Official Title: A Phase II, Safety, and Efficacy Study of Tiragolumab Plus Atezolizumab and Atezolizumab Monotherapy in Patients With Metastatic and/or Recurrent PD-L1-Positive Cervical Cancer

NCT Number: NCT04300647

Document Date: Protocol Amendment Version 8: 06-October-2023

PROTOCOL

TITLE:	**A PHASE II, SAFETY, AND EFFICACY STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH METASTATIC AND/OR RECURRENT PD-L1–POSITIVE CERVICAL CANCER**
PROTOCOL NUMBER:	WO42017
VERSION NUMBER:	8
EUDRACT NUMBER:	2019-004895-21
IND NUMBER:	147026
NCT NUMBER:	NCT04300647
TEST PRODUCTS:	Tiragolumab (RO7092284) Atezolizumab (RO5541267)
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Region-Specific Protocol		
Version	**Date Final**	**Region**	**Version**	**Date Final**
8	See electronic date stamp on the final page of this document.	—	—	—
7	11 Feb 2023	—	—	—
6	21 December 2022	—	—	—
5	16 February 2022	—	—	—
4	25 March 2021	—	—	—
3	8 January 2021	—	—	—
2	19 June 2020	—	—	—
1	23 December 2019	VHP	1	12 May 2020

VHP = Voluntary Harmonization Procedure.

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol WO42017 Version 8 has been amended to extend the study timeline and recommend the removal of further assessment of imaging scans by Independent Review Committee (IRC). Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The synopsis has been simplified to align with current protocol guidelines.
- The list of approved indications for atezolizumab has been updated to include alveolar soft part sarcoma (Section 1.7).
- Language has been added to state that further imaging scans do not need to be assessed by the IRC because the Sponsor has decided no additional assessments are necessary (Sections 3.1.1, 4.5.6, 6.4.1, 6.4.2.1, 6.4.2.2, 6.4.2.4, and 9.5, Appendix 2).
- The post-trial access language has been updated to state that, as the study is nearing closure and the patients will be transitioning to the continued access program, the timing of the end of the study and the length of the study has been extended to allow additional time for the last patient still on the study to transition into continued access program (Section 3.2).
- The medical term “Wegener granulomatosis” has been replaced by the term “granulomatosis with polyangiitis” to align with the updated preferred term in MedDRA (Section 4.1.2).
- Collection of information on long-term survival follow-up after treatment discontinuation has been removed as it will no longer be needed, in order to reduce site burden as the protocol analysis has been conducted (Section 4.6.1, Appendix 1).
- The pharmacokinetic, immunogenicity, and biomarker sample collection schedule has been changed so that samples are no longer collected at treatment discontinuation visit or disease progression visit because the Sponsor has decided no additional sample collection is needed (Appendix 2).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator’s Brochure, Version 20 and Tiragolumab Investigator’s Brochure, Version 7.

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

TITLE:	**A PHASE II, SAFETY, AND EFFICACY STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH METASTATIC AND/OR RECURRENT PD-L1–POSITIVE CERVICAL CANCER**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, SAFETY, AND EFFICACY STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH METASTATIC AND/OR RECURRENT PD-L1–POSITIVE CERVICAL CANCER**
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IND NUMBER:	147026
NCT NUMBER:	NCT04300647
TEST PRODUCTS:	Atezolizumab (RO5541267) Tiragolumab (RO7092284)
PHASE:	Phase II
INDICATION:	Cervical cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

STUDY RATIONALE

This Phase II study will evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and atezolizumab monotherapy in patients with metastatic and/or recurrent programmed death -ligand 1 (PD-L1)-positive (tumor cells and tumor associated immune cells [redacted] cervical carcinoma.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy	• Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or a partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Imaging scans do not need to be assessed by IRC.

Secondary Objective	Corresponding Endpoints
• To evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab	• Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the IRC according to RECIST v1.1 • Disease control rate (DCR), defined as the proportion of patients with a CR, PR, or stable disease (SD), as determined by an IRC according to RECIST v1.1 • Best clinical response rate (BCR), defined as the proportion of patients with a CR, PR, or SD, and the DOR as clinically determined by the investigator • Progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause, whichever occurs first • Overall survival (OS) after randomization, defined as the time from randomization to death from any cause • OS rate at 6 months and 12 months, defined as the proportion of patients who have not experienced death from any cause at 6 months and 12 months post-randomization, respectively – Imaging scans do not need to be assessed by IRC.
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety and tolerability of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy	• 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) – [redacted]

Pharmacokinetic objective	Corresponding Endpoints
• To characterize the pharmacokinetics of tiragolumab and atezolizumab	• Serum concentrations of tiragolumab at specified timepoints • Serum concentrations of atezolizumab at specified timepoints
Immunogenicity objective	**Corresponding Endpoints**
• To evaluate the immune response to tiragolumab and atezolizumab	• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs to tiragolumab and to atezolizumab during the study [redacted] • [redacted]

[redacted]

OVERALL DESIGN AND STUDY POPULATION

This Phase II, global, open-label, randomized study is designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy in patients with metastatic and/or recurrent PD-L1–positive cervical cancer after progression or recurrence from at least one platinum-based but no more than two prior systemic therapies.

Approximately 160 patients will be enrolled in the global enrollment phase of this study. Women with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 who have metastatic and/or recurrent PD-L1–positive cervical cancer are eligible.

Additional patients may be subsequently randomized [redacted]

Screening Period

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for an additional two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are rescreened within 60 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log.

During screening, tumor specimens from each potentially eligible patient will be prospectively tested for PD-L1 expression, as assessed by a central laboratory, using the [redacted]. Only patients who are PD-L1–positive with [redacted] will be enrolled.

Treatment Period

Eligible patients will be randomized in a 3:1 ratio to receive either tiragolumab in combination with atezolizumab or atezolizumab alone.

Eligible patients will be stratified by ECOG Performance Status (0 versus 1), prior use of chemoradiotherapy or radiotherapy (yes versus no), and treatment history (persistent versus recurrent disease).

In the doublet arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered by IV infusion Q3W also on Day 1 of each 21-day cycle.

In the atezolizumab monotherapy arm, patients will receive atezolizumab at a fixed dose of 1200 mg 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 of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for equivocal disease progression per RECIST v1.1 will be permitted to continue treatment (tiragolumab in combination with atezolizumab or atezolizumab alone) if they meet all of the criteria specified.

During the study, serum samples will be collected to monitor tiragolumab in combination with atezolizumab and atezolizumab pharmacokinetics and to detect the presence of antibodies to tiragolumab and atezolizumab. Patient samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, will also be collected for [redacted] assessments.

Patients will undergo tumor assessments at baseline and every 6 weeks ($\pm$7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks ($\pm$7 days) regardless of treatment delays until unequivocal radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above 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.

Response will be assessed according to RECIST v1.1. Objective response was previously determined at a single timepoint by the IRC according to RECIST v1.1. Imaging scans do not need to be assessed by IRC.

Crossover is allowed from the atezolizumab monotherapy arm to the tiragolumab plus atezolizumab arm after unequivocal progressive disease has been recorded during atezolizumab monotherapy, at the discretion of the investigator and after consultation with the

Medical Monitor. For patients who crossover from atezolizumab monotherapy to tiragolumab plus atezolizumab, the tumor assessment just preceding crossover will serve as a rebaseline scan against which all subsequent scans will be compared.

After initiation of study treatment, all adverse events will be reported according to the adverse event reporting period. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigators become aware of any serious adverse events or adverse events of special interest that are believed to be related to prior treatment with study drug(s). These events should be reported using the Adverse Event electronic Case Report Form (eCRF). 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 protocol-related procedures until a final outcome can be reported.

After study treatment discontinuation, survival follow -up information will no longer be collected.

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 study treatment at the investigator's discretion provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values indicating unequivocal progression of disease)
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

End of Study

The end of this study is defined as the date when the "last patient last visit" occurs (i.e., when the last patient has recorded her last visit). The end of study has been extended until all patients on active treatment in the study roll over to the continued access program.

At study closure, patients will still receive study treatment through the continued access program.

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

Phase:	*Phase II*	***Population Type:***	*Adults*
Control Method:	*None*	***Population Diagnosis or Condition:***	*Histologically confirmed recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix (neuroendocrine, clear cell, and sarcoma histologies are not allowed) after progression on or after 1–2 lines of prior systemic chemotherapy in the metastatic/recurrent setting that is not amenable to curative treatment with systemic chemotherapy, surgery, and/or radiotherapy* – *At least one prior line of platinum-based systemic chemotherapy* – *Radiosensitizing cisplatin given with*

			radiotherapy is not considered a line of systemic chemotherapy
Interventional Model:	*Double group*	***Population Age:***	*≥18 years*
Test Products:	*Atezolizumab Tiragolumab*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*Not applicable*	***Study Treatment Assignment Method:***	*Not applicable*
Number of Arms:	*Two*	***Number of Participants to Be Enrolled:***	*160*

STUDY TREATMENT

In the doublet arm, a fixed dose of 1200 mg atezolizumab will be administered by IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered by IV infusion Q3W also on Day 1 of each 21-day cycle. In the atezolizumab monotherapy arm, atezolizumab will be administered at a fixed dose of 1200 mg by IV infusion Q3W on Day 1 of each 21-day cycle.

DURATION OF PARTICIPATION

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

COMMITTEES

Independent Committees:	*Independent review committee (IRC)*
Other Committees:	Internal Monitoring Committee (IMC)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ASTCT	American Society for Transplantation and Cellular Therapy
BCR	best clinical response
[redacted]	
CE-IVD	Conformité Européenne–In Vitro Diagnostic
CIN	cervical intraepithelial neoplasia
CIT	cancer immunotherapy
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
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EAE	experimental autoimmune encephalitis
[redacted]	
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
Fc	fragment crystallizable
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
[redacted]	
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HLH	hemophagocytic lymphohistiocytosis
HPV	human papilloma virus
IC	immune cell
ICH	International Council for Harmonisation
IFN	Interferon
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRC	independent review committee
IRR	infusion-related reaction
IVD	in vitro diagnostic
IxRS	interactive voice or web-based response system
MAb	monoclonal antibody
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NK	natural killer (cell)
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PVR	poliovirus receptor
Q3W	every 3 weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation	Definition
SITC	Society for Immunotherapy of Cancer
SD	stable disease
T3	triiodothyronine
TC	tumor cell
TIC	tumor cells and tumor-associated immune cells
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TNF(-α)	tumor necrosis factor(–α)
TPS	tumor proportion score
TTE	*transthoracic echocardiogram*
ULN	upper limit of normal
VCA	viral-capsid antigen
VHP	Voluntary Harmonization Procedure
[redacted]	

1. BACKGROUND

1.1 BACKGROUND ON CERVICAL CANCER

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related death globally. More than 569,847 women are diagnosed with cervical cancer annually worldwide, resulting in more than 311,365 deaths (Bray et al. 2018). Almost 90% of cervical cancer deaths occur in developing countries. In the United States, there are 13,000 new cases of invasive cervical cancer and approximately 4000 cancer related deaths each year (American Cancer Society 2016). About a fifth of all global cervical cancer cases in 2018 occurred in China; approximately 106,000 new cases and 48,000 deaths from the disease occurred in China (Arbyn et al. 2020).

Treatment for early stage (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] Stages IA1 to IB1) and locally advanced (FIGO Stages IB2 to IVA) cervical cancer consists of surgery and definitive chemoradiotherapy, respectively, and can be quite effective in eliciting a remission. However, if cancer recurs or fails to resolve with primary treatment, prognosis is quite poor with 5-year survival rates of approximately 15%, which is comparable to that of patients with de novo metastatic (Stage IVB) disease (American Cancer Society 2016). With few exceptions, the standard of care for recurrent, persistent, or de novo metastatic disease is chemotherapy plus bevacizumab based on the Gynecology Oncology Group 240 trial, which showed that bevacizumab added to chemotherapy improved median overall survival (OS) compared with chemotherapy alone (17 vs. 13.3 months, respectively) (Tewari et al. 2014).

Currently, no globally-accepted standard of care exists after recurrence or progression on chemotherapy plus bevacizumab. As such, treatment options for these patients largely comprise various cytotoxic chemotherapy agents, administered as either a single agent or in combination. However, given the historically low response rates of approximately 10%−15%, increasing focus has been given to whether cytotoxic chemotherapies represent an acceptable standard of care over best supportive care given the impact and burden such agents can impart on patient quality of life.

Cervical cancer has been identified to be a direct consequence of infections by specific high-risk genotypes of human papilloma virus (HPV), most commonly HPV16 and HPV18 (Clifford et al. 2003; Mayadev et al. 2019). The notion that immune cells (ICs) can control HPV infections has been supported by results from studies showing spontaneous regression of HPV papillomas, and conversely other studies showing increased rates of HPV-related cancers among immunosuppressed and immune-deficient patients (Kadish et al. 2002; Lyford-Pike et al. 2013; Tong et al. 2015). The dynamic immune response to viral infections involves a balance of activating and deactivating signals with epitopes of viral peptides identified on antigen-presenting cells. Historically low efficacy rates of existing therapies, coupled with the engagement of the

immune response owing to HPV infection of the cervical epithelial cells, makes cervical cancer a particularly attractive opportunity for novel immunotherapy-based approaches.

1.2 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 immunoglobulin 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 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 co-expressed with other checkpoint immune receptors such as programmed death−1 (PD-1), and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (TCs) (Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014; Wang et al. 2015; Manieri et al. 2017).

TIGIT is expressed in a wide variety of human tumors, including most solid tumors, such as non−small cell lung cancer (NSCLC), breast cancer, and melanoma, and is highly correlated with T-cell infiltration and programmed death−ligand 1 (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). High expression of TIGIT-positive ICs has also been reported in cervical cancer samples by both IHC and by RNA sequencing (Cattaruzza et al. 2017; Anderson et al. 2019). High expression of TIGIT in immune-infiltrating cells in cervical cancer may have prognostic significance as well (Wang et al. 2019). The TIGIT ligand PVR is also reported to be highly expressed in infiltrating NK cells in cervical cancer as compared to NK cells in normal cervical tissue (Textor et al. 2008).

1.3 PD-L1/PD-1 PATHWAY IN CANCER

Programmed death−ligand 1 (PD-L1) is a cell surface protein that is broadly expressed by TCs and tumor-infiltrating ICs in many human cancers, including cervical 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 T cells 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 represent an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Neoantigens, such as cancer antigens or viral antigen in HPV-related cancer, are recognized by T cells by means of antigen-presenting cells, leading to T-cell activation. Immunotolerance in the tumoral microenvironment includes PD-1 overexpression on tumoral-infiltrating lymphocytes and PD-L1 overexpression on TCs, leading to the inhibition of activated effector T cells, through inhibitory checkpoint signals. By inhibiting the interaction between PD-1 and PD-L1, anti–PD-1/PD-L1 antibodies block the inhibitory checkpoint signals and restore endogenous anti-tumor immunity.

Therapeutic blockade of the PD-1/PD-L1 interaction has demonstrated modest, yet sustained disease control in cervical cancer. Indeed, pembrolizumab monotherapy for patients with recurrent, metastatic cervical cancer produced a response rate of $<15\%$, whereas nivolumab monotherapy also resulted in a comparable response rate of approximately 20% (Chung et al. 2019; Naumann et al. 2019). While these response rates were modest, the totality of evidence, including disease control, duration of response (DOR), and safety profile, led to the U.S. Food and Drug Administration's (FDA's) accelerated approval of pembrolizumab for the treatment of metastatic/recurrent cervical cancer in 2018 (Keytruda U.S. Package Insert). Despite this regulatory approval, the efficacy of this monotherapy approach leaves much room for improvement.

Because of this, antagonists that target additional inhibitory receptors have the potential to enhance such anti-tumor T-cell responses. One approach has been to combine anti–PD-1 with anti-cytotoxic T lymphocyte–associated protein 4 (anti–CTLA-4) (Naumann et al. 2019). Although the observed improvement in response rate supported this immune doublet strategy, the tolerability of this particular immune doublet was challenging. Refining and testing other co-inhibitory antagonists have emerged as attractive combination partners for anti–PD-L1/PD-1 on the basis of their complementary mechanism of action.

1.4 PD-L1/PD-1 INHIBITION IN VIRAL-ASSOCIATED TUMORS

There is a strong rationale for adopting an immunotherapeutic approach to treating cervical cancer given the prevalence of HPV tumorigenesis and associated viral antigen production. A higher expression of PD-L1 has been described in virus-induced cancers, including cervical cancer (Chung et al. 2019), and an upregulation of PD-1 and PD-L1 has been observed in high-risk HPV-related cervical intraepithelial neoplasia (Crafton and Salani 2016).

The viral reactive T cells in patients with cervical cancer with chronic HPV are key, as anti-tumor immunity may be driven by these T cells, in addition to T cells that are specific to tumor-associated antigens. Two important viral proteins, E6 and E7, are directly responsible for the development of HPV-induced tumorigenesis (Tomaic 2016). The presentation of viral antigens by APC activates naive T cells to proliferate and

differentiate into effector T cells and therefore initiates an HPV-specific immune response, recognizing and eliminating virus-infected cells.

1.5 COMBINED INHIBITION OF THE TIGIT AND PD-L1/PD-1 PATHWAYS AS A 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 preclinical 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 preclinical 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 preclinical and clinical studies for tiragolumab.

1.6.1 Preclinical Data with Tiragolumab

The preclinical 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 preclinical pharmacology studies demonstrate that tiragolumab binds to TIGIT and prevents TIGIT–PVR interactions. Tiragolumab is a human IgG1 MAb and therefore binds to Fcγ 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 preclinical PK behavior observed for tiragolumab is consistent with that expected for a receptor targeting human IgG1 MAb. The pivotal repeat-dose toxicity study demonstrated that weekly IV administration of tiragolumab [redacted] was well tolerated in cynomolgus monkeys, and no findings were directly attributed to tiragolumab administration. 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 for the safety plan).

Overall, the preclinical 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 preclinical studies.

1.6.2 Clinical Experience with Tiragolumab

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 NSCLC, head and neck squamous cell carcinoma, urinary bladder cancer, and renal cell cancer.

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.

Available safety data and preliminary 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 II Study GO40290 are summarized below.

1.6.2.2 Clinical Safety of Tiragolumab

[redacted]

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 portion of the study 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.

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 or tiragolumab in combination with atezolizumab in Study GO30103.

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

Study GO40290 is an ongoing, global Phase II, randomized, double-blinded, placebo-controlled study in first-line setting of NSCLC. The co-primary endpoints were confirmed objective response rate (ORR) and investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors, Version 1.1

(RECIST v1.1). Secondary endpoints included DOR, OS, safety, pharmacokinetics, and immunogenicity.

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

As of the primary clinical cutoff date of 30 June 2019, 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% had non-squamous histology compared with 40.7% of patients who had squamous histology, and 10.4% of patients were never smokers versus 89.6% who had smoked.

In all randomized patients with TPS ≥1%, the confirmed ORR was higher in the tiragolumab plus atezolizumab arm (31.3%) than in the placebo plus atezolizumab arm (16.2%); investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm compared with the placebo plus atezolizumab arm (stratified HR=0.57; 95% CI: 0.37 to 0.90; median PFS: 5.4 vs. 3.6 months, respectively).

The improvement in ORR and PFS observed with the combination of tiragolumab plus atezolizumab compared with placebo plus atezolizumab appears to be driven by the subgroup of patients with high PD-L1 expression (TPS ≥50%). In the subgroup of patients with TPS≥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%]). Investigator-assessed PFS was improved in the tiragolumab plus atezolizumab arm relative to the placebo plus atezolizumab arm (unstratified HR=0.33; 95% CI: 0.15 to 0.72; median PFS: not reached vs. 3.9 months, respectively).

The safety profile was comparable between the tiragolumab plus atezolizumab arm and the placebo plus atezolizumab arm for all grade adverse events (98.5% vs. 95.6%, respectively), Grade ≥3 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 that in the placebo plus atezolizumab arm (72.1%).

Grade ≥3 adverse events (with a ≥2% difference between arms) that occurred at a higher frequency in the tiragolumab plus atezolizumab arm were pneumonia (9.0% vs. 4.4%), pleural effusion (6.0% vs.1.5%), increased lipase (6.0% vs. 2.9%), and hypokalemia (3.0% vs. 0%). Grade≥3 adverse events that occurred at a higher frequency in the placebo plus atezolizumab arm were pulmonary embolism

(0% vs. 2.9%), increased amylase (0% vs. 2.9%), and asthenia (0% vs. 2.9%). Grade 5 adverse events that occurred in the tiragolumab plus atezolizumab arm were [redacted] 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 (reported for 1 patient each).

Using a comprehensive medical concepts strategy, 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 (≥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 reactions (IRRs) (preferred term of infusion-related reaction) (28.4% vs. 10.3%). One Grade 3 adverse event of rash was observed in the tiragolumab plus atezolizumab arm. All other events of rash and IRRs were of Grade 1 or 2 severity. No events of rash or IRR led to tiragolumab or atezolizumab discontinuation.

1.6.2.3 Clinical Pharmacokinetics and Immunogenicity of Tiragolumab and Atezolizumab

Clinical Pharmacokinetics and Immunogenicity of Tiragolumab

[redacted]

[redacted]

As of December 2019 in the Phase Ia portion of Study GO30103, [redacted]

As of October 2019 in Study GO40290, [redacted]

[redacted]

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

Clinical Pharmacokinetics and Immunogenicity of Atezolizumab

Overall, atezolizumab exposures increased dose proportionally over the dose range of [redacted], including the fixed dose of 1200 mg administered Q3W. The clearance and terminal half-life of atezolizumab was estimated to be 0.2 L/day and 27 days, respectively, based on a Phase I population-PK analysis that included 472 patients from Studies PCD4989g and JO28944. ADAs to atezolizumab have been observed in some patients at all dosing levels, but the presence of ADAs did not appear to have a clinically relevant impact on pharmacokinetics, safety, or efficacy of atezolizumab at the 1200-mg dose.

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

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

Atezolizumab is currently being explored in cervical cancer as part of various treatment regimens, including with radiotherapy (NCT03614949 and NCT03738228) and chemotherapy with bevacizumab (NCT03556839). While efficacy data for atezolizumab in these combinations are not available, early safety evaluation did not identify unique disease-specific safety signals. A pilot study (NCT02921269) of atezolizumab in conjunction with bevacizumab in 11 biomarker-agnostic patients with cervical cancer showed no confirmed responders, despite achieving disease stabilization in 4 patients.

This lack of initial efficacy precluded activation of the expansion cohort; however, no safety signals were identified (Friedman et al. 2019).

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

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

1.8 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study will enroll patients with metastatic and/or recurrent PD-L1–positive cervical cancer after progression or recurrence from systemic therapy to receive either tiragolumab in combination with atezolizumab or atezolizumab monotherapy. Based on results from the Phase II GO40290 study, the combination of tiragolumab plus atezolizumab in the experimental arm may represent a potentially efficacious treatment option for patients with PD-L1–positive cervical cancer and can offer a reasonable benefit–risk balance for patients in this study. Atezolizumab monotherapy has been extensively studied in a wide number of tumor types. Atezolizumab is well tolerated, and adverse events have been broadly consistent across tumor types.

Tumors may use more than one mechanism to evade the immune system. Therefore, using more than one method to activate the immune response may show synergistic effects. Based on the above data, the combination of tiragolumab plus atezolizumab is expected to have enhanced efficacy and safety profiles similar to atezolizumab monotherapy.

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cervical 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 injection.

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

Severe SARS-CoV-2 infection appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and 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 immune checkpoint inhibitors and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between 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 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 tiragolumab and/or atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

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

2. OBJECTIVES AND ENDPOINTS

This Phase II study will evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and atezolizumab monotherapy in patients with metastatic and/or recurrent PDL1−positive (tumor cells and tumor-associated immune cells [redacted]) cervical carcinoma. Specific objectives and corresponding endpoints for the study are outlined in the following sections.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a complete response (CR) or a partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by an independent review committee (IRC) according to RECIST v1.1

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoints:

- DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the IRC according to RECIST v1.1
- Disease control rate (DCR), defined as the proportion of patients with a CR, PR, or stable disease (SD), as determined by an IRC according to RECIST v1.1
- Best clinical response (BCR) rate, defined as the proportion of patients with a CR, PR, or SD, and the DOR as clinically determined by the investigator
- PFS after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause, whichever occurs first
- PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause at 6 months post-randomization
- OS after randomization, defined as the time from randomization to death from any cause
- OS rate at 6 months and 12 months, defined as the proportion of patients who have not experienced death from any cause at 6 months and 12 months *post−randomization*, respectively

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoint:

- 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)

[redacted].

2.3 PHARMACOKINETIC OBJECTIVE

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

- Serum concentrations of tiragolumab at specified timepoints
- Serum concentrations of atezolizumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

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

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

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This Phase II, global, open-label, randomized study is designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy in patients with metastatic and/or recurrent PD-L1–positive cervical cancer after progression or recurrence from at least one platinum-based but no more than two prior systemic therapies.

Approximately 160 patients will be enrolled in the global enrollment phase of this study. Women with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 who have metastatic and/or recurrent PD-L1–positive cervical cancer are eligible (for the complete list of eligibility criteria, refer to Sections 4.1.1 and 4.1.2).

Additional patients may be subsequently randomized in a [redacted]

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 an additional two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are rescreened within 60 days after previously signing the consent form. The investigator will maintain a record of reasons for screen failure.

During screening, tumor specimens from each potentially eligible patient will be prospectively tested for PD-L1 expression, as assessed by a central laboratory, using the [redacted].
Only patients who are PD-L1–positive with [redacted] will be enrolled.

Eligible patients will be randomized in a 3:1 ratio to receive either tiragolumab in combination with atezolizumab or atezolizumab alone.

Eligible patients will be stratified by ECOG Performance Status (0 versus 1), prior use of chemoradiotherapy or radiotherapy (yes versus no), and treatment history (persistent versus recurrent disease).

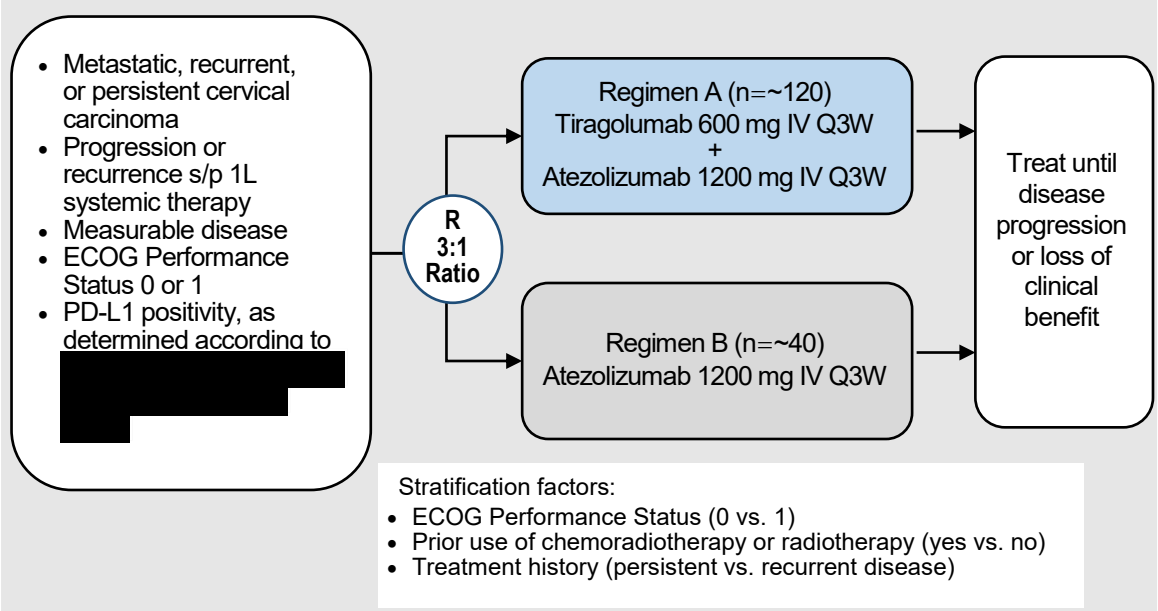
In the doublet arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered by IV infusion Q3W also on Day 1 of each 21-day cycle.

In the atezolizumab monotherapy arm, patients will receive atezolizumab at a fixed dose of 1200 mg 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 of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for equivocal disease progression per RECIST v1.1 will be permitted to continue treatment (tiragolumab in combination with atezolizumab or atezolizumab alone) if they meet all of the criteria specified.

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

Figure 1 Study Schema



1L = first line; [redacted] ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death–ligand 1; Q3W = every 3 weeks; R = randomization; s/p = status-post.
Note: Crossover is allowed from the atezolizumab monotherapy arm to the tiragolumab plus atezolizumab arm after unequivocal progressive disease has been recorded during atezolizumab monotherapy, at the discretion of the investigator and after consultation with the Medical Monitor.

During the study, serum samples will be collected to monitor tiragolumab in combination with atezolizumab and atezolizumab pharmacokinetics and to detect the presence of

antibodies to tiragolumab and atezolizumab (see Appendix 2 for the sampling schedule). Patient samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, will also be collected for [redacted] assessments.

Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (± 7 days) regardless of treatment delays until unequivocal radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above 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.

Response will be assessed according to RECIST v1.1 (see Appendix 3). Objective response will be determined at a single timepoint by the IRC according to RECIST v1.1. *As of protocol amendment version 8, imaging scans no longer need to be sent to or assessed by IRC.*

Crossover is allowed from the atezolizumab monotherapy arm to the tiragolumab plus atezolizumab arm after unequivocal progressive disease has been recorded during atezolizumab monotherapy, at the discretion of the investigator and after consultation with the Medical Monitor. For patients who crossover from atezolizumab monotherapy to tiragolumab plus atezolizumab, the tumor assessment just preceding crossover will serve as a rebaseline scan against which all subsequent scans will be compared.

After initiation of study treatment, all adverse events will be reported according to the adverse event reporting period (see Section 5.3.1). After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigators become aware of any serious adverse events or adverse events of special interest that are believed to be related to prior treatment with study drug(s). These events should be reported using the Adverse Event electronic Case Report Form (eCRF).
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 protocol-related procedures until a final outcome can be reported.

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. All patients will be periodically contacted for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator). If the patient withdraws from the study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status only.

3.1.2 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 study treatment at the investigator's discretion provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values indicating unequivocal progression of disease)
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.3 Safety Monitoring

The Sponsor will monitor patient safety throughout the study. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events; deaths; vital signs; and laboratory abnormalities, the Sponsor will review all cumulative data at regular intervals during the study.

3.1.4 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) composed of representatives from safety science, clinical science, and statistics, who are independent from the study team, will be established. Representatives from other functions may be added on an ad hoc basis depending on the nature of the findings. The primary responsibility of the IMC is to evaluate the safety, not efficacy, of treatment arms being evaluated. The IMC will share responsibility with the study team for the monitoring of patient safety.

The IMC may meet during the course of the study. The IMC may conduct an ad hoc meeting should an unexpected safety concern arise, as specified in the IMC Charter. At the time of each review of cumulative data, the IMC may make recommendations in consideration of the totality of the available data. Specific operational details such as the committee's composition, timing of meetings, and members' roles and responsibilities will be detailed in an 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 (i.e., when the last patient has recorded her last visit). *The end of study has been extended until all patients on active treatment in the study roll over to the continued access program.*

3.3 RATIONALE FOR STUDY DESIGN

This Phase II study design is based on the hypothesis that the combination of tiragolumab plus atezolizumab and atezolizumab monotherapy may elicit more responses (either a CR or a PR) and prolong the durability of such responses in patients with metastatic and/or recurrent PD-L1–positive cervical carcinoma.

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab, as outlined in the Tecentriq prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the MTD of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg atezolizumab Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

[redacted]

[redacted]

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

[redacted]

3.3.4 Rationale for Open-Label Study

Given that this study is designed to generate efficacy and safety data in this cervical cancer population, an open-label study design was chosen to enable rapid assessment and shared decision-making between physicians and patients in the study.

To ensure the objectivity of tumor-response data collected in an open-label study, the primary efficacy endpoint is IRC-determined ORR per RECIST v1.1. In addition, the strategy and timing for interim and final analysis of the primary endpoint have been prespecified in the protocol to ensure adequate duration of surveillance in the study.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

3.3.5.1 Rationale for Collection of Mandatory Archival and/or Pretreatment Biopsy Tumor Specimens

In this Phase II study, archival and/or fresh tumor specimens from patients will be tested for PD-L1 expression by a central laboratory and only patients with PD-L1–positive tumors (defined by expression of PD-L1 detected with the [redacted] at [redacted] by central laboratory assessment) will be enrolled. The efficacy endpoints will be analyzed in all randomized patients who receive at least one dose of study treatment. In addition, as part of an [redacted] efficacy analysis, investigator-assessed PFS and OS will also be analyzed in PD-L1 subgroups.

In addition, archival and/or pretreatment biopsy tumor specimens obtained from patients [redacted]

immunobiology, mechanisms of resistance, or tumor types or subtypes, and tumor mutational burden. The evaluation of biomarkers may help to identify which patients may potentially benefit most from tiragolumab plus atezolizumab and may help to guide future development of novel therapeutic and diagnostic options. DNA and/or RNA extraction and analysis may be performed to enable next-generation sequencing (NGS) and to evaluate expression of genes to assess their association with efficacy and/or to identify selected somatic mutations and disease pathways to increase the understanding of cervical cancer pathobiology.

3.3.5.2 Rationale for Collection of Blood Samples for Biomarker Analyses

Blood samples will be collected at screening and/or at baseline, during therapy, and at first evidence of radiographic progression or loss of clinical benefit. [redacted]

3.3.5.3 Rationale for Next-Generation Sequencing, Whole Genome Sequencing, or Whole Exome Sequencing in Tumor and/or Blood Samples

Tumor tissue and blood samples collected in this study may be used for DNA and RNA extraction to enable analysis by means of NGS techniques to identify mutations (somatic and possibly germline) and gene expression profiles that may be predictive of response or of resistance to tiragolumab plus atezolizumab. These analyses may also help identify susceptibility to developing adverse events, understand the mechanisms of response or resistance to treatment, and increase the knowledge and understanding of the biology of cervical cancer.

[redacted]

Genomics is increasingly informing researchers' understanding of disease pathobiology. [redacted] 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

[redacted]

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

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression and/or tumor immune infiltration, this study will allow patients randomized to continue to receive study treatment 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 3.1.2).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 160 patients with metastatic and/or recurrent PD-L1–positive cervical cancer will be enrolled in the global enrollment phase. [redacted]

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
- Life expectancy ≥ 12 weeks
- Ability to comply with the study protocol
- ECOG Performance Status of 0 or 1 (see Appendix 4)
- Histologically confirmed recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix (neuroendocrine, clear cell, and sarcoma histologies are not allowed) after progression on or after 1–2 lines of prior systemic chemotherapy in the metastatic/recurrent setting that is not amenable to curative treatment with systemic chemotherapy, surgery, and/or radiotherapy

  At least one prior line of platinum-based systemic chemotherapy.

Radiosensitizing cisplatin given with radiotherapy is not considered a line of systemic chemotherapy.

- Measurable disease, defined as:
  - At least one lesion that can be accurately and reliably measured in at least one dimension using computed tomography (CT) or magnetic resonance imaging (MRI) scan. Positron emission tomography (PET-CT) may be used if the CT portion is of diagnostic quality.
  - Tumors within a previously irradiated field cannot serve as a “target lesion”; however, they may serve as a “non-target lesion.”
- Formalin-fixed, paraffin-embedded (FFPE) cervical cancer tissue specimen (archival or tissue obtained from biopsy at screening) that is PD-L1 positive, as determined by the [redacted], with positivity defined as [redacted] as determined by a central laboratory.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - [redacted]
- [redacted]
- [redacted]

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Recovery from the effects of surgery, radiotherapy, or chemoradiotherapy

  At least 6 weeks must have elapsed from the last administration of chemoradiotherapy, and at least 3 weeks must have elapsed from the last administration of radiotherapy alone.
- 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, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, 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.

4.1.2 Exclusion Criteria

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

- FFPE cervical cancer tissue specimens (archival or tissue obtained from biopsy at screening) that is PD-L1 negative, as determined by the [redacted], with negativity defined as [redacted], as determined by a central laboratory
- Pregnant or breastfeeding, or intending to become pregnant during study treatment, within 90 days after the final dose of tiragolumab, or within 5 months after the final dose of atezolizumab

  Women of childbearing potential must have a negative pregnancy test result within 14 days prior to Cycle 1, Day 1.
- Treatment with investigational therapy with therapeutic intent within 28 days prior to randomization
- Planned surgery during the study
- Current treatment with anti-viral therapy for [redacted]
- Substance abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Bilateral hydronephrosis that cannot be alleviated by ureteral stents or percutaneous drainage
- History of other malignancy within 5 years prior to screening, except for those with an expected negligible risk for metastases or death (e.g., 5-year OS $>$ 90%) after curative treatment

  Examples include appropriately treated basal or squamous cell skin carcinoma, FIGO Stage I Grade 1 uterine cancer or ductal carcinoma in situ of the breast.
- Active or untreated CNS or brain metastases
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $\geq$ 1 week prior to randomization
- Leptomeningeal disease
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, total serum calcium $>$ 12 mg/dL, or corrected serum calcium greater than ULN)
- Known, clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse

- Active or history of autoimmune disease or immune deficiency, [redacted]
- [redacted]
- Active tuberculosis
- Severe infection per investigator judgment at the time of randomization, including, but not limited to, use of systemic antibiotics, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Significant cardiovascular disease, such as cardiac disease New York Heart Association Class II or greater, myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criterion or with a left ventricular ejection fraction $<50\%$ must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the study

- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk for treatment complications
- Illnesses or conditions that interfere with the patient's capacity to understand, follow, and/or comply with study procedures
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study

  Patients must not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, for 90 days following the last dose of tiragolumab, and for 5 months following the last dose of atezolizumab.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–CTLA-4, anti-TIGIT, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to randomization
- Treatment with systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 1 week prior to randomization 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, fully humanized, or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the tiragolumab or atezolizumab formulations

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's

identification number and treatment assignment from the web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms of tiragolumab in combination with atezolizumab or atezolizumab monotherapy. Randomization will occur in a 3:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. [redacted] Randomization will be stratified according to the following criteria:

- ECOG Performance Status (0 vs. 1)
- Prior use of chemoradiotherapy or radiotherapy (yes vs. no)
- Treatment history (persistent vs. recurrent disease)

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMPs) for this study are tiragolumab and atezolizumab.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Tiragolumab

Tiragolumab will be supplied by the Sponsor as a sterile liquid in a [redacted]. The vial contains approximately [redacted] of tiragolumab.

For further information on the formulation and handling of tiragolumab, please see the pharmacy manual and/or the Tiragolumab Investigator's Brochure.

4.3.1.2 Atezolizumab

Atezolizumab will be supplied by the Sponsor as a [redacted]. The vial contains approximately [redacted] of atezolizumab solution.

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

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

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

After the atezolizumab infusion, patients in the atezolizumab in combination with tiragolumab cohort will receive 600 mg tiragolumab administered by IV infusion on Day 1 of each 21-day cycle. The tiragolumab and atezolizumab doses are fixed and are not dependent on body weight.

Administration of tiragolumab and atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

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

Details on treatment administration (e.g., dose and timing) 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 5.1.2.3 and Appendix 7.

4.3.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

For anaphylaxis precautions, Appendix 6. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Atezolizumab Monotherapy Infusions

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

IRR = infusion-related reaction.

Guidelines for medical management of IRRs are provided in the Appendix 7.

No dose modification for atezolizumab is allowed.

4.3.2.2 Tiragolumab and Atezolizumab

In the doublet arm, 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 by IV infusion Q3W also on Day 1 of each 21-day cycle (see Section 3.1.1). The tiragolumab and atezolizumab dose are fixed and are not dependent on body weight.

For anaphylaxis precautions, refer to Appendix 6. Tiragolumab and atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Tiragolumab and Atezolizumab Infusions

	First Infusion	Subsequent Infusions
Atezolizumab infusion	• No premedication is permitted for the first 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 (±10) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion.	• If the patient experienced an IRR during any previous infusion of atezolizumab, premedication with antihistamines, antipyretics, and/or analgesics 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 infusion of atezolizumab	• 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.

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

	First Infusion	Subsequent Infusions
Infusion of tiragolumab	[redacted]	
Observation period after infusion of tiragolumab		

IRR = infusion-related reaction.

4.3.3 Investigational Medicinal Product Accountability

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied

IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Continued Access to Atezolizumab and/or Tiragolumab

The Sponsor will offer continued access to Roche IMPs (tiragolumab and/or atezolizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (tiragolumab and/or atezolizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive Roche IMPs (tiragolumab and/or atezolizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for cervical cancer.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for cervical cancer.
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country.

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

Patients may be eligible to receive tiragolumab and/or atezolizumab as part of an extension study, as described in Section 3.2.

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 drug 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]

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent study treatment infusions only, at the discretion of the investigator.

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 4.4.1 and 4.4.2) 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 7).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

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

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 7 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 4.4.2.2) 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. All activities should be performed and documented for each patient.

Patients will undergo tumor assessments as described in Section 4.5.6.

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.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for an additional re-screening opportunities as described in Section 3.1.1.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

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

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

4.5.3 Physical Examinations

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

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

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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

4.5.5 Performance Status

Performance status will be measured using the ECOG Performance Status and will be assessed at regular intervals throughout the study as specified in the schedule of activities (see Appendix 1). For further details, see Appendix 4.

4.5.6 Tumor and Response Evaluations

Screening and subsequent tumor assessments must include CT scans (with oral and/or IV contrast, unless contraindicated) or MRI scans of the chest-abdomen-pelvis. MRI scans with contrast of the chest, abdomen, and pelvis may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). A non-contrast CT scan of the chest may be used in lieu of an MRI of the chest.

In all patients with clinical evidence suspicious for CNS involvement, a CT scan with contrast or MRI scan with contrast (if CT contrast is contraindicated) of the brain must be performed at screening to evaluate CNS metastasis. If a CT scan with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline. Patients with active or untreated CNS metastases are not eligible for the study (see Section 4.1.2).

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

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

Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Day 1 of Cycle 1 may be used rather than repeating tests. All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. At subsequent (post-screening) tumor assessments, patients with a history of irradiated brain metastases at screening are not required to undergo brain scans unless clinically indicated (e.g., in patients with neurologic symptoms). The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

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

Response was previously assessed by the IRC on the imaging modalities detailed above, using RECIST v1.1 (see Appendix 3). As of protocol amendment version 8, imaging scans no longer need to be sent to or assessed by IRC. 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. Results must be reviewed by the investigator before dosing at the next cycle.

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

Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first *at the discretion of the investigator*.

Investigator assessment of overall tumor response at all timepoints will be only based on RECIST v1.1 (see Appendix 3). This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable; see Appendix 3) 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, hemoglobin, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
- Chemistry panel (serum or plasma): sodium, potassium, glucose, BUN or urea, creatinine, albumin, total calcium, total and direct bilirubin, ALP, ALT, AST, and LDH
- Coagulation: PT (or INR) and aPTT (or PTT)
- 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)

- Pregnancy test

  All women of childbearing potential will have a urine or serum pregnancy test ≤14 days prior to Cycle 1, Day 1. Urine pregnancy tests will be performed at specified subsequent visits. A positive urine pregnancy test must be confirmed by a quantitative serum pregnancy test and an ultrasound confirming intrauterine pregnancy.

- Urinalysis (glucose, protein, ketones, blood, leukocyte esterase, nitrites, WBC, bacteria, and epithelial cells); dipstick permitted

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis. Instruction manual and supply kits will be provided for these central assessments. Refer to the laboratory manual for additional details on sample handling.

Assessments Performed on Blood Samples

The following assessments will be performed on the blood samples:

- PK assays

  Serum samples will be obtained for measurement of tiragolumab or atezolizumab concentrations using validated immunoassays.

- ADA assays

  Serum samples will be obtained for measurement of ADAs to tiragolumab or to atezolizumab using validated assays.

[redacted]

Blood will be obtained for DNA extraction and used as a control to support the identification of somatic mutations in tissue and plasma circulating tumor DNA.

- Auto-antibody assays

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

Assessments Performed on Tissue Samples

The following assessments will be performed on tumor tissue samples:

- Archival or newly collected tumor tissue sample obtained at baseline for determination of PD-L1 and for [redacted]

  [redacted]

[redacted]

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

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

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum and tumor tissue samples collected for biomarker research and/or biomarker assay development will be destroyed no later than 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than 18 months after the final closure of the study

database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination, if requested.

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, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

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

4.5.8 Electrocardiograms

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

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

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 she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy

- Loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.2 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 ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, *no further information on survival follow-up will be collected as of protocol version 8.*

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

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

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on anticipated mechanism of action, results from nonclinical studies, published data on similar molecules, clinical experience with tiragolumab alone and in combination with atezolizumab in Phase I and II studies, and the clinical safety profile of atezolizumab as a single agent. The anticipated important safety risks for tiragolumab, atezolizumab, and tiragolumab in combination with atezolizumab are outlined below (see Sections 5.1.2, 5.1.1, and 5.1.3, respectively). Refer to the Tiragolumab Investigator's Brochure and the Atezolizumab Investigator's Brochure for a complete summary of safety information for each respective study drug.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of tiragolumab and atezolizumab 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 7.

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the NCI CTCAE v5.0.

Safety assessments will include the incidence, nature, and severity of adverse events, protocol-mandated vital signs, laboratory abnormalities, and other protocol-specified tests that are deemed critical to the safety evaluation of the study. Adverse events will be graded according to the NCI CTCAE v5.0. Refer to Sections 5.4–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

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

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: 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 7 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]

5.1.2.1 Infusion-Related Reactions

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

[redacted]

Refer to Section 4.3.2 for detailed guidance on administration of atezolizumab as well as tiragolumab in this study. Refer to Appendix 6 for guidance on anaphylaxis precautions, and Appendix 7 for guidance on management of IRRs.

[redacted]

Refer to Appendix 7 for guidance on the management of immune-mediated hepatitis.

5.1.2.3 Lymphopenia

The IgG1 backbone of tiragolumab with the intact Fc-effector function may lead to ADCC-mediated reduction in lymphocyte count. [redacted]

Patients with a lymphocyte count $<$ 500 cells/mL will be excluded from this study (see Section 4.1.2), and CBCs will be monitored regularly during the study (see Appendix 7).

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 in an EAE using suboptimal doses. In contrast to the wild-type B6 mice, the majority of the TIGIT–/–mice developed severe EAE (Joller et al. 2011).

[redacted]

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 7.

[redacted]

5.1.3 Risks Associated with Combination Use of Tiragolumab and Atezolizumab

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

Refer to Section 6 of the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. 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 CIT will also be excluded from participation in this study. [redacted] (see Section 4.1.2).

5.1.4 Management of Adverse Events

5.1.4.1 Dose Modifications

[redacted]

5.1.4.2 Treatment Interruption

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed. The Medical Monitor is available to advise as needed.

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

5.1.4.3 Management Guidelines for Tiragolumab- and Atezolizumab-Specific Adverse Events

General guidelines for management of patients who experience adverse events, including HLH and *macrophage activation syndrome (*MAS*)*, are presented in Appendix 7.

Guidelines for management of patients who experience adverse events associated with tiragolumab and/or atezolizumab, including immune-mediated adverse events, are provided in Appendix 7.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- [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:

[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.

[redacted]

[redacted]

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 [redacted]

There may be significant overlap in signs and symptoms of IRRs and [redacted]. Whereas IRRs occur during or within 24 hours after treatment administration, time to onset of [redacted] may vary. Differential diagnosis should be applied, particularly for [redacted] (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, [redacted], 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 as a diagnosis (e.g., "infusion-related reaction" or "[redacted]") on the Adverse Event eCRF. Avoid ambiguous terms such as "systemic reaction." [redacted] on the Adverse Event eCRF. Associated signs and symptoms should be recorded on the dedicated

Infusion-Related Reaction eCRF or [redacted], 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 [redacted].

NCI CTCAE v5.0 and [redacted] should be used when reporting severity of [redacted] on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with [redacted] on the dedicated [redacted]. Organ toxicities associated with [redacted] should not influence overall CRS grading.

Guidelines for medical management of IRRs and [redacted] are provided in Appendix 7, Table 7, and Table 8, respectively.

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

5.3.5.2 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., ALP 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 cervical cancer 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).

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 Cervical Cancer

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

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

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

- Medication error: accidental deviation in the administration of a drug

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

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

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

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

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

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported for the period defined in Section 5.3.1. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study treatment, within 90 days after the final dose of tiragolumab, or within 5 months after the final dose of atezolizumab. 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 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 embryo–fetal 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 embryo–fetal toxicity is not considered an adverse event.

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

5.4.3.3 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (see 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 Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

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

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase II, global, open-label, randomized study designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy in approximately 160 patients with metastatic and/or recurrent PD-L1–positive cervical cancer after progression or recurrence from systemic therapy.

Efficacy analyses will be conducted in all randomized patients who receive at least one dose of study treatment. Patients will be grouped according to treatment received, excluding treatment received during a potential crossover period.

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

The global population will include all patients enrolled during the global enrollment phase, and the [redacted] Separate analyses will be performed for the global population and the [redacted].

More details of analyses are provided in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

A total of 160 patients will be enrolled in this study and randomized in a 3:1 ratio (tiragolumab in combination with atezolizumab and atezolizumab monotherapy). The overall statistical power for several assumptions of the true underlying ORR in tiragolumab in combination with atezolizumab arm is given in Table 6 and takes the following considerations into account:

- Primary statistical test is a [redacted] at a one-sided [redacted] significance level, and the doublet arm will be compared to a historical reference of 14.6% (Chung et al. 2019).
- [redacted]

No type-I error control is applied for descriptive comparisons, including that of the atezolizumab monotherapy ORR to the historical reference. The probability of the observed ORR in the atezolizumab monotherapy arm being greater than a reference point at the time of final ORR analysis is also shown in Table 7.

Table 6 Overall Statistical Power in the Comparison of ORR in Tiragolumab in Combination with Atezolizumab Arm to a Reference Point of 14.6%

Reference ORR	True Underlying ORR in Tiragolumab in Combination with Atezolizumab
14.6% [a] (MDO [b] = [redacted])	[redacted]

MDO = minimum detectable observation; ORR = overall response rate.

[a] Source: Chung et al. 2019.

[b] MDO is defined as the smallest observed ORR leading to statistical significance at final analysis.

Table 7 Probability of Observed ORR in Atezolizumab Monotherapy Arm Greater than a Reference Point at the Final Analysis for ORR

Reference ORR	True Underlying ORR in Atezolizumab Monotherapy
14.6% [a]	[redacted]

ORR = overall response rate.

[a] Source: Chung et al. 2019.

[redacted]

[redacted]

[redacted]

[redacted]

[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.

6.4 EFFICACY ANALYSES

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 according to treatment received, excluding treatment received during a potential crossover period.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the IRC according to RECIST v1.1. *As of protocol amendment version 8, imaging scans no longer need to be sent to or assessed by IRC.*

The primary efficacy analysis population will consist of all randomized patients who receive at least one dose of study treatment, with patients grouped according to treatment received.

The primary efficacy analysis will take place once all patients have been enrolled and a minimum follow-up of approximately 6 months after the second tumor assessment, or approximately 9 months after randomization, has been achieved among the patients who remain in follow-up for ORR assessment, whichever is earlier.

In the primary analysis, patients whose ORR assessment was missing will be counted as not achieving a response. A one-sample z-test for proportion will be used for comparing the ORR of the tiragolumab in combination with atezolizumab arm to the historical reference. An estimate of the ORR and its 95% CI (Clopper-Pearson; Clopper and Pearson 1934) will be calculated for each treatment arm.

A sensitivity analysis will be performed for the primary endpoint of confirmed ORR on the ITT population (all randomized patients).

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoints as described below.

6.4.2.1 Duration of Response

DOR is defined for patients who had an objective response as the time from the first occurrence of a documented objective response (CR or PR) to the date of disease progression or death from any cause (whichever occurs first), as determined by the IRC according to RECIST v1.1. *As of protocol amendment version 8, imaging scans no longer need to be sent to or assessed by IRC.* Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of CR or PR, data for DOR will be censored at the date of the first occurrence of CR or PR plus1 day.

The analysis of DOR is based on a non-randomized subset of patients (those who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes only. In particular, 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 Disease Control Rate

DCR is defined as the proportion of patients with a CR, PR, or SD, as determined by the IRC according to RECIST v1.1. *As of protocol amendment version 8, imaging scans no*

longer need to be sent to or assessed by IRC. The methodologies described for the analysis of ORR will be the same as used for the analysis of DCR.

6.4.2.3 Best Clinical Response

BCR is defined as the proportion of patients with a CR, PR, or SD, as determined by the investigator. The methodologies described for the analysis of ORR will be the same as used for the analysis of BCR. DOR determined by the investigator will also be provided, and the methodology will be the same as used for the analysis of the IRC DOR.

6.4.2.4 Progression-Free Survival, Including the 6-Month Progression-Free Survival Rate

PFS is defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the IRC according to RECIST v1.1. *As of protocol amendment version 8, imaging scans no longer need to be sent to or assessed by IRC.*

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 Kaplan-Meier approach will also be used to estimate 6-month PFS rate in each arm.

6.4.2.5 Overall Survival, Including the 6-Month and 12-Month Overall Survival Rate

OS is defined as the time from randomization to death from any cause.

The methodologies described for the analysis of PFS will be the same as used for the analysis of OS.

[redacted]

6.4.4 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

The safety analyses will include all randomized patients who receive at least one dose of study drug, with patients grouped according to treatment received. Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, and study treatment exposures and will be presented by treatment arm. Verbatim descriptions of adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries. The following treatment-emergent adverse events will be summarized separately: adverse events leading to withdrawal of study drug, adverse

events leading to dose reduction or interruption, Grade ≥3 adverse events, adverse events leading to death, serious adverse events, and adverse events of special interest (see Section 5.2.3). Relevant laboratory values will be summarized by time, with NCI CTCAE v5.0 Grade 3 and Grade 4 values identified, where appropriate. Changes in NCI CTCAE grade will be tabulated by treatment arm.

6.5 SAFETY ANALYSES

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

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

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs, study treatment exposures, and immunogenicity as measured by ADAs and will be presented by treatment arm.

Verbatim descriptions of adverse events will be mapped to MedDRA terms. Severity for all events will be graded by the investigator according to NCI CTCAE v5.0, and [redacted] All adverse events will be summarized by treatment arm. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately: adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade ≥3 adverse events, Grade 5 adverse events, serious adverse events, and adverse events of special interest.

All deaths and causes of death will be summarized.

Relevant laboratory values will be summarized by treatment arm, with NCI CTCAE Grade 3 and Grade 4 values identified, where appropriate.

6.6 PHARMACOKINETIC ANALYSES

PK samples of tiragolumab and atezolizumab will be collected in this study as outlined in Appendix 2. Tiragolumab and atezolizumab serum concentration data (minimum serum concentration and maximum serum concentration) will be tabulated and summarized.

Descriptive statistics will include 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 assessments, with patients grouped according to treatment received.

The number and proportion of treatment-emergent ADA-positive patients and ADA-negative patients during both the treatment and follow-up periods will be summarized by treatment arm.

[redacted]

[redacted]

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor 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.

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.

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 is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered on 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, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 100 sites globally will participate to randomize approximately 160 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, biomarker analyses, and PK analyses), as specified in Section 4.5.7. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Tumor response and progression will be evaluated by an IRC. *As of protocol amendment version 8, imaging scans no longer need to be sent to or assessed by IRC.*

An IMC will be employed to 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 summaries of clinical study results may be available in health authority databases for public access, as required by local regulation,

and reports 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/Procedure (Window)	Screening Days –28 to –1 [b]	All Treatment Cycles [a] Every 21 days (±3 Days) [c]	Treatment Discontinuation ≤ 30 Days after Final Dose	Long-Term Survival Follow-Up [d] Approximately Every 3 Months after Disease Progression or Loss of Clinical Benefit [d]
Informed consent	x			
Archival or fresh tumor tissue specimen for PD-L1 testing (20 FFPE slides required; blocks preferred) [e, f]	x			
Demographics (age, sex, and self-reported ethnicity/race)	x			
Medical and cervical cancer history, and baseline conditions	x			
Vital signs [g]	x	x	x	
Weight	x	x	x	
Height	x			
Complete physical examination [h]	x			
Limited physical examination [h]		x		
ECOG Performance Status	x	x	x	
ECG [i]	x			
Hematology [j]	x	x	x	
Chemistry [k]	x	x	x	
Coagulation test (PT [or INR] and aPTT [or PTT])	x		x	

Appendix 1: Schedule of Activities

Assessment/Procedure (Window)	Screening Days –28 to –1[b]	All Treatment Cycles[a] Every 21 days (±3 Days)[c]	Treatment Discontinuation ≤ 30 Days after Final Dose	Long-Term Survival Follow-Up[d] Approximately Every 3 Months after Disease Progression or Loss of Clinical Benefit[d]
Pregnancy test[l]	x[l]	x	x	
TSH, free T3, and free T4[m]	x	x	x	
[redacted]				
Urinalysis[o]	x			
Arm A: atezolizumab plus tiragolumab administration[p]		x		
Arm B: atezolizumab administration[p]		x		
Tumor response assessment[q]	x	x[r]		x[s]
[redacted]				
Concomitant medications[t]	x	x	x	
Adverse events[u]		x	x	x[u]
Survival and anti-cancer follow-up[v]				x

Appendix 1: Schedule of Activities

ADA = anti-drug antibody; CT = computed tomography; [redacted] ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; [redacted]; MRI = magnetic resonance imaging; NA = not applicable; PCR = polymerase chain reaction; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

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

[b] Adequate hematologic and end-organ function, defined by laboratory test results, must be obtained within 14 days prior to randomization.

[c] Cycle 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤ 4 days prior to Cycle 1, Day 1 are not required to be repeated for the Cycle 1, Day 1 infusion.

[d] This visit *was previously* conducted by telephone. Approximately every 3 months as defined as every 84 days ± 7 days. *Long-term survival follow-up is no longer needed as of protocol version 8.*

[e] [redacted]

[f] Biomarker samples should not be collected for patients enrolling from [redacted]. Samples collected should match the number of slides allowed per [redacted].

[g] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.4.

[h] Complete physical examination must include pelvic examination. Limited physical examination will be a symptom-directed physical examination, as clinically indicated; see Section 4.5.3 for details.

[i] 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.

[j] Hematology consists of WBC count, hemoglobin, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).

[k] Chemistry panel (serum or plasma) includes sodium, potassium, glucose, BUN or urea, creatinine, albumin, total calcium, total and direct bilirubin, ALP, ALT, AST, and LDH.

[l] Pregnancy test should be performed for women of childbearing-potential only. Pregnancy test (serum or urine) must be performed ≤14 days prior to Cycle 1, Day 1. A positive urine pregnancy test must be confirmed by a quantitative serum pregnancy test and an ultrasound confirming intrauterine pregnancy.

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

[n] [redacted]

[o] Urinalysis is required at screening and can be by dipstick (glucose, protein, ketones, blood, leukocyte esterase, nitrites, WBC, bacteria, and epithelial cells).

[p] The initial cycle of atezolizumab plus tiragolumab or atezolizumab monotherapy should be administered over [redacted] minutes for each agent. Subsequent infusions of each agent should be infused over [redacted] minutes if the previous infusion was tolerated without an infusion-related reaction, or [redacted] minutes if patient experienced an infusion-related reaction with the previous infusion (see Section 4.3.2). For the tiragolumab and atezolizumab doublet, the tiragolumab must be administered after the atezolizumab.

[q] At screening and subsequent visits, CT scans (with oral and/or IV contrast, unless contraindicated) or MRI scans of the chest-abdomen-pelvis will be performed. A CT (with contrast) or MRI scan of the brain must be done at screening to evaluate CNS metastases in symptomatic patients, as clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Refer to Section 4.5.6.

[r] Perform every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1, regardless of treatment delays. After completing the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays, until unequivocal radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after RECIST v1.1–defined disease progression), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

[s] If a patient discontinues study treatment for any reason other than radiographic RECIST v1.1–defined disease progression (e.g., toxicity, symptomatic deterioration), tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [±7 days]) for 48 weeks following Day 1 of Cycle 1, and then every 9 weeks [±7 days] thereafter) until unequivocal radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs, first, even if the patient starts another anti-cancer therapy after discontinuing study treatment. See Section 4.6.1 for details.

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

[u] [redacted] After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6). These events should be reported on the Adverse Event eCRF.

[v] *As of protocol version 8, survival follow-up information will no longer be collected. The study will no longer* contact the patients for survival and new anti-cancer therapy information.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

[redacted]

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

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

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 10 mm but $<$ 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, 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, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

All lesions (or sites of disease) not selected as target lesions (measurable or non measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple nontarget 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.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

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.

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.

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Appendix 4
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease 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 5
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 reaction or pericardial disorder while receiving another immunostimulatory anticancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Appendix 6
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 7
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Tiragolumab and/or Atezolizumab

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

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

- [redacted]

DOSE MODIFICATIONS

[redacted]

TREATMENT INTERRUPTION

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

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study.

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

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

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
[redacted]	

[redacted]

HEPATIC EVENTS

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

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

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
[redacted]	

Table 2 Management Guidelines for Hepatic Events

[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.

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

Event	Management
[redacted]	

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

Event	Management
[redacted]	

[redacted]

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]	

Table 4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	

Table 4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	

Table 4 Management Guidelines for Endocrine Events

Event	Management
[redacted]	

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
[redacted]	

Table 5 Management Guidelines for Ocular Events

Event	Management
[redacted]	

IMMUNE-MEDIATED CARDIAC EVENTS

In high-risk patients (including those with abnormal baseline cardiac troponin levels, when available), transthoracic echocardiogram (TTE) monitoring should be considered, as clinically indicated, and based on local clinical practice. 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.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, *TTE for evaluation of left ventricular ejection fraction and global longitudinal strain*, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

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).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer (*e.g.,* metastatic disease*), cancer treatment (e.g.,* chest radiotherapy), cardiac injury *(e.g., injury due to* myocardial infarction or *iatrogenesis*), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, *TTE*, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6. Withhold treatment with tiragolumab and/or atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
[redacted]	

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

[redacted]

INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of Cycle 1 of tiragolumab or atezolizumab. However, patients who experience an infusion-related reaction (IRR) with Cycle 1 of tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

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

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
[redacted]	

Table 7 Management Guidelines for Infusion-Related Reactions

[redacted]

CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of tiragolumab or atezolizumab. However, patients who experience cytokine-release syndrome (CRS) with tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and *interferon*-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis

should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Guidelines for medical management of CRS are provided in Table 8.

Table 8 Management Guidelines for Cytokine-Release Syndrome

Event	Management
[redacted]	

Table 8 Management Guidelines for Cytokine-Release Syndrome

Table 8 Management Guidelines for Cytokine-Release Syndrome

[redacted]

PANCREATIC EVENTS

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

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
[redacted]	

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. Although uncommon,

cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 10.

Table 10 Management Guidelines for Dermatologic Events

Event	Management
[redacted]	

Table 10 Management Guidelines for Dermatologic Events

[redacted]

NEUROLOGIC DISORDERS

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

Table 11 Management Guidelines for Neurologic Disorders

Event	Management
[redacted]	

Table 11 Management Guidelines for Neurologic Disorders

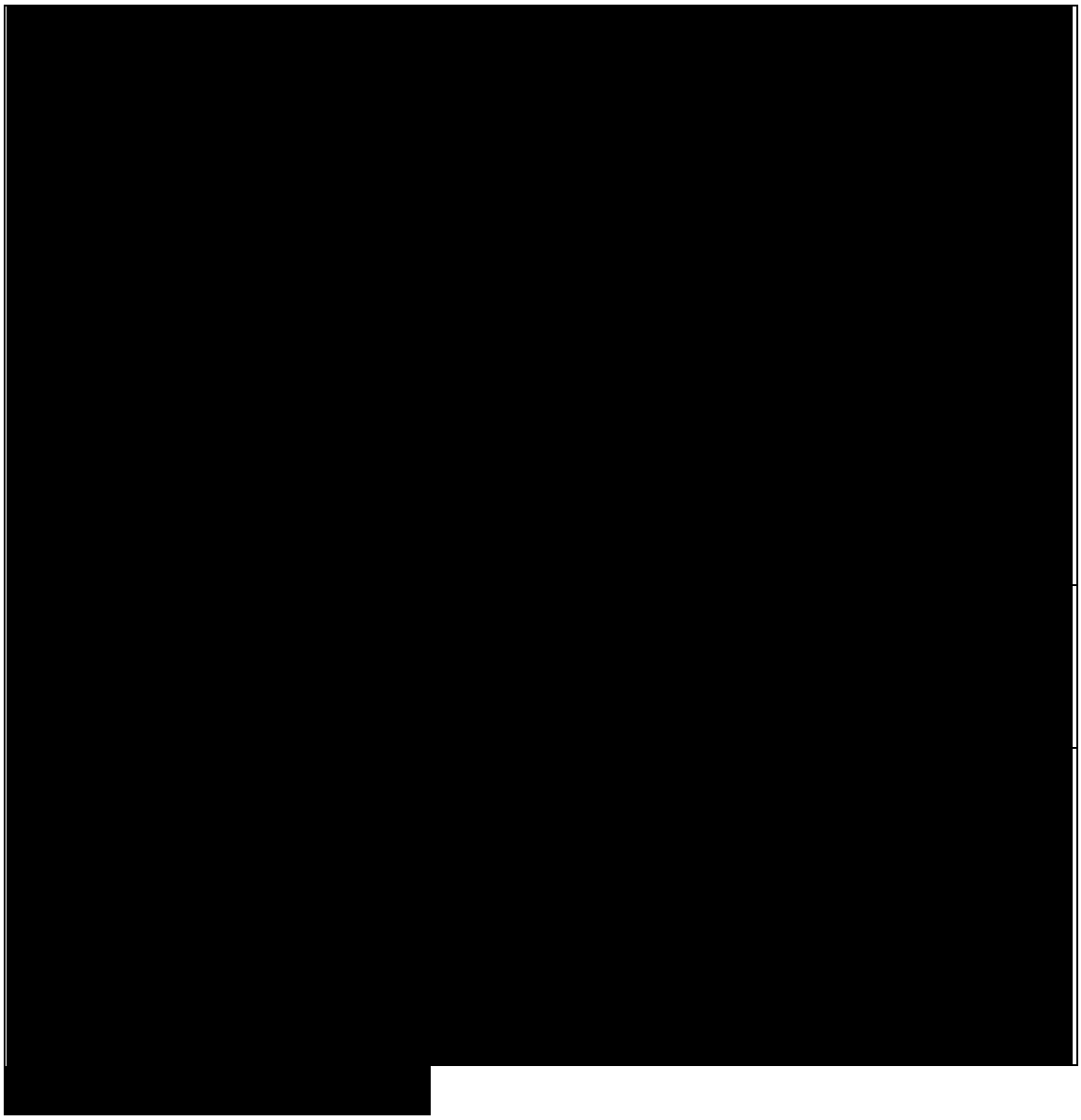

Table 11 Management Guidelines for Neurologic Disorders

[redacted]

Table 12 Management Guidelines for Immune-Mediated Myelitis

Event	Management
[redacted]	

[redacted]

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not

limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

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

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

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
[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]

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. Initial diagnosis is based on clinical (muscle weakness, muscle

pain, skin rash in dermatomyositis), biochemical (serum creatine kinase/*creatine phosphokinase* increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients may initially present with low grade nondescript symptoms including mild pain and weakness; thus, there should be a low threshold for suspicion of myositis.* Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis *(see section on immune-mediated myocarditis) and myasthenia gravis (bulbar symptoms such as dysphagia, dysphonia, and dyspnea; see section on neurologic disorders).*

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]	

Table 15 Management Guidelines for Immune-Mediated Myositis

Event	Management
[redacted]	

[redacted]

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected HLH should be treated according to the guidelines in Table 16.

Table 16 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis

Event	Management
[redacted]	

HLH = hemophagocytic lymphohistiocytosis

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