Official Title: A Phase II, Randomized, Double Blind Study of Atezolizumab Plus Tiragolumab and Atezolizumab Plus Placebo as First-Line Treatment in Patients with Recurrent/Metastatic PD-L1 Positive Squamous Cell Carcinoma of the Head and Neck

NCT Number: NCT04665843

Document Date: Protocol Amendment Version 6: 06-Dec-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND STUDY OF ATEZOLIZUMAB PLUS TIRAGOLUMAB AND ATEZOLIZUMAB PLUS PLACEBO AS FIRST-LINE TREATMENT IN PATIENTS WITH RECURRENT/METASTATIC PD-L1–POSITIVE SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
PROTOCOL NUMBER:	BO42533
VERSION NUMBER:	6
TEST PRODUCTS:	Atezolizumab (RO5541267) Tiragolumab (RO7092284)
STUDY PHASE:	Phase II
REGULATORY AGENCY IDENTIFIERS:	IND Number: 151530 EudraCT Number: 2020-002852-19 EU CT Number: 2023-509449-10-00 NCT Number: NCT04665843
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 Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
6	See electronic date stamp on the final page of this document.	—	—	—
5	13 December 2022	—	—	—
4	19 February 2022	—	—	—
2	6 October 2020	France	3	23 March 2021
1	8 July 2020	—	—	—

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol BO42533 has been amended primarily to update the risks and adverse event management guidelines for atezolizumab to align with the Atezolizumab Investigator's Brochure, Version 20 and to prepare the protocol for the switch to submission under the Clinical Trials Regulation (CTR). Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The synopsis has been simplified to align with CTR and other guidelines (front matter).
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.7).
- A section describing duration of participation has been added to align with CTR requirements (Section 3.3).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements (Section 4.3 and Appendix 17).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 20 (Appendix 16).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND STUDY OF ATEZOLIZUMAB PLUS TIRAGOLUMAB AND ATEZOLIZUMAB PLUS PLACEBO AS FIRST-LINE TREATMENT IN PATIENTS WITH RECURRENT/METASTATIC PD-L1–POSITIVE SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
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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 to the contact provided below.

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{Address}

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND STUDY OF ATEZOLIZUMAB PLUS TIRAGOLUMAB AND ATEZOLIZUMAB PLUS PLACEBO AS FIRST-LINE TREATMENT IN PATIENTS WITH RECURRENT/METASTATIC PD-L1–POSITIVE SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 151530 EudraCT Number: 2020-002852-19 EU CT Number: 2023-509449-10-00 NCT Number: NCT04665843

STUDY RATIONALE

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 recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN). PD-1 inhibitors in the first-line (1L) (pembrolizumab) and the second-line (2L)-plus settings (pembrolizumab and nivolumab) have demonstrated improvement in survival compared with standard chemotherapy, which has led to the recent approvals of pembrolizumab and nivolumab for the treatment of SCCHN, and validates the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in SCCHN. Furthermore, the safety profile of PD-L1/PD-1 antibodies as monotherapy appears to be more tolerable than many of the chemotherapy combinations given in the 1L setting, which are associated with substantial toxicities and are often poorly tolerated by elderly patients and patients with poor performance status.

Despite the activity in the 1L setting with pembrolizumab monotherapy in PD-L1–positive patients, durable clinical benefit is limited to a minority of patients, highlighting the need to explore novel therapies that may improve upon these outcomes. As described in Section 1.3, it is hypothesized that the combination of anti–T-cell immunoreceptor with Ig and ITIM domains (TIGIT) with anti–PD-L1/PD-1 agents may result in activation of anti-tumor immune responses, leading to enhanced killing of tumor cells and improved clinical responses in patients with metastatic SCCHN.

In the Phase Ib portion of Study GO30103, evaluating tiragolumab in combination with atezolizumab, partial responses occurred in patients with metastatic cancers, including SCCHN, with varying degrees of PD-L1 and/or TIGIT expression. The combination of atezolizumab plus tiragolumab was well tolerated in the Phase Ib portion of the study, and the addition of tiragolumab did not alter the safety profile of atezolizumab, regardless of the tumor type. Therefore, this study is designed to evaluate the anti-tumor effects and safety of atezolizumab plus tiragolumab and atezolizumab plus placebo as 1L treatment in patients with PD-L1 positive recurrent/metastatic SCCHN. The primary efficacy endpoint of confirmed objective response rate in both the atezolizumab plus tiragolumab and atezolizumab plus placebo arm will be compared with a [redacted]

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab plus tiragolumab and atezolizumab plus placebo	• Confirmed objective response rate, defined as the proportion of patients with a confirmed objective response (i.e., complete response or partial response on two consecutive occasions ≥4 weeks apart), as determined by the investigator according to RECIST v1.1
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of atezolizumab plus tiragolumab and atezolizumab plus placebo	• Duration of response 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 • PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause • PFS rate at 6 months • OS rate at 6 months and 12 months • Time to confirmed deterioration in patient reported physical functioning, as measured by the Patient Reported Outcomes Measurement Information System® Item Bank v2.0–Physical Functioning–Short Form 10b
• To evaluate the safety of atezolizumab plus tiragolumab and atezolizumab plus placebo	• Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 – Severity for cytokine release syndrome will also be determined according to the American Society for Transplantation and Cellular Therapy consensus grading scale.
• To characterize the pharmacokinetics of atezolizumab and tiragolumab	• Serum concentrations of atezolizumab and tiragolumab at specified timepoints
• To evaluate the immune response to atezolizumab and tiragolumab	• Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study • Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study

ADA = anti-drug antibody; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

OVERALL DESIGN AND STUDY POPULATION

DESCRIPTION OF STUDY

This is a Phase II, randomized, double-blind, global study designed to evaluate the efficacy and safety of atezolizumab plus tiragolumab and atezolizumab plus placebo as first-line (1L) treatment in recurrent/metastatic PD-L1–positive SCCHN. Eligible patients will include male and female patients age ≥ 18 years with Eastern Cooperative Oncology Group Performance Status of 0 or 1 who have recurrent disease that is not suitable for local therapy with curative intent and/or metastatic PD-L1–positive SCCHN (tumor-associated immune cell ≥ 5%), and have not received prior systemic therapy for recurrent/metastatic disease.

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

Phase:	Phase II	**Population Type:**	Adult patients
Control Method:	[redacted]	**Population Diagnosis or Condition:**	Recurrent/metastatic PD-L1–positive squamous cell carcinoma of the head and neck
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Product{s}:	Tiragolumab, atezolizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Treatment Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 120 patients

STUDY TREATMENT

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

- Arm A: atezolizumab 1200 mg IV→tiragolumab 600 mg IV
- Arm B: atezolizumab 1200 mg IV→placebo 600 mg IV

No dose modification for atezolizumab, tiragolumab, or placebo is allowed.

DURATION OF PARTICIPATION

Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. The total duration of study participation for each individual is expected to range from 1 day to more than 24 months.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first-line
2L	second-line
5-FU	fluorouracil
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ALK	anaplastic lymphoma kinase
ASTCT	American Society for Transplantation and Cellular Therapy
BICR	blinded independent central review
[redacted]	
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
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
EBNA	Epstein-Barr virus nuclear antigen
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
[redacted]	
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
[redacted]	
HR	hazard ratio

Abbreviation	Definition
IC	immune cell
ICH	International Conference for Harmonisation
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
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/web response system
MAb	monoclonal antibody
MAS	macrophage activation syndrome
MIS	Most Important Symptoms
MN	mobile nursing
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NE	not estimable
NGS	next-generation sequencing
NK	natural killer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PGI-CI	Patient Global Impression of Change and its Importance
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
[redacted]	
PROMIS®	Patient-Reported Outcomes Measurement Information System®
PVR	poliovirus receptor

Abbreviation	Definition
Q3W	every 3 weeks
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SITC	Society for Immunotherapy of Cancer
SmPC	Summary of Product Characteristics
SOC	standard of care
T3	triiodothyronine
T4	thyroxine
TC	tumor cell
TIC	tumor and immune cell
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
TTCD	time to confirmed deterioration
ULN	upper limit of normal
USPI	U.S. Package Insert
VCA	viral capsid antigen
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Head and neck cancers are a cause of significant morbidity and mortality, accounting for 890,000 new cases and 450,000 deaths globally in 2018 (Bray et al. 2018). Head and neck cancers are a heterogeneous group, comprising of cancers that begin in the mucosal surfaces of the upper aerodigestive tract and affect the oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx. The dominant histological type is squamous cell carcinoma, and accounts for over 90% of all malignant disease in the head and neck region of the body. The risk factors for squamous cell carcinoma of the head and neck (SCCHN) disease include tobacco use, alcohol consumption, and infection with human papillomavirus (HPV; Sankaranarayanan et al. 1998; Wyss et al. 2013; Vokes et al. 2015).

Historically, SCCHN has been a disease for older males with heavy lifelong tobacco use, high alcohol consumption, poor diet, and bad dentition. The effects of tobacco and alcohol, when used separately or in combination, have been shown to increase the risk for head and neck cancers (Blot et al. 1988). Long-term smoking and alcohol use is also a contributing factor in the development of second primary tumors within the head and neck region, esophagus, and lung in patients with SCCHN due to the field cancerization effect (Slaughter et al. 1953; Erkal et al. 2001). However, more patients are now being diagnosed with oropharyngeal cancers in their forties (Shiboski et al. 2005), and HPV infection, especially HPV-16, has been associated with the development of these types of cancers (Gillison et al. 2000; Mendenhall and Logan 2009). Although patients with HPV-positive SCCHN cancers tend to be younger and less likely to have a history of significant smoking and alcohol use, they have a history of multiple sexual partners and orogenital-sexual activity. HPV-associated SCCHN tumors tend to have a better prognosis and a lower rate of second primary tumors (Ang et al. 2010). Patients with head and neck cancer report significant and persistent physical (i.e., mucositis, loss of taste, and dysphagia), functional (i.e., pain, difficulty swallowing, voice impairment, and poor dental status), and psychosocial problems (Ojo et al. 2012).

Approximately one-third of patients newly diagnosed with SCCHN present with Stage I or II (early stage) disease. These patients are treated with either primary surgery or definitive radiotherapy. The 5-year overall survival (OS) rate in patients with Stage I or II disease is between 70% and 90% (Brockstein et al. 2020). Radiotherapy or surgery are equally effective treatments, and the choice of therapy is dependent upon the anatomic site, the surgical expertise, accessibility of the tumor, and the functional outcomes and morbidity associated with each modality.

The majority of patients with SCCHN present with locally advanced disease (Stage III–IVB). Although these patients are treated with multimodality definitive local therapy, locally advanced disease is associated with a high risk of local recurrence and

distant metastasis, and has a poor prognosis (median OS of approximately 20 months) (Adelstein et al. 2003). Patients who are HPV negative with Stage IVA and IVB SCCHN have a 5-year survival rate of $<25\%$ (Denis et al. 2004), and patients who are HPV positive with Stage III disease have a 5-year survival rate of 50% (Vokes et al. 2015; O'Sullivan et al. 2016).

Despite advances in diagnosis and treatment of early stage or locally advanced SCCHN, more than 65% of these patients will develop recurrent or metastatic disease (Argiris et al. 2008; Chow 2020). In addition, approximately 10% of SCCHN patients will present with metastatic SCCHN at initial diagnosis (Ridge et al. 2011; Siegel et al. 2019). For patients with locally recurrent disease, salvage surgery is curative only for select patients with resectable locoregional recurrence, and re-irradiation is often limited by prior radiotherapy history and associated toxicity and morbidity (Argiris et al. 2008; Chow 2020). As a result, for patients with recurrent or metastatic SCCHN, systemic therapy is a standard-of-care (SOC) therapy and mainstay of palliation. For these patients, the prognosis is poor with a median survival of 6–15 months in most clinical trials, depending upon patient and disease-related-factors (Clavel et al. 1994; Forastiere et al. 1998; Gibson et al. 2005; Vermorken et al. 2008; Burtness et al. 2019).

1.2 FIRST-LINE TREATMENT FOR RECURRENT/METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

1.2.1 First-Line Chemotherapy for Recurrent/Metastatic SCCHN

Platinum-based systemic chemotherapy has been considered the SOC for first-line (1L) recurrent/metastatic SCCHN for decades. The Phase III EXTREME trial established the combination of cetuximab with fluorouracil (5-FU) and platinum chemotherapy (cisplatin or carboplatin) as the SOC for 1L recurrent/metastatic SCCHN based on improvements in OS of 10.1 months compared with 7.4 months (hazard ratio [HR]: 0.80; 95% CI: 0.64 to 0.99; $p=0.04$), and progression-free survival (PFS) of 5.6 months compared with 3.3 months (HR: 0.54) when compared with 5-FU and platinum chemotherapy (Vermorken et al. 2008). Despite survival improvements, outcomes are still poor, and this regimen is associated with substantial toxicity and is generally poorly tolerated by elderly patients and/or patients with poor performance status and comorbidities. Therefore, novel systemic therapies are needed for the treatment of recurrent/metastatic SCCHN.

1.2.2 First-Line Immunotherapy for Recurrent/Metastatic SCCHN

The anti–PD-1 antibody, pembrolizumab, with or without chemotherapy, has recently emerged as a 1L treatment option for eligible patients with recurrent/metastatic SCCHN, based on results of the KEYNOTE-048 trial. This Phase III trial randomized previously untreated patients with recurrent/metastatic SCCHN to pembrolizumab alone, pembrolizumab and chemotherapy (platinum and 5-FU), or cetuximab and chemotherapy (cetuximab, platinum, 5-FU [EXTREME trial regimen]) (Burtness et al. 2019).

Anti–PD-1 and Chemotherapy for First-Line Recurrent/Metastatic SCCHN

The KEYNOTE-048 trial demonstrated a statistically significant improvement in the primary endpoint of OS in patients with a PD-L1 combined positive score (CPS) ≥1 and in the total population of patients who were treated with pembrolizumab and chemotherapy compared with patients who were treated with cetuximab and chemotherapy. In the CPS ≥1 population, the median OS was 13.6 months in the pembrolizumab and chemotherapy arm compared with 10.4 months in the cetuximab and chemotherapy arm (HR: 0.65; 95% CI: 0.53 to 0.80; $p < 0.0001$). In the total population, the median OS was 13 months in the pembrolizumab and chemotherapy arm compared with 10.7 months in the cetuximab and chemotherapy arm (HR: 0.77; 95% CI: 0.63 to 0.93; $p = 0.0034$).

There was no statistically significant improvement in PFS observed with pembrolizumab and chemotherapy compared with cetuximab and chemotherapy in both PD-L1 populations (CPS ≥ 1 [HR: 0.82; 95% CI: 0.67 to 1.00]; total population [HR: 0.92; 95% CI: 0.77 to 1.10; $p = 0.1697$]). Response rates were similar for pembrolizumab and chemotherapy compared with cetuximab and chemotherapy in all PD-L1 populations, although the median duration of response (DOR) for pembrolizumab and chemotherapy was numerically longer in the total patient population. Patients with a CPS ≥ 1 demonstrated a DOR of 6.7 months compared with 4.3 months, and the total population demonstrated a DOR of 6.7 months compared with 4.3 months.

Pembrolizumab in combination with platinum-based and 5-FU chemotherapy was approved by the U.S. Food and Drug Administration (FDA) for metastatic or unresectable, recurrent SCCHN regardless of PD-L1 status, and by the European Medicines Agency (EMA) for patients whose tumors express PD-L1 with a CPS ≥ 1 (Keytruda® U.S. Package Insert [USPI]; Keytruda® Summary of Product Characteristics [SmPC]).

Anti–PD-1 as Monotherapy for First-Line Recurrent/Metastatic SCCHN

In the KEYNOTE-048 trial, a statistically significant improvement in OS was demonstrated with pembrolizumab monotherapy compared with cetuximab and chemotherapy in the patient populations with a PD-L1 CPS ≥ 20 and CPS ≥ 1. In patients with CPS ≥ 20, OS benefit was observed with pembrolizumab monotherapy compared with cetuximab and chemotherapy with a median OS of 14.9 months compared with 10.7 months, respectively (HR: 0.61; 95% CI: 0.45 to 0.83; $p = 0.0007$). In patients with CPS ≥ 1, the median OS was 12.3 months with pembrolizumab monotherapy compared with 10.3 months with cetuximab and chemotherapy (HR: 0.78; 95% CI: 0.64 to 0.96; $p = 0.0086$). There was no statistically significant OS improvement demonstrated in the total population with a median OS of 11.6 months compared with 10.7 months (HR: 0.85, 0.71 to 1.03).

There was no improvement in PFS observed with pembrolizumab monotherapy compared with cetuximab and chemotherapy in PD-L1 populations with a CPS ≥ 20

(HR: 0.99; 95% CI: 0.75 to 1.29; p = 0.4562) and a CPS ≥ 1 (HR: 1.16; 95% CI: 0.96 to 1.39). Response rates were lower with pembrolizumab monotherapy compared with cetuximab and chemotherapy in both PD-L1 populations. Patients with a CPS ≥ 20 demonstrated a response rate of 23% compared with 36%, and patients with a CPS ≥ 1 demonstrated a response rate of 19% compared with 35%. However, responses were more durable with pembrolizumab monotherapy compared with cetuximab and chemotherapy, as demonstrated by the longer median DOR of 22.6 months compared with 4.2 months in patients with a CPS ≥ 20 who were treated with pembrolizumab and patients with a CPS ≥ 1 with a median DOR of 23.4 months compared with 4.5 months.

Based on these data, pembrolizumab as monotherapy was approved by the U.S. FDA and the EMA for the treatment of patients with 1L metastatic or unresectable, recurrent SCCHN whose tumors express PD-L1 with a CPS ≥ 1 (Keytruda® USPI; Keytruda® SmPC).

Overall, chemotherapy-free options with 1L immunotherapy offers patients with recurrent/metastatic SCCHN expressing PD-L1 OS benefit as well as a more tolerable toxicity profile. Despite improvements in OS with anti–PD-1 agents, only a subset of patients will benefit. Consequently new molecules and combinations, including novel immunotherapy combinations, are needed to address this unmet medical need.

1.3 TIGIT PATHWAY IN CANCER AS A 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 Ig super family (Yu et al. 2009; Manieri et al. 2017). TIGIT is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as the 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 and viral infections, demonstrating the role of TIGIT in inhibiting T-cell responses (Joller et al. 2011; Johnston et al. 2014). TIGIT expression is elevated 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 (TC) (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including SCCHN, and is highly correlated with T-cell infiltration and PD-1 expression (Johnston et al. 2014). Fluorescence-activated cell sorting analysis of fresh tumor samples showed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells. TIGIT expression ranges from 30% to 80% and from 50% to 80% on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, respectively (Johnston et al. 2014). TIGIT has been shown to be overexpressed on tumor-infiltrating $CD8^+$ and $CD4^+$ T cells in SCCHN mouse models, as well as SCCHN

patients. In addition, TIGIT was expressed on murine T-regulatory cells and correlated with immune suppression (Wu et al. 2019).

Therefore, TIGIT is a potential target for therapeutic intervention aimed at restoring the immune response against the tumor, including in SCCHN. Agents that inhibit the activity of TIGIT may relieve an important source of tumor-associated immune suppression and may enhance the activity of other immune-based therapies, such as atezolizumab, an inhibitor of PD-L1. Early nonclinical results using genetically deficient mice and blocking antibodies reveal a key role for TIGIT in regulating T-cell responses. Together these data support the hypothesis that anti-TIGIT in combination with anti–PD-L1 may reactivate anti-tumor immunity in SCCHN to provide clinical benefit to patients.

1.4 PD-L1/PD-1 PATHWAY IN CANCER

PD-L1 is a cell surface protein that is broadly expressed in TCs and tumor-infiltrating immune cells (ICs) in many human cancers, including lung cancer. PD-L1 binds to PD-1 and B7.1, two known inhibitory receptors whose expression on activated T-cells is sustained in states of chronic stimulation such as chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to a functional inactivation or inhibition of T cells. Aberrant expression of PD-L1 on TCs has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Inhibitors of PD-L1 and PD-1 have demonstrated clinical efficacy in a wide range of tumor types, including SCCHN. The evidenced benefit has led to approvals of anti–PD-1 antibodies (such as pembrolizumab and nivolumab) for the treatment of recurrent/metastatic SCCHN in the 1L and/or second-line (2L)-plus setting. Nevertheless, many patients with SCCHN treated with PD-L1/PD-1 blockade alone do not experience sustained clinical benefit, underscoring the need to explore cancer immunotherapy combinations with the potential to overcome intrinsic or acquired resistance to checkpoint inhibition. Antagonists that target additional inhibitory receptors have the potential to enhance such anti-tumor T-cell responses. Hence, such co-inhibitory antagonists have emerged as attractive combination partners for anti–PD-L1/PD-1 on the basis of their complementary mechanism of action.

1.5 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, TIGIT acts to limit anti-tumor immune responses in the context of the tumor microenvironment. Interference with TIGIT–PVR interaction may enhance the magnitude and quality of the

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 infiltrating T cells in several human tumors, inhibition of the TIGIT/PVR pathways may complement and potentiate the anti-tumor activity of a PD-L1 pathway inhibitor such as atezolizumab.

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 preclinical model, tumor-infiltrating T cells demonstrate increased interferon (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 treatment. Notably, co-inhibition of TIGIT and PD-L1 in this syngeneic tumor model was not associated with loss of body weight or any other observable adverse responses.

On the basis of these nonclinical studies, this study hypothesizes that the combination of anti-TIGIT antibody with anti–PD-L1/PD-1 therapy may result in activation of anti-tumor immune responses, leading to enhanced killing of TCs and improved clinical responses in patients with metastatic cervical cancer than with either agent alone.

1.6 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/monoclonal antibody (MAb) that binds TIGIT and prevents its interaction with PVR. The recombinant antibody is produced in Chinese hamster ovary 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).

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

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

1.6.1 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, and to identify a Phase Ia and Phase Ib starting dose for tiragolumab. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with tiragolumab.

The completed nonclinical pharmacology studies demonstrate that tiragolumab binds to TIGIT and prevents TIGIT–PVR interactions. Tiragolumab is a human IgG1 Mab and

therefore binds to Fc-γ receptors and is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC). However, neither complement-dependent cytotoxicity nor increased cytokine release were detected in the nonclinical models following tiragolumab treatment compared with the control-treated models. In the CT26 syngeneic colon tumor model, co-inhibition of the TIGIT/PVR and PD-L1/PD-1 pathways improves anti-tumor activity compared with inhibition of only one pathway with either monotherapy in the absence of loss of body weight or any other observable adverse responses. Taken together, the data provide a rationale for evaluating the combination of anti-TIGIT with anti–PD-L1 agents in clinical studies.

Because tiragolumab does not cross-react with rodent TIGIT, the pharmacokinetics and toxicokinetics of tiragolumab were investigated in cynomolgus monkeys. 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.

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

1.6.2 Clinical Experience with Tiragolumab

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

1.6.2.1 Ongoing Clinical Studies with Tiragolumab

Tiragolumab has been tested in Study GO30103, a first-in-human, combined Phase Ia/Phase Ib, open-label, dose-escalation, multicenter study. The study evaluated 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 portion of the study) or in combination with 1200 mg atezolizumab administered by IV infusion every 21 days (Phase Ib) to patients with locally advanced or metastatic malignancies. The

most common cancer types of patients enrolled in the study include non–small cell lung cancer (NSCLC), head and neck squamous cell carcinoma, urinary bladder cancer, and renal cell cancer. Refer to the Tiragolumab Investigator's Brochure for further details.

The combination of tiragolumab plus atezolizumab was further evaluated in patients with NSCLC in Study GO40290, an ongoing, Phase II, global randomized, double-blind, placebo-controlled study. This study was designed to evaluate the combination of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated, locally advanced, unresectable or metastatic PD–L1-selected NSCLC without epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations (tumor proportion score [TPS] $\geq$ 1%).

Safety data and efficacy data for single-agent tiragolumab from Phase I Study GO30103 and safety and efficacy data for the combination of tiragolumab and atezolizumab from Phase I Study GO30103 and Phase II Study GO40290 are summarized below.

1.6.2.2 Clinical Safety of Tiragolumab

In the Phase I study (GO30103), as of 2 December 2019, tiragolumab had been administered to 189 safety-evaluable patients in both the Phase Ia and Phase Ib portions of the study.

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

The safety profile of tiragolumab administered to patients as a single agent and in combination with atezolizumab in Study GO30103 is observed to be consistent across the different tumor indications.

Clinical Safety of Single-Agent Tiragolumab: Study GO30103

In Study GO30103, as of 2 December 2019, 42 patients had been enrolled in the Phase Ia portion. Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the adverse events observed in patients treated with single-agent tiragolumab in Study GO30103.

Clinical Safety of Tiragolumab plus Atezolizumab: Study GO30103

In Study GO30103, as of 2 December 2019, 170 patients had been enrolled in the Phase Ib portion, including 23 patients who crossed over from the Phase Ia portion following disease progression.

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 and atezolizumab across various tumor types in the Phase Ib portion of Study GO30103.

Clinical Safety of Tiragolumab plus Atezolizumab in Patients with NSCLC: Study GO40290

In the Phase II, randomized, double-blind 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%). 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).

Using a comprehensive strategy to summarize adverse events by medical concepts, immune-mediated adverse events were reported with a higher frequency in the tiragolumab plus atezolizumab arm (65.7%) compared with the placebo plus atezolizumab arm (47.1%). The difference ($\geq$10% difference between arms) was predominantly attributed to events of immune-mediated rash (preferred terms of rash, maculopapular rash, dermatitis, pruritic rash, eczema, erythema, and folliculitis) (38.8% vs. 14.7%) and infusion-related reaction (IRR; 28.4% vs. 10.3%).

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 in Study GO40290.

1.6.2.3 Clinical Activity of Tiragolumab plus Atezolizumab

Clinical Activity of Single-Agent Tiragolumab across Various Tumor Types: Study GO30103

As of the clinical cutoff date of 2 December 2019, tumor response assessment data using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) were available for 42 patients in the Phase Ia, single-agent tiragolumab portion of the study with advanced cancer in the Phase I Study GO30103.

In Phase Ia, there were no complete or partial responses (PR). A best overall response of stable disease (SD) per RECIST was observed in 8 of 42 patients with post-baseline tumor assessments at tiragolumab dose levels of 8 mg (n=1), 100 mg (n=2), 400 mg (n=4), and 1200 mg (n=1).

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the clinical activity in patients treated to date with tiragolumab as a single agent across tumor types.

Clinical Activity of Tiragolumab plus Atezolizumab across Various Tumor Types: Study GO30103

As of the clinical cutoff date of 2 December 2019, tumor response assessment data using RECIST v1.1 were available for 171 patients in Phase Ib tiragolumab plus atezolizumab portion of the study with advanced cancer in the Phase I Study GO30103.

In Phase Ib, a confirmed complete response (CR) was observed in 4 of 171 patients at tiragolumab dose levels of 400 mg (n = 3) and 600 mg (n = 1) in combination with 1200 mg atezolizumab. A PR was observed in 23 of 171 patients at tiragolumab dose levels of 30 mg (n = 2), 400 mg (n = 6), and 600 mg (n = 15) in combination with 1200 mg atezolizumab, including 2 patients who crossed over from the Phase Ia portion following disease progression at the 600 mg dose level. SD was observed in 39 of 171 patients at tiragolumab dose levels of 2 mg (n = 1), 8 mg (n = 3), 30 mg (n = 2), 100 mg (n = 3), 400 mg (n = 12), 600 mg (n = 17), and 1200 mg (n = 1) in combination with 1200 mg atezolizumab, including 8 patients who crossed over from the Phase Ia portion following disease progression.

Refer to the Tiragolumab Investigator's Brochure for further details and the most current information on the clinical activity in patients treated to date with tiragolumab plus atezolizumab across tumor types.

Clinical Activity of Tiragolumab plus Atezolizumab in Patients with NSCLC: Study GO40290

A total of 135 patients with a PD-L1 TPS ≥ 1% were included in the intent-to-treat (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 ≥ 50% relative to 57.0% of patients with a TPS 1%–49%; 59.3% of patients had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never-smokers compared with 89.6%

who had smoked. The median age of patients was 68 years in both the tiragolumab plus atezolizumab and placebo plus atezolizumab arms. Key demographic and baseline characteristics were generally balanced between treatment groups. There were more female patients (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.

As of the clinical cutoff date of 30 June 2019, the confirmed ORR in all randomized patients who received at least one dose of study treatment. Patients were grouped according to treatment received, and 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 in the placebo plus atezolizumab arm (n=29; 17.2% [95% CI: 1.8% to 32.7%]). With an additional 6 months of follow-up (clinical cutoff date of 2 December 2019), the confirmed ORR benefit was maintained in all randomized patients who received at least one dose of study treatment. Patients were grouped according to treatment received (37% in tiragolumab plus atezolizumab arm vs. 21% in the placebo plus atezolizumab arm) and in the TPS $\geq$50% population (66% in the tiragolumab plus atezolizumab arm vs. 24% in the placebo plus atezolizumab arm) (Rodriguez-Abreu et al. 2020). Responders in the tiragolumab plus atezolizumab arm included patients with both squamous and non-squamous histology.

As of the primary clinical cutoff date of 30 June 2019, the investigator-assessed PFS in all randomized patients who received at least one dose of study treatment. Patients were grouped according to treatment received and investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group compared with 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 $\geq$50%, investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group compared with 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). With an additional 6 months of follow-up (clinical cutoff date of 2 December 2019), the PFS benefit was maintained in all randomized patients who received at least one dose of study treatment. Patients were grouped according to treatment received (stratified HR=0.58; 95% CI: 0.38 to 0.89; median PFS 5.5 vs. 3.88 months) and the TPS $\geq$50% population (unstratified HR=0.30; 95% CI: 0.15 to 0.61; median PFS: NE vs. 4.11 months) (Rodriguez-Abreu et al. 2020). DOR and OS data were not yet mature as of the clinical cutoff date.

1.6.2.4 Clinical Pharmacokinetics and Immunogenicity of Tiragolumab and Atezolizumab

Clinical Pharmacokinetics and Immunogenicity of Tiragolumab

As of 2 December 2019, a preliminary PK analysis had been conducted based on available data (2−1200 mg of tiragolumab Q3W in the Phase Ia portion and 2−1200 mg

of tiragolumab Q3W in combination with 1200 mg atezolizumab Q3W in the Phase Ib portion of Study GO30103) using standard non-compartmental PK methods (refer to the Tiragolumab Investigator's Brochure for details). The pharmacokinetics of tiragolumab in combination with atezolizumab appeared to be consistent with the pharmacokinetics of tiragolumab administered as a single agent.

Preliminary population-PK analyses demonstrated that tiragolumab exposures increased dose proportionally following IV administration at doses ranging from 100 mg to 1200 mg Q3W as monotherapy or in combination with 1200 mg atezolizumab Q3W. Preliminary population-PK analysis estimated tiragolumab clearance at 0.28 L/day with a linear drug-elimination half-life of approximately 15 days.

As of December 2019, in the Phase Ia portion of GO30103, no treatment-emergent anti-drug antibodies (ADAs) against tiragolumab were detected. In the Phase Ib portion of GO30103, 3 out of 154 (1.9%) evaluable patients were positive for treatment-emergent ADAs against tiragolumab.

[redacted]

Preliminary data suggest that there was no apparent effect of tiragolumab ADAs on pharmacokinetics. However, the small number of ADA-positive patients was not adequate to assess the effect of ADAs on the pharmacokinetics of tiragolumab.

Refer to the Tiragolumab Investigator's Brochure for further details on the clinical pharmacokinetics and immunogenicity of tiragolumab.

Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

[redacted]

Refer to the Atezolizumab Investigator's Brochure for details on the clinical pharmacokinetics and immunogenicity of atezolizumab.

1.7 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 antitumor 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 cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, NSCLC, small-cell lung cancer, and 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.

1.7.1 Clinical Efficacy of Atezolizumab in SCCHN

In the Phase I PCD4989g study, 10 patients with metastatic SCCHN regardless of PD-L1 status were initially enrolled (Bahleda et al. 2017). Once PD-L1 was identified as a potential biomarker, 22 additional patients were enrolled and received atezolizumab IV Q3W (15 mg/kg or 20 mg/kg, or 1200 mg). Objective response and disease progression were determined using investigator-assessed RECIST v1.1.

With a minimum 14-month follow-up period, there were 32 efficacy-evaluable patients with SCCHN (n = 7 [IC0/1: < 5% PD-L1 expression on IC], n = 25 [IC2/3: ≥ 5% PD-L1 expression on IC]) as of 31 December 2016. Of these 32 patients, 84% were male, 66% had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 1, and 34% had an ECOG Performance Status of 0. The median age was 62 years (range: 32–78 years), patients were heavily pre-treated (53% had ≥ 2 prior lines of therapy), and 66% were current or former tobacco users. Primary tumor sites included the oropharynx (56%), oral cavity (22%), nasopharynx (13%), larynx (6%), and hypopharynx (3%). Of the 28 non-nasopharyngeal patients, 46% tested positive for HPV, 43% tested negative for HPV, and 11% had unknown HPV status (Colevas et al. 2018).

The confirmed ORR of the 32 enrolled patients was 22% (95% CI: 9.3% to 40.0%), and the median DOR was 7.4 months (95% CI: 2.8 to 45.8 months). The median PFS was 2.6 months (range: 0.5–48.4 months), and the median OS was 6.0 months (range: 0.5–51.6 months, censored value) (Colevas et al. 2018).

The encouraging response and long-term survival shown in this heavily pre-treated advanced recurrent/metastatic SCCHN cohort suggests that patients may derive clinical benefit from atezolizumab treatment.

1.7.2 Clinical Safety of Atezolizumab in SCCHN

The safety of atezolizumab monotherapy in metastatic SCCHN patients was evaluated in the Phase I PCD4989g study (Bahleda et al. 2017; Colevas et al. 2018). Of the 32 safety-evaluable SCCHN patients, 21 (66%) patients experienced a treatment-related adverse event of any grade, with the most common being fatigue (22%), rash (16%), asthenia (9%), diarrhea (9%), influenza-like illness (9%), nausea (9%), and pyrexia (9%). Serious treatment-related adverse events (Grade 3–4) were reported in 3 patients (9%) and treatment-related adverse events (Grade 3–4) were reported in 4 patients (13%). Two patients experienced a Grade 3 event of tumor lysis syndrome, and three patients experienced a Grade 3 event of pruritus, hyponatremia, and colitis, respectively. The only adverse event that led to treatment withdrawal was colitis (Grade 3). There was one Grade 4 treatment-emergent adverse event (cardiac tamponade), and no Grade 5 treatment-emergent adverse event was observed.

Based on these safety data, atezolizumab monotherapy treatment has an acceptable safety profile in the SCCHN population and is consistent with that seen in larger populations for other tumor types. No new safety findings have been observed in the SCCHN patient population in the PCD4989g study.

1.8 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.8.1 Study Rationale

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 recurrent/metastatic SCCHN. PD-1 inhibitors in the 1L (pembrolizumab) and the 2L-plus settings (pembrolizumab and nivolumab) have demonstrated improvement in survival compared with standard chemotherapy, which has led to the recent approvals of pembrolizumab and nivolumab for the treatment of SCCHN, and validates the inhibition of the PD-L1/PD-1 pathway for achieving clinical benefit in SCCHN. Furthermore, the safety profile of PD-L1/PD-1 antibodies as monotherapy appears to be more tolerable than many of the chemotherapy combinations given in the 1L setting, which are associated with substantial toxicities and are often poorly tolerated by elderly patients and patients with poor performance status.

Despite the activity in the 1L setting with pembrolizumab monotherapy in PD-L1–positive patients, durable clinical benefit is limited to a minority of patients, highlighting the need to explore novel therapies that may improve upon these outcomes. As described in Section 1.3, it is hypothesized that the combination of anti-TIGIT with anti–PD-L1/PD-1 agents may result in activation of anti-tumor immune responses, leading to enhanced killing of TCs and improved clinical responses in patients with metastatic SCCHN.

In the Phase Ib portion of Study GO30103, evaluating tiragolumab in combination with atezolizumab, PRs occurred in patients with metastatic cancers, including SCCHN, with varying degrees of PD-L1 and/or TIGIT expression. The combination of atezolizumab plus tiragolumab was well tolerated in the Phase Ib portion of the study, and the addition of tiragolumab did not alter the safety profile of atezolizumab, regardless of the tumor type. Therefore, this study is designed to evaluate the anti-tumor effects and safety of atezolizumab plus tiragolumab and atezolizumab plus placebo as 1L treatment in patients with PD-L1 positive recurrent/metastatic SCCHN. The primary efficacy endpoint of confirmed ORR in both the atezolizumab plus tiragolumab and atezolizumab plus placebo arm [redacted]

1.8.2 Benefit–Risk Assessment

This study will enroll SCCHN patients with recurrent disease not suitable for local therapy with curative intent and/or metastatic disease, and who have not received prior systemic therapy for recurrent/metastatic disease. [redacted]

To better understand the risks and benefits related to participation in this study, patients will be fully informed of the current 1L treatment options available for recurrent/ metastatic SCCHN. For all patients, combination chemotherapy often consisting of a platinum agent remains an SOC option for the 1L treatment of recurrent/metastatic SCCHN. Recently, pembrolizumab in combination with chemotherapy has been approved in the United States as a 1L treatment option for recurrent/metastatic SCCHN patients regardless of PD-L1 status, and in the European Union for patients whose tumors express PD-L1 (CPS $\geq$ 1). Pembrolizumab as monotherapy is approved in both the United States and the European Union for patients whose tumors express PD-L1 (CPS $\geq$ 1).

As a result of the available treatment options, patients will be informed that although single-agent atezolizumab is not currently approved for the 1L treatment of recurrent/ metastatic SCCHN, atezolizumab monotherapy has been evaluated in previously-treated metastatic SCCHN patients in Study PCD4989g and demonstrated evidence of clinical efficacy (Section 1.7.1). The ORR and median PFS observed with atezolizumab in the

Phase I PCD4989g study are comparable with that reported with other PD-1 inhibitors approved in the United States and the European Union in the 2L-plus recurrent/ metastatic setting (ORR: 13% to18% and median PFS: 2.0 to 2.1 months with nivolumab and pembrolizumab) (Ferris et al. 2016; Seiwert et al. 2016; Cohen et al. 2019). No new safety signals were observed in this cohort of SCCHN patients treated with atezolizumab in the PCD4989g study (Section 1.7.2).

[redacted] the combination of atezolizumab plus tiragolumab was well tolerated in both the Phase 1b (GO30103) and Phase II (GO40290) studies. Immune-mediated adverse events, although reported at a higher frequency for the atezolizumab plus tiragolumab arm in the Phase II GO40290 study, were generally mild, manageable and transient in nature (Section 1.6.2.2).

Based upon the available clinical data, 1L treatment with atezolizumab for all patients in this study offers the potential for clinical benefit in patients with PD-L1–positive recurrent/ metastatic SCCHN. Furthermore, the combination of atezolizumab plus tiragolumab may benefit patients beyond treatment with atezolizumab plus placebo. As the potential toxicities of atezolizumab plus tiragolumab or atezolizumab plus placebo do not overlap with the toxicity profile of chemotherapy, patients who do not respond to study treatment are considered likely to be able to subsequently receive standard therapies for which they would have otherwise been eligible. In totality, the overall benefit–risk ratio is considered to be appropriate for this study population because patients will be selected for enrollment based on tumor PD-L1 expression, all patients will receive treatment with atezolizumab regardless of treatment arm, and nonclinical and clinical data suggest the combination of atezolizumab plus tiragolumab may increase clinical efficacy compared with atezolizumab alone without increased toxicity.

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 (Wykes and Lewin 2018; Schorer et al. 2020) 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, the 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).

However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

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

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

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

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab plus tiragolumab and atezolizumab plus 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 plus tiragolumab and atezolizumab plus 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.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When

administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of 1L treatment with atezolizumab plus tiragolumab and atezolizumab plus placebo in patients with recurrent and/or metastatic PD-L1 positive [redacted] SCCHN. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus tiragolumab and atezolizumab plus placebo on the basis of the following endpoint:

- 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

2.1.2 Secondary Efficacy Objective

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

- 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
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
- OS, defined as the time from randomization to death from any cause
- PFS rate at 6 months
- OS rate at 6 months and 12 months
- Time to confirmed deterioration (TTCD) in patient-reported physical functioning, as measured by the Patient-Reported Outcomes Measurement Information System® (PROMIS®) Item Bank v2.0–Physical Functioning–Short Form 10b

[redacted]

- [redacted]

[redacted]

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of atezolizumab plus tiragolumab and atezolizumab plus placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)

  Severity for CRS will also be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading scale.

[redacted]

- [redacted]

2.3 PHARMACOKINETIC OBJECTIVE

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

- Serum concentrations of atezolizumab and tiragolumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

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

- Prevalence of ADAs to atezolizumab at baseline and incidence of ADAs to atezolizumab during the study
- Prevalence of ADAs to tiragolumab at baseline and incidence of ADAs to tiragolumab during the study

[redacted]

- [redacted]

[redacted]

- [redacted]

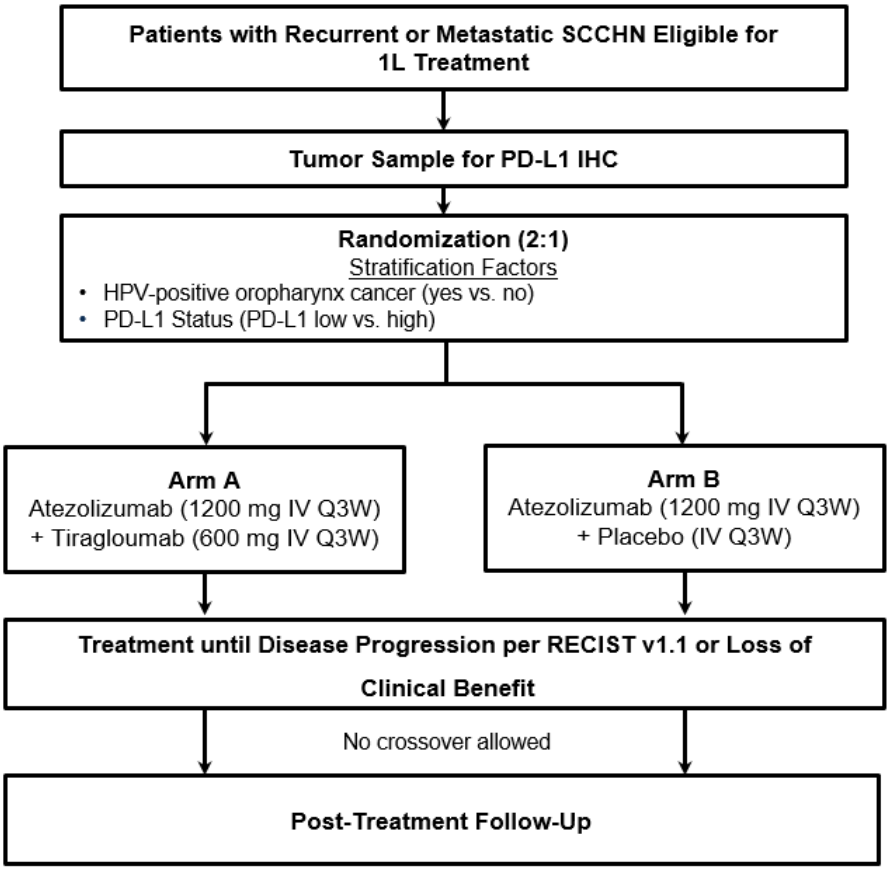
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, randomized, double-blind, global study designed to evaluate the efficacy and safety of atezolizumab plus tiragolumab and atezolizumab plus placebo as 1L treatment in recurrent/metastatic PD-L1–positive SCCHN.

Figure 1 presents an overview of the study design. A schedule of assessments is provided in Appendix 1. The schedule of patient-report outcomes (PROs) is presented in Appendix 2, and the PK, immunogenicity, [redacted]

Figure 1 Study Schema



1L = first-line; HPV = human papillomavirus; IHC = immunohistochemistry; IV = intravenous; Q3W = every 3 weeks; [redacted] SCCHN = squamous cell carcinoma of head and neck; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Male and female patients age ≥ 18 years with ECOG Performance Status of 0 or 1 who have recurrent disease that is not suitable for local therapy with curative intent and/or metastatic PD-L1–positive SCCHN [redacted], and have not received prior systemic therapy for recurrent/metastatic disease are eligible.

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities in Appendix 1. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) 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 4.1.1 and Section 4.1.2. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

During screening, tumor specimens from each potentially eligible patient will be prospectively tested for PD-L1 expression, [redacted] Only patients who are PD-L1 positive with a [redacted] assessed centrally will be eligible. [redacted]

Eligible patients will be stratified by HPV status for oropharynx cancer (HPV-positive oropharynx cancer: yes vs. no) and PD-L1 status (PD-L1: low vs. high). [redacted]

Eligible patients will be randomized in a 2:1 ratio to receive either atezolizumab plus tiragolumab (Arm A) or atezolizumab plus placebo (Arm B).

- **Arm A**: Patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered to patients by IV infusion Q3W on Day 1 of each 21-day cycle.
- **Arm B**: Patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by placebo administered by IV infusion Q3W on Day 1 of each 21-day cycle.

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 or radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for disease progression per RECIST v1.1, but continue to have clinical benefit, will be permitted to continue treatment (atezolizumab plus tiragolumab or atezolizumab plus placebo) if they meet all of the criteria specified in Section 3.1.1 and provide written consent.

Patients will undergo tumor assessments at baseline, every 6 weeks (± 7 days) for the first 30 weeks following Day 1 of Cycle 1, and every 9 weeks (± 7 days) after completion of the Week 30 tumor assessment. Tumor assessments will continue per schedule regardless of treatment delays until radiographic disease progression per RECIST v1.1 or loss of clinical benefit for patients who continue study treatment after radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, scans must be performed at any time if progressive disease or loss of clinical benefit is suspected. Radiographic images will be submitted to an independent review facility

(IRF) for a quality and completeness check, for potential blinded independent central review (BICR), and for temporary storage prior to transferring images to the Sponsor for the long-term retention and eventual secondary or exploratory use.

Patients who discontinue study treatment (for any reason, including, but not limited to, clinical decline or toxicity) in the absence of radiographic disease progression per RECIST v1.1 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 the Sponsor, whichever occurs first, regardless of whether a patient starts a new anti-cancer therapy.

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (Appendix 4).

In order not to confound the OS endpoint, crossover will not be allowed from Arm B (atezolizumab plus placebo) to Arm A (atezolizumab plus tiragolumab).

Patients will be asked to complete PRO questionnaires during the study treatment and at the study treatment discontinuation visit (see Appendix 2 for PRO schedule).

Serum samples will be collected to monitor atezolizumab and tiragolumab PK and to detect the presence of antibodies to atezolizumab and tiragolumab. [redacted]

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.

After study treatment discontinuation, survival follow-up information will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first (see Section 4.6.1). All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from survival follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from survival follow-up, study staff may use a public information source (e.g., county records) to obtain information about survival status.

3.1.1 Treatment after Disease Progression

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

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of 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 only on RECIST v1.1.

3.1.2 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will evaluate safety data analysis. The IMC Chair will be a medical oncologist who is not the Medical Monitor and is not associated with the study. Other IMC members may include, but are not limited to, a drug safety scientist, biostatistician, biomarker scientist, and clinical pharmacologist.

The IMC will review the safety data approximately every 6 months or more frequently if recommended by the IMC Chair or the Medical Monitor. The safety data may include, but is not limited to, demographic data, adverse event data (including serious adverse events and adverse events of special interest), study conduct data, and relevant laboratory data.

The responsibility, membership, and communication flow of the IMC is further described in the IMC Charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs, which is expected to occur approximately 24 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 43 months.

3.3 *DURATION OF PARTICIPATION*

Treatment will continue until disease progression per RECIST v1.1. The total duration of study participation for each individual is expected to range from 1 day to more than 24 months.

3.4 RATIONALE FOR STUDY DESIGN

[redacted]

3.4.3 Rationale for Patient Population

Despite recent improvements in treatment for recurrent/metastatic SCCHN, the prognosis for these patients remains poor, with a median OS of approximately 6 to 15 months reported in clinical trials (Clavel et al. 1994; Forastiere et al. 1998; Gibson et al. 2005; Vermorken et al. 2008; Burtness et al. 2019). Historically, platinum-based chemotherapy combinations have been the SOC for 1L treatment of recurrent/ metastatic SCCHN; however, these regimens are associated with significant toxicity and the duration of benefit is limited (Vermorken et al. 2008).

Recently, pembrolizumab monotherapy was approved in both the United States and the European Union as a 1L treatment option for recurrent/metastatic SCCHN patients

whose tumors express PD-L1 (CPS ≥ 1). This approval was based on the Phase III KEYNOTE-048 trial that demonstrated significant improvement in OS with pembrolizumab monotherapy compared with platinum-based chemotherapy and cetuximab in PD-L1–positive (CPS ≥ 1) patients (Burtness et al. 2019) (Section 1.2.2). Despite the activity of pembrolizumab monotherapy in the 1L setting, durable clinical benefit is limited to a minority of patients.

TIGIT is a novel immune checkpoint inhibitor that is often co-expressed with PD-L1 on tumor-infiltrating lymphocytes. In nonclinical models, combined blockade of both TIGIT and PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent treatments. [redacted]

On the basis of these results, this study will enroll SCCHN patients with recurrent disease not suitable for local therapy with curative intent and/ or metastatic disease, and who have not received prior systemic therapy for recurrent/metastatic disease, and whose tumors are PD-L1 positive [redacted] as determined [redacted] to receive 1L treatment with either atezolizumab plus tiragolumab or atezolizumab plus placebo.

[redacted]

[redacted]

3.4.5 Rationale for Atezolizumab Plus Placebo Arm

For the reasons described in Sections 1.8.2 and Section 3.4.3, patients with PD-L1 positive recurrent/metastatic SCCHN will be enrolled in this Phase II study. All patients, regardless of treatment arm, will receive atezolizumab.

As described in Section 1.8.2, all patients will be fully informed of their available treatment options. Although atezolizumab is not currently approved for the 1L treatment of recurrent/metastatic SCCHN, efficacy and safety of atezolizumab monotherapy in previously treated metastatic SCCHN patients was evaluated in the Phase I PCD4989g study (n = 32; of whom 53% had ≥ 2 prior lines of therapy). In this heavily pre-treated patient population, the confirmed ORR was 22% (95% CI: 9.3% to 40.0%), and the median DOR was 7.4 months (95% CI: 2.8 to 45.8 months). Additional efficacy results from PCD4989g are described in Section 1.7.1. Of note, the ORR and median PFS observed with atezolizumab in SCCHN patients in Study PCD4989g is comparable with that reported with other PD-1 inhibitors approved in the United States and the European Union for 2L-plus recurrent/metastatic SCCHN (Section 1.8.2). There were no new safety signals observed with atezolizumab treatment in this cohort of SCCHN patients (Section 1.7.2).

On the basis of these results, patients with recurrent/metastatic SCCHN randomized to Arm B will receive atezolizumab plus placebo. This group will be critical to informing the [redacted]

This study is double-blind and will administer placebo that is identical in appearance to tiragolumab. The placebo will be comprised of the same excipients but without the respective tiragolumab drug substance. Utilization of placebo will minimize potential biases in patient care, disease assessment, adverse event reporting, or additional testing.

3.4.6 Rationale for Stratification

In order to balance disease-related risk factors between the two treatment arms, randomization will be stratified. The stratification factors are as follows:

- HPV-positive oropharynx cancer: yes vs. no
- PD-L1 status: PD-L1 low vs. PD-L1 high

The chosen stratification factors are important prognostic and/or predictive factors for patients with SCCHN and are proposed to be included for the following reasons:

- HPV status is a prognostic indicator and patients with HPV-positive oropharyngeal carcinoma have a better prognosis (Fakhry et al. 2014; Vokes et al. 2015; O'Sullivan et al. 2016). Therefore, HPV status for oropharyngeal cancer has been included as a stratification to control for any impact on outcome.
- PD-L1 status has been shown to predict OS benefit with anti–PD-1 monotherapy in the 1L recurrent/metastatic setting. In the KEYNOTE-048 study, there was enrichment of OS benefit with pembrolizumab monotherapy observed in patients with PD-L1 CPS $\geq$20 (Burtness et al. 2019). PD-L1 status will be included as a stratification factor to ensure balance across treatment arms.

3.4.7 Rationale for Treatment Beyond Initial Radiographic Progression

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic

evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression and/or tumor immune infiltration, this study will allow randomized patients to receive either atezolizumab plus tiragolumab or atezolizumab plus placebo after apparent radiographic progression, provided the benefit–risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the investigator, after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see Section 3.1.1).

[redacted]

[redacted]

[redacted].

3.4.9 Rationale for Patient-Reported Outcome Assessments

Head and neck malignancies and their treatments affect a variety of body functions, and patients often report changes in breathing, swallowing, and speaking. As all of these functions are highly relevant for survival and/or social life, head and neck cancer can cause significant physical, emotional, and social problems, considerably reducing a patient's quality of life.

PROs are an important tool that help inform clinicians about the patient's perspective on their disease and treatment that may not be adequately captured by clinical measurements alone. In this study, the National Institutes of Health-funded PROMIS® will be utilized. PROMIS® has been developed with input from patients (DeWalt et al. 2007; Garcia et al. 2007), created and validated using advanced psychometrics methods (i.e., item-response theory) leading to short PROs with good measurement properties (Atkinson et al. 2017), and are unidimensional (only measures one latent variable) and do not require the removal of a subscale from a multidimensional questionnaire. The PROMIS® system exists as an item bank used for computer adaptive testing and as a fixed short-form; only the short-form will be used in this study, as it allows the same set of questions to be asked over time.

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting adverse event information directly from patients can provide a better understanding of treatment characteristics and their effects. [redacted] These symptoms were identified as being salient to patients' experience with atezolizumab plus tiragolumab on the basis of the recent work to identify common adverse events associated with immunotherapies (Hansen et al. 2020). Supplemental recommendations on which symptoms to measure in head and neck cancer were considered (Cella et al. 2011; Chera et al. 2014).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 120 patients with PD-L1–positive recurrent/metastatic SCCHN eligible for 1L treatment will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Histologically or cytologically confirmed recurrent/metastatic SCCHN involving the oropharynx, oral cavity, larynx, or hypopharynx, that is considered incurable by local therapies
- Known results from HPV status test for oropharyngeal carcinoma
- No prior systemic therapy for metastatic and/or recurrent SCCHN
- Measurable disease per RECIST v1.1
- Tumor PD-L1 expression with a
- ECOG Performance Status of 0 or 1

- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9 g/dL)
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:
  - Creatinine $\leq 1.5 \times$ ULN or creatinine clearance (measured or calculated by Cockcroft-Gault formula or per institutional guidelines) ≥ 50 mL/min
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulant
-
-
-
  -
  -
-

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 5 months after the final dose of atezolizumab and for 90 days after the final dose of tiragolumab/placebo.

  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.

- 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 or pregnant female partner, men must remain abstinent or use a condom during treatment with tiragolumab/placebo and for 90 days after the final dose of tiragolumab/placebo to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

4.1.2 Exclusion Criteria

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

- Disease suitable for local therapy with curative intent

- Progressive or recurrent disease within 6 months of the last dose of curative intent systemic treatment for locally advanced SCCHN
- Rapidly progressing disease in the opinion of the treating investigator
- Grade ≥2 unresolved toxicity related to surgery or other prior therapies

[redacted]

- Symptomatic, untreated, or actively progressing CNS metastases

[redacted]

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

- History of leptomeningeal disease
- Uncontrolled tumor-related pain

[redacted]

- Uncontrolled or symptomatic hypercalcemia

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 14 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  [redacted]

  – [redacted]

  – [redacted]

  – [redacted]

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

  [redacted]

- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, planned, or anticipated need for a major surgical procedure during the study
- History of additional malignancy other than SCCHN within 5 years prior to randomization, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>$90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia

- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  [redacted]

- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment, within 5 months after the final dose of atezolizumab, or within 90 days after the final dose of tiragolumab/placebo.
- [redacted]
- [redacted]

  [redacted]

- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti-TIGIT, anti–PD-L1, and anti–PD-1 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 initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - [redacted]
  - [redacted]

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or tiragolumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment, within 5 months after the final dose of atezolizumab, or within 90 days after the final dose of tiragolumab/placebo.

[redacted]

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established (including determination of tumor PD-L1 status by central testing), the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: atezolizumab plus tiragolumab (Arm A) or atezolizumab plus placebo (Arm B). Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- HPV-positive oropharynx cancer (yes vs. no)
- PD-L1 status (PD-L1: low vs. high)
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study.

While PK and immunogenicity samples must be collected from patients assigned to the both treatment arms (Arms A and B) to maintain the blinding of treatment assignment,

PK and ADA assay results of tiragolumab/placebo for patients assigned to atezolizumab plus placebo arm (Arm B) are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the atezolizumab plus placebo arm (Arm B) will not be analyzed for tiragolumab PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Post-baseline immunogenicity samples from patients assigned to the atezolizumab plus placebo arm (Arm B) will not be analyzed for tiragolumab ADAs 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 investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

Unblinding will not be permitted if an investigator is deciding whether a patient should initiate subsequent treatment with a non–health authority-approved therapy for that indication. Unblinding may be permitted if an investigator is deciding whether a patient should initiate subsequent treatment with a health authority-approved therapy for that indication. In the event that these criteria for non-emergency unblinding are met and 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. 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 study drug. The patient may continue to receive treatment, and the investigator and patient will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are atezolizumab, tiragolumab, and placebo. *Appendix 17 identifies all IMPs, auxiliary medicinal products, and non-IMPs for this study.*

All patients will receive atezolizumab in combination with either tiragolumab or with placebo.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Atezolizumab

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

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

4.3.1.2 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 further information on the formulation and handling of tiragolumab and placebo, refer to the pharmacy manual and/or the Tiragolumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

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

- Arm A: atezolizumab 1200 mg IV →tiragolumab 600 mg IV
- Arm B: atezolizumab 1200 mg IV→placebo 600 mg IV

For Cycle 1, premedication administered for atezolizumab and tiragolumab/placebo is not permitted.

Administration of atezolizumab and tiragolumab/placebo will be performed in a monitored setting where there is immediate access to trained personnel, adequate equipment, and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 15. Guidelines for medical management of IRRs are provided in Appendix 16.

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

Atezolizumab (1200 mg) and tiragolumab/placebo (600 mg) will be administered at a fixed dose. Details on treatment administration (e.g., date of administration and infusion start and stop time) 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.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4 and Appendix 16.

4.3.2.1 Atezolizumab

All patients will receive 1200 mg atezolizumab administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.1). The atezolizumab dose is fixed and is not dependent on body weight.

Atezolizumab infusions will be administered per the instructions outlined Table 1.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 4.6.1, Section 5.1.4, and Appendix 16.

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

Table 1 Administration of First and Subsequent Atezolizumab Infusions

	Day 1, Cycle 1 Infusion	Day 1 Infusion of Subsequent Cycles
Atezolizumab infusion	• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion.	• If the patient experienced an IRR with any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic medications may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • 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 recorded during the infusion.
Observation period after atezolizumab infusion	• After the infusion of atezolizumab, the patient begins a 60-minute observation period. • Vital signs should be recorded at 30 (± 10) minutes after the infusion of atezolizumab. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous atezolizumab infusion well without infusion-associated adverse events, the observation period after the next and following infusions may be reduced to 30 minutes. • If the patient experienced infusion-associated adverse events in the previous infusion, the observation period should be 60 minutes. • If clinically indicated, vital signs should be recorded at 30 (± 10) minutes after the infusion of atezolizumab.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs are provided in the Appendix 16.

4.3.2.2 Tiragolumab/Placebo

Following the administration of atezolizumab and an observation period (see Table 1), patients will receive 600 mg tiragolumab/placebo administered by IV infusion on Day 1 of each 21-day cycle (see Section 3.1). 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 Section 4.6.1, Section 5.1.4, and Appendix 16.

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

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

	Day 1, Cycle 1 Infusion	Day 1 Infusion of Subsequent Cycles
Infusion of tiragolumab/ placebo	• No premedication is permitted prior to the tiragolumab/ placebo infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within [redacted] minutes prior to the infusion. • Tiragolumab/placebo should be infused over [redacted] minutes. • Vital signs should be recorded 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 doses, at the discretion of the investigator. • Vital signs should be recorded within [redacted] minutes prior to the tiragolumab/placebo infusion. • Tiragolumab/placebo should be infused over [redacted] minutes if the previous infusion was tolerated without an infusion-related reaction, or [redacted] minutes if the patient experienced an infusion-related reaction with the previous infusion. • Vital signs should be recorded during the infusion if clinically indicated.
Observation period after infusion of tiragolumab/ placebo	• After the infusion of tiragolumab/placebo, the patient begins a [redacted] minute observation period. • Vital signs should be recorded at [redacted] minutes after the infusion of tiragolumab. • 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 infusion-associated adverse events, the observation period may be reduced to [redacted] minutes. • If the patient experienced an infusion-associated adverse event in the previous infusion, the observation period should be [redacted] minutes. • If clinically indicated, vital signs should be recorded at [redacted] minutes after the infusion of tiragolumab/placebo. • 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.

IRR = infusion-related reaction.

Guidelines for medical management of IRRs are provided in Appendix 16.

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]
- [redacted]

Guidelines for treatment interruption or discontinuation are provided in Section 5.1.4.2 and Appendix 16.

4.3.3 Investigational Medicinal Product Handling and Accountability

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

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, 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.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Atezolizumab and Tiragolumab

Patients may be eligible to receive atezolizumab and/or tiragolumab as part of a post-trial access program or an extension study. 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 in addition to protocol-mandated treatment 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]

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 15).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to Appendix 16 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]

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

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1, Appendix 2, and Appendix 3. 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.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The Sponsor will define the assessments eligible for MN and select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional, but will not include study drug infusions, which must be performed at this study site.

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.

[redacted]

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

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 a consent form at that time to acknowledge deferring 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 medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

4.5.3 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status Scale (see Appendix 5) at the timepoints specified in the schedule of activities in Appendix 1.

4.5.4 Physical Examinations

A complete physical examination must be performed at screening, and 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 (see Appendix 1). 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.

4.5.5 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 1 and Table 2 for details on the measurements of vital signs during study treatment.

4.5.6 Tumor and Response Evaluations

Screening assessments and subsequent tumor assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or magnetic resonance imaging (MRI) (with contrast) of the head and neck (base of skull to clavicle). A CT scan with contrast of the pelvis should be performed as clinically indicated or as per local SOC at screening and subsequent response evaluations. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed, and MRI scans with contrast of the head and neck, abdomen, and pelvis (as applicable) must be performed. Further investigations, such as bone scans should also be performed if clinically indicated at baseline and at subsequent response evaluations.

A CT scan with contrast or MRI scan with contrast (if CT with contrast is contraindicated) of the brain should be done as clinically indicated to evaluate CNS metastasis at screening and at subsequent response evaluations. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2). Patients with a history of irradiated brain metastasis at screening are not required to undergo brain scans at subsequent response evaluations unless clinically indicated.

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

Tumor assessments performed as SOC prior to obtaining informed consent may be used rather than repeating tests, provided the scans are of diagnostic quality and are performed within 28 days of randomization.

The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used at screening must be used for all subsequent tumor assessments. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation.

Patients will undergo tumor assessments at baseline, every 6 weeks (± 7 days) for the first 30 weeks following Day 1 of Cycle 1, and every 9 weeks (± 7 days) after completion of the Week 30 tumor assessment. Tumor assessments will continue per schedule regardless of treatment delays until radiographic disease progression per RECIST v1.1 or loss of clinical benefit for patients who continue study treatment after radiographic

disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, scans must also be performed at any time if progressive disease or loss of clinical benefit is suspected.

Patients who discontinue study treatment (for any reason, including, but not limited to clinical decline or toxicity) in the absence of radiographic disease progression per RECIST v.1.1 will continue to undergo tumor response assessments per the schedule described above, regardless of whether a new anti-cancer therapy is started. Tumor assessments will continue until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first

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 only be based on RECIST v1.1. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

Investigator assessment of overall tumor response at all timepoints will be only based on RECIST v1.1. 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, and evaluation of any newly identified lesions 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: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- [redacted]

  - [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- For patients with SCCHN involving the oropharynx: HPV status of tumor tissue [redacted]
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. During study treatment urine pregnancy tests will be performed on Day 1 of every cycle. Urine pregnancy test will also be performed at the treatment discontinuation visit. 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 (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

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

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody
- Serum sample for C-reactive protein
- Serum samples for atezolizumab and tiragolumab PK analysis through use of a validated assay

- Serum samples for assessment of ADAs to atezolizumab and tiragolumab through use of a validated assay
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11.1), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- [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, [redacted], will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of [redacted] analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine, which is only applicable to biopsies obtained at disease progression). The

aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

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

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

4.5.9 Clinical Outcome Assessments

PRO instruments will be completed to more fully characterize the clinical profile of atezolizumab plus tiragolumab and atezolizumab plus placebo. In addition, PRO instruments will enable the capture of each patient's direct experience with atezolizumab plus tiragolumab and atezolizumab plus placebo.

PRO data will be collected through use of the following instruments:

- PROMIS® Item Bank v2.0–Physical Functioning–Short Form 10b
- [redacted]
- [redacted]
- [redacted]
- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change and its Importance (PGI-CI)
- Most Important Symptoms (MIS)
- [redacted]

PRO questionnaires (i.e., PROMIS®, PGI-S/PGI-CI, MIS, and [redacted]) will be completed during treatment and at the treatment discontinuation visit, refer to Appendix 2 for schedule of PRO assessments.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments used to characterize the clinical profile of atezolizumab plus tiragolumab and atezolizumab plus placebo will be self-administered or interviewer-administered (as appropriate) at the clinic at specified timepoints during the study (see schedule of PRO assessments in Appendix 2). PRO data will be obtained through use of PROMIS®, PGI-S/PGI-CI, MIS, and [redacted] questionnaires.

At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Paper PRO questionnaires, translated into the local language as appropriate, scheduled for administration during a clinic visit must be completed by the patient at the investigational site at the start of the clinic visit prior to other study assessments and before administration of study treatment to avoid as much as possible, any assessment bias. Patients will complete paper versions of the questionnaires, which will be provided by site staff. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to complete the measures on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 15 minutes on Day 1 of Cycles 1 and 2, and less than 10 minutes for each subsequent cycle.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

PROMIS® Item Bank v2.0–Physical Functioning–Short Form 10b,

PROMIS® Item Bank v2.0–Physical Functioning–Short Form 10b consists of 10 questions designed to measure self-reported capability of physical activities including the functioning of upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living

(see Appendix 6). All questions are scored on a 1–5 scale, with a score of 5 equating to the patient's highest ability to function and a score of 1 equating to the patient's lowest ability to function. The recall period is 7 days.

Patient Global Impression of Severity (PGI-S)

The Patient Global Impression of Severity (PGI-S) is a one-item, self-reported measure used to assess the patient's impression about the severity of his or her overall condition during the preceding 7 days (see Appendix 10). The PGI-S utilizes a 5-point response scale, with a score of 5 equating to "very severe" and the score of 1 equating to "none" (adapted from Guy et al. 1976).

Patient Global Impression of Change and Its Importance (PGI-CI)

The Patient Global Impression of Change is a one-item, self-reported measure used to assess the patient's impression about changes to their condition compared with when they began the study (see Appendix 11). It utilizes a 7-point response scale, with a score of 7 equating to "very much worse" and a score of 1 equating to "very much improved" (adapted from Guy et al. 1976). In a subsequent question to the Patient Global Impression of Change, the patient is asked to indicate if the change experienced was important to them, the response options are "yes," "no," or "not applicable," if the patient did not experience any change.

Most Important Symptoms (MIS)

The purpose of the MIS questionnaire is to identify which symptoms have been most troublesome to the patient in the past 7 days. The MIS is based on the importance rating scale from the University of Washington Quality of Life Questionnaire Scale 2.0 and later, with the addition of a number of symptoms related to the disease and/or treatment (Rogers et al. 2002). Patients are asked to pick up to 4 symptoms that have been the most troublesome in the past week (see Appendix 12).

[redacted]

[redacted]

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

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants specifically occurred in tumors that are predictive of response to study drug, are associated with progression to a more severe disease state. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.10) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS 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.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

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

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

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not

been granted approval for RBR sampling, this section of the protocol (Section 4.5.11.2) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to atezolizumab, tiragolumab, head and neck cancer, or drug safety:

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

The samples above may be sent to one or more laboratories for analysis of microbial communities through whole metagenomic sequencing, microbial culture, germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome 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.

RBR 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).

4.5.11.4 Confidentiality

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

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

Given the complexity and exploratory nature of the analyses of RBR 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.

4.5.11.5 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.

4.5.11.6 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.

4.5.11.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Radiographic disease progression per RECIST v1.1

  Exception: Patients will be permitted to continue study treatment after RECIST v1.1 criteria for progressive disease are met, if they meet all of the criteria outlined in Section 3.1.1 for treatment beyond radiographic progression.
- For patient treated beyond radiographic progression per RECIST v1.1: loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see Section 3.1.1 for details)

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 ≤[redacted] days after the final dose of study treatment (see Appendix 1). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit, in which case all assessments associated with the treatment discontinuation visit should be performed at that time.

If a patient is discontinued from study treatment because of an adverse event (including adverse events of special interest; see Section 5.2.3) considered to be related to study treatment and the event is ongoing [redacted] days after the final dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

See the schedule of activities provided in Appendix 1, Appendix 2, and Appendix 3 for the respective assessments to be performed at the treatment discontinuation visit.

4.6.1.1 Follow-up Assessments

After treatment discontinuation all patients will continue in follow-up as outlined in the schedule of activities (Appendix 1).

Tumor Assessments

Patients who discontinue study treatment (for any reason, including, but not limited to clinical decline or toxicity) in the absence of radiographic disease progression per RECIST v.1.1 must continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1), regardless of whether a patient starts a new anti-cancer therapy, until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, scans must be performed at any time if progressive disease is suspected.

Survival and Subsequent Therapies

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent for survival follow-up or the Sponsor terminates the study) (see Appendix 1). Information on subsequent anti-cancer therapies will include systemic therapies (e.g., chemotherapy, targeted therapy, immunotherapy), surgery (e.g., resection of local and/or metastatic disease), and radiation procedures (e.g., radiotherapy to a tumor lesion).

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 (i.e., requests to withdrawn from all survival follow-up), this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study (i.e., survival follow-up) will not be replaced.

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on 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. The anticipated important safety risks for atezolizumab, tiragolumab, and atezolizumab in combination with tiragolumab are outlined below (see Sections 5.1.1, 5.1.2, and 5.1.3, respectively). Refer to the Atezolizumab Investigator's Brochure and the Tiragolumab 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. Administration of atezolizumab and tiragolumab/placebo 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 16. Refer to Sections 5.4–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

An IMC will periodically review safety data during the study (see Section 3.1.2).

In general, patients with active infection are excluded from study participation (see Section 4.1.2). In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with 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 16 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Risks Associated with Tiragolumab

[redacted]. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 16 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks for tiragolumab.

5.1.2.1 Infusion-Related Reactions

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

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

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab/placebo will be administered over [redacted] minutes followed by a [redacted] minute observation period, and subsequent infusions as well as observation times may be shortened only if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Refer to Sections 4.3.2.1 and 4.3.2.2 for detailed guidance on administration of atezolizumab and tiragolumab/placebo in this study. Refer to Appendix 15 for guidance on anaphylaxis precautions, and see Appendix 16 for guidance on management of IRRs and risks associated with tiragolumab.

[redacted]

[redacted]

5.1.2.3 Lymphopenia

[redacted]

[redacted]

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

5.1.2.4 Immune-Mediated Adverse Events

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

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

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

Management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 16.

5.1.2.5 Embryofetal Toxicity

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

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

5.1.3 Risks Associated with the Combination of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential 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. Based on the mechanism of action of tiragolumab and atezolizumab, additional immune-mediated adverse events are potential overlapping toxicities associated with combination use of tiragolumab plus atezolizumab.

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section 5.1) in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section 4.1.2). Patients previously treated with approved or experimental cancer immune therapies will also be excluded from participation in this study. [redacted]

5.1.4 Management of Adverse Events

5.1.4.1 Dose Modifications

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

5.1.4.2 Treatment Interruptions

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

[redacted]

[redacted]

Dose interruptions may be allowed for reason(s) other than toxicity, such as surgical procedures. The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

After both study treatments have been discontinued, the patient will be monitored for safety and efficacy as defined in Section 4.6.1.

5.1.4.3 Management Guidelines for Atezolizumab and Tiragolumab-Specific Adverse Events

General guidelines for management of patients who experience adverse events, including HLH and macrophage activation syndrome (MAS), are described in Appendix 16. Guidelines for management of patients who experience adverse events associated with atezolizumab and/or tiragolumab, including immune-mediated adverse events, are provided in Appendix 16.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 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). Adverse events of special interest for this study are as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [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 [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 [d]
5	Death related to adverse event [d]

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

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

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

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

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

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

The ASTCT CRS consensus grading scale (see Table 4) should be used in addition to NCI CTCAE when reporting severity of CRS (see Section 5.3.5.1 for details on CRS reporting).

Table 4 ASTCT CRS Consensus Grading Scale

Grade	Symptoms
1	• Fever [a] with or without constitutional symptoms (such as myalgia, arthralgia, or malaise) • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low-flow oxygen [b] by nasal cannula or blow-by
3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor [c] – Hypoxia requiring high-flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring two or more vasopressors [c] – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)
5	• Death due to CRS in which another cause is not the principal factor leading to this outcome

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

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

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

[c] Vasopressin should not be taken into consideration when determining number of vasopressors.

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.

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

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

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine release syndrome" on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the

dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF, as appropriate.

If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF.

NCI CTCAE v5.0 and the ASTCT CRS consensus grading scale (see Section 5.3.3) should be used when reporting severity of CRS on the Adverse Event eCRF.
NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

Guidelines for medical management of IRR and CRS are provided in Appendix 16 (Table 7 and Table 8, respectively).

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:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

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

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/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 atezolizumab and tiragolumab/placebo, 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] or other PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of

treatment-related symptoms [redacted] with investigator reports of adverse events. Sites are not expected to review the [redacted] or other 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 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitor is available 24 hours per day, 7 days per week. Details will be provided separately. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur prior to Study 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 Serious Adverse Event/Special Situation Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and 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 [redacted] days after the final dose of study treatment [redacted] In addition, adverse events of special interest will be reported until [redacted] days after the final dose of study treatment, regardless of [redacted] Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Special Situation Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and 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 study treatment or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab/placebo. 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 treatment with tiragolumab/placebo or within 90 days after the final dose of tiragolumab/placebo. 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 and adverse events of special interest (reporting periods defined in Section 5.3.1) all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study 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 Serious Adverse Event/ Special Situation Reporting 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 IMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase II, randomized, double-blind study designed to evaluate the efficacy and safety of atezolizumab plus tiragolumab and atezolizumab plus placebo in approximately 120 patients with metastatic and/or recurrent PD-L1–positive SCCHN.

The analysis of confirmed ORR, PFS, OS, and TTCD will be performed on all randomized patients who receive at least one dose of study treatment. Patients will be grouped based on actual treatment received. DOR will be assessed in patients who have a confirmed objective response.

Safety analyses will be conducted on all randomized patients who receive 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 atezolizumab plus tiragolumab arm in the safety analyses if the patient receives any amount of tiragolumab, regardless of the initial treatment assignment at randomization.

6.1 DETERMINATION OF SAMPLE SIZE

A total of 120 patients will be enrolled in this study and randomized in a 2:1 ratio (atezolizumab plus tiragolumab and atezolizumab plus placebo). [redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

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

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of any component of study drug, unless otherwise noted.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is confirmed ORR. 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 who do not meet these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders. Confirmed ORR is defined as the proportion of patients who had a confirmed objective response.

The primary efficacy analysis will take place once all patients have been enrolled and a [redacted]

The analysis population for the efficacy analyses will consist of all randomized patients who receive at least one dose of study treatment. Patients will be grouped based on actual treatment received. An estimate of the confirmed ORR and its 95% CI will be calculated using the Wilson score method for each treatment arm.

A sensitivity analysis will be performed for the primary endpoint of confirmed ORR on all randomized patients grouped according to their assigned treatment.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Duration of Response

DOR will be assessed in patients who have achieved a confirmed objective response, as determined by the investigator according to RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a confirmed objective response until the first date of progressive disease, as determined by the investigator according to RECIST v1.1, or death from any cause, 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 the last tumor assessment date. Kaplan-Meier methodology will be used to estimate the median DOR for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DOR for each treatment arm (Brookmeyer and Crowley 1982).

6.4.2.2 Progression-Free Survival, Including Progression-Free Survival Rate at 6 Months

PFS 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 or have not died by the data cutoff date will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982). The PFS rates at 6 months 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.

6.4.2.3 Overall Survival, Including Overall Survival Rate at 6 Months and 12 Months

OS 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 post-baseline information will be censored at the date of randomization.

OS and OS rate at 6 months and 12 months will be analyzed using the same methods as described in Section 6.4.2.2.

6.4.2.4 Patient-Reported Outcomes

TTCD for physical functioning using the PROMIS® Item Bank v2.0–Physical Functioning–Short Form 10b is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration. Confirmed clinically meaningful deterioration in physical function is defined as a clinically meaningful decrease from baseline that must be held for at least two consecutive assessments, or an initial clinically meaningful decrease from baseline followed by death. A T-score change >4 points is considered to be clinically meaningful for the physical functioning subscale score (Yost et al. 2011).

TTCD will be assessed in all randomized patients who received at least one dose of study treatment. Patients will be grouped based on actual treatment received. Patients who have not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date will be censored at the last time when they completed an assessment. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. TTCD [redacted] will be analyzed using the same methods as for PFS.

[redacted]

[redacted]

[redacted]

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of atezolizumab or tiragolumab/placebo.

Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the atezolizumab plus tiragolumab 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 and graded according the NCI CTCAE v5.0, and severity for CRS will also be graded by the investigator according to the ASTCT Consensus Grading Scale. All adverse events will be summarized by treatment arm and NCI CTCAE grade. CRS will also be summarized by treatment arm and ASTCT consensus grade. In addition, serious adverse events, immune-mediated 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.

All deaths and causes of deaths will be summarized by treatment arm.

Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data, including ADA results, will be summarized.

6.6 PHARMACOKINETIC ANALYSES

PK samples of tiragolumab and atezolizumab will be collected in this study as outlined in Appendix 3. Tiragolumab and atezolizumab serum concentration data (minimum serum concentration and maximum serum concentration) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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 assessment, with patients grouped according to treatment received. The number and proportion of treatment-emergent ADA-positive patients and ADA-negative patients will be summarized by treatment arm.

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

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format 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, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as 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 Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient’s willingness to continue 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 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of [redacted] analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). 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).

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.

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.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective

requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 60 sites globally will participate to randomize approximately 120 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, [redacted], 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 IMC will monitor and evaluate patient safety throughout the study.

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.

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Appendix 1
Schedule of Activities

Assessment/Procedures	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (every 21 Days) (± 3 days for Cycle ≥ 2)	Treatment Discontinuation [b] ≤ [redacted] Days after Final Dose	Follow-Up
Informed consent [c] • Prescreening ICF for PD-L1 testing, (if applicable) • Main ICF for study participation	x			
[redacted] [d]	x			
HPV status (only for patients with oropharyngeal carcinoma) [e]	x			
Demographic data (sex, age, and self-reported race/ethnicity)	x			
Medical history, including SCCHN history and baseline conditions	x			
Vital signs [f]	x	x	x	
Weight	x		x	
Height	x			
Complete physical examination [g]	x			
Limited physical examination [g]		x [h]	x	
ECOG Performance Status [h]	x	x [h]	x	
ECG [i]	x	As clinically indicated		
Hematology [j]	x [u]	x [h]	x	

Appendix 1: Schedule of Activities

Assessment/Procedures	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (every 21 Days) (± 3 days for Cycle ≥ 2)	Treatment Discontinuation [b] ≤ [redacted] Days after Final Dose	Follow-Up
Chemistry [k]	x [u]	x [h]	x	
Pregnancy test (for women of childrearing potential only)	x [l]	x [l]	x [l]	
Coagulation (INR and aPTT)	x [u]		x	
TSH, free T3 (or total T3), free T4 [m]	x	x [m]	x	
[redacted] [n]	x			
[redacted] [o]	x [n, o]	x [o]	x [o]	
Urinalysis [p]	x	As clinically indicated		
Concomitant medications [q]	x [q]	x	x	
Tumor response assessment [r, s]	x [r]	x [s]		
Adverse events [t]	x [t]	x [t]	x [t]	x [t]
PROs [v]		Refer to Appendix 2.		
Atezolizumab IV infusion [x]		x		
Tiragolumab/placebo IV infusion [x]		x		
Serum sample for autoantibody sample (central laboratory) [y]		x [y]		
Serum sample for C-reactive protein (central laboratory) [y]		x [y]		
[redacted]				

Appendix 1: Schedule of Activities

Assessment/Procedures	Screening [a]	Treatment	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (every 21 Days) (± 3 days for Cycle ≥ 2)	Treatment Discontinuation [b] ≤ [redacted] Days after Final Dose	Follow-Up
[redacted]				
Informed consent to continue treatment beyond radiographic disease progression per RECIST v1.1		At time of initial radiographic progression		
Disease progression tumor biopsy (if clinically feasible)		At time of radiographic progression [aa]		
Survival follow-up and anti-cancer treatment				x [bb]

ADA = anti-drug antibody; FFPE = formalin-fixed paraffin-embedded; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; [redacted] CF = Informed Consent Form; PGI = Patient Global Impression; PK = pharmacokinetic; PRO = patient-reported outcome; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SCCHN = squamous cell carcinoma of the head and neck; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

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

[a] Results of SOC tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than [redacted] days after their final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed and signing of the ICFs can occur outside the 28-day screening period. Patients have the option to sign the Prescreening ICF to consent to PD-L1 tissue testing during prescreening, prior to signing the main ICF for all screening procedures and study participation. Sites should consider prescreening for PD-L1 status to confirm PD-L1 eligibility prior to initiation of screening procedures. If prescreening is not performed, sites are encouraged to consider completing the PD-L1 test as early as possible during screening to confirm PD-L1 eligibility status.

[d] [redacted]

[e] [redacted]

[f] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.5.

[g] Complete and limited physical examinations are defined in Section 4.5.4.

[h] ECOG Performance Status, a limited physical examination, and specified local laboratory assessments may be obtained ≤96 hours before Day 1 of each cycle. Specified assessments performed ≤ 96 hours before Cycle 1, Day 1 for screening are not required to be repeated on Cycle 1, Day 1.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

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

[k] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH.

[l] All women of childbearing potential will have a serum pregnancy test at screening, within 14 days prior to Cycle1, Day1. Urine pregnancy tests must be performed on Day 1 of every cycle and at end of treatment visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be collected at screening, on Day 1 of Cycle 1, and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.). [redacted]

[n] A[redacted]

[redacted]

[o] [redacted]

[p] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] Concomitant medications include prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements. Any medications the patient has used within 7 days prior to initiation of study treatment should be documented. At subsequent visits, changes to current medications or medication used since the last document will be recorded.

[r] Tumor assessments performed as SOC prior to obtaining informed consent may be used rather than repeating tests provided the scans are of diagnostic quality and are performed within 28 days of randomization. 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. The same radiographic modality (e.g., computed tomography [CT] scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used at screening must be used for all subsequent tumor assessments. Screening assessments and subsequent tumor assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or magnetic resonance imaging (MRI) (with contrast) of the head and neck (base of skull to clavicle). A CT scan with contrast of the pelvis should be performed as clinically indicated, or as per local SOC, at screening, and subsequent response evaluations. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed, and MRI scans with contrast of the head and neck, abdomen, and pelvis (as applicable) must be performed. Further investigations, such as bone scans should also be performed, if clinically indicated, at baseline and at subsequent response evaluations. A CT scan with contrast or MRI scan with contrast (if CT with contrast is contraindicated) of the brain should be done as clinically indicated to evaluate CNS metastasis at screening and at subsequent response evaluations.
If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2). Patients with a history of irradiated brain metastasis at screening are not required to undergo head scans at subsequent response evaluations unless clinically indicated. 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.

[s] Patients will undergo tumor assessments at baseline, every 6 weeks (± 7 days) for the first 30 weeks following Day 1 of Cycle 1, and every 9 weeks (± 7 days) after completion of the Week 30 tumor assessment. Tumor assessments will continue per schedule, regardless of treatment delays, until radiographic disease progression per RECIST v1.1 or loss of clinical benefit for patients who continue study treatment after radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. At the investigator's discretion, scans must also be performed at any time if progressive disease or loss of clinical benefit is suspected. Patients who discontinue study treatment (for any reason, including, but not limited to, clinical decline or toxicity) in the absence of radiographic disease progression per RECIST v.1.1 will continue to undergo tumor response assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

[t] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] days after the 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]. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6).

[u] Specified screening laboratory test results must be obtained within 14 days prior to randomization.

[v] PRO assessments: Patient-Reported Outcomes Measurement Information System® [PROMIS®] Item Bank v2.0–Physical Functioning–Short Form 10b, [redacted] Patient Global Impression of Severity, Patient Global Impression of Change and its Importance, Most Important Symptoms, and Patient-Reported Outcomes Common Terminology Criteria for Adverse Events will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. See Appendix 2 for schedule of PRO assessments.

[x] Patients should receive their first dose of study drug the day of randomization, if possible. [redacted]. Atezolizumab will be administered prior to tiragolumab/placebo. Patients will receive atezolizumab by continuous IV infusion every 21 days on Day 1 of each 21-day cycle as indicated. For atezolizumab, the initial dose will be delivered over 60 (± 15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Following atezolizumab, patients will receive tiragolumab or placebo by continuous IV infusion every 21 days on Day 1 of

each 21-day cycle as indicated. For tiragolumab or placebo, the initial dose will be delivered over [redacted] minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over [redacted] minutes.

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

[z] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[aa] Patients will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.7 for tissue sample requirements.

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, unless the patient withdraws consent or the Sponsor terminates the study. If a patient requests to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study (i.e., survival follow-up), the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Appendix 2 Schedule of Patient-Reported Outcome Assessments

Visit	Timepoint	Sample Type(s)
Cycles 1 and 2, Day 1	Predose and prior to disease status assessments [a]	• PROMIS® Item Bank v2.0–Physical Functioning–Short Form 10b • [redacted] • [redacted] • [redacted] • [redacted] • MIS • PGI-S
Cycle 3, Day 1 and every other cycle until treatment discontinuation (i.e., Cycles 5, 7, 9, etc.)	Predose and prior to disease status assessments [a]	• [redacted] • MIS • PGI-S • PGI-CI
Cycle 4, Day 1 and every other cycle until treatment discontinuation (i.e., Cycles 6, 8, 10, etc.)	Predose and prior to disease status assessments [a]	• PROMIS® Item Bank v2.0–Physical Functioning–Short Form 10b • [redacted] • [redacted] • [redacted] • PGI-S • PGI-CI
Treatment discontinuation visit	At visit	• As indicated based on alternating schedule of assessment per cycle.

MIS = Most Important Symptoms; PGI-CI = Patient Global Impression of Change and its Importance; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; PRO = patient-reported outcome; [redacted]
PROMIS = Patient-Reported Outcomes Measurement Information System

[a] To be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. In scenarios where other clinical activities performed ≤ 96 hours before the visit dates (e.g., those specified in Appendix 1 footnote h) are intended for treatment determination, PROs can be completed ≤ 96 hours before the scheduled visit, prior to those clinical activities.

[redacted]

[redacted]

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.

CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions 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 complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

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

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

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

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

NEW LESIONS

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

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

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

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

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

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

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

REFERENCES

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

Appendix 5
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 6
Patient-Reported Outcomes Measurement Information System®: PROMIS® Item Bank v2.0–Physical Function–Short Form 10b

PROMIS® Item Bank v2.0 – Physical Function – Short Form 10b

Physical Function – Short Form 10b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA56	Are you able to get in and out of a car?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA9	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFH28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA6	Does your health now limit you in bathing or dressing yourself?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFH3	Does your health now limit you in putting a trash bag outside?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFH44	Does your health now limit you in doing moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix 10
Patient Global Impression of Severity (PGI-S)

Patient Global Impression of Severity (PGI-S)

Please choose the response below that best describes the severity of your overall status over the past week.

None	☐
Mild	☐
Moderate	☐
Severe	☐
Very severe	☐

Appendix 11
Patient Global Impression of Change and its Importance (PGI-CI)

Patient Global Impression of Change (PGI-C)

Since the start of the study, my overall status is:

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

Patient-reported Importance of Change

In the previous question, you reported the change you have experienced since starting this trial. Was this change important to you?

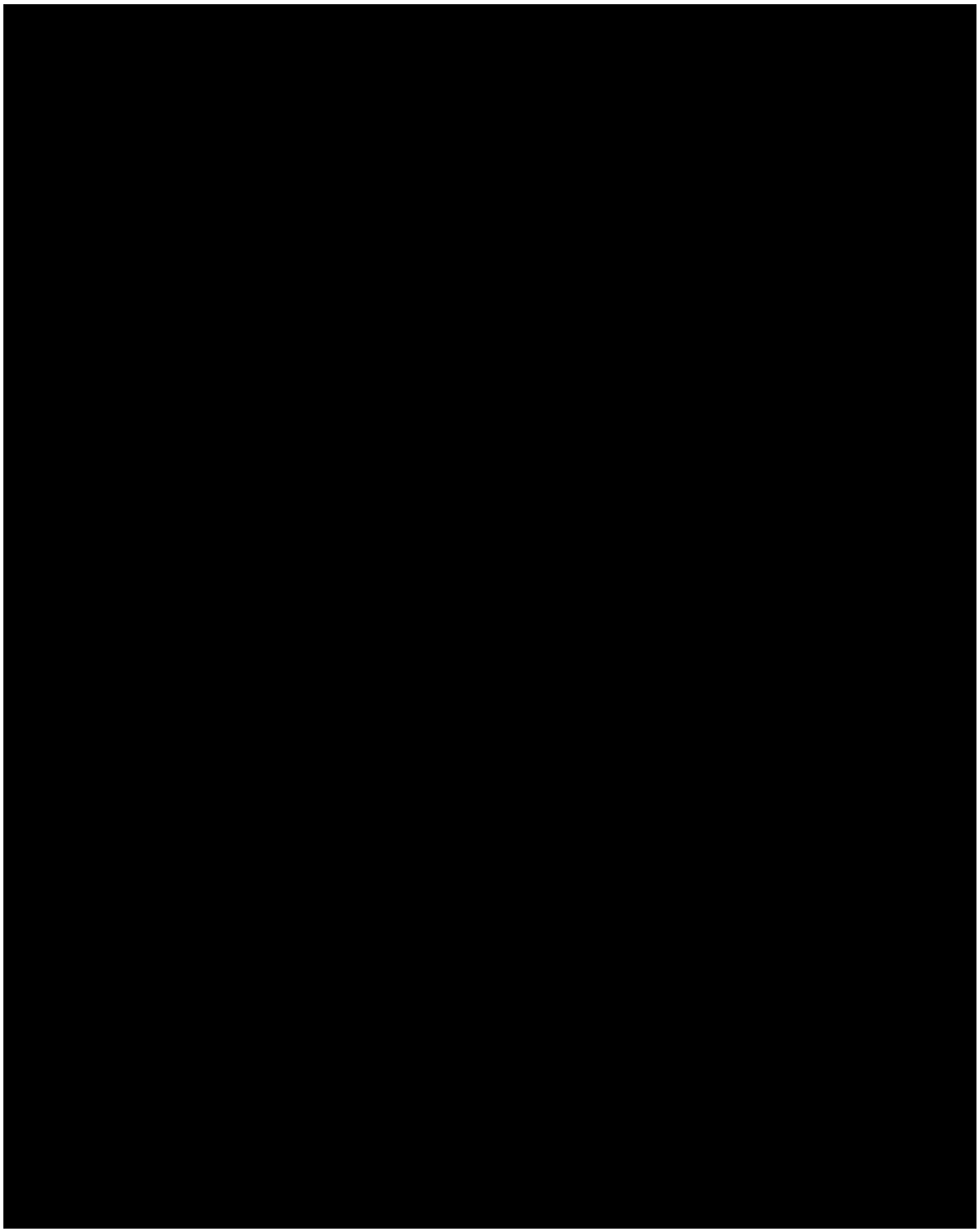
- ☐ Yes
- ☐ No
- ☐ Not applicable

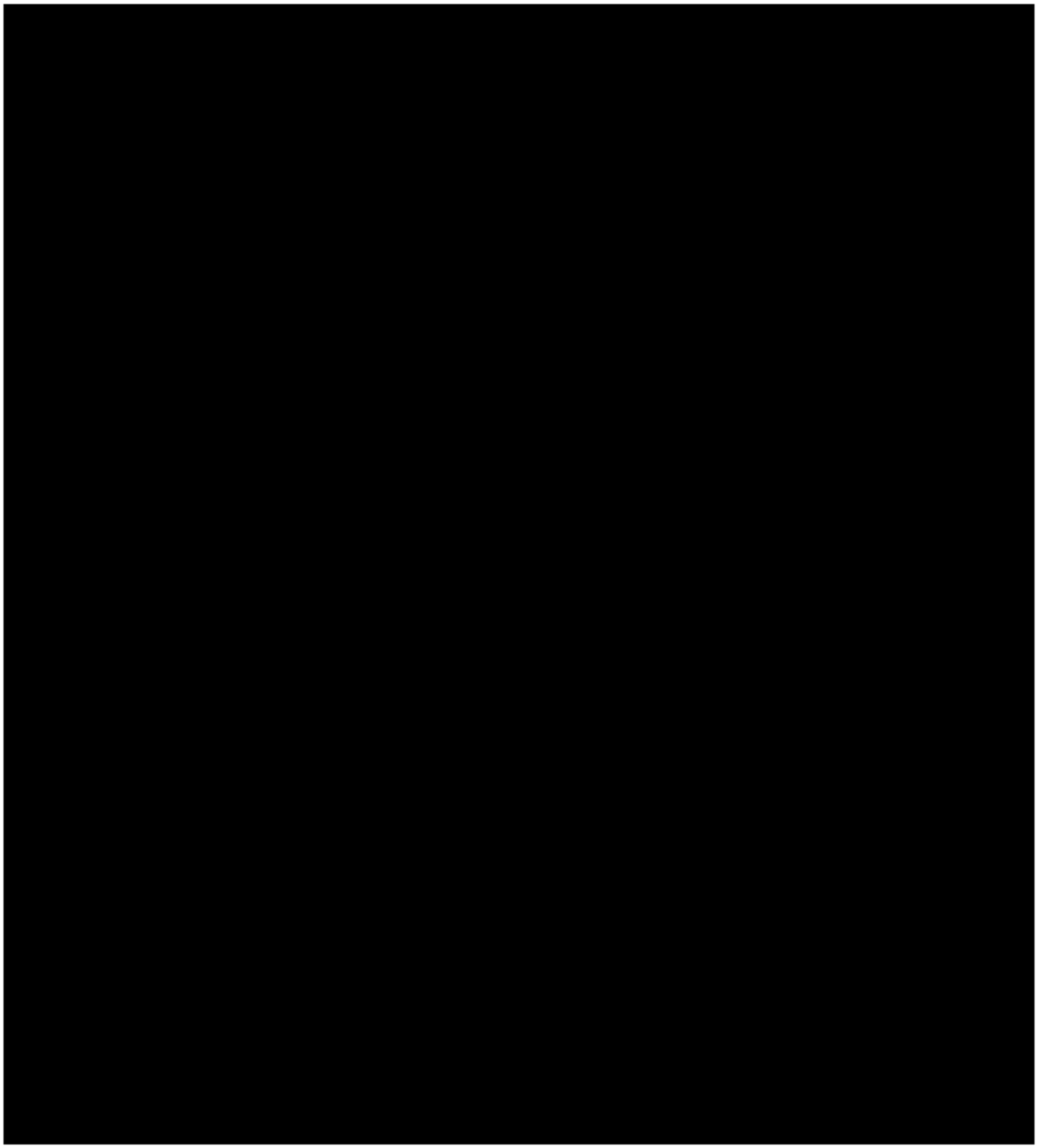
(selected *No change* in PGI-C)

Appendix 12
Most Important Symptoms

Which issues have been the most important to you during the past 7 days?
Check ☑ up to 4 boxes.

☐ Chewing or swallowing	☐ Constipation	☐ Coughing
☐ Diarrhoea	☐ Dry mouth or sticky saliva	☐ Dry or itchy skin
☐ Loss of appetite	☐ Nausea or vomiting	☐ Pain
☐ Skin rash	☐ Disturbed sleep	☐ Speech
☐ Swelling	☐ Taste or smell	☐ Tired / fatigue





Appendix 14
Preexisting Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

Appendix 15
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

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

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 16
Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Toxicities associated or possibly associated with atezolizumab and/or tiragolumab 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.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab and/or tiragolumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.

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

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

[redacted]

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

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

[redacted] The decision to re-challenge patients with atezolizumab and tiragolumab should be based on the investigator's benefit–risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab and tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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.

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. Coronavirus disease 2019 (COVID-19) evaluation should be performed

per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

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

[redacted]

a [redacted]

b [redacted]

c [redacted]

d [redacted]

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

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

d

HEPATIC EVENTS

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

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

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

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Table 2 Management Guidelines for Hepatic Events

Event	Management
[redacted]	• [redacted] • [redacted]
[redacted]	**All events:** • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

[redacted]

a [redacted]

b [redacted]

c [redacted]

GASTROINTESTINAL EVENTS

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

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

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

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

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

GI = gastrointestinal.

a [redacted]

b

c

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

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

GI = gastrointestinal.

a [redacted]

b

c

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) 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.

Table 4 Management Guidelines for Endocrine Events

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

[redacted]

a [redacted]

b [redacted]

c [redacted]

Table 4 Management Guidelines for Endocrine Events (cont.)

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

[redacted]

a [redacted]

b

c

Table 4 Management Guidelines for Endocrine Events (cont.)

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

[redacted]

a [redacted]

b

c

Table 4 Management Guidelines for Endocrine Events (cont.)

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

[redacted]

a [redacted]

b

c

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

OCULAR EVENTS

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

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Table 5 Management Guidelines for Ocular Events

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

a [redacted]

b

c

IMMUNE-MEDIATED CARDIAC EVENTS

[redacted]

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

IMMUNE-MEDIATED MYOCARDITIS

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

[redacted]

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

IMMUNE-MEDIATED PERICARDIAL DISORDERS

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

[redacted]

[redacted]

[redacted]

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
[redacted]	• [redacted]

[redacted]

INFUSION-RELATED REACTIONS

[redacted]

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab and tiragolumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours

of atezolizumab or tiragolumab administration and are generally mild to moderate in severity.

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

[redacted]

Table 7 Management Guidelines for Infusion-Related Reactions

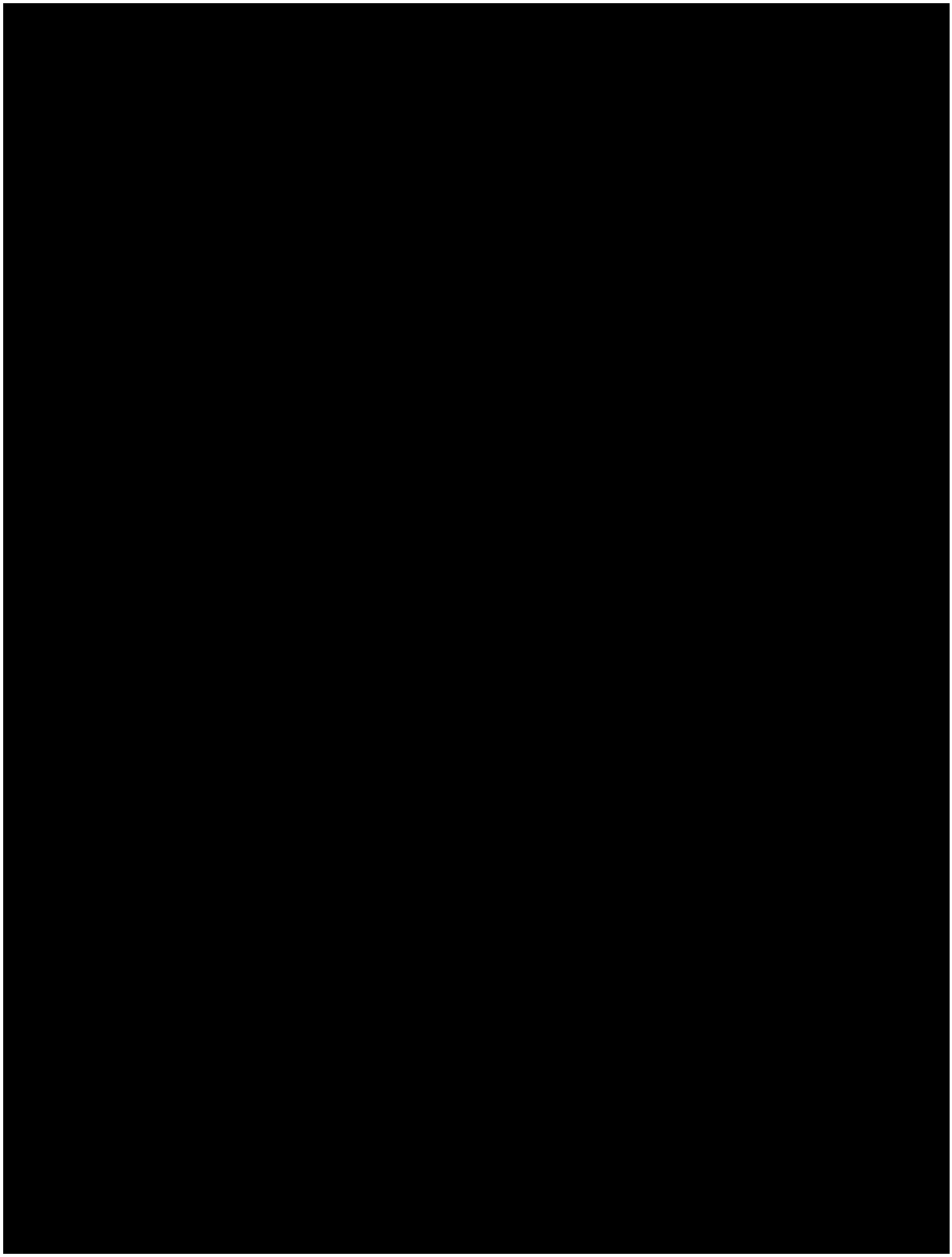
Event	Management
[redacted]	• [redacted]
[redacted]	• [redacted]
[redacted]	• [redacted]

IRR = infusion-related reaction.

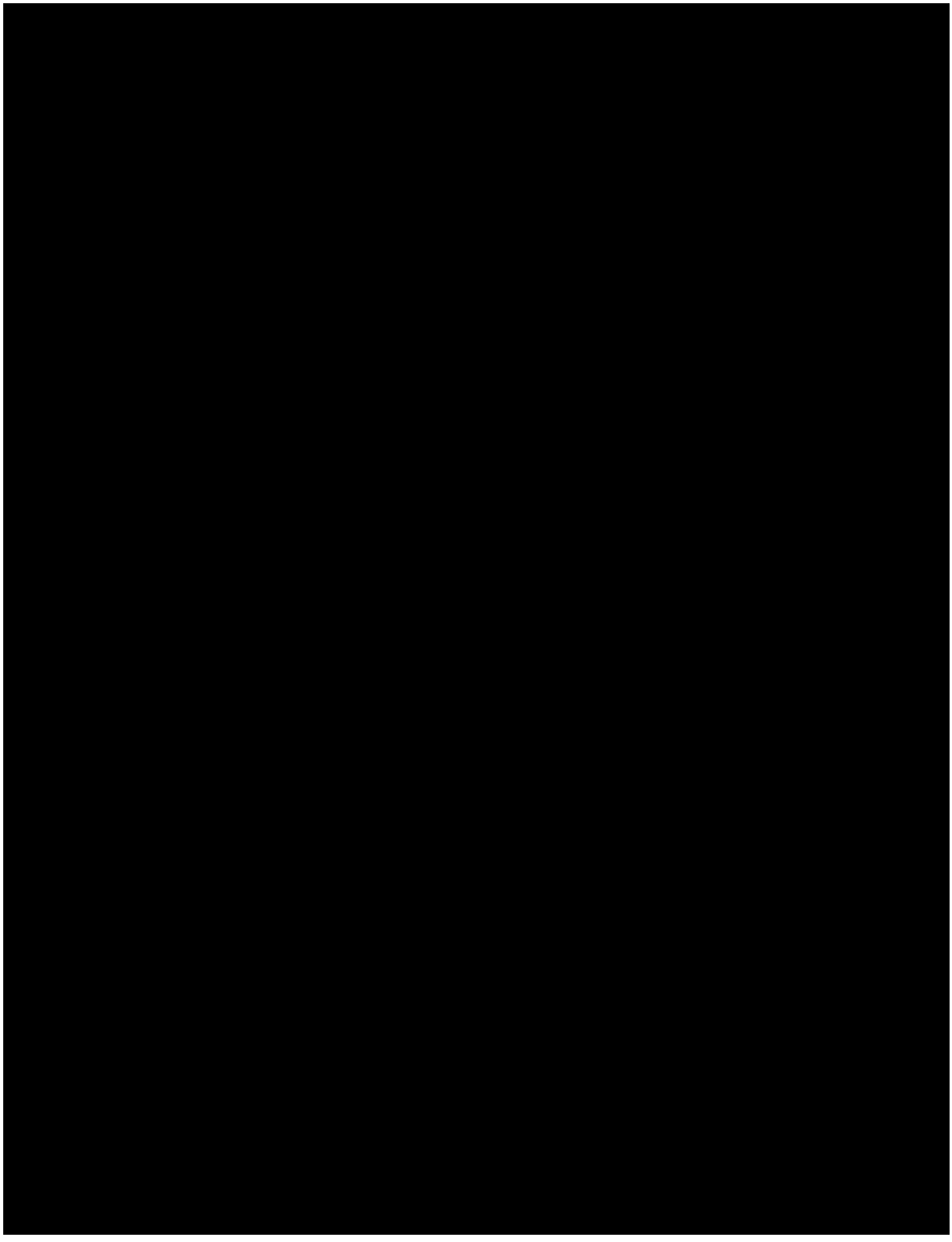
[a] [redacted]

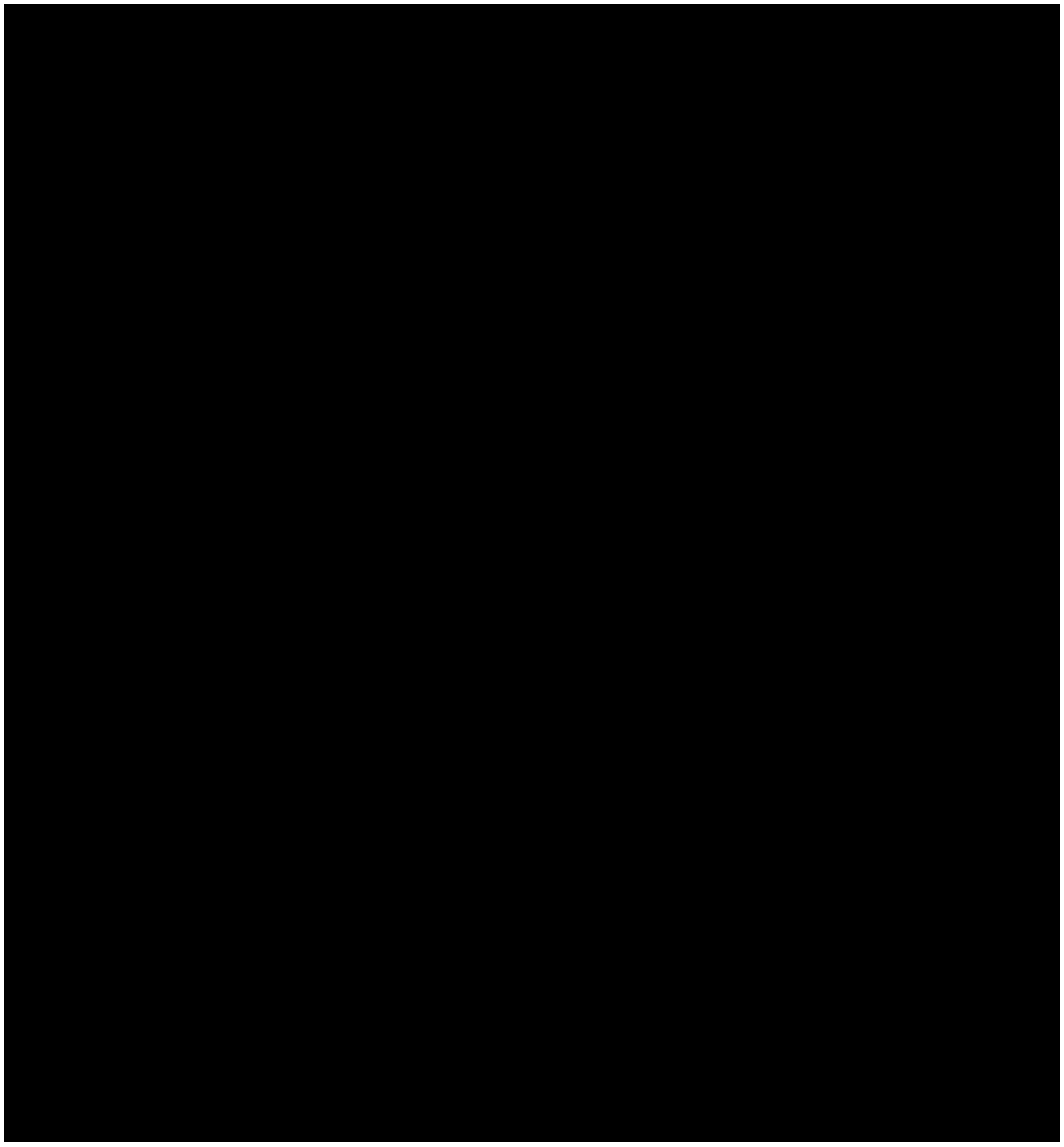
Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab



Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab





PANCREATIC EVENTS

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

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

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

GI = gastrointestinal; ULN = upper limit of normal.

[redacted]

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

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

GI = gastrointestinal; ULN = upper limit of normal.

a [redacted]

b

c

DERMATOLOGIC EVENTS

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

Table 10 Management Guidelines for Dermatologic Events

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

[redacted]

Table 10 Management Guidelines for Dermatologic Events (cont.)

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

a [redacted]

b

c

NEUROLOGIC DISORDERS

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

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Table 11 Management Guidelines for Neurologic Disorders

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

a [redacted]

b

c

Table 11 Management Guidelines for Neurologic Disorders (cont.)

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

[redacted]

a [redacted]

b

c

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Table 12 [redacted]

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

IVIG =intravenous immunoglobulin.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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

[redacted]

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

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[redacted]	• [redacted]

RENAL EVENTS

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

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

Table 14 Management Guidelines for Renal Events

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

[redacted]

a [redacted]

b

c

IMMUNE-MEDIATED MYOSITIS

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

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

Table 15 Management Guidelines for Immune-Mediated Myositis

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

[redacted]

a [redacted]

b [redacted]

c [redacted]

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

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

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

Event	Management
[redacted]	• [redacted]

[redacted]

a [redacted]

b

c

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

[redacted]

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

[redacted].

Appendix 16: Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

[redacted]

Event	Management
[redacted]	• [redacted]

[redacted]

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Appendix 17
Investigational, Auxiliary, and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A17-1 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*

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

[a] *Atezolizumab is used for an indication not included in the Local Product Information for that product.*

Table A17-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in U.K.*	*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*

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

[a] *Atezolizumab is used for an indication not included in the Local Product Information for that product.*

Signature Page for Protocol - BO42533 - TIRAGOLUMAB - v6 - Global/Core - Publish
System identifier: RIM-CLIN-514213

Approval Task	[redacted] Company Signatory 06-Dec-2023 00:21:59 GMT+0000