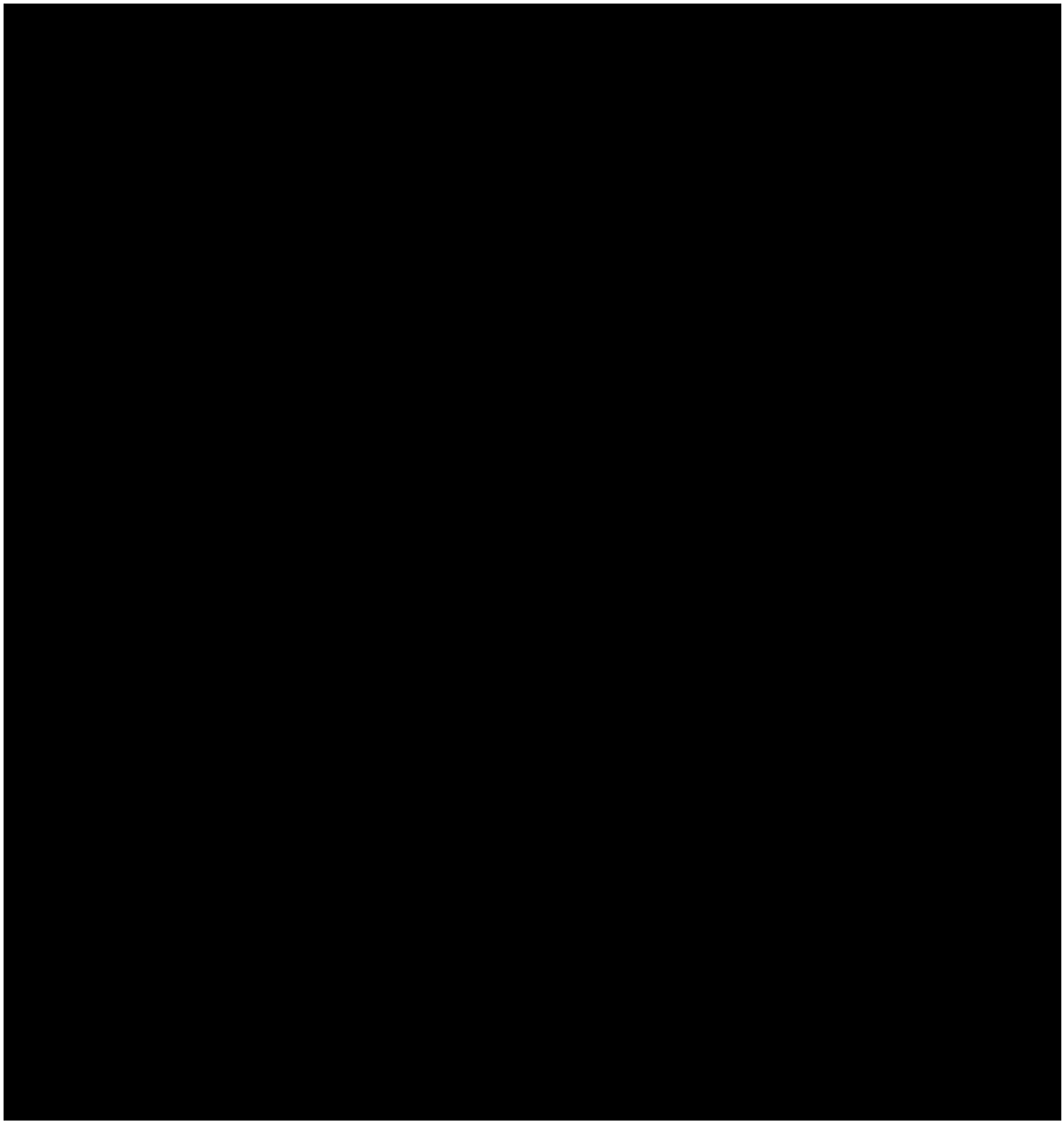

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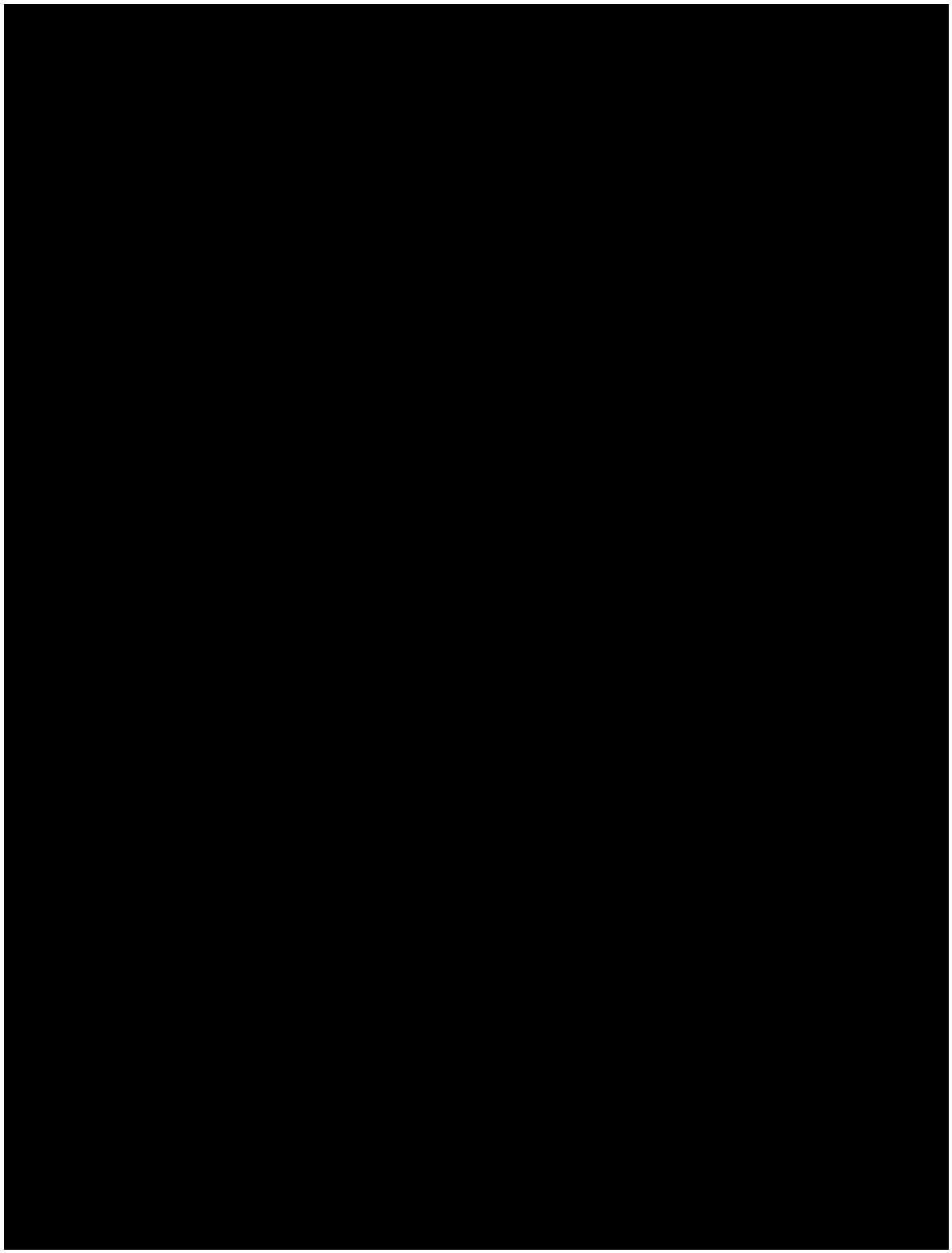


[redacted]

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 A14-9.

[redacted]

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

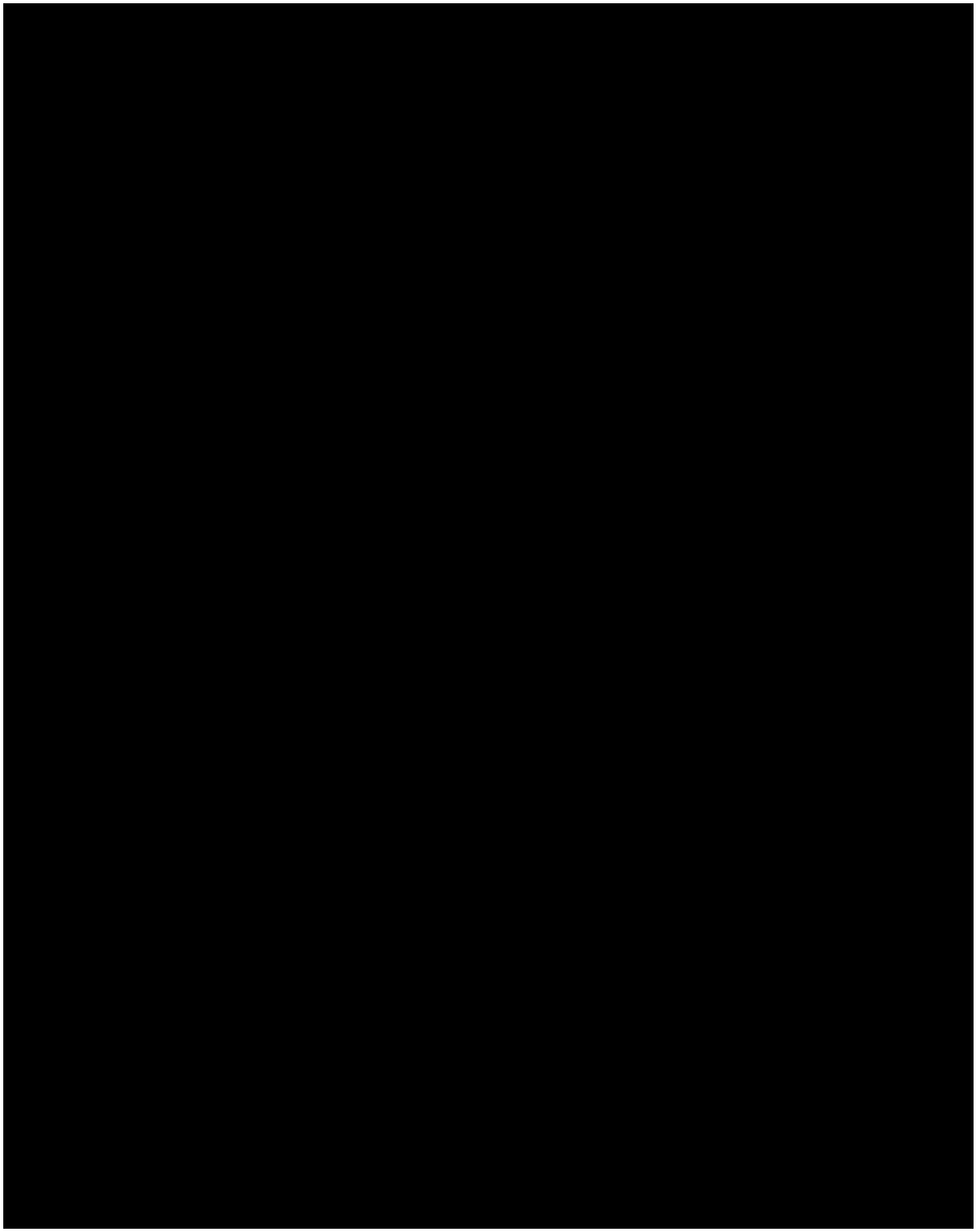
[redacted]

DERMATOLOGIC EVENTS

[redacted] Management guidelines for dermatologic events are provided in Table A14-10.

[redacted]

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab



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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. [redacted]

[redacted]

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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.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

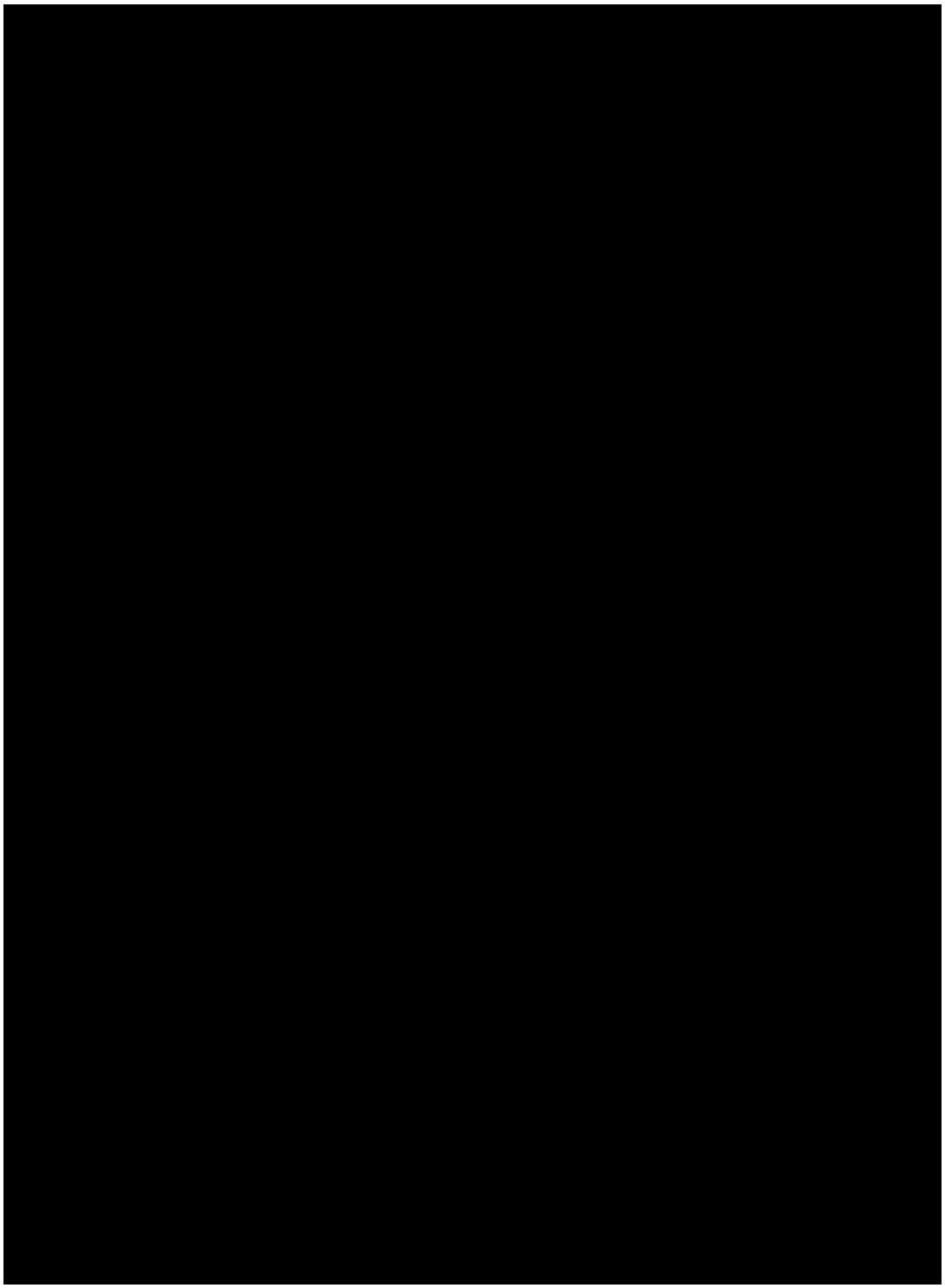
Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A14--13.

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 A14--14.

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab



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 A14--15.

[redacted]

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

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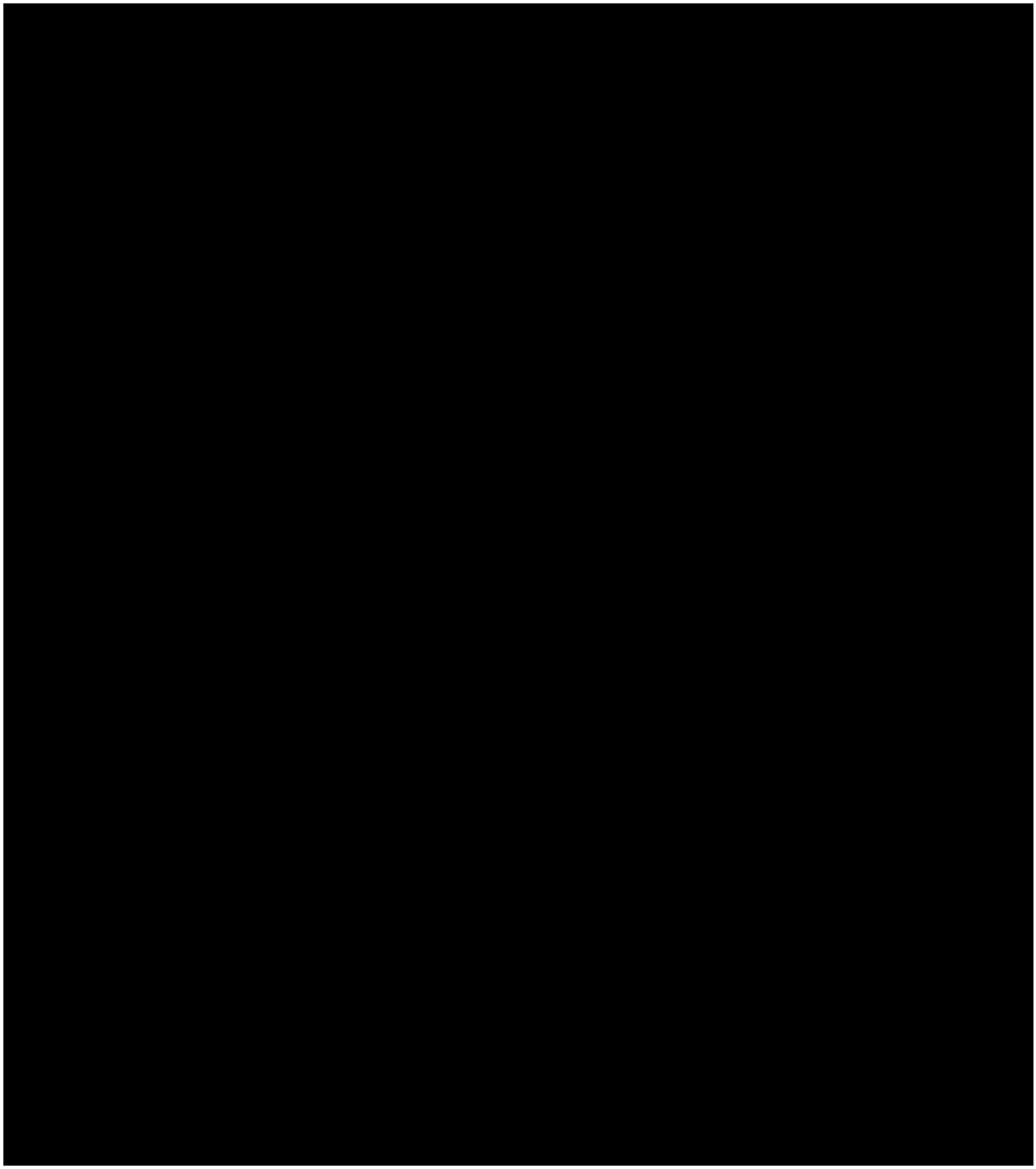

Appendix 14: Risks Associated with Tiragolumab or Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab or Atezolizumab

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