Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Treatment Combinations in Patients With Melanoma (Morpheus-Melanoma)

NCT Number: NCT05116202

Document Date: Protocol Version 4: 8-May-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH MELANOMA (MORPHEUS-MELANOMA)**
PROTOCOL NUMBER:	BO43328
VERSION NUMBER:	4
TEST COMPOUNDS:	Atezolizumab (RO5541267), tiragolumab (RO7092284), RO7247669
STUDY PHASE:	Phase Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 155538 EudraCT Number: 2021-002147-29 EU CT No.: 2022-502939-19-00 Clinical Investigation Identification Number (CIV ID): Not applicable NCT Number: NCT05116202
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	*See electronic date stamp on final page of this document.*	—	—	—
3	13 December 2022	—	—	—
2	24 February 2022	—	—	—
1	19 July 2021	France	1	22 September 2021

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol BO43328 has been amended primarily to add two new treatment arms to Cohort 1. Changes to the protocol, along with a rationale for each change, are summarized below:

- The RO7247669 600 mg treatment arm has been added for Cohort 1 to evaluate the efficacy, safety, and pharmacokinetics of a lower dose of RO7247669 based on emerging data (new Appendix 15). The following sections of the protocol have been updated to reflect the addition of this new treatment arm: Sections 1.3, 3.1.2, 3.1.3, 3.1.5, 4.1.2, 4.4, 4.5, 4.5.1, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7.2, 4.5.8, 4.5.9.1, 4.5.9.2, 4.5.11, 4.6.1, Appendix 9, Figure 2, and Tables 4 and 5.
- The RO7247669 600 mg + tiragolumab treatment arm has been added for Cohort 1 to evaluate the efficacy, safety, and pharmacokinetics of a lower dose of RO7247669 in combination with tiragolumab based on emerging data (new Appendix 16). The following sections of the protocol have been updated to reflect the addition of this new treatment arm: Sections 1.3, 3.1.2, 3.1.3, 3.1.5, 4.1.2, 4.4, 4.5, 4.5.1, 4.5.2, 4.5.3, 4.5.4, 4.5.5, 4.5.6, 4.5.7.2, 4.5.8, 4.5.9.1, 4.5.9.2, 4.5.11, 4.6.1, Appendix 9, Figure 2, and Tables 4 and 5.
- Figure 3 was updated to clarify that collection of archival tissue may take place during screening (Section 3.1.2).
- The sample sizes have been updated to 195–290 patients in Cohort 1 and 8–46 patients in Cohort 2 to reflect the number of patients currently enrolled (as of 20 March 2023) in the trial and the addition of the two new treatment arms (Section 3.1.2, Section 6.1, Figure 2, and Table 4).
- Text has been added to clarify that for most arms, approximately 20 patients will be enrolled during the preliminary phase. Approximately 40 patients will be enrolled in the RO7247669 600 mg and RO7247669 600 mg + tiragolumab arms during the preliminary phase to ensure a more precise benefit–risk assessment in arms with the lower dose of RO7247669 (Section 3.1.2 and Figure 2).
- Text was added to indicate that pausing enrollment while conducting the safety evaluation phase after 6 patients will not be needed for a lower dose of a study drug that has already completed a safety evaluation for a higher dose (Section 3.1.3), but a formal safety evaluation will be still conducted and the same stopping criteria will apply as for higher dose arms.
- Text has been updated to indicate that tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization/enrollment do not have to be repeated at screening. The previous timeframe was 14 days; the extension will reduce patient burden (Section 4.5.7.1 and Appendix 10).
- It has been clarified that in Cohort 1, tumor assessments performed outside the protocol mandated time window do not have to be repeated (Section 4.5.7.2).

- Text has been clarified to indicate that fresh tumor tissue will be processed as described in the laboratory manual (Section 4.5.9.2)
- Table 6 has been updated to clarify that archival tissue collection during screening for Cohorts 1 and 2 is mandatory, if tissue is available (Section 4.5.9.2).
- Text has been added to indicate that after the end of the reporting period for non-serious adverse events (defined as 30 days after the final dose of study treatment), all treatment-related non-serious adverse events that lead to surgery delay will continue to be reported until 135 days after the final dose of study treatment. This will allow reporting of these adverse events, which are outside of the allowed 30 day reporting period, in the event of delay in surgery (Section 5.6 and footnotes in schedule of activities for all appendices).
- Text has been modified to clarify that patients who do not proceed to complete lymph node dissection will be classified as non-responders (Section 6.4.1).
- Text has been added to specify that weight, limited physical examination, 12-lead ECG, and Eastern Cooperative Oncology Group assessments may be performed within 24 hours prior to dosing during the treatment period in order to provide additional flexibility for patients and study sites (schedule of activities for Appendices 11–16).
- Language has been added to indicate the approval of relatlimab by the U.S. Food and Drug Administration for the treatment of unresectable or metastatic melanoma (Section 1.1.1.2 and Appendices 12, 14, 15, and 16).
- Text has been updated describing Study NP41300 to align with the RO7247669 Investigator's Brochure Version 4 (Appendices 12, 14, 15, and 16).
- Throughout the protocol, the dose of RO7247669 has been updated to indicate the use of either 2100 or 600 mg.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH MELANOMA (MORPHEUS-MELANOMA)**
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SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE TREATMENT COMBINATIONS IN PATIENTS WITH MELANOMA (MORPHEUS-MELANOMA)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 155538 EudraCT Number: 2021-002147-29 EU CT No.: 2022-502939-19-00 Clinical Investigation Identification Number (CIV ID): Not applicable NCT Number: NCT05116202

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of treatment combinations in cancer immunotherapy (CIT)-naive patients with resectable Stage III melanoma (Cohort 1) and in patients with Stage IV melanoma (Cohort 2). *Four* checkpoint inhibitors, namely ipilimumab, pembrolizumab, nivolumab, *and relatlimab* are now approved by the U.S. Food and Drug Administration for the treatment of unresectable or advanced disease. For patients with macroscopic Stage III melanoma, surgery followed by adjuvant immunotherapy within 1 year of either nivolumab or pembrolizumab treatment is generally indicated. Patients with clinically detectable Stage III melanoma are ideal candidates for neoadjuvant therapy because they represent a high-risk patient population with poor outcomes when treated with upfront surgery alone. Neoadjuvant therapy also has the advantage of providing information on pathologic response, which is valuable to estimate prognosis and to guide the choice of adjuvant therapy and follow-up. This study protocol was developed in accordance with International Neoadjuvant Melanoma Consortium guidelines to create the needed consistency amongst neoadjuvant trials in order to facilitate optimal data organization for future regulatory review. Its exploratory analysis plan will strengthen translational research across the melanoma disease continuum.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints for Cohort 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment	• pRR (defined as the proportion of patients with pCR, pnCR, and pPR) at time of surgery, as determined by independent pathologic review
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• pRR (defined as the proportion of patients with pCR, pnCR, and pPR) at time of surgery, as determined by local pathologic assessment • EFS, defined as the time from randomization to any of the following events (whichever occurs first): Disease progression that precludes surgery, as assessed by the investigator according to RECIST v1.1; local, regional or distant disease recurrence; or death from any cause • RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause • OS, defined as the time from randomization to death from any cause

Table 1 Objectives and Corresponding Endpoints for Cohort 1 (cont.)

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of treatment	• ORR, defined as the proportion of patients with a CR or PR as determined by the investigator according to RECIST v1.1, prior to surgery Responses will be assessed and determined according to RECIST v1.1 but are not required to be confirmed by later imaging.
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of treatment	• Incidence, , nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v5.0 CRS severity will also be determined according to the ASTCT CRS Consensus Grading Scale. • Incidence and nature of immune-related adverse events Grade ≥ 3 during the first 12 weeks • Rate and duration of delayed surgery due to treatment-related adverse events • Surgical complication rates according to ClavienDindo- surgical classification after CLND

ASTCT = American Society for Transplantation and Cellular Therapy; CLND = completion lymph node dissection; CR = complete response; CRS = cytokine-release syndrome; EFS = event-free survival; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; pnCR = pathologic near complete response; pPR = pathologic partial response; PR = partial response; pRR = pathologic response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Table 2 Objectives and Corresponding Endpoints for Cohort 2

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment	• ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• PFS after randomization/enrollment, defined as the time from randomization/enrollment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • OS after randomization/enrollment, defined as the time from randomization/enrollment to death from any cause • OS at specific timepoints (e.g., 6 months)

Table 2 Objectives and Corresponding Endpoints for Cohort 2 (cont.)

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of treatment	• 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 investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥ 12 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of treatment	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v5.0 CRS severity will also be determined according to the ASTCT CRS Consensus Grading Scale.

ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine-release syndrome; DOR = duration of response; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with resectable Stage III (Cohort 1) or Stage IV (Cohort 2) melanoma. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status), or introduce additional cohorts of patients with other types of melanoma.

Two cohorts will be enrolled in parallel in this study. Cohort 1 will consist of patients with resectable Stage III melanoma with measurable lymph node metastases according to Response Evaluation Criteria in Solid Tumors, Version 1.1 that can be biopsied, who have no history of in-transit metastases within the last 6 months, and who have not received systemic CIT for their disease, for example, PD-1/PD-L1 and/or CTLA-4 blocking agents or other agents. Cohort 2 will consist of patients with Stage IV melanoma who experienced disease progression during or after at least one but not more than two lines of treatment for metastatic disease. Up to two lines of checkpoint inhibition therapy (monotherapy or combination therapy) are allowed. Patients with BRAF-mutant disease may have received an additional line of targeted therapy (either before, intermittent with, or after the checkpoint inhibition therapy) or may have received targeted therapy and checkpoint inhibition therapy concurrently as one combination treatment. Patients with BRAF-mutant melanoma with rapidly progressive disease who have not been previously treated with approved targeted therapies are not eligible.

In each cohort, eligible patients will initially be randomly assigned to one of several treatment arms (see below). Currently, there are no arms open for enrollment in Cohort 2.

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

Phase:	Phase Ib/II	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Cohort 1: resectable Stage III melanoma Cohort 2: Stage IV (metastatic) cutaneous melanoma
Interventional Model:	Parallel	**Population Age:**	≥ 18 years
Test Compound{s}:	Atezolizumab (RO5541267), tiragolumab (RO7092284), RO7247669	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Nivolumab, ipilimumab	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	*6*	**Number of Participants to Be Enrolled:**	Cohort 1: Approximately *195–290* patients Cohort 2: Approximately *8–*46 patients

STUDY TREATMENT

Table 3 Study Treatments for Cohorts 1 and 2

Study Treatments for Cohort 1	
Treatment Group	Administration Method and Schedule
Nivolumab plus ipilimumab (Nivo + Ipi) (Control Arm) (21-day cycles)	• Nivolumab 3 mg/kg IV on Day 1 of each cycle • Ipilimumab 1 mg/kg IV on Day 1 of each cycle
RO7247669 *2100 mg* (21-day cycles)	• RO7247669 2100 mg by IV infusion on Day 1 of each cycle
RO7247669 2100 mg plus tiragolumab (CIT combination) (21-day cycles)	• *RO7247669 2100 mg by IV infusion on Day 1 of each cycle* • *Tiragolumab 600 mg IV on Day 1 of each cycle*
Atezolizumab plus tiragolumab (CIT combination) (21-day cycles)	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle
RO7247669 600 mg (21-day cycles)	• *RO7247669 600 mg by IV infusion on Day 1 of each cycle*
RO7247669 600 mg plus tiragolumab (CIT combination) (21-day cycles)	• *RO7247669 600 mg by IV infusion on Day 1 of each cycle* • *Tiragolumab 600 mg IV on Day 1 of each cycle*
Study Treatment for Cohorts 1 and 2 [a]	
RO7247669 *2100 mg* plus tiragolumab (CIT combination) (21-day cycles)	• RO7247669 2100 mg IV on Day 1 of each cycle [b] • Tiragolumab 600 mg IV on Day 1 of each cycle

CIT = cancer immunotherapy; Ipi = ipilimumab; Nivo = nivolumab.

[a] There are currently no arms open for enrollment in Cohort 2.

[b] After the safety run-in has been completed, the Sponsor may explore lower doses (e.g., 1200 mg and 600 mg).

There will be no dose modifications for atezolizumab, tiragolumab, or RO7247669 in this study. Treatment with atezolizumab, tiragolumab, or RO7247669 may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. Guidelines for the management of atezolizumab-, tiragolumab-, and RO7247669-specific adverse events are described in Appendix 9 of the protocol.

DURATION OF PARTICIPATION

In Cohort 1, the total duration of study participation for each individual from screening until the treatment completion visit and start of adjuvant treatment is expected to be approximately 17 weeks (not including long-term follow-up). After the treatment period, participants may continue onto long-term follow-up, where information will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months until death.

In Cohort 2, the total duration of study participation for each individual is expected to be up to 5 years (including long-term follow-up).

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee; Scientific Oversight Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ASTCT	American Society for Transplantation and Cellular Therapy
Atezo	atezolizumab
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CIT	cancer immunotherapy
CLND	complete lymph node dissection
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CR	complete response
CRS	cytokine-release syndrome
CSR	Clinical Study Report
CT	computed tomography
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T lymphocyte–associated protein 4
DOR	duration of response
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
ICH	International Council for Harmonisation

Abbreviation	Definition
IFN	interferon
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INMC	International Neoadjuvant Melanoma Consortium
Ipi	ipilimumab
IPRF	Independent Pathology Review Facility
IRB	Institutional Review Board
iRECIST	modified RECIST v1.1 for immune-based therapeutics
IRR	infusion-related reaction
IxRS	interactive web-based response system
LAG-3	lymphocyte activation gene-3
LVEF	left ventricular ejection fraction
MEK	mitogen-activated protein kinase kinase
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
Nivo	nivolumab
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
pCR	pathologic complete response
PD-1	programmed death-1
PD-1–LAG-3	programmed death-1 lymphocyte activation gene-3
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
pnCR	pathologic near complete response
pPR	pathologic partial response
PR	partial response

Abbreviation	Definition
pRR	pathologic response rate
PS	performance status
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RFS	relapse-free survival
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SITC	Society for Immunotherapy of Cancer
SmPC	Summary of Product Characteristics
SOC	Scientific Oversight Committee
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
Tira	tiragolumab
TnI	troponin I
TnT	troponin T
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiogram
ULN	upper limit of normal
VCA	viral capsid antigen
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA

Melanoma is a malignant tumor of melanocytes. This potentially deadly form of skin cancer is one of the fastest growing malignancies (Algazi et al. 2010; Finn et al. 2012). More than 300,000 people worldwide are currently diagnosed with melanoma each year, and 57,000 people die of the disease (Ferlay et al. 2018). The clinical outcomes of patients with melanoma are highly dependent on the stage at presentation.
When melanoma is diagnosed early (Stage I and II), it is generally curable with surgery as the treatment of choice, with a long-term survival rate of around 90% for Stage I melanoma (Balch et al. 2009). However, most people with more advanced melanoma have a poor prognosis (Finn et al. 2012). Patients with lymph-node involvement (Stage III) have a high risk of local and distant relapse after surgery, and the 5-year survival rate is 32%–93% in this patient group (Gershenwald et al. 2017). Few patients have metastatic disease (Stage IV) at presentation, but some develop metastases after their initial definitive treatment. Immunotherapy and targeted therapies have improved the outcomes of those patients, and the 5-year survival rate is around 50% (Larkin et al. 2015; Wolchok et al. 2017; Larkin et al. 2019; Robert et al. 2019; Long et al. 2020). Despite recent therapeutic advances, melanoma continues to be a serious health issue, with a high medical need and a steadily increasing incidence over the past 30 years (Bataille 2009).

1.1.1 Treatment for Melanoma

Remarkable progress has been made in melanoma research over the last decade. The U.S. Food and Drug Administration (FDA) has approved 13 new melanoma therapies since 2011, including both targeted and immune-based therapies (Luke et al. 2017). Current standard of care includes treatment with immune checkpoint inhibitors (CPIs), either alone or in combination, as well as targeted therapies, including BRAF and MEK inhibitors. Interleukin (IL)-2, oncolytic viral, and interferon (IFN) therapies are also viable treatment options for a subset of patients.

1.1.1.1 Targeted Therapies

Targeted therapies have demonstrated efficacy in improving overall survival (OS) and have been approved by the FDA for the BRAF-mutant subtype of metastatic melanoma. Combination therapies with BRAF and MEK inhibitors show improved outcomes over treatment with a single-agent inhibitor alone. However, most patients acquire resistance to therapy and relapse. Therefore, treatment with dabrafenib (a selective BRAF inhibitor) in combination with trametinib (a selective MEK inhibitor) was tested in the adjuvant setting in the COMBI-AD trial in patients with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive melanoma. This combination improves relapse-free survival (RFS) and OS, and has been approved by the FDA for adjuvant use (Long et al. 2017). In addition, there is further improvement in progression-free survival (PFS) when a PD-L1 inhibitor (atezolizumab) is added to the combination of BRAF plus MEK inhibitors (vemurafenib plus cobimetinib). The Phase III IMspire150 study of patients

with previously untreated $BRAF^{V600}$ mutation-positive advanced melanoma demonstrated that the triple combination helped reduce the risk of disease worsening or death compared to placebo plus vemurafenib and cobimetinib (Gutzmer et al. 2020). The IMspire150 study was the first Phase III study to combine targeted therapy and immunotherapy to show a benefit for patients with $BRAF^{V600}$ mutation-positive advanced melanoma, and this triplet therapy has been approved by the FDA.

1.1.1.2 Immunotherapies

A variety of immunotherapies have been approved for the treatment of melanoma, and immunotherapy has shown benefit regardless of PD-L1 expression or BRAF mutations.

Four CPIs, namely ipilimumab, pembrolizumab, nivolumab, *and relatlimab* are now approved by the FDA for the treatment of unresectable or advanced disease. Each has shown improved OS against different comparators. Treatments shown to be effective in the unresectable or metastatic disease setting have also proven to be effective adjuvant therapies for patients with resectable Stage III melanomas. The current standard of care is surgery followed by adjuvant anti–PD-1 or targeted therapy.

Ipilimumab, a monoclonal antibody targeting CTLA-4, demonstrated significant improvement in OS in two randomized trials (Hodi et al. 2010; Robert et al. 2011), and was the first CPI approved for use in unresectable or metastatic melanoma. It was also the first CPI to be approved by the FDA as adjuvant therapy, and it has demonstrated improved OS at a dose of 10 mg/kg when compared with placebo in the European Organisation for Research and Treatment of Cancer 18071 study (Eggermont et al. 2016). The subsequent Intergroup E1609 trial demonstrated better outcomes with low-dose (3 mg/kg) ipilimumab; this dose has been approved for metastatic disease (Tarhini et al. 2020). Anti–PD-1 monotherapy (pembrolizumab or nivolumab) shows improved efficacy outcomes with better safety profiles compared with treatment using single-agent anti–CTLA-4 (ipilimumab) or the investigator's choice of chemotherapy.

Pembrolizumab was initially approved for the treatment of patients with advanced or unresectable melanoma who progressed after ipilimumab and/or BRAF therapy (Ribas et al. 2015a; Robert et al. 2015b). It is now approved for the treatment of patients with unresectable or metastatic melanoma, as well as for the adjuvant treatment of patients with melanoma with lymph node involvement following complete resection.

Nivolumab was originally approved in advanced melanoma patients without BRAF mutation (Robert et al. 2015a). It is now approved for patients with unresectable or metastatic melanoma, and for patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection in the adjuvant setting.

The combination of anti–PD-1 and anti–CTLA-4 immunotherapies (nivolumab plus ipilimumab) further prolonged PFS and OS compared with ipilimumab or nivolumab alone, and this combination has been approved for previously untreated patients with

unresectable or metastatic melanoma (Larkin et al. 2015). The CheckMate 238 study compared nivolumab with ipilimumab. At a median follow-up of 51 months, nivolumab improved RFS and distant metastasis-free survival while reducing toxicity. The OS was similar in the two groups (Ascierto et al. 2020).

Relatlimab is now approved with nivolumab for patients with unresectable or metastatic melanoma. The combination of relatlimab and nivolumab improved PFS compared to nivolumab alone in patients with untreated advanced melanoma (Tawbi et al. 2022).

1.1.2 Treatment for Stage III Melanoma

For patients with macroscopic Stage III melanoma, surgery followed by adjuvant immunotherapy with one year of either nivolumab or pembrolizumab is generally indicated (Weber et al. 2017; Eggermont et al. 2018). These agents are PD-1 inhibitors. For patients with a tumor that contains a $BRAF^{V600}$ mutation, targeted therapy with BRAF and MEK inhibitors represents an alternative therapy, especially for patients with Stage III disease who are unable to receive adjuvant immunotherapy due to active autoimmune disease or due to the need for immunosuppressive therapy.

Clinical trial data suggest that 40% of patients with macroscopic Stage III melanoma relapse within 3 years after surgery (Bloemendal et al. 2019). Moreover, a substantial subset of patients (15%–25%) relapse soon after surgery and before starting adjuvant therapy (Weber et al. 2017), resulting in a 3-year RFS of the intent-to-treat population of less than 50%. Patients with clinical or palpable lymph node involvement have a 5-year survival rate of 20% to 59%, with certain subgroups of patients (based on number of involved nodes, extracapsular extension, or iliac involvement in groin metastases) showing even worse survival rates of around 5% at 5 years (Hauschild et al. 2018; Ascierto et al. 2020; Eggermont et al. 2020).

1.1.2.1 Neoadjuvant Immunotherapy Treatment in Stage III Melanoma

Nonclinical studies demonstrated improved survival and increased anti-tumor immunity when immune CPI therapy was given before surgery as compared with adjuvant application (Liu et al. 2016; Brockwell et al. 2017; Bourgeois-Daigneault et al. 2018; Brooks et al. 2018; O'Donnell et al. 2019). Patients with clinically detectable Stage III melanoma are ideal candidates for neoadjuvant therapy because they represent a high-risk patient population with poor outcomes when treated with upfront surgery alone. Neoadjuvant therapy also has the advantage of providing information on pathologic response, which is valuable to estimate prognosis and to guide the choice of adjuvant therapy and follow-up (Tetzlaff et al. 2018). Moreover, the availability of tumor tissue before and following therapy enables efficient exploration of possible mechanisms of resistance and response as well as identification of baseline biomarkers. Neoadjuvant therapy for melanoma is now an active area of research, with numerous completed and ongoing trials that have disparate designs, endpoints, and analyses (Menzies et al. 2021). The International Neoadjuvant Melanoma Consortium (INMC) was created by

experts in medical oncology, surgical oncology, pathology, radiation oncology, radiology, and translational research who developed recommendations for investigating neoadjuvant therapy in melanoma to align future trial designs and correlative analyses (Amaria et al. 2019).

Six melanoma neoadjuvant trials were conducted recently with BRAF/MEK-targeted therapy or PD-1-based immunotherapy (reviewed by Amaria et al. 2019). These trials demonstrated that neoadjuvant therapies can achieve high pathologic complete response (pCR) rates and impressive RFS in Stage III melanoma (Menzies et al. 2021; Rozeman et al. 2021). The initial data are particularly promising for the neoadjuvant combination of nivolumab plus ipilimumab. Treatment with nivolumab plus ipilimumab results in pathologic response rates (pRRs) between 70%–80%, is well tolerated, and may reduce surgical morbidity (Rozeman et al. 2019; Blank et al. 2020).

This study protocol was developed in accordance with INMC guidelines to create the needed consistency amongst neoadjuvant trials in order to facilitate optimal data organization for future regulatory review. Its exploratory analysis plan will strengthen translational research across the melanoma disease continuum.

1.1.2.2 Treatment for Metastatic Melanoma

Current standard of care includes treatment with immune CPIs, either alone or in combination, as well as treatment with targeted BRAF and MEK inhibitor therapies. IL-2, oncolytic viral, and IFN therapy remain options for a subset of patients. Radiation therapy may have a palliative role for symptomatic localized areas of disease. Cytotoxic chemotherapy (single agent or combination) has not been shown to improve OS in patients with advanced melanoma. Response rates are typically less than 20%, and median response durations are 4 to 6 months. Consequently, the role of chemotherapy (e.g., dacarbazine, temozolomide, carboplatin/paclitaxel, and fotemustine) is limited to patients who have progressed after optimal treatment with other systemic therapy options.

1.2 STUDY RATIONALE

This randomized Phase Ib/II umbrella study is designed to accelerate the development of treatments or treatment combinations by identifying early signals and establishing proof-of-concept clinical data in patients with resectable melanoma. Single-agent immune CPIs or targeted therapies, dual CPI combinations, and CPIs in combination with targeted therapies have shown promising objective response rates (ORRs) and OS and are approved for use in patients with melanoma.

The currently prevailing cancer immunotherapy (CIT) approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors such as PD-1/PD-L1. Other approaches build on the removal or inhibition of tumor-promoting cell types or employ immune stimulation via cytokines, engagement of costimulatory receptors, or antibody-directed T-cell activation.

CIT has demonstrated clear clinical efficacy, with significant survival benefit observed across multiple advanced malignancies, and there is evidence that PD-1/PD-L1 checkpoint blockade can generate pCR and durable responses in patients with melanoma (Rozeman et al. 2019; Blank et al. 2020). Although these targets have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates that a series of stepwise events is necessary for the generation of an effective anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune-evasion mechanisms. Thus, the need to identify and circumvent the various factors that account for the absence of, or escape from, an effective anti-cancer immune response will be critical for propagating cancer immunity and advancing the field of CIT. The combination of PD-1/PD-L1 blocking with agents targeting different immune-evasion mechanisms may further increase response rates and decrease rates of disease recurrence in this population.

The potential risks for patients will be immune-related adverse events associated with the study treatments. Adverse events could potentially impact the timely conduct of surgery. Further, although post-surgery recovery could be altered when applying neoadjuvant CIT, these theoretical concerns have not been borne out by data from recent studies in the neoadjuvant setting (Blank et al. 2018; Rozeman et al. 2019). The current study is designed with the flexibility to open new treatment arms as novel treatment combinations become available and to close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving control arm treatment. More importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination. To improve the confidence of clinical signal detection in the experimental arms, this study will include a control arm (currently available in Cohort 1).

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) is summarized in Table 1. The control and experimental treatment regimens are described in Section 3.1 (see also Table 1). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental IMPs, are provided in the respective appendix for that treatment arm, as outlined in Appendix 11 through *Appendix 16*.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target(s)	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Immune checkpoint inhibitor
RO7247669	PD-1, LAG-3	Bispecific, dual immune checkpoint inhibitor [a]
Tiragolumab	TIGIT	TIGIT antagonist, improves the activation and effectiveness of T-cell and NK-cell tumor-killing activity [b]

IMP = investigational medicinal product; LAG-3 = lymphocyte activation gene-3; NK = natural killer; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; TIGIT = T-cell immunoreceptor with Ig and ITIM domains.

[a] Codarri et al. 2019.

[b] Stanietsky et al. 2009; Yu et al. 2009; Johnston et al. 2014.

1.3 COVID-19 BENEFIT–RISK ASSESSMENT

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

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 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 is altered by CIT.

Severe SARS-CoV-2 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines 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 immune CPI therapies (e.g., atezolizumab, tiragolumab, and RO7247669). At this time, there is insufficient evidence for causal association between immune CPI therapies and an increased risk of severe outcomes from SARS-CoV-2.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with immune CPI therapies 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 is a paucity of data concerning the possible interactions between CIT treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies could positively or negatively impact COVID-19 vaccination efficacy and safety (Society for Immunotherapy of Cancer [SITC] 2020).

Per the 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 CPIs) with the understanding that there are limited safety and efficacy data in these patients (NCCN COVID-19 vaccination and cancer patients). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccine and treatment with CIT (SITC 2020).

For patients enrolling in this study with atezolizumab, tiragolumab, and RO7247669, the decision to administer the vaccine should be individualized by the physicians in consultation with the patient, based on the risk of SARS-CoV-2 infection/complications and potential benefit from the vaccine, the general condition of the patient, underlying disease, and the severity of COVID-19 outbreak in a given area/region. For further details on permitted and prohibited therapies, see Sections A11–4.2 (nivolumab + ipilimumab [Nivo + Ipi]), A12–4.2 (RO7247669 *2100 mg*), A13–4.2 (atezolizumab + tiragolumab [Atezo + Tira]), A14–4.2 (RO7247669 *2100 mg* + Tira Cohorts 1 and 2), *A15–4.2 (RO7247669 600 mg), and A16–4.2 (RO7247669 600 mg + Tira)*. The SITC and NCCN recommendations referenced above and institutional guidelines should be considered by the investigator in decision making. When administered, SARS-CoV-2 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the SARS-CoV-2 vaccine is considered a concomitant medication and should be documented as such (Section 4.4).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of treatment combinations in CIT-naive patients with resectable Stage III melanoma (Cohort 1) and in patients with Stage IV melanoma (Cohort 2).

Specific objectives and corresponding endpoints for the study are outlined below for Cohort 1 (see Table 2) and Cohort 2 (see Table 3).

Table 2 Objectives and Corresponding Endpoints for Cohort 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment	• pRR (defined as the proportion of patients with pCR, pnCR, and pPR) at time of surgery, as determined by independent pathologic review
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• pRR (defined as the proportion of patients with pCR, pnCR, and pPR) at time of surgery, as determined by local pathologic assessment • EFS, defined as the time from randomization to any of the following events (whichever occurs first): Disease progression that precludes surgery, as assessed by the investigator according to RECIST v1.1; local, regional or distant disease recurrence; or death from any cause • RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause • OS, defined as the time from randomization to death from any cause • ORR, defined as the proportion of patients with a CR or PR as determined by the investigator according to RECIST v1.1, prior to surgery Responses will be assessed and determined according to RECIST v1.1 but are not required to be confirmed by later imaging.
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• Landmark EFS, defined as the time from randomization to any of the following events (whichever occurs first): Disease progression that precludes surgery, as assessed by the investigator according to RECIST v1.1; local, regional or distant disease recurrence; or death from any cause at specific timepoints (1, 2, 3, and 5 years) • Landmark RFS, defined as the time from surgery to the first documented recurrence of disease or death from any cause at specific timepoints (1, 2, 3, and 5 years) • Landmark OS, defined as the time from randomization to death from any cause at specific timepoints (1, 2, 3, and 5 years)

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CLND = completion lymph node dissection; CR = complete response; CRS = cytokine-release syndrome; EFS = event-free survival; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; pnCR = pathologic near complete response; pPR = pathologic partial response; PR = partial response; pRR = pathologic response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Table 2 Objectives and Corresponding Endpoints for Cohort 1 (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of treatment	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v5.0 CRS severity will also be determined according to the ASTCT CRS Consensus Grading Scale. • Incidence and nature of immune-related adverse events Grade ≥ 3 during the first 12 weeks • Rate and duration of delayed surgery due to treatment-related adverse events • Surgical complication rates according to Clavien-Dindo surgical classification after CLND
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of treatment	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure and the efficacy and safety of treatment	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate, on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate, on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered	• For drugs for which ADA formation is measured: Presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs	• For drugs for which ADA formation is measured: Relationship between ADA status and efficacy, safety, or PK endpoints

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CLND = completion lymph node dissection; CR = complete response; CRS = cytokine-release syndrome; EFS = event-free survival; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; pnCR = pathologic near complete response; pPR = pathologic partial response; PR = partial response; pRR = pathologic response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Table 2 Objectives and Corresponding Endpoints for Cohort 1 (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.9) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CLND = completion lymph node dissection; CR = complete response; CRS = cytokine-release syndrome; EFS = event-free survival; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; pCR = pathologic complete response; PK = pharmacokinetic; pnCR = pathologic near complete response; pPR = pathologic partial response; PR = partial response; pRR = pathologic response rate; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RFS = relapse-free survival.

Table 3 Objectives and Corresponding Endpoints for Cohort 2

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of treatment	• ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• PFS after randomization/enrollment, defined as the time from randomization/enrollment to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • OS after randomization/enrollment, defined as the time from randomization/enrollment to death from any cause • OS at specific timepoints (e.g., 6 months) • 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 investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥12 weeks or a CR or PR, as determined by the investigator according to RECIST v1.1
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of treatment	• ORR, PFS, DOR, and disease control as determined by the investigator according to iRECIST
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of treatment	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v5.0 CRS severity will also be determined according to the ASTCT CRS Consensus Grading Scale.

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine-release syndrome; DOR = duration of response; eCRF = electronic Case Report Form; iRECIST = modified RECIST v1.1 for immune-based therapeutics; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.
Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Overall response per iRECIST (see Appendix 2) will not be captured in the eCRF, but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

Table 3 Objectives and Corresponding Endpoints for Cohort 2 (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To characterize the PK profile of drugs that are administered as part of treatment	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure and the efficacy and safety of treatment	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoint**
• To evaluate the immune response to drugs that are administered	• For drugs for which ADA formation is measured: Presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs	• For drugs for which ADA formation is measured: Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.9) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; CR = complete response; CRS = cytokine-release syndrome; DOR = duration of response; eCRF = electronic Case Report Form; iRECIST = modified RECIST v1.1 for immune-based therapeutics; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Overall response per iRECIST (see Appendix 2) will not be captured in the eCRF, but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

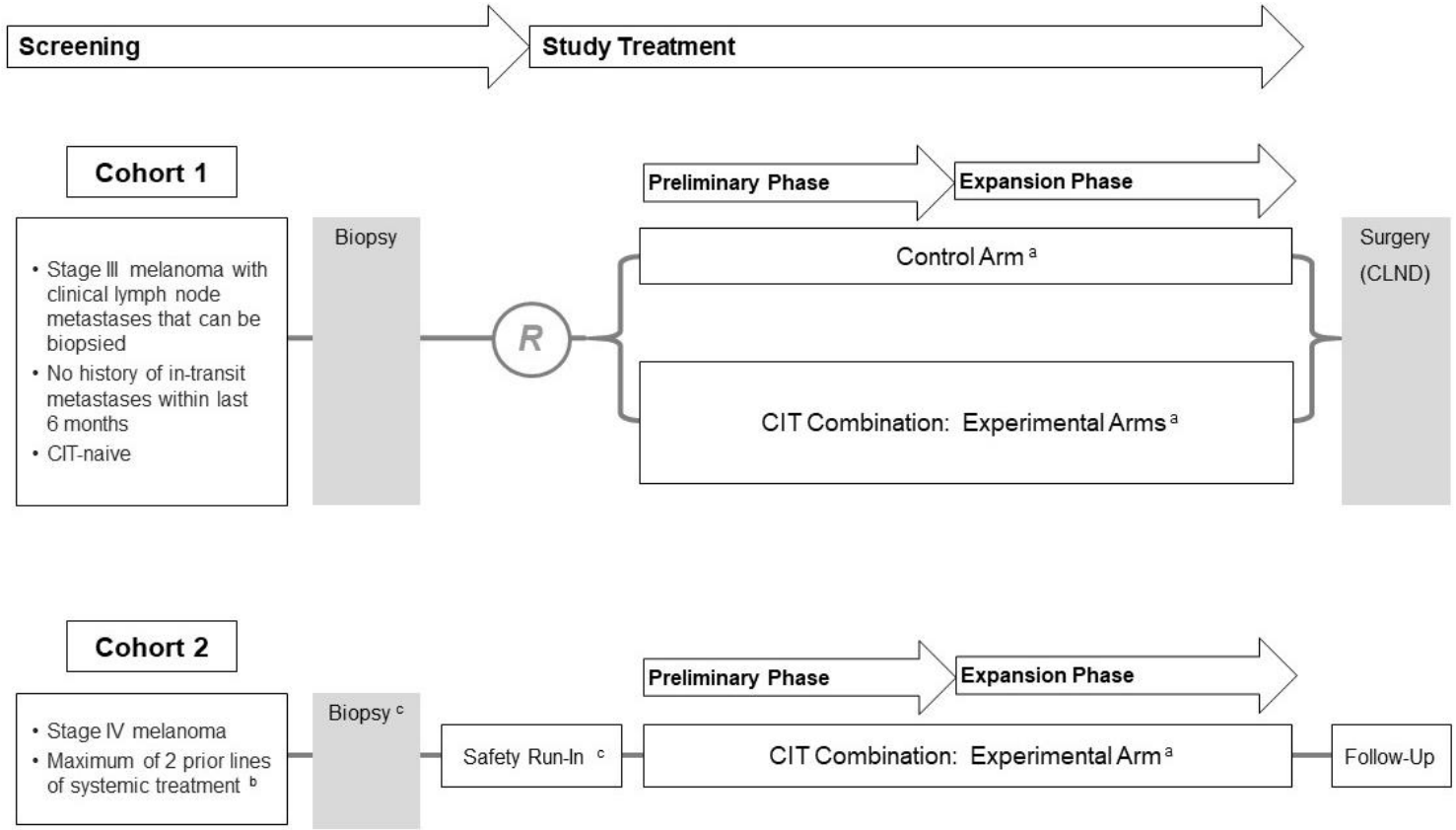
This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with resectable Stage III (Cohort 1) or Stage IV (Cohort 2) melanoma. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status), or introduce additional cohorts of patients with other types of melanoma.

When additional treatment options become available, patients may be eligible to receive treatment with a different treatment combination in an additional study stage (Stage 2). When a Stage 2 treatment is available, this will be introduced by amending the protocol.

Two cohorts will be enrolled in parallel in this study. Cohort 1 will enroll patients with resectable Stage III melanoma with measurable lymph node metastases according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) that can be biopsied, who have no history of in-transit metastases within the last 6 months, and who have not received systemic CIT for their disease, e.g., PD-1/PD-L1 and/or CTLA-4 blocking agents or other agents. Cohort 2 will enroll patients with Stage IV melanoma who experienced disease progression during or after at least one but not more than two lines of treatment for metastatic disease. Up to two lines of checkpoint inhibition therapy (monotherapy or combination therapy) are allowed. Patients with BRAF-mutant disease may have received an additional line of targeted therapy (either before, intermittent with, or after the checkpoint inhibition therapy) or may have received targeted therapy and checkpoint inhibition therapy concurrently as one combination treatment. Patients with BRAF-mutant melanoma with rapidly progressive disease who have not been previously treated with approved targeted therapies are not eligible.

In each cohort, eligible patients will be assigned to one of several treatment arms (see Section 3.1.2). For the study design, see Figure 1.

Figure 1 Study Design



CIT = cancer immunotherapy; CLND = complete lymph node dissection; R = randomization.

Note: All treatment arms (except the safety run-in) will include a mandatory on-treatment biopsy (see Section 4.5.9 for details).

[a] Refer to Table 4 for a summary of available treatment regimens.

[b] Patients with BRAF-mutant disease may have received an additional line of targeted therapy.

[c] Enrollment will begin with a 6-patient safety run-in phase. Biopsies are optional for patients enrolled in the safety run-in.

3.1.2 Treatment Assignment

In Cohort 1, patients will be randomly assigned to a control arm (nivolumab plus ipilimumab [Nivo + Ipi]) or an experimental arm consisting of RO7247669 *2100 mg*, atezolizumab in combination with tiragolumab (Atezo + Tira), RO7247669 *2100 mg* in combination with tiragolumab (RO7247669 *2100 mg* + Tira), *RO7247669 600 mg, or RO7247669 600 mg in combination with tiragolumab (RO7247669 600 mg + Tira)*. Patients will be stratified by geographic region (Australia vs. Rest of the World) and baseline LDH (≤ the upper limit of normal [ULN] vs. > ULN). Details on the treatment regimens are provided in the respective appendices, Appendix 11 through *Appendix 16*, as specified in Table 4 and Figure 2.

In Cohort 2, patients will be enrolled into an experimental arm consisting of RO7247669 *2100 mg* in combination with tiragolumab (RO7247669 *2100 mg* + Tira). Enrollment will begin with a 6-patient safety run-in phase. Patients from French investigational sites are excluded from the safety run-in phase and may only be enrolled into the preliminary phase, which succeeds the safety-run-in. Details on the treatment regimens are provided in Appendix 14 as specified in Table 4 and Figure 2.

Approximately *203–336* patients will be enrolled during the study, including approximately 6 patients who will be enrolled in the safety run-in phase of Cohort 2. Enrollment within the experimental arms will take place in two phases: a preliminary phase, followed by an expansion phase. *For most arms, approximately 20 patients will be enrolled during the preliminary phase. Approximately 40 patients will be enrolled in the RO7247669 600 mg and RO7247669 600 mg + Tira arms during the preliminary phase to ensure a more precise benefit–risk assessment in arms with the lower dose of RO7247669*. If clinical activity (pathologic response in Cohort 1) is observed in an experimental arm during the preliminary phase, approximately 20 additional patients may be enrolled in that arm during the expansion phase.

The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Experimental arms with insufficient clinical activity or unacceptable toxicity will not be expanded. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, in order to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

The randomization ratio will depend on the number of experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm is no more than 35%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 4 Treatment Regimens

Cohort	Study Treatment [a]	Number of Patients (Sponsor Assignment) [b]	Number of Patients (Random Assignment) [c]		Appendix
		Safety Run-in Phase	Preliminary Phase	Expansion Phase [d]	
1	Control arm: Nivo + Ipi	N/A	Variable [c]		Appendix 11
1	RO7247669 *2100 mg*	N/A	20 [e]	20	Appendix 12
1	Atezo + Tira	N/A	20 [e]	20	Appendix 13
1	RO7247669 *2100 mg* + Tira [f]	N/A	20 [e]	20	Appendix 14
1	*RO7247669 600 mg*	*N/A*	*40*	*20*	*Appendix 15*
1	*RO7247669 600 mg + Tira*	*N/A*	*40*	*20*	*Appendix 16*
2	RO7247669 *2100 mg* + Tira	~6	20	20	Appendix 14

Atezo = atezolizumab; Ipi = ipilimumab; Nivo = nivolumab; Tira = tiragolumab.

[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all experimental arms may not be open for enrollment at the same time.

[b] During the safety run-in phase, patients will be assigned to available treatment arms. The treatment assignment ratio will depend on the number of experimental arms that are open for enrollment (see Section 4.2 for more information).

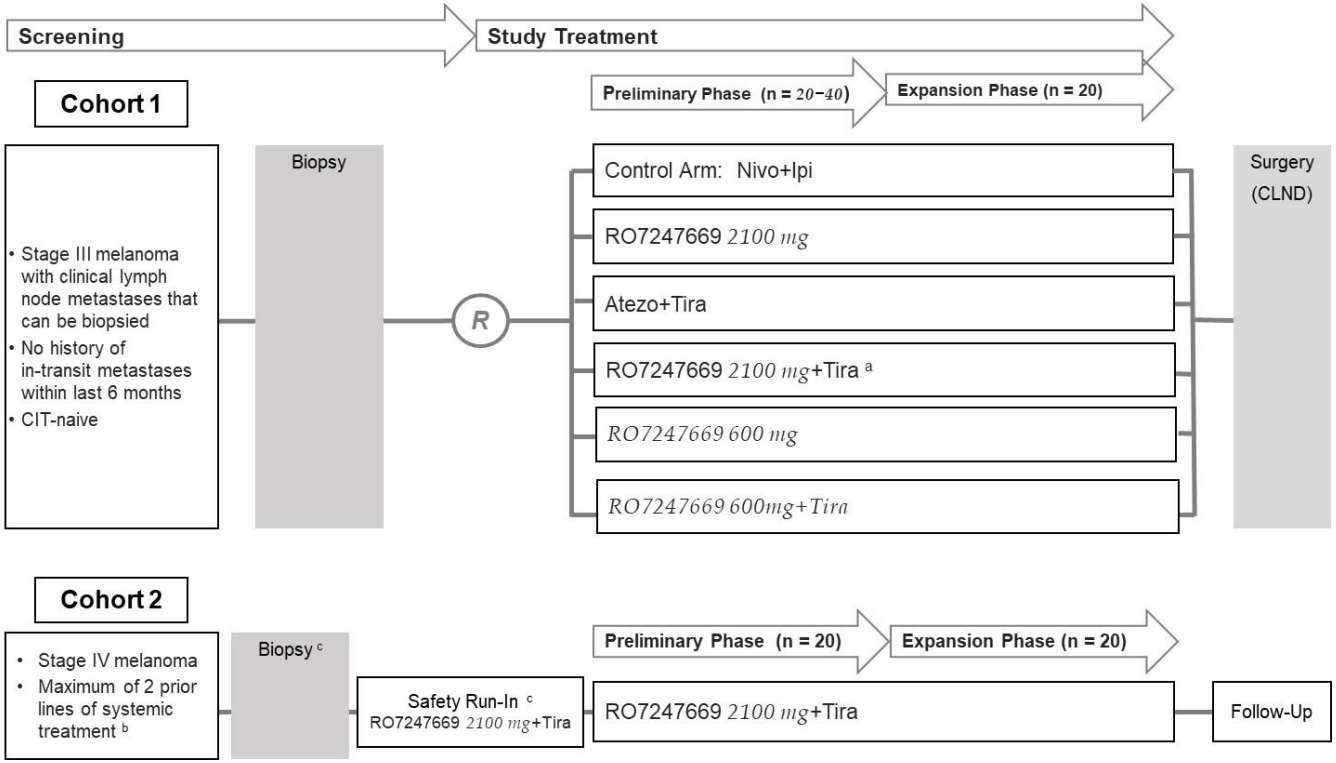
[c] The randomization ratio will depend on the number of experimental arms that are open for randomization (e.g., if an arm is added or randomization into an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm is no more than 35%. See Section 4.2 for more information.

[d] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 20 additional patients will be enrolled in that arm during the expansion phase. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion.

[e] Enrollment will be suspended in the Cohort 1 RO7247669 *2100 mg*, Atezo + Tira, and RO7247669 *2100 mg* + Tira arms to allow for a safety evaluation in a minimum of 6 patients (see Section 3.1.3).

[f] Enrollment in the RO7247669 *2100 mg* + Tira arm will open in Cohort 1 after safety assessment of the treatment combination in Cohort 2.

Figure 2 Study Schema



Atezo = atezolizumab; CIT = cancer immunotherapy; CLND = completion lymph node dissection; Ipi = ipilimumab; Nivo = nivolumab; R = randomization; Tira = tiragolumab.

Note: All treatment arms (except the safety run-in) will include a mandatory on-treatment biopsy (see Section 4.5.9 for details).

[a] Enrollment in the RO7247669 2100 mg + Tira arm will open in Cohort 1 if the stopping criteria are not met during the safety run-in phase in Cohort 2.

[b] Patients with BRAF-mutant disease may have received an additional line of targeted therapy.

[c] Enrollment in the RO7247669 2100 mg + Tira arm will begin with a 6-patient safety run-in phase in Cohort 2. Biopsies are optional for patients enrolled in the safety run-in.

In Cohort 1, patients in the control arm and the experimental arms will receive neoadjuvant treatment during a 6-week period. After completion of neoadjuvant treatment, or in case of discontinuation due to toxicity and in absence of disease progression, patients will undergo surgery (completion lymph node dissection [CLND]) in Week 7. After the treatment completion/discontinuation visit and at the discretion of the investigator, patients will start either adjuvant therapy or observation (see Figure 3).

Because of the possibility of an initial increase in the size of metastatic lymph nodes caused by immune-cell infiltration in the context of a T-cell response (termed pseudoprogression) with CITs, suspected clinical or radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment until surgery. Before discontinuation of study treatment and/or cancellation of surgery, progression should be confirmed by biopsy or repeated radiographic assessment by an additional expert reviewer. All patients are expected to proceed with surgery, provided that there are no distant metastases and the surgeon considers the disease to be completely resectable.

In Cohort 2, patients will continue to receive treatment 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 (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab and other CITs, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT combination will be permitted to continue treatment if they meet all of the following criteria:

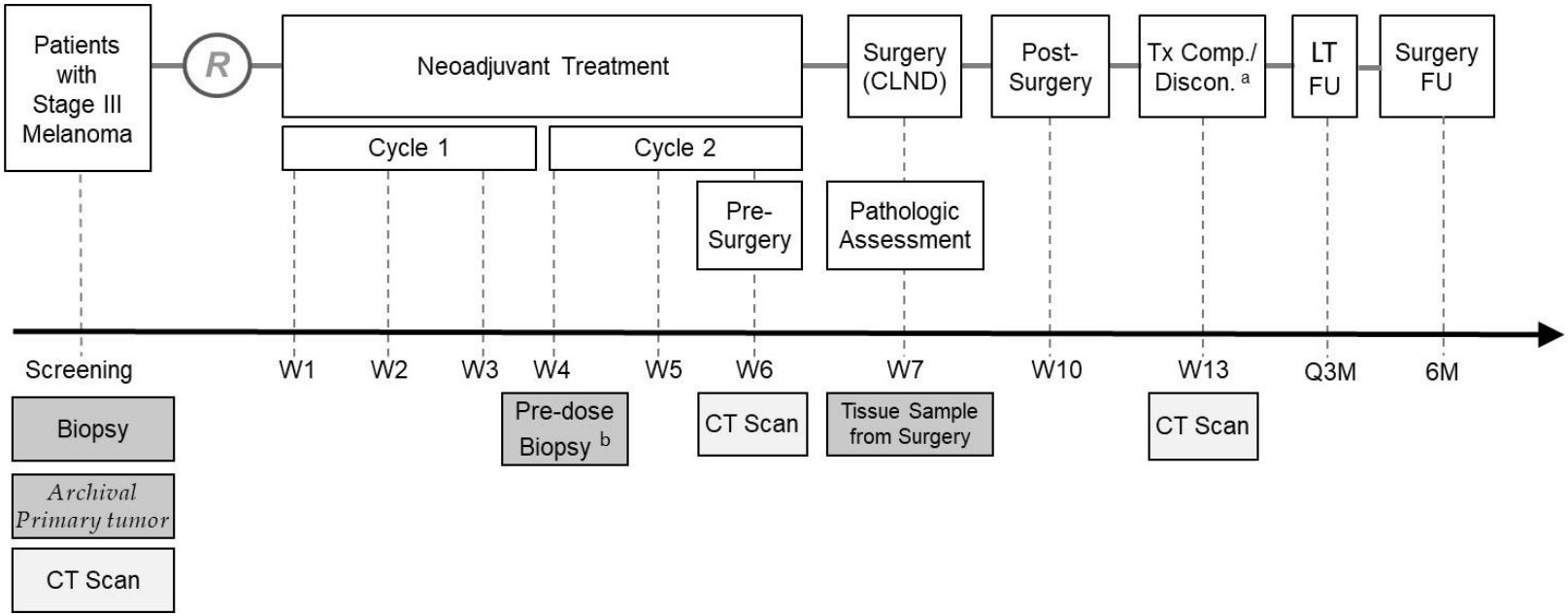
- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients eligible for treatment beyond progression will be informed by the investigator that they may be foregoing other treatment options known to confer clinical benefit while continuing to receive the study treatment. 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 for medical conditions that the investigator or Sponsor determines may jeopardize the patient's safety if he/she continues in the study.

If at a subsequent tumor assessment, pseudoprogression is ruled out and progression of the disease is confirmed, the patient will be discontinued from study treatment.

Figure 3 Detailed Study Schema (Cohort 1)



CLND = completion lymph node dissection; Comp. = completion; CT = computed tomography; Discon. = discontinuation; FU = follow-up; LT = long-term; M = month; R = randomization; Q3M = every 3 months; Tx = treatment; W = week.

[a] At the discretion of the investigator, patients will start either adjuvant therapy or observation commencing in Week 13.

[b] The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.

3.1.3 Safety Evaluation Phase (Cohort 1)

To evaluate the toxicities of the experimental treatments in the neoadjuvant setting, enrollment will be suspended after approximately 6 patients have been enrolled to allow for a safety evaluation.

The safety evaluation will be based on safety data from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and who have completed safety follow-up assessments until surgery. Notably, timely conduct of surgery (CLND) is an indicator of treatment tolerability. During the 6-patient safety evaluation, or following safety evaluations, if ≥30% of patients experience one or more of the following events that is considered to be at least possibly related to study treatment, enrollment for that combination will be put on hold while the Sponsor evaluates the benefit–risk profile of that treatment:

- A treatment-related Grade ≥3 adverse event that does not improve (with or without treatment) to Grade 2 or better within 2 weeks
- A treatment-related adverse event causing >2-week delay in surgery
- A treatment-related serious adverse event
- A treatment-related adverse event that requires permanent discontinuation of study drug
- Death, except those that are incontrovertibly related to disease progression or extraneous causes such as accidents

If no new safety signals are detected, enrollment will be resumed in that arm.

For the same study drug or study drug combination, if a higher dose arm has passed the safety evaluation for a minimum of 6 patients, enrollment will be not suspended after 6 patients are enrolled in the lower dose arms pending the outcome of the safety evaluation. However, the Sponsor will still conduct a formal safety evaluation from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent for a given combination) and who have completed safety follow-up assessments until surgery. The stopping rules outlined above will also apply to the lower dose arms at this safety evaluation.

3.1.4 Safety Run-In Phase (Cohort 2)

To assess the safety and tolerability of novel combinations that are tested clinically for the first time, an initial safety run-in phase will be implemented in Cohort 2. Approximately 6 patients with metastatic disease will be treated with the novel combination and assessed for safety and tolerability for a minimum of 28 days.

A minimum of 6 patients in Cohort 2 must complete the initial safety run-in phase. If the combination is determined to be tolerable, enrollment for the preliminary phase may be opened, and the same arm in Cohort 1 can be opened for enrollment (refer to Section 3.1.2 for details). Patients in the safety run-in phase will be enrolled and treated

in a sequential manner, with at least one week between the first patient and the remaining patients.

The assessment will be based on safety data from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent) and who have completed safety follow-up assessments for at least 28 days. During the 6-patient safety run-in phase, or following safety evaluations, if ≥30% of patients experience one or more of the following events that is considered to be at least possibly related to study treatment, enrollment for that combination will be put on hold while the Sponsor evaluates the benefit–risk profile of that treatment:

- A treatment-related Grade ≥3 adverse event that does not improve (with or without treatment) to Grade 2 or better within 2 weeks
- A treatment-related serious adverse event
- A treatment-related adverse event that requires permanent discontinuation of study drug
- Death, except those that are incontrovertibly related to disease progression or extraneous causes such as accidents

If no new safety signals are detected, the combination will also be initiated in Cohort 1.

3.1.5 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). CRS severity will also be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading Scale.

Patients in Cohort 1 will receive neoadjuvant treatment for 2 cycles (6 weeks) and will undergo surgery (CLND) in Week 7. All patients are expected to proceed with surgery, provided that there are no distant metastases and the surgeon considers the disease to be completely resectable. Pathologic response will be assessed locally and by independent pathologic review.

Patients who discontinue treatment due to unacceptable toxicity and continue to have no evidence of metastatic disease will still be eligible for surgery and proceed with CLND after the adverse event has resolved and re-staging confirms Stage III disease.
If patients have confirmed disease progression, patient management and treatment selection will be at the discretion of the treating physician. These patients will remain in the study for follow-up.

Patients will undergo radiological tumor assessments in Week 6 (from Day 1 of Cycle 1) prior to surgery (CLND) (see Section 4.5.7 for details). Response will be assessed and

determined by the investigator in accordance with RECIST v1.1, but confirmation by later imaging studies is not required (see Appendix 1).

Patients in Cohort 2 will undergo tumor assessments every 9 weeks (from Day 1 of Cycle 1) for the first 54 weeks and then every 12 weeks thereafter (see Section 4.5.7). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Response per modified RECIST v1.1 for immune-based therapeutics (iRECIST) (see Appendix 2) will be determined programmatically by the Sponsor on the basis of investigator-assessed individual lesion data.

For Cohort 1 and Cohort 2, if clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm and the corresponding control arm be submitted for evaluation by an independent review facility.

For all patients, blood samples will be collected at baseline and during the study for biomarker research, including blood-based next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) testing.

Tumor and blood samples will be collected at baseline and during the study for biomarker assessments. Baseline tumor tissue samples will be collected from all patients (except patients in the Cohort 2 safety run-in phase) by biopsy of a metastatic lymph node (Cohort 1) or other metastatic lesion (Cohort 2) at screening. In addition, archival primary tumor tissue will be submitted from all patients if available. For patients in Cohort 1, on-treatment tissue samples will be collected by biopsy on Day 1 of Cycle 2 (up to 72 hours prior to drug administration), and at surgery (CLND). For patients enrolled in Cohort 2, on-treatment tissue samples will be collected by biopsy on Day 8 of Cycle 2. These samples will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.4.7 and details on tissue sample collection in Section 4.5.9). If possible, baseline screening samples should be collected after all other screening assessments have been evaluated for eligibility.

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and the other therapeutic agents, blood samples will be taken at various timepoints before and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

The schedule of activities for each treatment arm is presented in Sections A11–6 (Nivo + Ipi), A12–6 (RO7247669 *2100 mg*), A13–6 (Atezo + Tira), A14–6 (RO7247669 *2100 mg* + Tira Cohort 1), A14–8 (RO7247669 *2100 mg* + Tira Cohort 2), *A15–6 (RO7247669 600 mg), and A16–6 (RO7247669 600 mg + Tira).*

3.1.6 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from clinical science, safety science, and biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, or enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

3.1.7 Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

3.1.8 Independent Pathology Review

An Independent Pathology Review Facility (or facilities) (IPRF[s]) will perform an independent review of resection tissue, and other clinical data as needed, for the primary efficacy analyses. Review will be performed according to the guidelines of Pathologic Assessment of Resection Specimens After Neoadjuvant Therapy for Metastatic Melanoma (Appendix 3) IPRF membership and procedures will be detailed in an IPRF charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit, including long-term follow-up visits conducted by telephone or in the clinic.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years.

3.3 DURATION OF PARTICIPATION

In Cohort 1, the total duration of study participation for each individual from screening until the treatment completion visit and start of adjuvant treatment is expected to be approximately 17 weeks (not including long-term follow-up):

- Screening: Up to 4 weeks; Days −28 to −1
- Treatment period: 13 weeks; participants will receive neoadjuvant treatment during a 6-week period and will undergo surgery at Week 7. After surgery and prior to commencing adjuvant treatment, treatment completion will be performed in Week 13.

After the treatment period, participants may continue onto long-term follow-up:

- Information on long-term follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

In Cohort 2, the total duration of study participation for each individual is expected to be up to 5 years:

- Screening: Up to 4 weeks; Days −28 to −1
- Treatment period: participants will continue to receive treatment 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 (e.g., symptomatic deterioration such as pain secondary to disease).
- Safety follow-up: 28 days after the last dose of treatment
- Long-term follow-up: Information on long-term follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected by telephone, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study).

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Patient Population

Cohort 1 will enroll patients with resectable Stage III melanoma with measurable lymph node metastases (according to RECIST v1.1) that can be biopsied, and who have no history of in-transit metastases within the last 6 months. Enrolled patients must not have received prior immunotherapy for their disease.

This same patient population was enrolled in the OpACIN and OpACIN-neo studies, including the PRADO extension cohort. These studies evaluated the neoadjuvant (and adjuvant) combination of nivolumab and ipilimumab in patients with resectable melanoma. Neoadjuvant therapy was found to have a statistically significant and

clinically meaningful benefit as compared with adjuvant therapy (Rozeman et al. 2019; Blank et al. 2020; Rozeman et al. 2021). In addition, the safety profile of the treatment was found to be tolerable in an optimized treatment schedule.

Despite the recently demonstrated benefit of checkpoint inhibition therapy, there is a continuing need for treatment regimens that are more efficacious (i.e., broader and deeper pathologic response in the surgical specimen) and better tolerated for patients with resectable melanoma. The multiple treatment options in this study are expected to stimulate the immune system through a variety of mechanisms (see Appendix 11 through *Appendix 16* for more details). The aim is to extend the benefit of CIT beyond that of current checkpoint inhibition to a larger population with resectable melanoma.

Cohort 2 will enroll patients with Stage IV melanoma who experienced disease progression during or after at least one but not more than two lines of treatment for metastatic disease. Up to two lines of checkpoint inhibition therapy (monotherapy or combination therapy) are allowed. Patients with BRAF-mutant disease may have received an additional line of targeted therapy (either before, intermittent with, or after the checkpoint inhibition therapy) or may have received targeted therapy and checkpoint inhibition therapy concurrently as one combination treatment. Patients with BRAF-mutant melanoma with rapidly progressive disease who have not been previously treated with approved targeted therapies are not eligible.

Novel combinations of compounds with a clinical and/or biological rationale for anti-melanoma activity that have not yet been tested clinically will be investigated in Cohort 2. Importantly, for individual compounds considered for novel combinations, safety and tolerability have been already established in other studies and a safe dose and schedule are available. The Cohort 2 safety run-in phase will assess the safety of the novel combination with regards to potential overlapping toxicities (see Section 3.1.4 for details).

3.4.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response (CR), partial response (PR), and stable disease (SD) have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudoprogression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells.

In Cohort 1, because of the possibility of an initial increase in the size of metastatic lymph nodes caused by immune-cell infiltration in the context of a treatment elicited

T-cell response in the absence of unacceptable toxicity, patients who meet the criteria for disease progression in the target lymph node metastases per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment until surgery. However, the appearance of novel, previously undetected non-lymph node lesions may indicate that the patient has in fact been understaged and rather presents with more advanced or Stage IV disease. Because of the potential for a response after pseudoprogression, this study will allow patients randomly allocated to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1.2). Patients should be discontinued for 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 3.1.2 for details).

3.4.3 Rationale for the Use of Modified RECIST for Immune-Based Therapeutics

Increasing clinical experience indicates that traditional response criteria (e.g., RECIST v1.1 and World Health Organization criteria) may not adequately assess the activity of immunotherapeutic agents because initial radiographic evidence of disease progression does not necessarily reflect therapeutic failure. Patients can experience a response in the presence of new lesions or after an increase in tumor burden. Thus, this study will employ iRECIST (Seymour et al. 2017; see Appendix 2), tumor response criteria that have been modified for unconventional tumor change patterns associated with CIT.

iRECIST was developed by the RECIST working group in an effort to create a common set of criteria that the CIT field could apply to clinical trials (Seymour et al. 2017). iRECIST accounts for responses that may occur following transient radiographic progression caused by immune-cell infiltration in tumors (leading to a transient increase in the size of existing lesions, including those that were previously undetectable and consequently appear as new lesions). iRECIST relies on collection of tumor assessment data after initial disease progression per RECIST v1.1.

Given the proposed immunomodulatory mechanism-of-action of atezolizumab and other CPIs and the possibility of observing delayed responses, exploratory efficacy endpoints will include analyses based on iRECIST. These analyses will allow for evaluation of iRECIST as an improved measure of the efficacy of immunotherapies relative to standard RECIST v1.1.

3.4.4 Rationale for Neoadjuvant Treatment in Melanoma in Cohort 1

Neoadjuvant therapy has several potential advantages over adjuvant therapy, and could even be superior to adjuvant therapy in this patient population. In particular, using neoadjuvant therapy could allow investigators to determine therapy efficacy in individual patients, which could guide the use of additional adjuvant therapy, if needed.

Neoadjuvant therapy could also reduce tumor burden before surgery, and the pathologic response data could be used as surrogate outcome markers for RFS and OS. In the case of T-cell checkpoint blockade, neoadjuvant therapies could have a potentially significant advantage. T-cell checkpoint-blocking antibodies enhance T-cell activation when an antigen is encountered. Drug exposure during the time the major tumor mass is still present may therefore potentially induce a stronger and broader tumor-specific T-cell response (Blank et al. 2018). Indeed, preclinical data provided support for the superior activity of T-cell checkpoint blockade when given before surgery (Liu et al. 2016).

Data from the recent OpACIN and OpACIN-neo studies show that two cycles of neoadjuvant ipilimumab plus nivolumab without additional adjuvant therapy induces durable RFS in more than 80% of patients, and further endorse pathologic response as a strong surrogate outcome marker for RFS (Rozeman et al. 2021).

3.4.5 Rationale for Pathologic Response Rate as Primary Endpoint in Cohort 1

The pathologic response to neoadjuvant therapy is a surrogate endpoint of improved patient outcomes in the treatment of several cancer types. The majority of neoadjuvant studies that are ongoing in melanoma are testing immunotherapy and use pathologic response as an endpoint (Mueller et al. 2021).

Several studies, including OpACIN and OpACIN-neo, have shown that pathologic response appears to be a strong surrogate marker for long-term benefit. A pooled analysis of the INMC confirmed that pathologic response strongly correlates with RFS and OS with neoadjuvant therapy in Stage III melanoma. It is further reported that particularly with combination immunotherapy, any degree of pathologic response with immunotherapy is sufficient to confer excellent survival.

Six neoadjuvant melanoma studies were conducted recently with BRAF/MEK-targeted therapy or PD-1-based immunotherapy, and demonstrated that neoadjuvant therapies achieve high pCR rates and RFS in Stage III melanoma. In the pooled analysis, pCR occurred in 40% of patients: 47% with targeted therapy and 33% with immunotherapy (43% combination and 20% monotherapy). pCR correlated with improved RFS (pCR 2-year 89% vs. no pCR 50%, $p < 0.001$) and OS (pCR 2-year OS 95% vs. no pCR 83%, $p = 0.027$). In patients achieving a pathologic response with immunotherapy, very few relapses were seen (2-year RFS 96%), and no patient had died from melanoma at time of the report. With pCR from targeted therapy, the 2-year RFS was only 79%, and OS was only 91% (Menzies et al. 2021).

3.4.6 Rationale for Using Nivo + Ipi as Comparator in Cohort 1

No standard of care exists for neoadjuvant treatment of resectable melanoma. The highest pathologic response rates have been observed in Stage IV disease and in Stage III disease in the neoadjuvant setting with the combination of nivolumab and

ipilimumab (Menzies et al. 2021). As pathologic response (especially pCR, but also *near* pCR) emerges as a potential surrogate endpoint for RFS benefit, the combination of nivolumab and ipilimumab was chosen as the active comparator for this study. In addition, given the positive data in several studies and the approval of the combination of nivolumab and ipilimumab for patients with advanced melanoma, this combination was considered to be the best comparator for the anticipated patient population in this study (Wolchok et al. 2013; Sznol et al. 2014). Furthermore, a Phase III study with the objective of establishing nivolumab combined with ipilimumab as a standard of care option for neoadjuvant therapy is planned (NADINA Trial).

The recommended dose for advanced melanoma is 1 mg/kg nivolumab and 3 mg/kg ipilimumab. This study will use alternative dosing of 3 mg/kg nivolumab and 1 mg/kg ipilimumab because this dosing schedule induced a lower rate of immune-mediated toxicity in the OpACIN-neo study, and thus was identified as the optimal dosing regimen in the neoadjuvant setting (Rozeman et al. 2019).

Randomized studies evaluating immunotherapy combinations will allow us to identify safe and effective neoadjuvant treatments for patients with resectable melanoma while also significantly increasing our understanding of cancer biology.

3.4.7 Rationale for Biomarker Assessments

Blood samples for biomarker assessments will be collected at baseline and during the study. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatments and treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell subpopulations, gene expression, and ctDNA) and drug dose and efficacy and safety endpoints may allow for the development of a blood-based biomarker to help define future treatments and predict which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be collected from all patients (except patients in the Cohort 2 safety run-in phase) by biopsy at screening. In addition, on-treatment tissue samples will be collected up to 72 hours prior to drug administration. If available, archival primary tumor tissue will be submitted from all patients.

Tumor samples will be evaluated for biomarkers such as tumor-infiltrating immune cells, PD-L1, CD8, and expression of targets specific to each drug combination. Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number, locations, densities and functional status of tumor-infiltrating immune cells, could provide validation of the postulated mechanism-of-action, confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved*, and/or response prediction capacity*. Differences in biomarkers and lymphocyte infiltration in baseline primary tumor compared to metastasis may be assessed.

Tumor tissue and blood samples may be analyzed through use of NGS methods such as whole exome sequencing (WES) to identify somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria outlined in Section 4.1.1.1 and Section 4.1.1.2 to qualify for Cohort 1. Patients must meet all of the criteria outlined in Section 4.1.1.1 and Section 4.1.1.3 to qualify for Cohort 2.

4.1.1.1 Shared Inclusion Criteria for Cohort 1 and Cohort 2

Patients must meet all of the following criteria to qualify for Cohort 1 and Cohort 2:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing Informed Consent Form
- ECOG performance status (PS) of 0 or 1
- Ability to comply with the protocol, in the investigator's judgment
- Availability of a representative tumor specimen that is suitable for biomarker testing via central laboratory

  Baseline tumor tissue samples will be collected from all patients (except patients in the Cohort 2 safety run-in phase) by biopsy of a metastatic lymph node (Cohort 1) or other metastatic lesion (Cohort 2) at screening.

  In addition, archival primary tumor tissue will be submitted from all patients. In exceptional cases where no archival primary tissue is available (e.g., for patients with unknown primary tumor), enrollment is permitted. For archival tissue, a formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) with sufficient size and tumor content representation, preferably including the invasive margin, or, if available, at least 16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

  Refer to Section 4.5.9 and to the laboratory manual for additional information on tumor specimens collected at screening.

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$ cells/L (500/μL)

    Borderline machine lymphocyte counts may be confirmed by a manual count.
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL)
  - Hemoglobin ≥ 90 g/L (9 g/dL)
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN with the following exceptions:

    For Cohort 2, patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.

    For Cohort 2, patients with documented liver or bone metastasis: ALP $\leq 5 \times$ ULN.
  - Total bilirubin $\leq 1.5 \times$ ULN, with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
  - Creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin ≥ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen (i.e., no new thrombosis, thromboembolic event, or bleeding episode within 3 months prior to study treatment start)
- Negative HIV test at screening, *with the following exception: Patients with a positive HIV test at screening are eligible provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu L$, and have an undetectable viral load.*

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.
- Negative hepatitis B surface antibody (HBsAb), and negative total hepatitis B core antibody (HBcAb) test at screening. If a patient has a negative hepatitis B surface antigen (HBsAg) test and a positive total HBcAb test at screening, an hepatitis B virus (HBV) DNA test must also be performed to rule out active HBV.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as outlined for each specific treatment arm in Appendix 11 through *Appendix 16*.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 11 through *Appendix 16*.

4.1.1.2 Inclusion Criteria for Cohort 1

Patients must meet all of the following criteria to qualify for Cohort 1:

- Histologically confirmed resectable Stage III melanoma (T: T0, Tx or T1–4; N: cN1–3, pN1b/2b/3b; M: M0 according to AJCC-8 [Gershenwald et al. 2017]) and no history of in-transit metastases within the last 6 months

  Patients may present with primary melanoma with concurrent regional nodal metastasis, or a history of primary melanoma or unknown primary melanoma with clinically detected regional nodal recurrence, and may belong to any of the following groups:

  – Primary cutaneous melanoma with concurrent clinically/radiologically apparent regional lymph node metastases
  – Clinically/radiologically detected recurrent melanoma at the proximal regional lymph node(s) basin
  – Clinically/radiologically detected nodal melanoma (if single site) arising from an unknown primary

- Fit and planned for CLND (as assessed by surgeon prior to randomization according to local guidelines)
- Measurable disease (at least one target lesion) according to RECIST v1.1

  At least one macroscopic lymph node metastasis (measurable according to RECIST v1.1) to be biopsied.

4.1.1.3 Inclusion Criteria for Cohort 2

Patients must meet all of the following criteria to qualify for Cohort 2:

- Life expectancy ≥ 3 months, as determined by the investigator
- Histologically confirmed Stage IV (metastatic) cutaneous melanoma according to AJCC-8 (Gershenwald et al. 2017)
- Disease progression during or following at least one but no more than two lines of treatment for metastatic disease

  Up to two lines of CPI therapy (monotherapy or combination therapy) are allowed. Patients with BRAF-mutant disease may have received an additional line of targeted therapy (either before, intermittent with, or after the CPI therapy), or may have received targeted therapy and CPI therapy concurrently as one combination treatment. Patients with BRAF-mutant melanoma with rapidly progressive disease who have not been previously treated with approved targeted therapies are not eligible. Patients who received adjuvant treatment with CPI therapy for localized melanoma require an additional line of CPI therapy in the metastatic setting. Patients who relapse or systemically progress

during or within 6 months of completion of adjuvant therapy are eligible and do not require an additional line of CPI therapy.

- Measurable disease (at least one target lesion) according to RECIST v1.1

  At least one metastasis (measurable according to RECIST v1.1).

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment in specific arms if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in Table 5.

Table 5 Arm-Specific Exclusion Criteria

Cohort	Treatment Arm	Applicable Exclusion Criteria
1	Nivo + Ipi (control)	Sections 4.1.2.1 and 4.1.2.2
	RO7247669 *2100 mg*	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
	Atezo + Tira	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.5
	RO7247669 *2100 mg* + Tira	Sections 4.1.2.1, 4.1.2.2, 4.1.2.4, and 4.1.2.5
	RO7247669 600 mg	*Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4*
	RO7247669 600 mg + Tira	*Sections 4.1.2.1, 4.1.2.2, 4.1.2.4, and 4.1.2.5*
2	RO7247669 *2100 mg* + Tira	Sections 4.1.2.1, 4.1.2.3, 4.1.2.4, and 4.1.2.5

Atezo = atezolizumab; Ipi = ipilimumab; Nivo = nivolumab; Tira = tiragolumab.

4.1.2.1 Exclusion Criteria for Cohort 1 and Cohort 2

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

- Mucosal and uveal melanoma

  Acral lentiginous melanoma is excluded for Cohort 1.

  For Cohort 2, acral lentiginous melanoma is permitted; however, the proportion of patients should not exceed 20% of response-evaluable patients.

- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Treatment with systemic immunostimulatory agents (including, but not limited to, IFN and IL-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- Known immunodeficiency or conditions requiring treatment with systemic immunosuppressive medication (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor–α agents), or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients on replacement doses of corticosteroids to manage hypopituitary or adrenal insufficiency are eligible for the study.

Patients who received acute, low-dose, systemic immunosuppressant medications, or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study. Patients requiring chronic low-dose systemic corticosteroid treatment (i.e., a maximal dose of corticosteroids ≤ 10mg/day equivalent prednisone) are eligible.

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

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 7) for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

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

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

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan. Patients with a history of CIT-related pneumonitis Grade < 2 are eligible.
- History of malignancy other than malignant melanoma within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer

- Active tuberculosis (TB)
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic or prophylactic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
- Significant cardiovascular disease such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Uncontrolled hypertension (defined as resting systolic blood pressure $>$150 mmHg and/or diastolic blood pressure $>$100 mmHg in two or more serial measurements)
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure other than CLND, during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, impair the ability of the patient to participate in the study, or may render the patient at high risk from treatment complications
- History of severe allergic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Known intolerance to any of the drugs required for premedication (acetaminophen, ranitidine, diphenhydramine, and methylprednisolone)
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Eligible only for the control arm

4.1.2.2 Exclusion Criteria for Cohort 1

Patients who meet any of the following criteria will be excluded from Cohort 1:

- Distantly metastasized melanoma
- History of in-transit metastases within the last 6 months
- Prior radiotherapy

- Prior immunotherapy, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies, and other systemic therapy for melanoma

4.1.2.3 Exclusion Criteria for Cohort 2

Patients who meet any of the following criteria will be excluded from Cohort 2:

- Symptomatic, untreated, or progressing CNS metastases

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.

  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

  – CNS metastases are stable for ≥4 weeks prior to initiation of study, or neurosurgical resection occurred ≥ 28 days prior to initiation of study treatment.

  – The patient has no requirement for corticosteroids as therapy for CNS disease for at least 14 days prior to initiation of study treatment.

  – Anti-convulsant therapy at a stable dose is permitted.

- Active or history of carcinomatous meningitis/leptomeningeal disease
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at screening.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg/dL, or corrected calcium >ULN)
- Any history of an immune-mediated Grade 4 adverse event attributed to prior CIT (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase) that resulted in permanent discontinuation of the prior immunotherapeutic agent

- All immune-mediated adverse events related to prior immunomodulatory therapy (other than endocrinopathy managed with replacement therapy or stable vitiligo) that have not resolved completely to baseline. Patients treated with corticosteroids for immune-mediated adverse events, except for corticosteroids replacement therapy for adrenal insufficiency (provided that the patient receives $\leq$10 mg prednisone/day or equivalent), must not have related symptoms or signs for $\geq$4 weeks following discontinuation of corticosteroids
- Adverse events related to any prior radiotherapy, chemotherapy, targeted therapy, CPI therapy or surgical procedure must have resolved to Grade 1 or better, except alopecia (any grade), Grade 2 peripheral neuropathy, and hypothyroidism and/or hypopituitarism on a stable dosage of hormone replacement therapy (e.g., thyroxine, hydrocortisone, prednisolone, others)

4.1.2.4 Exclusion Criteria for RO7247669-Containing Arms (Cohort 1 and Cohort 2)

Patients who meet any of the following criteria will be excluded from the RO7247669-containing arms:

- Prior treatment with an anti−LAG-3 agent
- History of myocarditis (regardless of etiology)
- Left ventricular ejection fraction (LVEF) $<$50% assessed by either transthoracic echocardiogram (TTE) or multiple-gated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to initiation of study treatment
- Troponin T (TnT) or troponin I (TnI) $>$institutional ULN

  Patients with TnT or TnI levels between $>$ 1 and $<2\times$ULN are eligible if repeat levels within 24 hours are $\leq 1\times$ULN. If repeat levels within 24 hours are between $>$1 and $<2\times$ULN, patients need to undergo a cardiac evaluation and may be considered for treatment if there are no clinically significant findings.

4.1.2.5 Exclusion Criteria for Tiragolumab-Containing Arms (Cohort 1 and Cohort 2)

Patients who meet any of the following criteria will be excluded from the tiragolumab-containing arms:

- Prior treatment with an anti-TIGIT agent
- Acute Epstein-Barr virus (EBV) infection or known or suspected chronic active EBV infection at screening

  Patients with a positive EBV viral capsid antigen (VCA) IgM test at screening are excluded from this arm. An EBV PCR test should be performed as clinically indicated to screen for active infection or suspected chronic active infection. Patients with a positive EBV PCR test are excluded from this arm.

4.2 METHOD OF TREATMENT ASSIGNMENT

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

For Cohort 1, this study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment over the course of the study.
The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%. The randomization ratios may be altered to increase enrollment in a particular arm.

Randomization will be stratified according to the following criteria:

- Geographic region: Australia vs. Rest of the World
- Baseline LDH: $\leq$ULN vs. $>$ULN

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Section 4.1.2. For example, the Atezo+Tira arm will be removed as an option for patients who are ineligible for that arm. If a patient is only eligible for the control arm, that patient will not be enrolled in the study.

For Cohort 2, patients will be assigned to receive treatment with RO7247669 $2100\ mg$+Tira. If additional treatment arms are opened at a later time, a permuted-block randomization method will be employed from this point forward.

Patients who do not receive at least one dose of each drug for their assigned treatment regimen will not be included in the efficacy analyses. Additional patients may be enrolled to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4.

4.3.1 Investigational Medicinal Product Handling and Accountability

The IMPs for this study are atezolizumab, tiragolumab, RO7247669, nivolumab, and ipilimumab. *Appendix 17* identifies all IMPs, non-investigational medicinal products, and auxiliary medicinal products for this study.

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

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

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or will 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 a drug accountability log.

Refer to the pharmacy manual and/or the applicable Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing study treatments in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions are provided in the respective appendix for each treatment arm (see Sections A11–4.2 [Nivo + Ipi], A12–4.2 [RO7247669 *2100 mg*], A13–4.2 [Atezo + Tira], and A14–4.2 [RO7247669 *2100 mg* + Tira Cohorts 1 and 2]*, A15–4.2 [RO7247669 600 mg], and A16–4.2 [RO7247669 600 mg + Tira]*).

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for screening in Appendix 10 and for each treatment arm in Sections A11–6 (Nivo + Ipi), A12–6 (RO7247669 *2100 mg*), A13–6 (Atezo + Tira), A14–6 (RO7247669 *2100 mg* + Tira Cohort 1), and A14–8 (RO7247669 *2100 mg* + Tira Cohort 2), *A15–6 (RO7247669 600 mg), and A16–6 (RO7247669 600 mg + Tira)*. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each infusion; 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) and may be obtained more than 28 days before initiation of study treatment. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening evaluations are to be performed within 28 days prior to initiation of study treatment (Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to Day 1 may be used as outlined in the schedule of activities (see Appendix 10 [screening], Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2]*, A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*). Such tests do not need to be repeated for screening or re-screening.

4.5.2 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. The patient's molecular profile for melanoma, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time 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.

Refer to the schedule of activities for information about the timing of medical history, molecular profile, concomitant medication, and demographic data collection (Appendix 10 [screening], Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2]*, A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include evaluations as per clinical practice (e.g., evaluations of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes.

New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height will be recorded at screening. Weight will be recorded at specified timepoints during the study.

Refer to the schedule of activities for information about the timing of physical examinations (Appendix 10 [screening], Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2*], A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*).

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured within 60 minutes prior to administration of each study treatment and, if clinically indicated, during or after treatment administration. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 10 [screening], Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2]*, A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*).

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Electrocardiograms

An ECG will be performed at screening, as clinically indicated, and as outlined in the schedules of activities (see Appendix 10 [screening], Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2]*, A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

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

4.5.6 Evaluation of Left Ventricular Function

Patients will undergo evaluation of LVEF, either by TTE or MUGA scan at screening and as outlined in the schedules of activities (see Appendix 10 [screening], Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*). Evaluation of LVEF must be performed using the same method for each patient. TTE measurements should be performed by the same operator whenever possible, following the most recent echocardiography society guidelines. Paper copies of reports will be kept as part of the patient's permanent study file at the site.

4.5.7 Tumor and Response Evaluations

4.5.7.1 Radiographic Procedures for Screening (Cohorts 1 and 2)

All measurable and evaluable lesions should be assessed and documented at screening as outlined in the schedule of activities (Appendix 10). Tumor assessments performed as standard of care prior to obtaining informed consent and within *28* days prior to randomization/enrollment do not have to be repeated at screening.

Screening assessments must include CT scans (with oral and/or IV contrast) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT scan with contrast or MRI scan of the head with contrast must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT or MRI scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease may be used as per RECIST v1.1.

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. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations as outlined in Section 4.5.7.2 (Cohort 1) or Section 4.5.7.3 (Cohort 2). The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

4.5.7.2 Cohort 1 Tumor, Response, and Disease Status Evaluations

Patients in Cohort 1 will be assessed for pathologic and radiologic response to treatment. Patients will undergo pathological tumor assessments after 6 weeks of treatment at surgery (CLND). The complete resection of Stage III lymph nodes (CLND) in Week 7 must be performed in compliance with the criteria for adequate surgical procedures for therapeutic lymph node dissection (see Appendix 4). CLND should be performed as planned if the patient is receiving corticosteroids or other anti-inflammatory drugs for the management of immune-mediated adverse events, provided these are being given at a stable or tapering dose and the severity of adverse events is Grade 2 or better. CLND may be delayed for up to 2 weeks if study treatment-related adverse events have not improved sufficiently at the time of planned surgery (see Section 3.1.3). Pathological response will be determined by local and independent pathologic review according to INMC guidelines (Tetzlaff et al. 2018; Appendix 3).

Patients will undergo radiographic tumor assessments at baseline and after 6 weeks of treatment before surgery (CLND) according to RECIST v1.1, as outlined for each arm in the schedules of activities (see Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*). At the treatment completion/discontinuation visit (Week 13), the disease status will be assessed by radiographic tumor assessments for the absence of recurrent disease. *Tumor assessments that have been performed outside the protocol-mandated time window do not have to be repeated. However, at the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.*

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator prior to treatment administration.

Disease Follow-Up and Confirmation of Disease Progression or Recurrence

During the neoadjuvant treatment, diagnosis of disease progression should be confirmed by clinical, laboratory, radiological, and/or histological findings. After surgery, prior to commencing adjuvant treatment or observation, the first planned tumor assessment will be performed in Week 13 to conclude the neoadjuvant therapy-surgery intervention window and should include a CT scan. After the treatment phase, during the follow-up phase, all patients must be followed to assess disease recurrence and survival as outlined for each arm in the schedules of activities (see Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1]*, A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]). Tumor assessments that have been performed outside the protocol-mandated time window do not have to be repeated. However, at the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.*

The designation of disease recurrence, whether local, regional, or distant, can be made only when clinical, laboratory, radiological and/or histological findings confirm the diagnosis.

During the post-surgery period, disease status should be clinically evaluated and documented every 3 months for the first 2 years; every 6 months in the third year and annually thereafter until a diagnosis of a recurrence (defined below). In addition to physical examinations, liver function tests, bone scans, chest X-ray/diagnostic CT scan, liver imaging, and/or other radiographic modalities may be considered when clinically indicated to exclude metastatic disease within timelines as per current local standard of practice.

The diagnosis of a progression or recurrence should be confirmed histologically whenever clinically possible. The earliest date of diagnosis of disease progression or

recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence. Recurrent disease includes local, regional, or distant recurrence: local recurrence is defined as tumor regrowth within 2 cm of the primary lesion's tumor bed; regional recurrence as any nodal or non-nodal tumor lesions that are more than 2 cm from the primary lesion but are not beyond the regional nodal basin; distant recurrence as any non-local/non-regional recurrence.

The definitions of and procedures for confirming disease recurrence, death, and other noteworthy events on follow-up are provided below. Documentation of recurrence will require specification of all sites involved to establish the pattern of recurrence.
The following criteria of treatment failure constitute the only acceptable evidence of disease recurrence:

- Lung: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease
- Liver: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease
- Central nervous system: A positive brain CT or MRI scan or CSF cytology
- Cutaneous, subcutaneous, and lymph node recurrence: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease
- Bone and other organs: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease identified on two different radiologic studies (i.e., positive nuclear bone scan or PET scan and contrast GI series or ultrasound, X-ray or CT of abdomen for abdominal disease)

4.5.7.3 Cohort 2 Tumor and Response Evaluations

Patients in Cohort 2 will undergo tumor assessments every 9 ($\pm$1) weeks (from Day 1 of Cycle 1) for the first 54 weeks and then every 12 ($\pm$2) weeks thereafter, regardless of dose delays, as outlined in the schedule of activities (see Section A14–8 [RO7247669 $2100\ mg+$Tira Cohort 2]). The exception is patients who continue treatment after radiographic disease progression. Such patients will undergo tumor assessments every 9 weeks until loss of clinical benefit as determined by the investigator (see Section 3.1.2 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy. Tumor assessments that have been performed outside the protocol-mandated time window do not have to be repeated. However, at the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable but will be documented at screening as a site of metastatic disease. Brain

metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated.

To facilitate evaluation of response per iRECIST in Cohort 2, tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable; see Appendix 1) at all subsequent assessments.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator prior to treatment administration.

Overall response per iRECIST (see Appendix 2) will not be captured in the eCRF, but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

4.5.8 Classification of Surgical Complications

Surgical complications will be scored according to Clavien-Dindo classification (Appendix 5). Complication rates for every grade will be reported and scored for patients that underwent CLND, as outlined for each arm in the schedules of activities (see Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*).

4.5.9 Laboratory, Biomarker, and Other Biological Samples

4.5.9.1 Local Laboratory Assessments

For information about the timing of local laboratory assessments, please refer to the schedule of activities for screening (Appendix 10) or the appropriate treatment arm (Sections A11–6 [Nivo + Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo + Tira], A14–6 [RO7247669 *2100 mg* + Tira Cohort 1], A14–8 [RO7247669 *2100 mg* + Tira Cohort 2], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg + Tira]*).

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)

- Chemistry panel (serum or plasma): includes sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care in the region), glucose, BUN or urea, creatinine, total protein, ferritin, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, amylase, lipase, and LDH. In addition, adrenocorticotropic hormone (ACTH), cortisol, S100, and erythrocyte sedimentation rate (ESR) will be assessed at screening and pre-surgery visits for patients enrolled in Cohort 1.
- Lipid panel: includes triglycerides, HDL, and LDL
- Coagulation: INR and aPTT
- Thyroid function testing: TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4
- Cardiac enzymes: troponin I or T
- C-reactive protein
- HIV serology, unless not permitted per local regulations
- HBV serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), total hepatitis B core antibody (HBcAb), and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

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

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- EBV serology:
  - EBV VCA IgM
  - EBV VCA IgG or Epstein-Barr nuclear antigen (EBNA) IgG
  - EBV PCR (only if clinically indicated)
- Cytomegalovirus (CMV) serology: CMV IgM and IgG

  If a patient has a positive CMV IgM test or $\geq 4 \times$ ULN increase in CMV IgG, quantitative PCR should used to determine if the patient has a CMV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Pregnancy tests will also be performed at treatment completion/discontinuation at Week 13 and during follow-up at 6 months in Cohort 1, and at 3 and 6 months in Cohort 2.

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).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

4.5.9.2 Central Laboratory Assessments

For information about the timing of central laboratory assessments, please refer to the schedule of activities for screening (Appendix 10) or the appropriate treatment arm (Sections A11–6 [Nivo+Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo+Tira], A14–6 [RO7247669 *2100 mg*+Tira Cohort 1], A14–8 [RO7247669 *2100 mg*+Tira Cohort 2], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg+Tira]*).

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

- Serum sample for analysis of autoantibodies: anti–nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody
- Serum samples for PK analysis through use of validated assays
- Serum samples for immunogenicity analysis through use of validated assays
- Plasma and blood for exploratory research on biomarkers including blood-based NGS/WES ctDNA assay to determine tumor-specific alterations
- Archival tumor tissue sample for exploratory research on biomarkers

  An archival primary tumor tissue sample, preferably as a FFPE tumor tissue block with representation and sufficient tumor content, including the invasive margin (preferred), or, if available, at least 16 slides containing unstained, freshly cut, serial sections, must be submitted along with an associated pathology report. For the Cohort 2 safety run-in phase, submission of an archival sample is preferred, but patients are eligible for the study if no archival sample is available. Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

- Fresh baseline and on-treatment tumor tissue for exploratory research on biomarkers

  Baseline tumor tissue samples will be collected from all patients (except patients in the Cohort 2 safety run-in phase) by biopsy of a metastatic lymph node (Cohort 1) or other metastatic lesion (Cohort 2) at screening. For patients in Cohort 1, on-treatment tissue samples will be collected by biopsy on Day 1 of Cycle 2 (up to 72 hours prior to drug administration), and at surgery (CLND). For patients enrolled in Cohort 2, on-treatment tissue samples will be collected

by biopsy on Day 8 of Cycle 2. An overview of planned tissue samples is provided in Table 6.

To mitigate potential risk associated with tumor biopsies, all patients undergoing fresh tumor biopsies must have tumor lesions from which biopsies can be safely obtained, as per clinical judgment of the treating physician. Collection of tumor biopsies should be guided by ultrasound, CT scan or other methods according to the location of the selected lesion. Collect at least 3 cores (preferably 4 cores) using a 14-gauge needle, ideally of at least 20 mm in length or equivalent size. Fresh tumor tissue will be processed as described in the laboratory manual .

The baseline and on-treatment biopsies should preferably be taken from the same tumor lesion/metastasis to ensure comparability. If the lesion biopsied at baseline cannot be biopsied on treatment (e.g., because lesion is no longer present or can no longer be safely biopsied), then an alternative lesion should be biopsied. Preferably the new lesion would be in a similar tissue. If feasible, biopsies may be repeated if the initial biopsy did not contain sufficient tumor material for analysis. The location of each biopsy will be documented in relation to each tumor lesion as determined by imaging.

Table 6 Overview of Mandatory Tissue Samples

Timepoint	Sample Type	Requirement
Cohort 1		
Screening	Archival tissue	Mandatory *(if available)*
Screening	Fresh biopsy	Mandatory
Cycle 2 Day 1 (up to 72 hours prior to drug administration)	Fresh biopsy	Mandatory
Surgery (CLND) Week 7	Fresh tissue from surgery	Mandatory
Cohort 2 (except safety run-in)		
Screening	Archival tissue	Mandatory *(if available)*
Screening	Fresh biopsy	Mandatory
Cycle 2 Day 8	Fresh biopsy	Mandatory

CLND = complete lymph node dissection

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of two consecutive high power fields of viable tumor, if possible including the invasive margin that preserves cellular context and tissue architecture, regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy, or excisional, incisional, punch biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and

lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations *and their functional and/or activation status*, T-cell receptor repertoire, or cytokines associated with T-cell activation. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. NGS methods may include whole genome sequencing (WGS) or WES of tissue and blood samples, but WGS or WES of blood samples will be performed only at participating sites (see Section 4.5.10).

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biologic samples will be destroyed no later than the time of completion of the final Clinical Study Report (CSR), with the following exceptions:

- Serum and plasma samples collected for PK analysis or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed.
- Blood, plasma, peripheral blood mononuclear cell (PBMC), and tumor tissue collected for biomarker research will be destroyed no later than 5 years after the final CSR has been completed, with the exception of the samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the Institutional Review Board (IRB)/Ethics Committee (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 the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

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

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

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

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

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to develop adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. The samples may be sent to one or more laboratories for analysis.

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

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

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

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

Refer to Section 4.5.9 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Tumor Biopsies

Patients will be given the option of consenting to additional tumor biopsies. If deemed clinically feasible by the investigator, consenting patients in Cohort 1 and Cohort 2 may undergo additional biopsies at the time of unacceptable toxicity, loss of clinical benefit, relapse (Cohort 1), or at any other time at the investigator's discretion for exploratory research on biomarkers. Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, loss of clinical benefit, relapse, or prior to the next anti-cancer therapy (whichever is sooner), as described in the schedule of activities (Sections A11–6 [Nivo+Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo+Tira], A14–6 [RO7247669 *2100 mg*+Tira Cohort 1], A14–8 [RO7247669 *2100 mg*+Tira Cohort 2], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg+Tira]*).

If deemed clinically feasible by the investigator, baseline and on-treatment tumor tissue samples may be collected from patients in the Cohort 2 safety run-in phase. Biopsies should be performed at screening and during treatment on Day 8 of Cycle 2 for exploratory research on biomarkers.

An overview of optional tissue samples is provided in Table 7 .

Table 7 Overview of Optional Tissue Samples

Timepoint	Sample Type	Requirement
Cohort 1		
Any time during study [a]	Fresh biopsy	Optional
Cohort 2 safety run-in		
Screening	Archival tissue	Optional
Screening	Fresh biopsy	Optional
Cycle 2 Day 8	Fresh biopsy	Optional
Any time during study [a]	Fresh biopsy	Optional
Cohort 2		
Any time during study [a]	Fresh biopsy	Optional

[a] To be collected at the time of unacceptable toxicity, loss of clinical benefit, relapse (Cohort 1), or at any other time at the investigator's discretion, if deemed clinically feasible.

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

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to provide optional biopsies.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.9. Refer to Section 4.5.9 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data derived from biomarker analyses.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

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

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

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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

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

- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) collected during the study, including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion

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

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

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

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

4.5.12.4 Confidentiality

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

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

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

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

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

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

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her samples, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.12.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non–protocol-specified anti-cancer therapy
- Pregnancy
- Cohort 1: Confirmed disease progression or dissemination prior to surgery. Patients who discontinue study treatment early because of an unacceptable toxicity should continue to be followed for both resolution of toxicity and disease recurrence as outlined in the schedule of activities (Sections A11–6 [Nivo+Ipi], A12–6 [RO7247669 *2100 mg*], A13–6 [Atezo+Tira], A14–6 [RO7247669 *2100 mg*+Tira Cohort 1], *A15–6 [RO7247669 600 mg], and A16–6 [RO7247669 600 mg+Tira]*).
- Cohort 2: 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.

For Cohort 1, regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment. For patients who progress or have loss of clinical benefit, the visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit.

For Cohort 2, 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 A14–8).

Information on long-term follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., country records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

4.6.2 Patient Discontinuation from Study

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

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

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. 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., country 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

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm in Appendix 11 through *Appendix 16*.

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 infectionis confirmed, the disease should be managed as per local or institutional guidelines.

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 each treatment arm are listed in the respective appendix for that treatment arm (see Appendix 11 through *Appendix 16*).

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 5.3.5.12–5.6.

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 Events Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

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

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

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

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

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

The ASTCT CRS Consensus Grading Scale (see Table 9) should be used in addition to NCI CTCAE when reporting severity of CRS (see Section 5.3.5.1 for details on CRS reporting).

Table 9 ASTCT CRS Consensus Grading Scale

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

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

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

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

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 10):

- 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 10 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

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

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

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

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

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 9, and guidelines for management of IRRs in the RO7247669 arms are provided in Appendix 12 *and Appendix 15*.

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 ($>3\times$ baseline value) 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 $>3\times$ **baseline value** in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ **baseline value** 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 disease 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 Melanoma

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 Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm

- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

    In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

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 atezolizumab, tiragolumab, and RO7247669, 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.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab, tiragolumab, and RO7247669, 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.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

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.

5.4 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 arm-specific appendices for details on pregnancy reporting requirements for each treatment arm)

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

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

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

5.4.1 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

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 continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 135 days after the final dose of study treatment or until initiation of new, systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

After the end of the reporting period for non-serious adverse events (defined as 30 days after the final dose of study treatment), all treatment-related non-serious adverse events that lead to surgery delay will continue to be reported until 135 days after the final dose of study treatment.

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.

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:

- Opdivo® EMA Summary of Product Characteristics (SmPC; nivolumab)
- Yervoy® EMA SmPC (ipilimumab)
- RO7247669 Investigator's Brochure
- Atezolizumab Investigator's Brochure
- Tiragolumab 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

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen, and safety analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment that patients actually receive. Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and ranges. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on treatments or treatment combinations when administered to patients with melanoma. Cohort 1 will consist of patients with resectable Stage III melanoma who have not received prior systemic therapy for their disease. Cohort 2 will consist of patients with Stage IV melanoma who experienced disease progression during or after at least one but not more than two lines of treatment for metastatic disease.

In Cohort 1, approximately *195–290* patients will be randomly allocated to the control and experimental arms during the study (*35–50* patients to the control arm and 20*–60* patients to each experimental arm). In Cohort 2, approximately *8–*46 patients will be assigned to an experimental arm. Please refer to Table 4 for further details.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm. Patient disposition will be summarized by treatment arm. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. Reasons for discontinuation of study drugs will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site [if applicable], and baseline ECOG PS) will be summarized overall and by treatment arm.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint in Cohort 1

The primary efficacy endpoint in Cohort 1 is pRR at time of surgery. pRR will be assessed after completion of neoadjuvant treatment (Week 7) at time of CLND.
The pRR is defined as the proportion of patients who achieve pCR (a complete absence of viable tumor in the treated tumor bed), pathologic near complete response (pnCR; $<$10% of viable tumor in the treated tumor bed); and pathologic partial response (pPR; $<$50% of the treated tumor bed is occupied by viable tumor cells) as determined by independent pathologic review. Patients with missing or no pathologic response assessment, *including patients who do not proceed to CLND,* will be classified as non-responders.

pRR will be calculated for each arm along with 95% CIs (Clopper-Pearson method). The difference in pRR between the experimental arms and the control arm will also be calculated, along with 95% CIs using the Wald method with continuity correction.

6.4.2 Secondary Efficacy Endpoints in Cohort 1

The secondary efficacy endpoints in Cohort 1 are pRR at time of surgery as determined by local pathologic assessment, event-free survival (EFS), RFS, OS, and ORR prior to surgery. pRR is defined in Section 6.4.1.

EFS is defined as the time from randomization to any of the following events (whichever occurs first): disease progression that precludes surgery, as assessed by the investigator according to RECIST v1.1 (see Section 4.5.7); local, regional, or distant disease recurrence; or death from any cause. Patients who have not experienced such events will be censored at the time of their last post-tumor tumor assessment.

RFS is defined as the time from surgery to the first documented recurrence of disease or death from any cause. For patients who do not have documented recurrence of disease or death, RFS will be censored at the day of the last tumor assessment.

OS is defined as the time from randomization to death from any cause. Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for RFS, EFS, and OS, 95% CIs will be constructed using the Brookmeyer and Crowley method. The RFS, EFS, and OS rate at specific timepoints will also be estimated using the Kaplan-Meier method, with 95% CIs calculated on the basis of Greenwood's estimate for the variance.

The ORR according to RECIST v1.1 will be assessed after completion of neoadjuvant treatment (Week 7) and is defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1. Patients with missing or no response assessments will be classified as non-responders. Note that ORR will be determined using unconfirmed pre-operative radiologic responses. Although RECIST v1.1 requires confirmatory imaging assessments to be completed at least 4 weeks after the initial response, due to the timing of CLND, these responses cannot be confirmed with subsequent imaging.

ORR will be calculated for each arm, along with 95% CIs (Clopper–Pearson method). The difference in ORR between the experimental arms and the control arm will also be calculated, along with 95% CIs using the Wald method with continuity correction.

6.4.3 Exploratory Efficacy Endpoints in Cohort 1

The exploratory efficacy endpoints in Cohort 1 are landmark EFS, landmark RFS, and landmark OS at specific timepoints (1, 2, 3, and 5 years). RFS, EFS, and OS are defined in Section 6.4.2.

Landmark EFS rates, landmark RFS rates, and landmark OS rates will be estimated for each study arm using the Kaplan-Meier method, with 95% CIs calculated through use of Greenwood's formula.

6.4.4 Primary Efficacy Endpoint in Cohort 2

The primary efficacy endpoint in Cohort 2 is ORR, as defined in Section 2 (see Table 3). ORR is determined by the investigator according to RECIST v1.1. Patients with missing or no response assessments will be classified as non-responders.

ORR, the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% CIs (Clopper–Pearson method).

6.4.5 Secondary Efficacy Endpoints in Cohort 2

The secondary efficacy endpoints in Cohort 2 are PFS, OS, OS at specific timepoints (e.g., 6 months), duration of response (DOR), and disease control, as defined in Section 2 (see Table 3). PFS, DOR, and disease control are determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a CR or PR.

For patients who do not have documented disease progression or death, PFS and DOR will be censored at the day of the last tumor assessment.

Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% CIs constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated using the Kaplan-Meier method, with 95% CIs calculated on the basis of Greenwood's estimate for the variance.

Disease control rate (the proportion of patients with SD for $\geq$12 weeks), a PR, or a CR, will be calculated for each treatment arm, with 95% CIs estimated through use of Clopper-Pearson's exact method.

6.4.6 Exploratory Efficacy Endpoints in Cohort 2

The exploratory efficacy endpoints are ORR, PFS, DOR, and disease control as determined by the investigator according to iRECIST (see Appendix 2).

ORR, PFS, DOR, and disease control will be analyzed through use of the same methods described in Sections 6.4.4 and Section 6.4.5. DOR will be derived for efficacy-evaluable patients with a CR or PR.

6.5 SAFETY ANALYSES

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 and also according to the ASTCT CRS Consensus Grading Scale for CRS.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms. Adverse event severity will be graded according to NCI CTCAE v5.0, and severity of CRS will also be graded by the investigator according to the ASTCT Consensus Grading (Lee et al. 2019). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and causes of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory test results will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

Additionally, in Cohort 1, the incidence, nature of immune-related adverse events Grade $\geq$ 3 during the first 12 weeks, and the rate and duration of delayed surgery due to treatment-related adverse events will be summarized by treatment arm. CLND may be delayed for up to 2 weeks if study treatment-related adverse events have not improved sufficiently at the time of planned surgery (see Section 3.1.3).

Additionally, surgical complications will be scored according to Clavien-Dindo classification (Appendix 5). Complication rates for every grade will be reported and scored for patients that underwent CLND.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and specified drugs given either alone or in

combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs will be plotted by treatment arm and cycle and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab or other study drug concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve.

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

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity may be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60-titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

For other study treatments where ADA is tested, positivity will be determined according to standard methods established in previous studies of that drug.

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

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy and safety endpoints (see Section 4.5.9 for more details).

6.9 INTERIM ANALYSES

Given the exploratory nature of this study, it is anticipated that interim analyses will be conducted during the study, with the earliest interim analysis taking place when at least one experimental arm has completed enrollment in the preliminary phase, and patients have completed their pathologic response assessment (Cohort 1), or when at least one experimental arm has completed enrollment in the preliminary phase and patients have been followed for a minimum of 9 weeks for the primary endpoint analysis (ORR) (Cohort 2). Further interim analyses may be conducted as deemed appropriate by Sponsor. In Cohort 1, a posterior probability may be used to guide further enrollment based on the interim analysis of clinical activity in the experimental arm compared with the control arm. If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, for example, the posterior probability of having a pRR improvement (e.g., 10%) is greater than a threshold (e.g., 70% confidence level), there may be further enrollment of 20 additional patients in the experimental arm (expansion phase).

In Cohort 2, a posterior probability may be used to guide further enrollment in a treatment arm based on an interim analysis of clinical activity in the experimental arm compared with a predefined ORR threshold, defined as an improvement over standard of care. For example, if available data suggest a standard of care ORR of 10%, and an ORR improvement of 10% is considered to be a clinical meaningful change, this would lead to an ORR threshold of 20% in the calculation of the posterior probability.

The ORR for standard of care treatment will be based on emerging internal and external data for in-class immune-modulating investigational and other compounds for the patient population in Cohort 2 who have received at least two lines of prior treatment at the time of the analysis.

The Sponsor may make a decision to expand enrollment in an arm based on the totality of available data including, but not limited to, duration of the observed responses, PFS, and potentially early OS data. Safety and biomarker data (available at the time of making this decision) will also be taken into consideration from the perspective of an adequate benefit-risk assessment.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final 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 his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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 9.5).

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 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.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. 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 4.5.9. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 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).
In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be 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.

9.6 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
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

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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.

For Cohort 1, responses will be assessed and determined according to RECIST v1.1, but are not required to be confirmed by later imaging studies.

A1–1 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.

A1–1.1 DEFINITION OF MEASURABLE LESIONS

A1–1.1.1 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

A1–1.1.2 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").

A1–1.2 DEFINITION OF NON-MEASURABLE LESIONS

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

A1–1.3 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 (PET) scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because 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.

A1–2 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.

A1–2.1 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.

A1–2.2 CHEST X-RAY

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

A1–2.3 CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a noncontrast 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 prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

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

A1–2.4 ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

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

A1–3 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.

A1–3.1 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 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 because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathologic 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 pathologic 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-pathologic and should not be recorded or followed.

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

A1–3.2 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.

A1–3.2.1 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, because a normal lymph node is defined as having a short axis of < 10 mm.

A1–3.2.2 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 because 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.

A1–3.2.3 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.

A1–3.3 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.

A1–4 RESPONSE CRITERIA

A1–4.1 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 pathologic lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

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

A1–4.2 CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of nontarget 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 schedules of activities.

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

  All lymph nodes must be non-pathologic 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

A1–4.3 SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

A1–4.3.1 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.

A1–4.4 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.

A1–4.5 CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A1-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A1-1 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.

A1–4.6 MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

A1–4.7 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

having "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 A1-1.

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.

A1–5 REFERENCES

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

Appendix 2
Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

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Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immunotherapy-specific response criteria adaptations to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; Eisenhauer et al. 2009) have been developed to allow for unconventional response and progression patterns. This includes modified RECIST v1.1 for immune-based therapeutics (iRECIST), which are described below.

A2–1 MODIFIED RECIST V1.1 FOR IMMUNE-BASED THERAPEUTICS (IRECIST)

iRECIST (Seymour et al. 2017) was developed by the RECIST working group in an effort to create a common set of criteria that the CIT field could apply to clinical trials. Response evaluation through use of iRECIST requires collection of tumor assessment data after radiographic progression per RECIST v1.1. Details regarding lesion evaluation are described below. When not otherwise specified, RECIST v1.1 conventions will apply.

Criteria for determining overall response at a single timepoint per iRECIST are also summarized below. Of note, overall response per iRECIST will not be captured in the electronic Case Report Form (eCRF), but will instead be calculated programmatically by the Sponsor on the basis of investigator-assessed individual lesion data recorded in the eCRF.

iRECIST response status is not a specific component of treatment discontinuation criteria, including decisions about whether to continue treatment beyond progression per RECIST v1.1. Investigators should instead take into account radiologic data and clinical status in making such decisions, as described in Section 3.1.1.

A2–1.1 EVALUATION OF LESIONS TO SUPPORT IRECIST RESPONSE ASSESSMENT AFTER DISEASE PROGRESSION PER RECIST V1.1

iRECIST is an extension of RECIST v1.1 that allows for response assessment following disease progression per RECIST v1.1. RECIST v1.1 rules for categorizing lesions as measurable or non-measurable and measuring lesions (see Appendix 1) also apply to iRECIST. After disease progression per RECIST v1.1, the same target and non-target lesions selected at baseline will continue to be followed, along with any new lesions that develop, to support iRECIST response evaluations, as described below and summarized in Table A2-1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

A2–1.1.1 Target Lesions

The target lesions selected at baseline should continue to be measured at all tumor assessment timepoints after disease progression per RECIST v1.1, according to RECIST v1.1 conventions.

A2–1.1.2 Non-Target Lesions

Non-target lesions selected at baseline should continue to be followed at all tumor assessment timepoints after disease progression per RECIST v1.1. At each timepoint, non-target lesions should continue to be categorized as "absent" (complete response [CR]), "unequivocal progression" relative to baseline (progressive disease [PD]), or "present without unequivocal progression" (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.

A2–1.1.3 New Lesions

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST v1.1 (e.g., non-lymph node lesions must be $\geq$10 mm on the longest diameter; new lymph nodes must be $\geq$15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint should be measured from that point on, if the maximum number of measurable new lesions has not been reached. However, for calculation of the sum of diameters for new lesions, iRECIST excludes measurements from new lesions that were not measurable at first appearance.

All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is $\geq$15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is $\geq$10 mm and $\leq$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short

axis of a lymph node is <10 mm, the lymph node should not be considered pathologic and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm. Measurable new lymph node lesions should continue to be measured at all subsequent timepoints, even if the short axis decreases to <15 mm (or even <10 mm).

Table A2-1 Guidelines for Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1

Lesion Type	Evaluation of Lesions to Support iRECIST Response Assessment after Disease Progression per RECIST v1.1
Target lesions	Measurements should be continued according to RECIST v1.1 conventions.
Non-target lesions	Non-target lesions should continue to be categorized as absent (CR), unequivocal progression (PD), or present without unequivocal progression (non-CR/non-PD), as defined by RECIST v1.1. In addition, any non-target lesions that were categorized as PD at the previous timepoint should be evaluated to determine whether there has been any further increase in size.
New lesions	New lesions should be evaluated for measurability per RECIST v1.1. All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints. Up to a maximum of five measurable new lesions total (with a maximum of two lesions per organ) should be selected and measured at each timepoint. All non-measurable new lesions (including those that subsequently become measurable) and additional measurable new lesions (in excess of five total or two per organ) should be assessed to determine whether there is any increase in size relative to the previous assessment timepoint.

CR = complete response; iRECIST = immune RECIST; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

A2–1.2 SUMMARY OF CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Timepoint response per iRECIST will be calculated programmatically by the Sponsor. A complete description of the iRECIST criteria can be found in a publication by Seymour et al. (2017).

A2–2 REFERENCES

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

Seymour L, Bogaerts J, Perrone A, et al., on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–52.

Appendix 3
Pathologic Assessment of Resection Specimens After Neoadjuvant Therapy for Metastatic Melanoma

Table 1. Quick reference guide to pathologic assessment of neoadjuvant treated melanoma specimens

Working definitions

- **Tumor bed**
  - The area of the tissue occupied by:
    - Viable tumor and/or
    - Evidence of tumoral regression, including:
      - Necrosis
      - Clusters/sheets of pigmented macrophages
      - Fibrosis/fibroinflammatory stroma
- **Pathologic complete response (pCR)**
  - Complete absence of viable tumor in the treated tumor bed
- ***Major PR/near pCR***
  - *< 10% of viable tumor in the treated tumor bed*
    - *This may represent a meaningful end point in the context of neoadjuvant immune checkpoint blockade*
- **Partial pathologic response (pPR)**
  - Less than 50% of the treated tumor bed is occupied by viable tumor cells. Note: percent tumor regression associated with improved patient outcomes for both targeted therapy and immunotherapy is an area of active investigation.

Gross evaluation of the surgical specimen after neoadjuvant therapy

- Three-dimensional macroscopic measurement of the ***largest grossly positive lymph node identified*** should be provided in the gross description.
- If the ***largest grossly positive lymph node measures ≤ 5 cm in greatest dimension:***
  - Each lymph node should be *submitted entirely at 3–4 mm serially sectioned intervals* (Figure 1A).
- For ***any grossly positive lymph node measuring > 5 cm in greatest dimension***, representative sections of the largest lymph nodes may be utilized.
  - For nodes >5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node (Figure 1B).
  - All lymph nodes <5 cm in specimens where the largest node(s) >5 cm should be submitted entirely (Figure 1A).

Microscopic templates:

(1) For viable melanoma

MELANOMA, METASTATIC TO **XX** OF **YY** LYMPH NODES (XX/YY).
Largest tumor deposit size:____×____mm[a]
Location: Subcapsular/Intraparenchymal
Extracapsular extension: Present/Not identified
See comment.

[a]For the measurements, we recommend including the following:

- Microscopic measurement of the largest deposit of continuous viable tumor in two dimensions (AA x BB mm)

(2) If no viable melanoma

FIBROSIS AND/OR NODULAR AGGREGATES OF PIGMENTED MACROPHAGES AND/OR (COMPLETELY) NECROTIC TUMOR CONSISTENT WITH MELANOMA (COMPLETELY REGRESSED WITH TREATMENT EFFECT), METASTATIC TO **XX** OF **YY** LYMPH NODES (XX/YY).
Largest tumor deposit size: ____×____mm (CORRESPONDS TO LARGEST AREA OF REGRESSED/NECROTIC MELANOMA—Gross measurement preferred over microscopic)
Location: Subcapsular/Intraparenchymal
Extracapsular extension: Present/not identified (corresponds to pigmented macrophages/fibrosis consistent with completely regressed melanoma)
See comment.

Comment:

Sections reveal (viable/partially viable/completely regressed) melanoma involving XX of YY lymph nodes. An evaluation of the complete tumor bed reveals[a, b]:

- AA% viable tumor
  - *This would correspond to the % of the tumor bed surface area that is occupied by viable tumor cells*
- Tumoral melanosis/necrosis: Present/not identified
  - *Extent: (% of the tumor bed occupied by tumoral melanosis and pigmented macrophages/necrosis)*
- Fibrosis/fibroinflammatory stroma: Present/absent
  - Extent: (% of the tumor bed occupied by fibrosis/fibroinflammatory stroma)

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[a]The sum of these three elements (% viable tumor, % tumoral melanosis/necrosis, and fibrosis/fibrinflammatory stroma should equal 100%).
[b]If multiple nodes or nodal basins are involved by disease (whether completely or partially necrotic), a summary statement should estimate the combined percentages of viable tumor cells, necrosis/melanosis and fibrosis occupying the surface area encompassed by the tumor bed comprising each of the involved nodes.

REFERENCES

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Appendix 4
Criteria for Adequate Surgical Procedures for Therapeutic Lymph Node Dissection

Complete lymph node dissection (CLND) after neoadjuvant melanoma treatment should be performed as planned if the patient is receiving corticosteroids or other anti-inflammatory drugs for the management of immune-mediated adverse events, provided these are being given at a stable or tapering dose and the severity of adverse events is Grade 2 or better. CLND may be delayed for up to 2 weeks if study treatment-related adverse events have not improved sufficiently at the time of planned surgery (see Section 3.1.3).

Criteria for adequate surgical procedures for therapeutic lymph node dissection:

Head and Neck

- Minimum of 15 pathologically investigated nodes
- Face, ear, and anterior scalp: parotidectomy plus (modified) radical neck dissection
- Posterior scalp: (modified or posterior) radical neck dissection plus suboccipital nodes. For this specific localization, a CLND will be considered as adequate if at least 5 lymph nodes (LN) have been investigated

Upper Extremity

- Minimum of 10 pathologically investigated nodes
- Axillary node dissection included at least 10 nodes taken from Levels I and II
- It is advised to routinely include the Level III nodes too
- Level III nodes should always be dissected if they were clinically involved

Lower Extremity

- Minimum of 5 pathologically investigative nodes
- If Cloquet's node is positive, a deep groin (external iliac and obturator) node dissection should be performed

(Modified) Radical Neck Dissection:

Classic or modified radical neck dissection may be performed for patients with melanoma of the head and neck. Minimum of 15 nodes must be pathologically investigated. As noted above, patients with melanoma located on the ear and anterior scalp and face will require superficial parotidectomy along with a (modified) radical neck procedure. The boundaries of the radical neck dissection are inferiorly the clavicle; the mandible, the mastoid and the tail of the parotid gland superiorly; the anterior border of the trapezius muscle posteriorly and the strap muscle of the larynx anteriorly. The sternocleidomastoid muscle, internal jugular vein, and/or spinal accessory nerve may be sacrificed or preserved at the surgeon's discretion. For posterior lesions the radical neck incision must be extended posteriorly or a second incision must be made so that the

sub-occipital/postauricular nodal group can be sampled. For posterior neck dissection, surgical and pathologic exploration of 5 nodes are sufficient to consider the procedure is adequate.

Axillary Lymphadenectomy:

For this study a complete axillary lymph node dissection will be performed including nodes at Levels I, II, and III (Level III does not have to be removed routinely, but is advised. In any case Level III should be dissected in case of preoperative nodal involvement). Axillary node dissection must include at least 10 nodes taken from Levels I and II and the Level III nodes dissected for palpable axillary nodes. Minimum of 10 nodes must be pathologically investigated. The boundaries of the dissection should include the axillary vein superiorly beginning at the thoracic outlet and coursing to the latissimus dorsi tendon. The lateral border of the dissection is the anterior edge of the lattisimus dorsi muscle. The posterior boundary is the subscapular muscle. The anterior border of the resection is the pectoralis major group. The inferior boundary of the dissection should be the juncture of the latissimus dorsi and the serratus anterior muscles.

The contents within these boundaries should be completely removed with the exception of the long thoracic nerve and the thoracodorsal nerve which should be identified during the dissection and preserved throughout. As stated, the pectoralis minor muscle may be divided or sacrificed with the specimen at the discretion of the surgeon. The preferable approach to the axilla is through a horizontal incision in the line of the skin crease, 3 or 4 cm below the apex of the skin fold of the axilla.

Inguinal Lymphadenectomy (Superficial Groin Dissection):

A superficial groin (femoral/inguinal) node dissection should be performed by excising all of the nodes inferior to the inguinal ligament and bounded by the medial border of the sartorius muscle in the lateral border of the adductor magnus muscle. The fatty and lymphatic tissues should be dissected carefully off of the femoral vessels and nerves all the way up to the inguinal canal and for 2–3 cm superior to the inguinal ligament (the superficial subcutaneous tissue cranial to the exit of the femoral canal). The saphenous vein is resected to ensure complete excision of the lymph nodes. Transposition of the sartorius muscle should be considered (but is not mandatory) to cover the femoral vessels after complete lymphatic excision. Ideally, this area should be entered through a curvilinear incision staring laterally over the inguinal ligament and curving medially and inferiorly ending over the mid-point of the adductor magnus muscle. For a superficial groin node dissection, a minimum of 5 nodes must be pathologically investigated.

Deep Groin (External Iliac and Obturator) Node Dissection:

Deep Inguinal and External Iliac Node Dissection can be most easily approached by incising the abdominal wall musculature 3 or 4 cm superior to the inguinal ligament. This incision is taken down through the external oblique, internal oblique and transversus muscles and the surgeon at that point stays extraperitoneal as in the approach to the iliac vessels for renal transplantation. With this approach, the external, internal, and common iliac arteries are exposed and the lymphatics coursing among the iliac vessels are excised. The obturator nodes along the obturator nerve and artery should also be resected through this approach. A full combined superficial and deep groin (ilio-inguinal) node dissection is advised in case of when Cloquet's node is positive or if there is other evidence of extended involvement to the deep nodes preoperatively.

Appendix 5
Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)[a] requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge,[b] the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

CNS = central nervous system; IC = intermediate care; ICU = intensive care unit.

[a] Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.

[b] For examples of complication grades, see Table 2 in Dindo et al. (2004).

REFERENCE

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–13.

Appendix 6
ECOG 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.

ECOG = Eastern Cooperative Oncology Group.

Appendix 7
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, tiragolumab, or RO7247669 for patients who have previously experienced a severe or life–threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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

Appendix 8
Anaphylaxis Precautions

A8–1 EQUIPMENT NEEDED

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

A8–2 PROCEDURES

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

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

Appendix 9
Guidelines for Management of Atezolizumab-, Tiragolumab-, and/or RO7247669-Specific Adverse Events

TABLE OF CONTENTS

Appendix 9: Guidelines for Management of Atezolizumab-, Tiragolumab-, and/or RO7247669-Specific Adverse Events

These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit risk balance when managing individual cases.

Tiragolumab and RO7247669 are in an early phase of clinical development, and not all risks are known as clinical evaluation is ongoing. Please refer to Section 6 of the Tiragolumab or RO7247669 Investigator's Brochure for a detailed description of anticipated safety risks associated with these molecules. Risks associated with atezolizumab are described in this appendix. Please refer to Section 6 of the Atezolizumab Investigator's Brochure for further information.

The expected pharmacologic activities of atezolizumab, tiragolumab, and RO7247669 are similar for checkpoint inhibitors as a class. Accordingly, the adverse event management guidelines described in this appendix, including those for continuing, withholding, resuming, and discontinuing study treatment, are applicable to atezolizumab, tiragolumab, and RO7247669, with these exceptions:

- For infusion-related reactions (IRRs) associated with RO7247669 as a monotherapy, please refer to Table A12-3 in Appendix 12 *and Table A15-3 in Appendix 15*.
- For IRRs associated with tiragolumab in combination with atezolizumab, please refer to Table A13-5 in Appendix 13.
- For IRRs associated with RO7247669 in combination with tiragolumab, please refer to Table A14-4 in Appendix 14 *and Table A16-4 in Appendix 16*.

Toxicities associated or possibly associated with atezolizumab, tiragolumab, and/or RO7247669 treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology when clinically indicated.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab, tiragolumab, and/or RO7247669 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. The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration or resumption of atezolizumab, tiragolumab, or RO724669.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections in this appendix or the treatment arm-specific appendices.

- 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 long-term follow-up. There should be a high level of suspicion that new symptoms are treatment related.
- In general, atezolizumab, tiragolumab, and/or RO7247669 therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab, tiragolumab, and/or RO7247669 for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab, tiragolumab, and/or RO7247669 for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab, tiragolumab, and/or RO7247669 can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab, tiragolumab, and/or RO7247669 treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.
- The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab, tiragolumab, and/or RO7247669. Resumption of atezolizumab, tiragolumab, and/or RO7247669 may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab, tiragolumab, and/or RO7247669 should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

A9–1 DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab, tiragolumab, or RO7247669 in this study.

A9–2 TREATMENT INTERRUPTION

Treatment with atezolizumab, tiragolumab, or RO7247669 may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab, tiragolumab, and/or RO7247669 can be resumed.

For Cohort 1, treatment with atezolizumab, tiragolumab, and/or RO7247669 should not be interrupted unless a patient experiences toxicity. If toxicity meets criteria for interrupting/withholding study drug(s), study drug(s) should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should only be considered if the benefit–risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

For Cohort 2, if RO7247669 and tiragolumab are withheld for 12 weeks or longer due to toxicity, the patient should be discontinued from RO7247669 and tiragolumab. However, RO7247669 and tiragolumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. RO7247669 and tiragolumab may be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. RO7247669 and tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) at the discretion of the investigator. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A9–3 PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A9-1.

Table A9-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669 and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c, d] • Oral or IV broad spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Table A9-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

BAL = bronchoscopic alveolar lavage.

[a] For Cohort 2, RO7247669 and tiragolumab, may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

[d] In case of pneumonitis, atezolizumab/tiragolumab/RO7247669 should not be resumed after permanent discontinuation.

A9–4 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 A9-2.

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

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

Table A9-2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days duration:** • Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–5 GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A9-3.

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 A9-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent of 1–2 mg/kg/day oral prednisone. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]

GI = gastrointestinal.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 3	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–6 ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A9-4.

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 A9-4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab/tiragolumab/RO7247669. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding atezolizumab/tiragolumab/RO7247669 • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab/tiragolumab/RO7247669 when symptoms are controlled and thyroid function is improving.
Grade 3 or 4 hypothyroidism	• Withhold atezolizumab/tiragolumab/RO7247669. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status) • Resume atezolizumab/tiragolumab/RO7247669 when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab/tiragolumab/RO7247669. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for Grade 2 hyperthyroidism. • Consider patient referral to endocrinologist.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 2 hyperthyroidism	• Consider withholding atezolizumab/tiragolumab/RO7247669. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab/tiragolumab/RO7247669 when symptoms are controlled and thyroid function is improving.
Grade 3 or 4 hyperthyroidism	• Withhold atezolizumab/tiragolumab/RO7247669. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to endocrinologist. • Resume atezolizumab/tiragolumab/RO7247669 when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab/tiragolumab/RO7247669. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab/tiragolumab/RO7247669. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab/tiragolumab/RO7247669 when symptoms resolve and glucose levels are stable.
Hypophysitis (panhypopituitarism), Grade 2 or 3	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (panhypopituitarism), Grade 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–7 OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A9-5.

Table A9-5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–8 IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table A9-6.

A9–9 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., 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 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, an echocardiogram, 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 A9-6.

A9–10 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 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 related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), 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, transthoracic echocardiogram, 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 A9-6. Withhold treatment with atezolizumab, tiragolumab and/or RO7247669 for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A9-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [b, c] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

[b] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[c] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

A9–11 INFUSION-RELATED REACTIONS

No premedication is indicated for the administration of the Day 1, Cycle 1 infusion of tiragolumab, atezolizumab, *or RO7247669*. However, patients who experience an infusion-related reaction (IRR) with the Day 1, Cycle 1 infusion of tiragolumab, atezolizumab, *or RO7247669* may receive premedication with antihistamines, antipyretic medication, 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, atezolizumab, *and RO7247669*. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of tiragolumab, atezolizumab, *or RO7247669* administration and are generally mild to moderate in severity. Refer to the beginning of this appendix (Appendix 9) for IRR management guidelines for each treatment arm.

A9–12 CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab, tiragolumab, or RO7247669. However, patients who experience cytokine-release syndrome (CRS) may receive premedication with antihistamines, anti-pyretic 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.

Guidelines for medical management of CRS are provided in Table A9-7.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (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's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table A9-7 Management Guidelines for Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics, and monitor closely for CRS.
Grade 2 [a] Fever [b] with at least one of the following: • Hypotension not requiring vasopressors • Hypoxia requiring low-flow oxygen [d] by nasal cannula or blowby	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab/tiragolumab/RO7247669, and contact the Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab/tiragolumab/RO7247669 may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretic medications, and/or analgesics and monitor closely for CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Table A9-7 Management Guidelines for Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with at least one of the following: • Hypotension requiring a vasopressor (with or without vasopressin) • Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [f] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with at least one of the following: • Hypotension requiring multiple vasopressors (excluding vasopressin) • Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [f] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator. The Medical Monitor will be available to advise as needed. • Hospitalize patient until complete resolution of symptoms.

Table A9-7 Management Guidelines for Cytokine-Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; MAS = macrophage activation syndrome; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute.

Notes: The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading scale. NCI CTCAE v5.0 and the ASTCT CRS consensus grading scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine-Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

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

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

[g] Refer to Riegler et al. (2019).

A9–13 PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up 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 A9-8.

Table A9-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue atezolizumab/tiragolumab/RO7247669. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]

GI = gastrointestinal.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–14 DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab, tiragolumab, and/or RO7247669 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 A9-9.

Table A9-9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab/tiragolumab/RO7247669. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab/tiragolumab/RO7247669 for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab/tiragolumab/RO7247669.

Table A9-9 Management Guidelines for Dermatologic Events (cont.)

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–15 NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table A9-10, with specific guidelines for myelitis provided in Table A9-11.

Table A9-10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.
Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • For general immune-mediated neuropathy: – If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] – If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • For facial paresis: – If event resolves fully, resume atezolizumab/tiragolumab/RO7247669. [b] – If event does not resolve fully while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-10 Management Guidelines for Neurologic Disorders (cont.)

Event	Management
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-11 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669 unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

A9–16 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 A9-12.

Table A9-12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–17 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 pre-renal and post-renal 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 A9-13.

Table A9-13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit−risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–18 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 increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A9-14.

Table A9-14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab/tiragolumab/RO7247669. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., $>$12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of $\leq$10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab/tiragolumab/RO7247669 for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab/tiragolumab/RO7247669. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab/tiragolumab/RO7247669, permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c]

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., $>$12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of $\leq$10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over $\geq$1 month to the equivalent of $\leq$10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

Table A9-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] For Cohort 2, RO7247669 and tiragolumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab/tiragolumab/RO7247669 can be resumed.

[c] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A9–19 HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

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 IL-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table A9-15.

Table A9-15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab/tiragolumab/RO7247669 and contact the Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact the Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over $\geq$1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

A9–20 REFERENCES

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Appendix 10
Study Details Specific to Screening

Assessment/Procedure	Protocol Section	Stage 1 Screening
Patient Information		Day –28 to Day –1
Informed consent	4.5.1	x
Demographic data	4.5.2	x
Medical history and baseline conditions		x
Clinical Assessments		Day –28 to Day –1 (unless otherwise indicated)
Molecular profile of melanoma (if available)	4.5.2	x
Weight	4.5.3	x
Height		x
Complete physical examination		x
Vital signs	4.5.4	x
12-Lead ECG	4.5.5	x
TTE or MUGA scan	4.5.6	x
ECOG Performance Status	Appendix 6	x
Baseline tumor assessments	4.5.7	x (Day–14 to Day–1) [a]
Concomitant medications	4.5.2	x (Day –7 to Day –1)
Adverse events [b]	5.3.1 and 5.5.1	x
Local Laboratory Assessments		Day –14 to Day –1
Hematology	4.5.9.1	x
Chemistry [c]		x
Lipid panel		x
Coagulation (INR and aPTT)		x
TSH, free T3 (or total T3), free T4		x
Cardiac enzymes		x
C-reactive protein		x
Viral serology		x
LDH		x
Pregnancy test	4.5.9.1	x (blood test)
Urinalysis		x

Appendix 10: Study Details Specific to Screening

Assessment/Procedure	Protocol Section	Stage 1 Screening
Central Laboratory Assessments		Day −28 to Day −1
Serum autoantibody sample	4.5.9.2	x
Blood and plasma samples for biomarkers [d]	4.5.9.2	x
Tumor biopsy [d]	4.5.9.2 and 4.5.11	x

ECOG = Eastern Cooperative Oncology Group; MUGA = multiple-gated acquisition; TTE = transthoracic echocardiogram.

[a] *Baseline tumor assessments should be performed within 14 days before initiation of study treatment. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization/enrollment do not have to be repeated at screening.*

[b] 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 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.

[c] In addition, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be assessed for patients in screening for Cohort 1.

[d] Screening samples should be collected, if possible, after all other screening assessments have been evaluated for eligibility.

Appendix 11
Study Details Specific to Nivo+Ipi Arm (Control)

TABLE OF CONTENTS

A11–1 BACKGROUND ON NIVO + IPI ARM

A11–1.1 BACKGROUND ON NIVOLUMAB

Nivolumab (Nivo) is a human monoclonal antibody that targets the human PD-1 receptor. Nivolumab is approved for the treatment of several cancer types, including melanoma. It is approved as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma, and as monotherapy for the adjuvant treatment of patients with melanoma.

For detailed information, refer to the local prescribing information for nivolumab.

A11–1.2 BACKGROUND ON IPILIMUMAB

Ipilimumab (Ipi) is a fully human monoclonal antibody that binds to CTLA-4 and inhibits its interaction with ligands on antigen-presenting cells.

Ipilimumab is approved for the treatment of several cancer types, including melanoma. It is approved as monotherapy or in combination with nivolumab for the treatment of advanced (unresectable or metastatic) melanoma, and as monotherapy for the adjuvant treatment of patients with melanoma.

For detailed information, refer to the local prescribing information for ipilimumab.

A11–2 RATIONALE FOR NIVO + IPI ARM

A11–2.1 COMBINATION TREATMENT WITH NIVOLUMAB AND IPILIMUMAB

Nivolumab in combination with ipilimumab is an approved treatment option for advanced (unresectable or metastatic) melanoma.

A11–2.2 CLINICAL STUDIES OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB IN MELANOMA

In the Phase III CheckMate 067 study, nivolumab monotherapy or combination therapy with nivolumab and ipilimumab was compared with ipilimumab monotherapy in patients with metastatic melanoma. The co-primary endpoints for this study were progression-free survival (PFS) and overall survival (OS). Nivolumab monotherapy and combination therapy with nivolumab + ipilimumab demonstrated superior survival benefit when compared with ipilimumab monotherapy. Combination therapy provided the greatest clinical benefit, with patients receiving this treatment having the highest overall response (OR) and complete response (CR) rates (58% and 22%, respectively, for nivolumab + ipilimumab combination therapy; 45% and 19% for nivolumab monotherapy; and 19% and 6% for ipilimumab monotherapy) (Larkin et al. 2015; Wolchok et al. 2017; Larkin et al. 2019).

As a result of clinical evidence demonstrated in the metastatic setting, combination therapy with nivolumab + ipilimumab was investigated in patients with macroscopic

Stage III melanoma. The OpACIN study (Blank et al. 2018) investigated the benefit of neoadjuvant versus adjuvant treatment with nivolumab+ipilimumab on relapse-free survival (RFS) and OS, and proposed superior benefit for the neoadjuvant use.

Combination treatment with nivolumab+ipilimumab presents more safety concerns than treatment with either nivolumab or ipilimumab alone, as serious toxicities and the need for treatment discontinuation occur more frequently in patients treated with nivolumab+ipilimumab (Schadendorf et al. 2017; Shoushtari et al. 2018). These toxicities have also been seen in patients with Stage III melanoma who received nivolumab+ipilimumab as neoadjuvant therapy, and they were severe enough to impact the timing of surgical intervention. Therefore, different schedules of treatment with nivolumab+ipilimumab combination therapy were explored in the OpACIN-neo study. An alternative off-label dosing regimen (nivolumab 3 mg/kg+ipilimumab 1 mg/kg) was found to retain comparable pathological response rates while decreasing toxicities (Rozeman et al. 2019).

A11–2.3 BENEFIT–RISK ASSESSMENT

Nivolumab and ipilimumab are approved treatment options for patients with melanoma and have demonstrated a favorable benefit–risk assessment. Moreover, combination therapy with nivolumab+ipilimumab is approved in the advanced setting for unresectable or metastatic melanoma.

More detailed information about known and expected benefits in the context of potential risks and expected adverse events related to nivolumab and ipilimumab administration is provided in the local prescribing information for each agent.

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, refer to Section 1.3.

A11–3 RATIONALE FOR DOSE AND SCHEDULE FOR NIVO+IPI ARM

The approved combination regimen for metastatic melanoma is nivolumab (1 mg/kg every 3 weeks [Q3W] for four doses)+ipilimumab (3 mg/kg Q3W for four doses), followed by nivolumab 3 mg/kg every two weeks. An alternative dosing regimen of nivolumab 3 mg/kg and ipilimumab 1 mg/kg was identified in the OpACIN-neo study as the optimal neoadjuvant dosing regimen in melanoma, with comparable clinical efficacy and improved tolerability (Rozeman et al. 2019).

Given the evidence of clinical efficacy in both the neoadjuvant and adjuvant settings, and the fact that nivolumab in combination with ipilimumab is approved for patients with advanced melanoma, combination treatment with nivolumab 3 mg/kg+ipilimumab 1 mg/kg was considered to be the best comparator for the anticipated patient population in this study (Wolchok et al. 2013; Sznol et al. 2014; Rozeman et al. 2019).

Nivolumab will be administered at a dose of 3 mg/kg IV and ipilimumab will be administered at a dose of 1 mg/kg IV Q3W on Day 1 of each 21-day cycle.

A11–4 MATERIALS AND METHODS SPECIFIC TO NIVO+IPI ARM

A11–4.1 TREATMENT IN NIVO+IPI ARM

A11–4.1.1 Formulation, Packaging, and Handling

A11–4.1.1.1 Nivolumab

The nivolumab drug product will be supplied by the Sponsor as a 10 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of nivolumab, refer to the local prescribing information for nivolumab.

A11–4.1.1.2 Ipilimumab

The ipilimumab drug product will be supplied by the Sponsor as a 5 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of ipilimumab, refer to the local prescribing information for ipilimumab.

A11–4.1.2 Dosage, Administration, and Compliance

Patients in the nivolumab+ipilimumab (Nivo+Ipi) control arm will receive treatment for 2 cycles (6 weeks) as outlined in Table A11-1 until surgery, or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A11-1 Treatment Regimen for Nivo+Ipi Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Nivolumab 3 mg/kg IV on Day 1 of each cycle • Ipilimumab 1 mg/kg IV on Day 1 of each cycle

Ipi=ipilimumab; Nivo=nivolumab.

Refer to the local prescribing information for each agent for detailed instructions on drug preparation, storage, and administration.

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12. For information on overdosing of nivolumab or ipilimumab, refer to the local prescribing information for each agent.

A11–4.1.2.1 Nivolumab

Nivolumab will be administered by IV infusion at a dose of 3 mg/kg on Day 1 of each 21-day cycle.

Administration of nivolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8.

For information on the formulation, packaging, and handling of nivolumab, refer to the local prescribing information.

A11–4.1.2.2 Ipilimumab

Ipilimumab will be administered by IV infusion at a dose of 1 mg/kg on Day 1 of each 21-day cycle.

Administration of ipilimumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8.

For information on the formulation, packaging, and handling of ipilimumab, refer to the local prescribing information.

A11–4.2 CONCOMITANT THERAPY FOR NIVO + IPI ARM

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

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for nivolumab or ipilimumab, refer to the local prescribing information for each agent.

A11–4.3 CONTRACEPTION REQUIREMENTS FOR NIVO + IPI ARM

Contraception requirements for women and men in the Nivo + Ipi arm are outlined below:

- Women of childbearing potential must agree to remain abstinent (refrain from heterosexual intercourse) or use contraception methods, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of study treatment.

  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 has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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 acceptable methods of contraception.
  If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 5 months after the final dose of nivolumab and/or ipilimumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A11–5 ASSESSMENT OF SAFETY FOR NIVO+IPI ARM

A11–5.1 SAFETY PLAN FOR NIVO+IPI ARM

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 study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

For detailed safety information, refer to the local prescribing information for each agent.

A11–5.1.1 Risks Associated with Nivolumab

Nivolumab has been associated with risks such as infusion-related reactions (IRRs) and immune-mediated adverse events. Refer to the local prescribing information for nivolumab for a detailed description of anticipated safety risks for nivolumab.

A11–5.1.2 Risks Associated with Ipilimumab

Ipilimumab has been associated with risks such as IRRs and immune-mediated adverse events. Refer to the local prescribing information for ipilimumab for a detailed description of anticipated safety risks for ipilimumab.

A11–5.1.2.1 Risks Associated with Combination Use of Nivolumab and Ipilimumab

Immune-related adverse reactions have occurred at higher frequencies in combination treatment of nivolumab with ipilimumab compared with either drug as monotherapy.

A11–5.1.2.2 Management of Patients Who Experience Adverse Events in Nivo+Ipi Arm

Guidelines for the management of patients who experience adverse events are provided in the local prescribing information for each drug.

A11–5.2 REPORTING REQUIREMENTS FOR PREGNANCIES IN NIVO+IPI ARM

A11–5.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of nivolumab or within 5 months after the final dose of ipilimumab. 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A11–5.2.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the final dose of nivolumab or within 5 months after the final dose of ipilimumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A11–5.2.3 Abortions

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

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

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

A11–5.2.4 Congenital Anomalies/Birth Defects

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

A11–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR NIVO+IPI ARM

Table A11-2 Schedule of Activities for Nivo+Ipi Arm

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
IMP Administration										
Nivolumab administration	A11–4.1.2		x	x						
Ipilimumab administration			x	x						
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [d]	4.5.3		x	x	x		x	x		x
Complete physical examination								x		
Limited physical examination [d]			x	x	x		x			x
Vital signs	4.5.4		x	x	x		x	x		x
12-Lead ECG [d]	4.5.5		x	x				x		
TTE or MUGA scan	4.5.6							x		
ECOG Performance Status [d]	Appendix 6		x	x	x		x	x		x

TABLE A11-2 SCHEDULE OF ACTIVITIES FOR NIVO+IPI ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Clinical Assessments (cont.)										
Surgery (CLND)	3.1.5, Appendix 4					x				
Tumor response assessments	4.5.7				x				As clinically indicated	
Disease status assessments	4.5.7.2				x			x [e]	x	
Concomitant medications	A11–4.2		x	x	x		x	x		
Adverse events [f]	5.3.1, 5.5.1, and 5.6		x	x	x		x [f]	x [f]	x [f]	x [f]
Clavien-Dindo assessment	4.5.8 and Appendix 5							x		x
Follow-up and anti-cancer treatment	4.6.1								x [g]	
Local Laboratory Assessments										
Hematology	4.5.9.1		x [h]	x [h]	x		x	x		x
Chemistry			x [h]	x [h]	x [i]		x	x		x
Lipid panel					x			x		

TABLE A11-2 SCHEDULE OF ACTIVITIES FOR NIVO+IPI ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Local Laboratory Assessments (cont.)										
Coagulation (INR and aPTT)	4.5.9.1		x [h]	x [h]	x					
TSH, free T3 (or total T3), free T4			x [h]		x		x	x		x
Cardiac enzymes			x [h]	x [h]	x [j]			x		
C-reactive protein			x [h]	x [h]	x		x	x		x
Pregnancy test			x [h]	x [h]	x		x	x		x [k]
Urinalysis			Perform as clinically indicated.					x		
Central Laboratory Assessments										
Serum autoantibody sample	4.5.9.2		Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
Blood and plasma samples for biomarkers			Refer to Section A11–7.						x (only if onsite)	Refer to Section A11–7.
Pre-dose tumor biopsy				x [l]						
Resected tissue						x				

TABLE A11-2 SCHEDULE OF ACTIVITIES FOR NIVO + IPI ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤ 7D after randomization)	D1 (+ 1D)	Wk 6 (≤ 8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥ 20D after surgery)	Wk 13	Every 3M (± 7D)	6M after surgery (± 7D)
Tumor biopsy (optional)	4.5.11		Perform at the time of unacceptable toxicity, loss of clinical benefit, relapse, or at any other time if deemed clinically feasible by the investigator.							

CLND = complete lymph node dissection; Comp. = completion; CT = computed tomography; D = day; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; M = month; MUGA = multiple-gated acquisition; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; Wk = week.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.

[c] Patients who proceed to surgery will have the surgery follow-up 6 months after surgery.

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] The disease status assessments at Week 13 should include a mandatory CT scan

TABLE A11-2 SCHEDULE OF ACTIVITIES FOR NIVO+IPI ARM (cont.)

[f] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.

[g] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first long-term follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first long-term follow-up visit 3 months after the final dose of study treatment. Information on long-term follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only.

[h] Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[i] At the pre-surgery visit, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be included in the chemistry panel.

[j] This is only applicable if elevated levels of cardiac enzymes were detected in previous assessments.

[k] If periods are missed or delayed before the 6-month follow-up visit, pregnancy testing should be repeated. This test can be performed by a local gynecologist.

[l] The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.

A11–7 SCHEDULE OF BIOMARKER SAMPLES FOR NIVO + IPI CONTROL ARM

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to the first infusion (–6 hr to 0 hr)	• Biomarkers (blood, plasma)
Day 1 of Cycle 2	Prior to infusion (–6 hr to 0 hr)	• Biomarkers (blood, plasma)
Surgery CLND Week 7	Prior to surgery (–24 hr to 0 hr)	• Biomarkers (blood, plasma)
Post-surgery Week 10 [a]	At visit	• Biomarkers (blood, plasma)
Treatment completion/ discontinuation visit Week 13	At visit	• Biomarkers (blood, plasma)
Long-term follow-up Every 3 months (±7 days) [b]	At visit	• Biomarkers (blood, plasma)
Surgery follow-up 6 months after surgery (±7 days)	At visit	• Biomarkers (blood, plasma)

CLND = complete lymph node dissection; Ipi = ipilimumab; Nivo = nivolumab.

[a] Week 10 biomarker samples must be obtained ≥20 days post-surgery.

[b] To be collected if visit is conducted on site.

A11–8 REFERENCES

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Appendix 12
Study Details Specific to RO7247669 *2100 mg* Arm

TABLE OF CONTENTS

A12–1 BACKGROUND ON RO7247669 *2100 mg* ARM

RO7247669 is a novel, Fc-silent IgG1-based bispecific antibody (bsAb) in 1 + 1 format that incorporates monovalent binding to two immune checkpoint proteins: PD-1 and LAG-3. RO7247669 is designed to target dysfunctional tumor antigen-specific T-lymphocytes expressing PD-1 and LAG-3 to establish or re-establish an effective anti-tumor immune response in cancer patients. This may result in improved therapeutic responses over currently available therapies. In addition, RO7247669 is engineered to prevent binding to Fc gamma receptors, thus potentially avoiding tumor-associated macrophage resistance mechanisms. Such mechanisms have been observed with IgG4-based anti–PD-1 antibodies, such as pembrolizumab and nivolumab (Arlauckas et al. 2017). Clinical evaluation of RO7247669 is ongoing in a first-in-human, dose-finding study (NP41300) as a single agent in cancer patients with and without prior checkpoint inhibitor (CPI) exposure.

Refer to the RO7247669 Investigator's Brochure for details on nonclinical and *other planned and ongoing* clinical studies.

A12–2 RATIONALE FOR RO7247669 *2100 mg* ARM

A12–2.1 TARGETING THE PD-1 AND LAG-3 ANTIGENS

Cancer immunotherapy agents, particularly immune CPIs, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, additional treatment options targeting immune checkpoints are needed because the majority of patients eventually progress after an initial response or else fail to respond to the PD-1/PD-L1 checkpoint blockade. This is believed to be due mainly to primary or secondary resistance mechanisms, to immunosuppressive activity of myeloid-derived suppressor cells, and/or to T-regulatory cells (Sharma et al. 2017).

To overcome resistance mechanisms, additional treatment options and multiple combinations with anti–PD-L1 therapy are being assessed. One potential reason for resistance to anti–PD-L1 therapy is the upregulation of alternative immune checkpoints with non-redundant regulatory functions (Sharma et al. 2017). LAG-3 is one such alternative immune checkpoint. LAG-3 is a member of the Ig superfamily that is structurally similar to CD4. LAG-3 is expressed on activated effector T cells and is constitutively expressed on T-regulatory cells and natural killer (NK) cells. The expression of both PD-1 and LAG-3 on tumor infiltrating lymphocytes (TILs) correlates with the degree of impairment of effector functions, which is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015). Hence, LAG-3 is a marker of T-cell dysfunctionality. LAG-3 also regulates T-cell functions, presumably including the function of T-regulatory cells. In chronic infections and cancer, LAG-3, together with PD-1, contributes to T-cell–acquired dysfunctionality and to the

inability of T cells to mount an effective/protective immune response upon interaction with the LAG-3 ligand, MHC-II.

The interaction of LAG-3 with MHC-II inhibits T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production (Goldberg and Drake 2011). The effect of LAG-3 expression on T-regulatory cells is controversial. An early report concluded that LAG-3 promotes T-regulatory cell-mediated immune suppression (Camisaschi et al. 2010). However, a more recent report from the same authors found that LAG-3 limits T-regulatory cell-mediated immune suppression (Zhang et al. 2017).

Expression of LAG-3 has been reported across various tumor types, including breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), melanoma, renal cell cancer (RCC), prostate cancer, and hepatocellular carcinoma (HCC). In patients with these tumor types, LAG-3 is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norstrom et al. 2016). Clinical evaluation of anti–LAG-3 agents, as single agents and in combination with other CPIs, is ongoing in several early phase studies in patients with advanced solid tumors (Long et al. 2018). Preliminary data demonstrate that anti–LAG-3 therapy is well tolerated, both as single agents and in combination with anti–PD-1 therapies, and the safety profiles are consistent with those of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). RO7247669 may therefore be a therapeutic option for patients with melanoma.

Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory immune checkpoints on the surface of effector T cells. LAG-3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG-3 enhances $CD8^+$ T-cell effector function and potentiates anti-tumor immunity in nonclinical models. Blockade of these two receptors in mice with colon, fibrosarcoma, or ovarian tumors resulted in tumor remission in approximately 80% of animals, compared with remission in 10% to 40% with blockade of either receptor using a single agent (Woo et al. 2012; Huang et al. 2015). TILs from patients with ovarian cancer showed that antigen-specific $CD8^+$ T cells co-expressing PD-1 and LAG-3 exhibited greater impairment in their ability to respond to cognate antigen stimulation compared with $CD8^+$ T cells that expressed one checkpoint molecule (Matsuzaki et al. 2010). In patients with NSCLC, overexpression of LAG-3 on TILs correlated with PD-1/PD-L1 expression and was linked to higher risk of recurrence and poor survival outcomes (He et al. 2017).

A12–2.2 CLINICAL STUDIES OF AGENTS TARGETING THE PD-1 AND LAG-3 PATHWAYS

Clinical data are available for early- *and late*-phase studies that evaluated the safety, tolerability, and preliminary anti-tumor activity of agents that target both the PD-1 and LAG-3 pathways. Evidence of clinical activity has been reported in some of these

studies. Overall, adverse events have been manageable to date, and the safety profiles appear similar to those of single-agent CPIs.

An ongoing Phase I/IIa study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody nivolumab and the anti–LAG-3 monoclonal antibody relatlimab in patients with advanced solid tumors. Preliminary data suggest that the combination of nivolumab and relatlimab may have an increased benefit compared with single-agent anti–PD-1. In a cohort of patients who had advanced melanoma who were previously treated with anti–PD-1/PD-L1 agents, the ORR was 11.5% (n = 61) with a disease control rate (DCR) of 49%. The anti–PD-1/PD-L1 treatment combination had an acceptable safety profile that was similar to the safety profile of nivolumab monotherapy (Ascierto et al. 2017).

Relativity-047 is a phase III study evaluating the combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) versus nivolumab alone in patients with untreated advanced melanoma. This study demonstrated that nivolumab and relatlimab improved progression-free survival (PFS = 10.1 months) over nivolumab (PFS = 4.6 months). The incidence of Grade 3 or 4 treatment-related adverse events was 18.9% in patients that received the nivolumab and relatlimab combination and 9.7% in patients that received nivolumab alonoe (Tawbi et al. 2022).

An ongoing Phase I/II study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody spartalizumab and the anti–LAG-3 monoclonal antibody LAG525 in patients with advanced solid tumors. Preliminary anti-tumor activity was observed during the Phase I dose-escalation portion of the study, including durable responses in 2 of 5 patients with triple-negative breast cancer (TNBC) and in 2 of 8 patients with mesothelioma. Analyses of tumor biopsies from the TNBC cohort also showed a trend of conversion from an immune-cold to an immune-activated phenotype. Common adverse events, i.e., adverse events reported in ≥ 10% of patients, included fatigue (18%), diarrhea (15%), and nausea (12%). The incidence of Grade 3–4 adverse events was 8% for both the combination (n = 121) and monotherapy (n = 119) arms (Hong et al. 2018).

An ongoing, first-in-human, dose-escalation, and dose-expansion Phase I study is evaluating the safety, tolerability, and clinical activity of the anti–PD-1/LAG-3 dual affinity re-targeting protein (DART®) bsAb MGD013 in patients with advanced solid tumors and hematologic malignancies. During the dose-escalation phase of the study, the maximum tolerated dose (MTD) was not reached, and the safety profile was consistent with anti–PD-1 monotherapy. During the dose-expansion phase, anti-tumor activity was observed in patients with TNBC (n = 23; ORR, 4.3%; DCR, 39.1%), CPI-naive NSCLC (n = 14; ORR, 14.3%; DCR, 64.3%), and epithelial ovarian cancer (n = 23; ORR, 8.7%; DCR, 52.2%). Expression of LAG-3 and an IFN-γ gene signature at baseline was

associated with objective responses (Luke et al. 2020). Clinical studies evaluating MGD013 as monotherapy and in combination with anti–HER-2 agents are ongoing.

A12–2.2.1 Study NP41300

Study NP41300 is an ongoing, first-in-human, dose-escalation, dose-expansion Phase I study to evaluate the safety, pharmacokinetics, and therapeutic activity of the anti–PD-1/LAG-3 bsAb RO7247669 as a single agent in patients with locally advanced and/or metastatic solid tumors. Part A, the dose-escalation phase of the study, is designed to determine the MTD and/or recommended dose for expansion (RDE) of RO7247669. Part B of the study is designed to evaluate the anti-tumor activity of RO7247669 at the MTD or RDE in tumor-specific expansion cohorts.

As of the data cut-off date of 1 March *2022*, RO7247669 was well tolerated in the patients enrolled in Part A of the study. No unexpected safety concern associated with RO7247669 was identified. No dose-limiting toxicities (DLTs) were observed up to the maximum dose tested (2100 mg every 2 weeks [Q2W]), and no MTD was identified. The maximum dose of 2100 mg was determined to be the recommended dose for the dose-expansion phase (Part B) of Study NP41300. *As of the data cutoff of 1 March 2022, 83 patients received treatment in Part B.*

As of the data cutoff date of 1 March *2022*, the DCR in Part A of the study was 51.4% (18 of 35 evaluable patients), and the ORR was 17.1% (6 of 35 patients). Among the patients treated with the proposed dose of 2100 mg Q2W, 7 of 13 patients had a best response of stable disease or better (DCR = 53.8%), including 4 patients with a confirmed partial response (PR; ORR = 30.8%). *Besides the confirmed partial responses (cPR) observed at the RDE, there were 2 cPRs at the 600 mg dose level (ORR =50.0%).*

As of the data cutoff date, 1 March 2022, in Part B of the study the DCR was 48.3% (28 of 58 patients) and the ORR was 5.2% (3 of 58 patients) among patients of the study treated at the RDE of 2100 mq Q2W (Cohorts B1, B2, and B3). Within patients treated with 600 mg Q2W (Cohort B5), the DCR was 40% (4 of 10 patients), and the ORR was 10% (1 of 10 patients). Among patients treated with 600 mg Q3W, the DCR was 28.6% (2 of 7 patients) and the ORR was 14.3% (1 of 7 patients).

Refer to the RO7247669 Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A12–2.3 BENEFIT–RISK ASSESSMENT

Despite limited clinical experience with RO7247669, the clinical efficacy and safety profiles of anti–PD-1/PD-L1 monoclonal antibodies are well characterized and established. In recent years, *four* checkpoint inhibitors, namely pembrolizumab,

nivolumab, ipilimumab, *and relatlimab* have been approved by the FDA for the treatment of unresectable or advanced melanoma.

The co-stimulatory action of RO7247669 on PD-1 and LAG-3 receptors may result in enhanced and/or more durable responses than either therapy modality alone. However, there may be a risk of exaggerated immune cell activation, particularly given the LAG-3 modulation of the immune response. Preliminary data from Study NP41300, and recent early phase studies of anti–LAG-3 antibodies showed that anti–LAG-3 therapy was generally well tolerated as monotherapy or in combination with anti–PD-1 therapies, and that it had a safety profile consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). The safety and efficacy of CPIs is established in the adjuvant setting, and CPIs are now being actively evaluated as neoadjuvant treatment and show promising early results (Herrscher and Robert 2020).

To evaluate the toxicities of the experimental treatments in the neoadjuvant setting, a minimum of 6 patients in the RO7247669 *2100 mg* arm must complete a safety evaluation before additional patients can be enrolled in that arm (refer to Section 3.1.3 for details).

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.3.

A12–3 RATIONALE FOR DOSE AND SCHEDULE FOR RO7247669 *2100 mg* ARM

A12–3.1 RATIONALE FOR RO7247669 DOSE AND SCHEDULE

RO7247669 will be administered at a fixed dose of 2100 mg Q3W (2100 mg on Day 1 of each 21-day cycle). A fixed dosing regimen of 2100 mg Q3W was selected based on available clinical pharmacokinetic, efficacy, and safety data from Study NP41300. During the dose-escalation Part A of the study, RO7247669 was well tolerated, and no specific safety concern associated with RO7247669 was identified. No DLT up to the highest dose of 2100 mg Q2W was observed, and no MTD was identified. Anti-tumor activity, as measured by radiographic PRs, was observed starting at a dose of 600 mg Q2W. PK results for RO7247669 were dose linear within the dose range tested in Study NP41300 and were therefore predicted to be in the range of target saturation. Peripheral receptor occupancy was >90% ~80 days after administration; therefore, Q3W administration should result in similar receptor occupancy as Q2W administration.

In addition, RO7247669 was well tolerated in both the dose range finding studies and Good Laboratory Practice (GLP) monkey toxicology studies up to the highest dose evaluated (100 mg/kg). Toxicology findings were consistent with the findings in cynomolgus monkey studies of marketed CPIs.

The supporting data for the selected dose can be found in the RO7247669 Investigator's Brochure.

A12–4 MATERIALS AND METHODS SPECIFIC TO RO7247669 *2100 mg* ARM

A12–4.1 TREATMENT IN RO7247669 *2100 mg* ARM

A12–4.1.1 Formulation, Packaging, and Handling

The RO7247669 drug product will be supplied by the Sponsor as a 50 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of RO7247669, refer to the pharmacy manual and the RO7247669 Investigator's Brochure.

A12–4.1.2 Dosage, Administration, and Compliance

Patients in the RO7247669 *2100 mg* arm will receive treatment for 2 cycles (6 weeks) as outlined in Table A12-1 until surgery, or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A12-1 Treatment Regimen for RO7247669 *2100 mg* Arm

Cycle Length	Dose, Route, and Regimen
21 days	• RO7247669 2100 mg by IV infusion on Day 1 of each cycle

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.
No safety data related to overdosing of RO7247669 are available to date.

RO7247669 will be administered by IV infusion at a fixed dose of 2100 mg on Day 1 of each 21-day cycle.

Administration of RO7247669 will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8.
RO7247669 infusions will be administered per the instructions outlined in Table A12-2.

Table A12-2 Administration of First and Second RO7247669 Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the first RO7247669 infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • RO7247669 should be infused over 60 (±10) minutes. • After the infusion of RO7247669, the patient begins a 60-minute observation period. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities. • 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 the first 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 and recorded on the eCRF. • RO77247669 should be infused over 30 (±10) minutes if the first infusion was tolerated without an IRR, followed by a 30-minute observation period. • If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.

eCRF = electronic Case Report Form; IRR = infusion-related reaction.

For patients who experience a Grade 2 infusion-related reaction (IRR), premedication with paracetamol 500–1000 mg orally [PO] or IV and diphenhydramine 25–50 mg PO or IV (or an alternative histamine $H_{1/2}$ antagonist at an adequate dose) is required prior to subsequent infusions. In case of Grade 3 or 4 IRRs related to study treatment, the patient should be permanently discontinued from the study treatment.

Guidelines for medical management of IRRs for RO7247669 are provided in Section A12–5.1.2.3.

No dose modification for RO7247669 is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.2.2.

A12–4.2 CONCOMITANT THERAPY FOR RO7247669 *2100 mg* ARM

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

A12–4.2.1 Permitted Therapy for RO7247669 *2100 mg* Arm

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

- Oral contraceptives with a failure rate of $< 1\%$ per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A12–4.2.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency. Other use of corticosteroids may be at the investigator's discretion. The Medical Monitor is available to advise as needed.
- Local therapy (e.g., surgery other than complete lymph node dissection [CLND] that is not considered to be related to melanoma)

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second RO7247669 infusion 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 as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or $H_{1/2}$-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

A12–4.2.2 Cautionary Therapy for RO7247669 *2100 mg* Arm

A12–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF)-α inhibitors may attenuate potential beneficial immunologic effects of treatment with RO7247669. 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 RO7247669 therapy (see Appendix 9 for details).

A12–4.2.2.2 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 A12–4.2.3) may be used during the study at the discretion of the investigator.

A12–4.2.3 Prohibited Therapy for RO7247669 *2100 mg* Arm

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until surgery or, if earlier, disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with RO7247669, and for 4 months after the final dose of RO7247669.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with RO7247669.

A12–4.3 CONTRACEPTION REQUIREMENTS FOR RO7247669 *2100 mg* ARM

Contraception requirements for women and men in the RO7247669 *2100 mg* arm are outlined below:

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

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 4 months after the final dose of RO7247669.

  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 acceptable methods of contraception.
  If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential who is not pregnant or a pregnant female partner, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period, for 4 months after the last dose of RO7247669 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A12–5 ASSESSMENT OF SAFETY FOR RO7247669 *2100 mg* ARM

A12–5.1 SAFETY PLAN FOR RO7247669 *2100 mg* ARM

The safety plan for patients in this study is based on clinical experience with RO7247669 in ongoing studies. The potential safety risks are outlined below (see Section A12–5.1.1). Guidelines for management of patients who experience specific adverse events are provided in Section A12–5.1.2 and Appendix 9.

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. Special caution will be taken by performing a planned safety evaluation phase for patients randomized to this arm (see Section 3.1.3).

Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A12–5.1.1 Risks Associated with RO7247669

Clinical evaluation of RO7247669 is ongoing, and not all risks are known. As an antagonist of PD-1 and LAG-3, RO7247669 is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Based on the mechanism-of-action of RO7247669, the safety profile is anticipated to be similar to other CPIs. Potential risks associated with RO7247669 include the following: IRRs (including anaphylaxis), immunogenicity, and immune-mediated adverse events. Refer to Section 6 of the RO7247669 Investigator's Brochure for a detailed description of anticipated safety risks for RO7247669.

A12–5.1.1.1 Infusion-Related Reactions and Anaphylaxis

Administration of therapeutic antibodies may cause IRRs, which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion and are predominantly reported following the first infusion. The incidence and severity of IRRs typically decrease with subsequent infusions. Based on in vitro data, the risk of proinflammatory cytokine-mediated IRRs on first administration of RO7247669 as a single agent is considered low.

Refer to Section A12–4.1.2 for detailed guidance on administration of RO7247669 in this study. Refer to Appendix 8 for guidance on anaphylaxis precautions and to Section A12–5.1.2.3 for guidance on the management of IRRs.

A12–5.1.1.2 Immunogenicity

Administration of therapeutic antibodies may cause the formation of anti-drug antibodies, which may negatively affect the safety of the therapeutic (e.g., allergic reactions, immune complex-mediated diseases).

A12–5.1.1.3 Immune-Mediated Adverse Events

The co-stimulatory action of RO7247669, in particular its effects on LAG-3, may lead to an exaggerated risk of immune cell activation that may result in the occurrence of enhanced, untoward, immune-mediated adverse events and increased cytokine release-mediated toxicities.

Toxicities from PD-1 blocking agents can involve any organ or tissue, although some immune-mediated adverse events occur much more frequently than others. The most frequently occurring immune-mediated adverse events affect skin, colon, endocrine organs, liver, and lungs. Others are very infrequent but may be very serious, even lethal, such as neurological disorders and myocarditis.

The limited data from recent early phase studies showed anti–LAG-3 therapy was generally well tolerated as a monotherapy or in combination with anti-PD-1 therapies, and data were consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018).

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A12–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Patients with a history of autoimmune disease will be excluded from this study. Please see Section 4.1.2 for details.

A12–5.1.2 Management of Patients Who Experience Specific Adverse Events in RO7247669 *2100 mg* Arm

A12–5.1.2.1 Dose Modifications

There will be no dose modifications for RO7247669 in this study.

A12–5.1.2.2 Treatment Interruption for Toxicities

RO7247669 treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7247669 can be resumed if warranted. In the neoadjuvant setting,

the study treatment is limited to a pre-surgery window of 6 weeks. Treatment during this period should not be interrupted, unless a patient experiences toxicity. If toxicity meets criteria for interrupting/withholding RO7247669, RO7247669 should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should only be considered if the benefit-risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

A12–5.1.2.3 Management Guidelines for Adverse Events

Guidelines for management of patients who experience specific adverse events are provided in Table A12-3.

Table A12-3 Guidelines for Management of Patients Who Experience Adverse Events in RO7247669 *2100 mg* Arm

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	
General guidance	• For anaphylaxis precautions, see Appendix 8. • For severe hypersensitivity reactions, permanently discontinue RO7247669. • For suspected CRS, see Appendix 9 for guidance on supportive care. • Determine tryptase concentration and IgE titer if clinical presentation of IRR suggests an anaphylactic or hypersensitivity reaction (hives, obstructive shortness of breath, urticaria, other histamine associated symptoms) and/or if the first IRR or CRS (≥ Grade 2) is observed at the second infusion. If tryptase and/or IgE are elevated, collect a second sample for IgE/tryptase analysis at least 48 hours after the onset of the reaction to rule out the possibility of an anaphylactic reaction.
IRR to RO7247669, Grade 1 or 2	• Slow infusion to ≤50% or interrupt infusion. • Give supportive treatment. Patients should be treated with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, if they have not been administered in the last 4 hours. IV fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice. • Upon symptom resolution, infusion may resume (if interrupted) at 50% starting rate. The infusion must remain at the lower rate resulting in symptom resolution for the remainder of the infusion. • For Grade 2 IRRs, subsequent doses of RO7247669 should be administered with pre-medication, including acetaminophen/paracetamol and an antihistamine such as diphenhydramine. • For Grade 2 wheezing or urticaria, patient must also be pre-medicated prior to subsequent doses (as described above). • If symptoms recur with the same or greater severity following the slower or interrupted infusion, the infusion must be stopped immediately. No further RO7247669 will be administered for the cycle.

CRS = cytokine-release syndrome; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS = macrophage activation syndrome.

Table A12-3 Guidelines for Management of Patients Who Experience Adverse Events in RO7247669 *2100 mg* Arm (cont.)

Event	Action to Be Taken
IRR to RO7247669, Grade 3–4	• Discontinue infusion immediately. • Give supportive treatment. • Permanently discontinue study treatment.
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, myositis, HLH, MAS, and systemic immune activation	• Guidelines for the management of these events are provided in Appendix 9.

CRS = cytokine-release syndrome; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS = macrophage activation syndrome.

A12–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR RO7247669 *2100 mg* ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the RO7247669 *2100 mg* arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A12–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN RO7247669 *2100 mg* ARM

A12–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 4 months after the final dose of RO7247669. 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for

follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A12–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 4 months after the final dose of RO7247669. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A12–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event,

recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

A12–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

A12–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR RO7247669 *2100 mg* ARM

Table A12-4 Schedule of Activities for RO7247669 *2100 mg* Arm

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
IMP Administration										
RO7247669 administration *(2100 mg)*	A12–4.1.2		x	x						
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [d]	4.5.3		x	x	x		x	x		x
Complete physical examination								x		
Limited physical examination [d]			x	x	x		x			x
Vital signs	4.5.4 and A12–4.1.2		x	x	x		x	x		x
12-Lead ECG [d]	4.5.5		x	x				x		
TTE or MUGA scan	4.5.6							x		

TABLE A12-4 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Clinical Assessments (cont.)										
ECOG Performance Status [d]	Appendix 6		x	x	x		x	x		x
Surgery (CLND)	3.1.5, Appendix 4					x				
Tumor response assessments	4.5.7				x				As clinically indicated	
Disease status assessments	4.5.7.2				x			x [e]	x	
Concomitant medications	A12–4.2		x	x	x		x	x		
Adverse events [f]	5.3.1, 5.5.1, and 5.6		x	x	x		x [f]	x [f]	x [f]	x [f]
Clavien-Dindo assessment	4.5.8 and Appendix 5							x		x
Follow-up and anti-cancer treatment	4.6.1								x [g]	
Local Laboratory Assessments										
Hematology	4.5.9.1		x [h]	x [h]	x		x	x		x
Chemistry			x [h]	x [h]	x [i]		x	x		x

TABLE A12-4 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Local Laboratory Assessments (cont.)										
Lipid panel	4.5.9.1				x			x		
Coagulation (INR and aPTT)			x [h]	x [h]	x					
TSH, free T3 (or total T3), free T4			x [h]		x		x	x		x
Cardiac enzymes			x [h]	x [h]	x [j]			x		
C-reactive protein			x [h]	x [h]	x		x	x		x
Pregnancy test			x [h]	x [h]	x		x	x		x [k]
Urinalysis			Perform as clinically indicated.					x		
Central Laboratory Assessments										
Serum autoantibody sample	4.5.9.2		Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
PK samples			Refer to Section A12–7.							
ADA samples			Refer to Section A12–7.							

TABLE A12-4 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤ 7D after randomization)	D1 (+ 1D)	Wk 6 (≤ 8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥ 20D after surgery)	Wk 13	Every 3M (± 7D)	6M after surgery (± 7D)
Blood and plasma samples for biomarkers	4.5.9.2		Refer to Section A12–7.						x (only if onsite)	Refer to Section A12–7.
Pre-dose tumor biopsy				x [l]						
Resected tissue						x				
Tumor biopsy (optional)	4.5.11		Perform at the time of unacceptable toxicity, loss of clinical benefit, relapse, or at any other time if deemed clinically feasible by the investigator.							

ADA = anti-drug antibody; CLND = complete lymph node dissection; Comp. = completion; CT = computed tomography; D = day; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; M = month; MUGA = multiple-gated acquisition; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; Wk = week.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.

[c] Patients who proceed to surgery will have the surgery follow-up 6 months after surgery.

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] The disease status assessments at Week 13 should include a mandatory CT scan.

TABLE A12-4 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* ARM (cont.)

[f] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.

[g] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first long-term follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first long-term follow-up visit 3 months after the final dose of study treatment. Information on long-term follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[h] Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[i] At the pre-surgery visit, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be included in the chemistry panel.

[j] This is only applicable if elevated levels of cardiac enzymes were detected in previous assessments.

[k] If periods are missed or delayed before the 6-month follow-up visit, pregnancy testing should be repeated. This test can be performed by a local gynecologist.

[l] The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.

A12–7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 *2100 mg* ARM

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to first infusion (–6 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
	30 (±10) minutes after the end of RO7247669 infusion	• RO7247669 PK (serum)
Day 1 of Cycle 2	Prior to infusion (–6 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
	30 (±10) minutes after the end of RO7247669 infusion	• RO7247669 PK (serum)
Surgery CLND Week 7	Prior to surgery (–24 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
Post-surgery Week 10 [a]	At visit	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
Treatment completion/ discontinuation Week 13	At visit	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
Long-term follow-up Every 3 months (±7 days) [b]	At visit	• Biomarkers (blood, plasma)
Surgery follow-up 6 months after surgery (±7 days)	At visit	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)

ADA = anti-drug antibody; CLND = complete lymph node dissection; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced, or sample collection may cease altogether.

[a] Week 10 biomarker samples must be obtained ≥20 days post-surgery.

[b] To be collected if visit is conducted on site.

A12–8 REFERENCES

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Appendix 13
Study Details Specific to Atezo+Tira Arm

TABLE OF CONTENTS

A13–1 BACKGROUND ON ATEZO + TIRA ARM

A13–1.1 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 enhances the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

A13–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa monoclonal antibody that binds TIGIT and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients.

Refer to the Tiragolumab Investigator’s Brochure for details on nonclinical and clinical studies.

A13–2 RATIONALE FOR ATEZO + TIRA ARM

A13–2.1 THE PD-L1 PATHWAY

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

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

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including non–small cell lung cancer (NSCLC), urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see the Atezolizumab Investigator's Brochure for detailed efficacy results).

Cancer immunotherapy agents, particularly immune checkpoint inhibitors, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active as monotherapy for many patients.

A13–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily (Yu et al. 2009). 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 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

concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (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. It is expressed in most solid tumors, such as NSCLC, breast cancer, and melanoma, as well as in hematological tumors, such as multiple myeloma (MM) and non-Hodgkin lymphoma (NHL). Fluorescence activated cell sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey at al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating $CD4^+$ T cells and in 50%–80% of tumor-infiltrating $CD8^+$ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Taken together, these data support the hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A13–2.3 COMBINATION TREATMENT WITH ANTI–PD-L1 AND ANTI-TIGIT AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated $CD8^+$ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Hence, targeting both TIGIT and PD-L1 with tiragolumab and atezolizumab, respectively, in patients, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including melanoma.

A13–2.4 CLINICAL STUDIES OF TIRAGOLUMAB AS A SINGLE AGENT OR IN COMBINATION WITH ATEZOLIZUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290) and in one clinical study in patients with in hematological malignancies (Study GO41036).

A13–2.4.1 Study GO30103

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study. It was designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including urothelial cancer, renal cell cancer, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, colorectal cancer (CRC), gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the clinical cutoff date of 2 December 2020, a total of 236 patients had been enrolled in Study GO30103. Forty-two patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and 217 patients were enrolled in the Phase Ib portion of the study to receive tiragolumab in combination with atezolizumab. The latter group included 23 patients who crossed over from the Phase Ia portion of the study.

The best observed response with tiragolumab monotherapy in the Phase Ia portion was prolonged stable disease in 8 of 42 patients, with some patients, including 1 patient with CRC, experiencing a decrease in tumor size.

In the Phase Ib portion, complete response was observed in 4 of 217 patients at tiragolumab dose levels of 400 mg (n = 3/48) and 600 mg (n = 1/104) in combination with 1200 mg atezolizumab. Partial response was observed in 27 of 217 patients at tiragolumab dose levels of 30 mg (n = 2/13), 400 mg (n = 6/48), and 600 mg (n = 18/104) in combination with 1200 mg atezolizumab, including two patients who crossed over from the Phase Ia portion at the 600 mg dose level. Stable disease was observed in 53 of 217 patients at tiragolumab dose levels of 2 mg (n = 1/8), 8 mg (n = 3/12), 30 mg (n = 2/13), 100 mg (n = 3/8), 400 mg (n = 12/48), 600 mg (n = 25/104), and 1200 mg (n = 7/24) in combination with 1200 mg atezolizumab, including 8 patients who crossed over from the Phase Ia portion of the study (2 patients at 8 mg, 1 patient at 30 mg, 2 patients at 100 mg, and 3 patients at 400 mg).

As of 2 December 2020, safety data were available for 235 safety-evaluable patients in Study GO30103. A total of 42 patients were treated in the Phase Ia portion with tiragolumab as a single agent (2 mg to 1200 mg), while 216 patients were treated in the Phase Ib portion with tiragolumab at dose levels of 2 mg to 1200 mg in combination with

atezolizumab at 1200 mg, including 23 patients who crossed over from the Phase Ia portion to the Phase Ib portion.

Tiragolumab was tolerated across all administered dose levels both as a single agent and in combination with atezolizumab. The maximum tolerated dose (MTD) was not reached, and the maximum administered dose was 1200 mg. No dose-limiting toxicities (DLTs) or clear dose-related trends in the incidence of adverse events were observed. Grade ≥3 adverse events, regardless of attribution to the study drug(s), were reported in 16 patients (38.1%) and 113 patients (52.3%) in the Phase Ia and Phase Ib portions, respectively. There were 14 reported deaths in the Phase Ia portion of the study, including 12 deaths due to malignant neoplasm progression, 1 death due to gastrointestinal hemorrhage in the context of progressive disease, and 1 death due to hepatic failure. The death due to hepatic failure was considered by the investigator to be related to study drug. One hundred eighteen deaths were reported in the Phase Ib portion of the study. This included 111 deaths due to progressive disease (31 cases were reported as adverse events during the adverse event reporting period and coded as malignant neoplasm progression or neoplasm malignant), 2 deaths due to pulmonary embolism, 1 death due to esophageal hemorrhage, 1 death due to sepsis, 1 death due to septic shock, 1 death due to COVID-19, and 1 death due to upper airway obstruction. Treatment-related serious adverse events were reported in 1 patient in the Phase Ia portion (hepatic failure) and in 10 patients (4.6%) in the Phase Ib portion. No patient discontinued study treatment due to adverse events in the Phase Ia portion of Study GO30103. Adverse events leading to treatment discontinuation were reported in 12 patients in the Phase Ib portion of the study, with a Grade 4 cardiac tamponade, a Grade 4 pneumonitis, and one event of Grade 2 arthralgia considered by the investigator to be related to the study drug(s). Adverse events of special interest were reported in 5 patients (11.9%) in the Phase Ia portion and 82 patients (38.0%) in the Phase Ib portion of the study.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile has been observed to be consistent across different solid tumor indications.

A13–2.4.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–positive NSCLC (defined as tumor proportion score [TPS] ≥1%).

As of the primary clinical cutoff date of 30 June 2019, 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).

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

In all randomized patients, the combination of tiragolumab plus atezolizumab improved the co-primary endpoints of investigator-assessed ORR and progression-free survival (PFS) compared with placebo plus atezolizumab, with median follow-up of 5.9 months. ORR for tiragolumab plus atezolizumab was 31.3% (95% CI: 19.5, 43.2) compared with placebo plus atezolizumab which was 16.2% (95% CI: 6.7, 25.7). Investigator-assessed median PFS for tiragolumab plus atezolizumab was 5.4 months (95% CI: 4.2 months, not reached) compared to placebo plus atezolizumab which was 3.6 months (95% CI: 2.7 months, 4.4 months), with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.37, 0.90). Investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified HR = 0.33; 95% CI: 0.15, 0.72; median PFS not reached vs. 3.9 months, respectively).

As of 2 December 2020, 67 safety-evaluable patients in the tiragolumab plus atezolizumab arm in Study GO40290 were treated with a median of 8 doses of tiragolumab and atezolizumab (range: 1–38) for a median of 5.0 months (range: 0.03–26.0). In the placebo plus atezolizumab arm, 68 safety-evaluable patients were treated with a median of 5 doses of placebo and atezolizumab (range: 1–37) for a median of 2.8 months (range: 0.03–26.3).

As of 30 June 2020, in the Phase II randomized, placebo-controlled Study GO40290, a total of 135 safety-evaluable patients were administered either tiragolumab (600 mg recommended Phase II/III dose) in combination with atezolizumab or placebo in combination with atezolizumab. The safety profile of tiragolumab plus atezolizumab was similar to that of placebo plus atezolizumab- for all-grade adverse events (98.5% vs. 97.1%), Grade ≥3 adverse events (53.7% vs. 50.0%), serious adverse events (47.8% vs. 39.7%), and adverse events leading to treatment discontinuation (13.4% vs. 11.8%). Adverse events of special interest were reported in 58.2% of patients in the tiragolumab plus atezolizumab arm and in 32.4% of patients in the placebo plus atezolizumab arm. One death due to Epstein-Barr virus (EBV) reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in this study, which was considered by the investigator to be related to the study drugs.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure or additional details on all ongoing and planned clinical studies.

A13–2.5 BENEFIT–RISK ASSESSMENT

The preliminary safety and efficacy data from the ongoing studies of tiragolumab as a single agent or in combination with atezolizumab across different solid tumor indications including melanoma, and hematologic malignancies support a favorable benefit–risk profile for tiragolumab. This favorable benefit–risk profile, the potential for TIGIT as a target for therapeutic intervention in melanoma, and the significant unmet medical need in this indication are key reasons for the current study.

To evaluate overlapping toxicities of the experimental treatments in the neoadjuvant setting (refer to Section A13–5.1.3 for details), a minimum of 6 patients in the Atezo + Tira arm must complete a safety evaluation before additional patients can be enrolled in that arm (refer to Section 3.1.3 for details).

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.3.

A13–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + TIRA ARM

A13–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab.

A13–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle).

The fixed dose of 600 mg IV Q3W was selected on the basis of available clinical pharmacokinetic, efficacy, and safety data from the combined Phase Ia/Phase Ib Study GO30103, with single-agent tiragolumab or tiragolumab in combination with atezolizumab. In the Phase Ia portion of the study with tiragolumab as a single agent, the MTD was not reached, and no DLTs were observed in dose-escalation. As of the clinical cutoff date, anti-drug antibodies to tiragolumab were rare in the Phase Ia or Phase Ib portions across all dose levels. Complete occupancy of peripheral TIGIT receptors on $CD4^+$, $CD8^+$, and NK cells was observed beginning at 30 mg of tiragolumab in both Phase Ia and Phase Ib portions of the study and remained sustained at all higher doses (unpublished Roche data on file).

Prolonged stable disease was observed in patients in the Phase Ia portion of the study at tiragolumab doses beginning at 400 mg. In the Phase Ib portion of the study with tiragolumab plus atezolizumab, the MTD was not reached. Anti-tumor activity, as measured by radiographic partial responses, was observed across doses for tiragolumab beginning at 30 mg and ranging up to 600 mg in combination with 1200 mg atezolizumab.

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

A13–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + TIRA ARM

A13–4.1 TREATMENT IN ATEZO + TIRA ARM

A13–4.1.1 Formulation, Packaging, and Handling

A13–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a 60 mg/mL concentrate for solution for infusion.

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

A13–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor as a 60 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of tiragolumab, refer to the pharmacy manual and the Tiragolumab Investigator's Brochure.

A13–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus tiragolumab (Atezo + Tira) arm will receive treatment for 2 cycles (6 weeks) as outlined in Table A13-1 until surgery, or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A13-1 Treatment Regimen for Atezo + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Tiragolumab 600 mg IV on Day 1 of each cycle

Atezo = atezolizumab; Tira = tiragolumab.

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.
No safety data related to overdosing of atezolizumab or tiragolumab are available to date.

A13–4.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of 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. For anaphylaxis precautions, see Appendix 8.
Atezolizumab infusions will be administered per the instructions outlined in Table A13-2.

Table A13-2 Administration of First and Second Atezolizumab Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Atezolizumab should be infused over 60 (±15) minutes. • After the infusion of atezolizumab, the patient begins a 30-minute observation period. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities. • 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 the first infusion, premedication with antihistamines, anti-pyretics, 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 and recorded on the eCRF. • 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. Record on the eCRF in case of abnormalities.

eCRF = electronic Case Report Form; IRR = infusion-related reaction

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Table A13-5.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.4.2.

A13–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in Table A13-3.

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. Tiragolumab infusions will be administered per the instructions outlined in Table A13-3.

Table A13-3 Administration of First and Second Tiragolumab Infusions

First Infusion	Second Infusion
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Tiragolumab should be infused over 60 (±15) minutes. • After the infusion of tiragolumab, the patient begins a 60-minute observation period. • Record vital signs on the eCRF every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed postinfusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an IRR with the first 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 and recorded on the eCRF. • Tiragolumab 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 infusion-related reaction with the previous infusion. • Patients should be observed for 30 minutes after completion of the tiragolumab infusion if the previous infusion was tolerated without an IRR, or for 60 minutes after completion of the tiragolumab infusion if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded on the eCRF every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.

eCRF = electronic Case Report Form; IRR = infusion-related reaction.

Guidelines for medical management of IRRs for tiragolumab are provided in Table A13-5.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A13–5.1.4.2.

A13–4.2 CONCOMITANT THERAPY FOR ATEZO + TIRA ARM

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

A13–4.2.1 Permitted Therapy for Atezo + Tira Arm

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

- Oral contraceptives with a failure rate of < 1% per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A13–4.2.3)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease (COPD) or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency. Other use of corticosteroids may be permitted at the investigator's discretion. The Medical Monitor is available to advise as needed.
- Local therapy (e.g., surgery other than complete lymph node dissection [CLND] that is not considered to be related to melanoma)

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second atezolizumab and tiragolumab 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 as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; refer to Appendix 8 for details).

A13–4.2.2 Cautionary Therapy for Atezo + Tira Arm

A13–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab and/or tiragolumab. Therefore, in situations in which systemic

corticosteroids, immunosuppressive medications, or TNF-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 and/or tiragolumab therapy (refer to Appendix 9 for details).

A13–4.2.2.2 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 A13–4.2.3) may be used during the study at the discretion of the investigator.

A13–4.2.3 Prohibited Therapy for Atezo + Tira Arm

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.4), and during study treatment until surgery, or if earlier, until disease progression is documented and the patient has discontinued study treatment.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab and/or tiragolumab, and for 5 months after the final dose of atezolizumab and/or tiragolumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and/or tiragolumab.

A13–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + TIRA ARM

Contraception requirements for men and women in the Atezo + Tira arm are outlined below:

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

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

  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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 90 days after the final dose of tiragolumab. Men must refrain from donating sperm during this same period.

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

A13–5 ASSESSMENT OF SAFETY FOR ATEZO + TIRA ARM

A13–5.1 SAFETY PLAN FOR ATEZO + TIRA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A13–5.1.1, A13–5.1.2, and A13–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A13–5.1.4 and Appendix 9.

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. Because of the potential for overlapping toxicities for atezolizumab and tiragolumab, special caution will be taken by performing a planned safety evaluation phase for patients randomized to this arm (see Section 3.1.3).

Administration of atezolizumab and tiragolumab 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. Adverse events will be reported as described in Sections 5.2–5.6.

A13–5.1.1 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 (SCARs). In addition, immune-mediated reactions may involve any organ system and lead to HLH. Refer to Appendix 9 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A13–5.1.2 Risks Associated with Tiragolumab

Infusion-related reactions and immune-mediated hepatitis are identified risks of tiragolumab. Lymphopenia is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 9 of the protocol and Section 6 of the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks of tiragolumab.

A13–5.1.2.1 Infusion-Related Reactions

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

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

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Refer to Section A13–4.1.2 for detailed guidance on administration of tiragolumab in this study. Please see Appendix 8 for guidance on anaphylaxis precautions and Table A13-5 for guidance on the management of IRRs.

A13–5.1.2.2 Immune-Mediated Hepatitis

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors (i.e., atezolizumab). A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

Refer to Appendix 9 for guidance on the management of immune-mediated hepatitis.

A13–5.1.2.3 Immune-Mediated Adverse Events

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

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

pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

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

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A13–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 9.

A13–5.1.2.4 Lymphopenia

The IgG1 backbone of tiragolumab with intact Fc-effector function may lead to ADCC-mediated reduction in lymphocyte count. Lymphopenia is a potential risk with tiragolumab. Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab, with or without atezolizumab.

Patients with a lymphocyte count $< 0.5 \times 10^9$/L (500/μL) will be excluded from the study (see Section 4.1.1), and complete blood counts will be monitored regularly during the study (see Appendix A13–6).

A13–5.1.2.5 Embryofetal Toxicity

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

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

A13–5.1.3 Risks Associated with Combination Use of Atezolizumab and Tiragolumab

Based on results from clinical data with tiragolumab and atezolizumab, there are known and potential overlapping toxicities in patients treated with tiragolumab plus atezolizumab. Because the expected pharmacologic activity of these two molecules is

to increase adaptive T-cell immune responses, there is the possibility of heightened immune responses.

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

Based on clinical experience to date, it is anticipated that immune-mediated adverse events following treatment with tiragolumab and atezolizumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune CPIs 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 Cohort 1. Owing to the risks of active viral infection and viral reactivation, patients with active infection (including, but not limited to, HIV, HBV, HCV, EBV, known and/or suspected chronic active EBV infection, or tuberculosis) and/or patients with recent severe infections will be excluded from this study (see Sections 4.1.1 and 4.1.2).

A13–5.1.4 Management of Patients Who Experience Specific Adverse Events in the Atezo + Tira Arm

A13–5.1.4.1 Dose Modifications

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

A13–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab and tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed, if warranted. In the neoadjuvant setting, the study treatment is limited to a pre-surgery window of 6 weeks. Treatment during this period should not be interrupted, unless a patient experiences toxicity. If toxicity meets criteria for interrupting/withholding atezolizumab and/or tiragolumab, atezolizumab and tiragolumab should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should only be considered if the benefit/risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to, but independent of, atezolizumab. Tiragolumab may also exacerbate the frequency or severity of atezolizumab-related adverse events or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and atezolizumab. If atezolizumab is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, atezolizumab should also be withheld or discontinued.

A13–5.1.5 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A13-4, Table A13-5, and Appendix 9.

For cases in which management guidelines are not covered in Appendix 9, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A13-4 Guidelines for Management of Patients Who Experience Adverse Events in the Atezo + Tira Arm

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	• Guidelines for management of IRRs are provided in Table A13-5. • For anaphylaxis precautions, see Appendix 8. • For severe hypersensitivity reactions, permanently discontinue the causative agent.
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, and systemic immune activation	• Guidelines for management of these events are provided in Appendix 9.

CRS = cytokine-release syndrome; GI = gastrointestinal; IRR = infusion-related reaction.

A13–5.1.5.1 Infusion-Related Reactions

No premedication is indicated for the administration of the Day 1, Cycle 1 infusion of tiragolumab or atezolizumab. However, patients who experience an IRR with the Day 1, Cycle 1 infusion of tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medication, 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 tiragolumab or atezolizumab administration and are generally mild to moderate in severity. Guidelines for medical management of IRRs during Cycle 1 are provided in Table A13-5. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table A13-5 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue tiragolumab and atezolizumab and contact the Medical Monitor. [a]

IRR = infusion-related reaction.

[a] If a study drug warrants permanent discontinuation, there should be no re-challenge of the drug. For combination regimens, both study drugs should be discontinued.

A13–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE ATEZO + TIRA ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the Atezo + Tira arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

- Myelitis
- Facial paresis

A13–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE ATEZO + TIRA ARM

A13–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab or within 90 days after the final dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A13–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the final dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health

Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A13–5.3.3 Abortions

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

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

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

A13–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

A13–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+TIRA ARM

Table A13-6 Schedule of Activities for Atezo+Tira Arm

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D –28 to D –1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
IMP Administration										
Atezolizumab administration	A13–4.1.2		x	x						
Tiragolumab administration			x	x						
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [d]	4.5.3		x	x	x		x	x		x
Complete physical examination								x		
Limited physical examination [d]			x	x	x		x			x
Vital signs	4.5.4 and A13–4.1.2		x	x	x		x	x		x
12-Lead ECG [d]	4.5.5		x	x				x		
TTE or MUGA scan	4.5.6							x		

TABLE A13-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤ 7D after randomization)	D1 (+ 1D)	Wk 6 (≤ 8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥ 20D after surgery)	Wk 13	Every 3M (± 7D)	6M after surgery (± 7D)
Clinical Assessments (cont.)										
ECOG Performance Status [d]	Appendix 6		x	x	x		x	x		x
Surgery (CLND)	3.1.5, Appendix 4					x				
Tumor response assessments	4.5.7				x				As clinically indicated	
Disease status assessments	4.5.7.2				x			x [e]	x	
Concomitant medications	A13–4.2		x	x	x		x	x		
Adverse events [f]	5.3.1, 5.5.1, and 5.6		x	x	x		x [f]	x [f]	x [f]	x [f]
Clavien-Dindo assessment	4.5.8 and Appendix 5							x		x
Follow-up and anti-cancer treatment	4.6.1								x [g]	

TABLE A13-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤ 7D after randomization)	D1 (+ 1D)	Wk 6 (≤ 8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥ 20D after surgery)	Wk 13	Every 3M (± 7D)	6M after surgery (± 7D)
Local Laboratory Assessments										
Hematology	4.5.9.1		x [h]	x [h]	x		x	x		x
Chemistry			x [h]	x [h]	x [i]		x	x		x
Lipid panel					x			x		
Coagulation (INR and aPTT)			x [h]	x [h]	x					
TSH, free T3 (or total T3), free T4			x [h]		x		x	x		x
Cardiac enzymes			x [h]	x [h]	x [j]			x		
C-reactive protein			x [h]	x [h]	x		x	x		x
Pregnancy test			x [h]	x [h]	x		x	x		x [k]
Urinalysis			Perform as clinically indicated.					x		
Central Laboratory Assessments										
Serum autoantibody sample	4.5.9.2		Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
PK samples			Refer to Section A13–7.							
ADA samples			Refer to Section A13–7.							

TABLE A13-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤ 7D after randomization)	D1 (+ 1D)	Wk 6 (≤ 8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥ 20D after surgery)	Wk 13	Every 3M (± 7D)	6M after surgery (± 7D)
Central Laboratory Assessments (cont.)										
Blood and plasma samples for biomarkers	4.5.9.2		Refer to Section A13–7.						x (only if onsite)	Refer to Section A13–7.
Pre-dose tumor biopsy				x [l]						
Resected tissue						x				
Tumor biopsy (optional)	4.5.11		Perform at the time of unacceptable toxicity, loss of clinical benefit, relapse, or at any other time if deemed clinically feasible by the investigator.							

ADA = anti-drug antibody; CLND = complete lymph node dissection; Comp. = completion; CT = computed tomography; D = day; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; M = month; MUGA = multiple-gated acquisition; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; Wk = week.

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

TABLE A13-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.

[c] Patients who proceed to surgery will have the surgery follow-up 6 months after surgery.

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] The disease status assessments at Week 13 should include a mandatory CT scan.

[f] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.

[g] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first long-term follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first long-term follow-up visit 3 months after the final dose of study treatment. Information on follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[h] Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[i] At the pre-surgery visit, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be included in the chemistry panel.

[j] This is only applicable if elevated levels of cardiac enzymes were detected in previous assessments.

TABLE A13-6 SCHEDULE OF ACTIVITIES FOR ATEZO + TIRA ARM (cont.)

[k] If periods are missed or delayed before the 6-month follow-up visit, pregnancy testing should be repeated. This test can be performed by a local gynecologist.

[l] The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.

A13–7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR ATEZO + TIRA ARM

Visit [a]	Time	Sample
Day 1 of Cycle 1	Prior to first infusion (–6 hr to 0 hr)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
	30 (± 10) minutes after the end of atezolizumab infusion	• Atezolizumab PK (serum)
	30 (± 10) minutes after the end of tiragolumab infusion	• Tiragolumab PK (serum)
Day 1 of Cycle 2	Prior to infusion (–6 hr to 0 hr)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
Surgery CLND Week 7	Prior to surgery (–24 hr to 0 hr)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
Post-surgery Week 10 a	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
Treatment completion/ discontinuation Week 13	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)

ADA = anti-drug antibody; Atezo = atezolizumab; CLND = complete lymph node dissection; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Week 10 biomarker samples must be obtained ≥ 20 days post-surgery.

[b] To be collected if visit is conducted on site.

Table A13-7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR ATEZO + TIRA ARM (cont.)

Visit	Time	Sample Type
Long-term follow-up Every 3 months (±7 days) [b]	At visit	• Biomarkers (blood, plasma)
Surgery follow-up 6 months after surgery (±7 days)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)

ADA = anti-drug antibody; Atezo = atezolizumab; CLND = complete lymph node dissection; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Week 10 biomarker samples must be obtained ≥ 20 days post-surgery.

[b] To be collected if visit is conducted on site.

A13–8 REFERENCES

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Appendix 14
Study Details Specific to RO7247669 *2100 mg*+Tira Arm (Cohorts 1 and 2)

TABLE OF CONTENTS

A14–1 BACKGROUND ON RO7247669 *2100 mg* + TIRA ARM

A14–1.1 BACKGROUND ON RO7247669

RO7247669 is a novel, Fc-silent IgG1-based bispecific antibody (bsAb) in 1 + 1 format that incorporates monovalent binding to two immune checkpoint proteins: PD-1 and LAG-3. RO7247669 is designed to target dysfunctional tumor antigen-specific T lymphocytes expressing PD-1 and LAG-3 to establish or re-establish an effective anti-tumor immune response in cancer patients. This may result in improved therapeutic responses over currently available therapies. In addition, RO7247669 is engineered to prevent binding to Fc gamma receptors, thus potentially avoiding tumor-associated macrophage resistance mechanisms. Such mechanisms have been observed with IgG4-based anti–PD-1 antibodies, such as pembrolizumab and nivolumab (Arlauckas et al. 2017). Clinical evaluation of RO7247669 is ongoing in a first-in-human, dose-finding study (Study NP41300), as a single agent in cancer patients with and without prior CPI exposure.

Refer to the RO7247669 Investigator's Brochure for details on nonclinical and *other planned and ongoing* clinical studies.

A14–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa monoclonal antibody that binds TIGIT and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients.

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

A14–2 RATIONALE FOR RO7247669 *2100 mg* + TIRA ARM

A14–2.1 TARGETING THE PD-1 AND LAG-3 ANTIGENS

Cancer immunotherapy agents, particularly immune CPIs, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, additional treatment options targeting immune checkpoints are needed, because the majority of patients eventually progress after an initial response or fail to respond to the PD-1/PD-L1 checkpoint blockade. This is believed to be mainly due to primary or secondary resistance

mechanisms, immunosuppressive activity of myeloid-derived suppressor cells and/or T-regulatory cells (Sharma et al. 2017).

To overcome resistance mechanisms, additional treatment options and multiple combinations with anti–PD-L1 are being assessed. One potential reason for resistance to anti–PD-L1 therapy is the upregulation of alternative immune checkpoints with non-redundant regulatory functions (Sharma et al. 2017). LAG-3 is one such alternative immune checkpoint. Structurally similar to CD4, LAG-3 is a member of the Ig superfamily. LAG-3 is expressed on activated effector T cells and is constitutively expressed on T-regulatory cells and natural killer (NK) cells. The expression of both PD-1 and LAG-3 on tumor infiltrating lymphocytes (TILs) correlates with the degree of impairment of effector functions, which is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015). Hence, LAG-3 is a marker of T-cell dysfunctionality. LAG-3 also regulates T-cell functions, presumably including the function of T-regulatory cells. In chronic infections and cancer, LAG-3, together with PD-1, contributes to T-cell–acquired dysfunctionality and to the inability of T cells to mount an effective/protective immune response upon interaction with the LAG-3 ligand, MHC-II.

The interaction of LAG-3 with MHC-II inhibits T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production (Goldberg and Drake 2011). The effect of LAG-3 expression on T-regulatory cells is controversial. An early report concluded that LAG-3 promotes T-regulatory cell-mediated immune suppression (Camisaschi et al. 2010). However, a more recent report from the same authors found that LAG-3 limits T-regulatory cell-mediated immune suppression (Zhang et al. 2017).

Expression of LAG-3 has been reported across various tumor types, including breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), melanoma, renal cell cancer (RCC), prostate cancer, and hepatocellular carcinoma (HCC). In patients with these tumor types, LAG-3 is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norstrom et al. 2016). Clinical evaluation of anti–LAG-3 agents, as a single-agent and in combination with other CPIs, is ongoing in several early phase studies in patients with advanced solid tumors (Long et al. 2018). Preliminary data demonstrate that anti–LAG-3 therapy is well tolerated, both as a single agent and in combination with anti–PD-1 therapies, and the safety profiles were consistent with those of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). RO7247669 therefore has the potential to be a therapeutic option for patients with melanoma.

Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory immune checkpoints on the surface of effector T cells. LAG-3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG-3 enhances $CD8^+$

T-cell effector function and potentiates anti-tumor immunity in nonclinical models. Blockade of these two receptors in mice with colon, fibrosarcoma, or ovarian tumors resulted in tumor remission in approximately 80% of animals compared with 10% to 40% with blockade of either receptor using a single agent (Woo et al. 2012; Huang et al. 2015). TILs from patients with ovarian cancer showed that antigen-specific $CD8^+$ T cells co-expressing PD-1 and LAG-3 exhibited greater impairment in their ability to respond to cognate antigen stimulation compared with $CD8^+$ T cells that expressed one checkpoint molecule (Matsuzaki et al. 2010). In patients with NSCLC, overexpression of LAG-3 on TILs correlated with PD-1/PD-L1 expression and was linked to higher risk of recurrence and poor survival outcomes (He et al. 2017).

A14–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily (Yu et al. 2009). TIGIT is expressed on the surface of activated T cell and NK cell subsets and interacts with high affinity with CD155 (also known as 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 concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (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. It is expressed in most solid tumors, such as NSCLC, breast cancer, and melanoma, as well as in hematological tumors, such as multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). Fluorescence activated cell sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey et al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating $CD4^+$ T cells and in 50%–80% of tumor-infiltrating $CD8^+$ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in regulating T-cell responses in cancer. Taken together, these data support the

hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A14–2.3 COMBINATION TREATMENT WITH ANTI–PD-1/ANTI–LAG-3 AND ANTI-TIGIT AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells including TIGIT and LAG-3. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated $CD8^+$ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Similarly, in-vivo proof-of-concept studies using different tumor mouse models have shown PD1-LAG-3 bsAbs to be superior in controlling tumor growth and promoting tumor eradication when compared with anti-PD-1 antibodies as monotherapy. Hence, targeting PD-1/LAG-3 and TIGIT with RO7247669 and tiragolumab, respectively, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including melanoma.

A14–2.4 CLINICAL STUDIES OF AGENTS TARGETING THE PD-1 AND LAG-3 PATHWAYS

Clinical data are available for early- *and late*-phase studies that evaluated the safety, tolerability, and preliminary anti-tumor activity of agents that target both the PD-1 and LAG-3 pathways. Evidence of clinical activity has been reported in some of these studies. Overall, adverse events have been manageable to date, and the safety profiles appear similar to those of single-agent CPIs.

An ongoing Phase I/IIa study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody nivolumab and the anti–LAG-3 monoclonal antibody relatlimab in patients with advanced solid tumors. Preliminary data suggest that the combination of nivolumab and relatlimab may have an increased benefit compared with single-agent anti–PD-1. In a cohort of patients who had advanced melanoma who were previously treated with anti–PD-1/PD-L1 agents, the objective response rate (ORR) was 11.5% (n = 61) with a disease control rate of 49%. The anti–PD-1/PD-L1 treatment combination had an acceptable safety profile that was similar to the safety profile of nivolumab monotherapy (Ascierto et al. 2017).

Relativity-047 is a phase III study evaluating the combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) versus nivolumab alone in patients with untreated advanced melanoma. This study demonstrated that nivolumab and relatlimab

improved progression-free survival (PFS = 10.1 months) over nivolumab (PFS = 4.6 months). The incidence of Grade 3 or 4 treatment-related adverse events was 18.9% in patients that received the nivolumab and relatlimab combination and 9.7% in patients that received nivolumab alonoe (Tawbi et al. 2022).

An ongoing Phase I/II study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody spartalizumab and the anti–LAG-3 monoclonal antibody LAG525 in patients with advanced solid tumors. Preliminary anti-tumor activity was observed during the Phase I dose-escalation portion of the study, including durable responses in 2 of 5 patients with triple-negative breast cancer (TNBC) and in 2 of 8 patients with mesothelioma. Analyses of tumor biopsies from the TNBC cohort also showed a trend of conversion from an immune-cold to an immune-activated phenotype. Common adverse events, i.e., adverse events reported in ≥10% of patients, included fatigue (18%), diarrhea (15%), and nausea (12%). The incidence of Grade 3–4 adverse events was 8% for both the combination (n = 121) and monotherapy (n = 119) arms (Hong et al. 2018).

An ongoing, first-in-human, dose-escalation, and dose-expansion Phase I study is evaluating the safety, tolerability, and clinical activity of the anti–PD-1/LAG-3 dual affinity re-targeting protein (DART®) bsAb MGD013 in patients with advanced solid tumors and hematologic malignancies. During the dose-escalation phase of the study, the maximum tolerated dose (MTD) was not reached, and the safety profile was consistent with anti–PD-1 monotherapy. During the dose-expansion phase, anti-tumor activity was observed in patients with TNBC (n = 23; ORR, 4.3%; disease control rate [DCR], 39.1%), CPI-naive NSCLC (n = 14; ORR, 14.3%; DCR, 64.3%), and epithelial ovarian cancer (n = 23; ORR, 8.7%; DCR, 52.2%). Expression of LAG-3 and an IFN-γ gene signature at baseline was associated with objective responses (Luke et al. 2020). Clinical studies evaluating MGD013 as monotherapy and in combination with anti–HER-2 agents are ongoing.

A14–2.4.1 Study NP41300

Study NP41300 is an ongoing, first-in-human, dose-escalation, dose-expansion Phase I study to evaluate the safety, pharmacokinetics, and therapeutic activity of the anti–PD-1/LAG-3 bsAb RO7247669 as a single-agent in patients with locally advanced and/or metastatic solid tumors. Part A, the dose-escalation phase of the study, is designed to determine the MTD and/or recommended dose for expansion (RDE) of RO7247669. Part B of the study is designed to evaluate the anti-tumor activity of RO7247669 at the MTD or RDE in tumor-specific expansion cohorts.

As of the data cutoff date, 1 March *2022*, RO7247669 was well tolerated in the patients enrolled in Part A of the study. No unexpected safety concern associated with

RO7247669 was identified. No dose-limiting toxicities (DLTs) were observed up to the maximum dose tested (2100 mg every 2 weeks [Q2W]), and no MTD was identified. The maximum dose of 2100 mg was determined to be the recommended dose for the dose-expansion phase (Part B) of Study NP41300. *As of the data cutoff of 1 March 2022, 83 patients received treatment in Part B.*

As of the data cutoff date, 1 March *2022*, the DCR in Part A of the study was 51.4% (18 of 35 evaluable patients), and the ORR was 17.1% (6 of 35 patients). Among the patients treated with the proposed dose of 2100 mg Q2W, 7 of 13 patients had a best response of stable disease or better (DCR = 53.8%), including 4 patients with a confirmed partial response (PR, ORR = 30.8%). *Besides the confirmed partial responses (cPR) observed at the RDE, there were 2 cPRs at the 600 mg dose level (ORR =50.0%).*

As of the data cutoff date, 1 March 2022, in Part B of the study the DCR was 48.3% (28 of 58 patients) and the ORR was 5.2% (3 of 58 patients) among patients of the study treated at the RDE of 2100 mq Q2W (Cohorts B1, B2, and B3). Within patients treated with 600 mg Q2W (Cohort B5), the DCR was 40% (4 of 10 patients), and the ORR was 10% (1 of 10 patients). Among patients treated with 600 mg Q3W, the DCR was 28.6% (2 of 7 patients) and the ORR was 14.3% (1 of 7 patients).

Refer to the RO7247669 Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A14–2.5 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290) and in one clinical study in patients with hematological malignancies (Study GO41036).

A14–2.5.1 Study GO30103

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study. It was designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including urothelial cancer, renal cell cancer, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, colorectal cancer (CRC), gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the clinical cutoff date of 2 December 2020, a total of 236 patients had been enrolled in Study GO30103. Forty-two patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and 217 patients were enrolled in the Phase Ib portion of the study to receive tiragolumab in combination with atezolizumab.

The latter group included 23 patients who crossed over from the Phase Ia portion of the study.

The best observed response with tiragolumab monotherapy in the Phase Ia portion was prolonged stable disease in 8 of 42 patients, with some patients, including 1 patient with CRC, experiencing a decrease in tumor size.

In the Phase Ib portion, complete response was observed in 4 of 217 patients at tiragolumab dose levels of 400 mg (n = 3/48) and 600 mg (n = 1/104) in combination with 1200 mg atezolizumab. Partial response was observed in 27 of 217 patients at tiragolumab dose levels of 30 mg (n = 2/13), 400 mg (n = 6/48), and 600 mg (n = 18/104) in combination with 1200 mg atezolizumab, including two patients who crossed over from the Phase Ia portion at the 600 mg dose level. Stable disease was observed in 53 of 217 patients at tiragolumab dose levels of 2 mg (n = 1/8), 8 mg (n = 3/12), 30 mg (n = 2/13), 100 mg (n = 3/8), 400 mg (n = 12/48), 600 mg (n = 25/104), and 1200 mg (n = 7/24) in combination with 1200 mg atezolizumab, including 8 patients who crossed over from the Phase Ia portion of the study (2 patients at 8 mg, 1 patient at 30 mg, 2 patients at 100 mg, and 3 patients at 400 mg).

As of 2 December 2020, safety data were available for 235 safety-evaluable patients in Study GO30103. A total of 42 patients were treated in the Phase Ia portion with tiragolumab as a single agent (2 mg to 1200 mg), while 216 patients were treated in the Phase Ib portion with tiragolumab at dose levels of 2 mg to 1200 mg in combination with atezolizumab at 1200 mg, including 23 patients who crossed over from the Phase Ia portion to the Phase Ib portion.

Tiragolumab was tolerated across all administered dose levels both as a single agent and in combination with atezolizumab. The MTD was not reached, and the maximum administered dose was 1200 mg. No DLTs or clear dose-related trends in the incidence of adverse events were observed. Grade ≥ 3 adverse events, regardless of attribution to the study drug(s), were reported in 16 patients (38.1%) and 113 patients (52.3%) in the Phase Ia and Phase Ib portions, respectively. There were 14 reported deaths in the Phase Ia portion of the study, including 12 deaths due to malignant neoplasm progression, 1 death due to gastrointestinal hemorrhage in the context of progressive disease, and 1 death due to hepatic failure. The death due to hepatic failure was considered by the investigator to be related to study drug. One hundred eighteen deaths were reported in the Phase Ib portion of the study. This included 111 deaths due to progressive disease (31 cases were reported as adverse events during the adverse event reporting period and coded as malignant neoplasm progression or neoplasm malignant), 2 deaths due to pulmonary embolism, 1 death due to esophageal hemorrhage, 1 death due to sepsis, 1 death due to septic shock, 1 death due to COVID-19, and 1 death due to upper airway obstruction. Treatment-related serious

adverse events were reported in 1 patient in the Phase Ia portion (hepatic failure) and in 10 patients (4.6%) in the Phase Ib portion. No patient discontinued study treatment due to adverse events in the Phase Ia portion of Study GO30103. Adverse events leading to treatment discontinuation were reported in 12 patients in the Phase Ib portion of the study, with a Grade 4 cardiac tamponade, a Grade 4 pneumonitis, and one event of Grade 2 arthralgia considered by the investigator to be related to the study drug(s). Adverse events of special interest were reported in 5 patients (11.9%) in the Phase Ia portion and 82 patients (38.0%) in the Phase Ib portion of the study.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile has been observed to be consistent across different solid tumor indications.

A14–2.5.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–positive NSCLC (defined as tumor proportion score [TPS] $\geq 1\%$).

As of the primary clinical cutoff date of 30 June 2019, 135 patients with a PD-L1 TPS $\geq 1\%$ were included in the intent-to-treat (ITT) population and were randomly assigned to receive tiragolumab plus atezolizumab ($n = 67$) or placebo plus atezolizumab ($n = 68$). As of the primary analysis, 47.8% of patients in the tiragolumab plus atezolizumab group versus 27.9% of patients in the placebo plus atezolizumab group were still receiving study treatment in the ITT population. In the TPS $\geq 50\%$ population, 65.5% of patients in the tiragolumab plus atezolizumab group versus 24.1% of patients in the placebo plus atezolizumab group were still receiving study treatment.

In all randomized patients, the combination of tiragolumab plus atezolizumab improved the co-primary endpoints of investigator-assessed ORR and progression-free survival (PFS) compared to placebo plus atezolizumab, with median follow-up of 5.9 months. ORR for tiragolumab plus atezolizumab was 31.3% (95% CI: 19.5, 43.2) compared with placebo plus atezolizumab which was 16.2% (95% CI: 6.7, 25.7). Investigator-assessed median PFS for tiragolumab plus atezolizumab was 5.4 months (95% CI: 4.2 months, not reached) compared with placebo plus atezolizumab which was 3.6 months (95% CI: 2.7 months, 4.4 months), with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.37, 0.90). Investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified $HR = 0.33$; 95% CI: 0.15, 0.72; median PFS not reached vs. 3.9 months, respectively).

As of 2 December 2020, 67 safety-evaluable patients in the tiragolumab plus atezolizumab arm in Study GO40290 were treated with a median of 8 doses of

tiragolumab and atezolizumab (range: 1–38) for a median of 5.0 months (range: 0.03–26.0). In the placebo plus atezolizumab arm, 68 safety-evaluable patients were treated with a median of 5 doses of placebo and atezolizumab (range: 1–37) for a median of 2.8 months (range: 0.03–26.3).

As of 30 June 2020, in the Phase II randomized, placebo-controlled Study GO40290, a total of 135 safety-evaluable patients were administered either tiragolumab (600 mg recommended Phase II/III dose) in combination with atezolizumab or placebo in combination with atezolizumab. The safety profile of tiragolumab plus atezolizumab was similar to that of placebo plus atezolizumab- for all-grade adverse events (98.5% vs. 97.1%), Grade ≥3 adverse events (53.7% vs. 50.0%), serious adverse events (47.8% vs. 39.7%), and adverse events leading to treatment discontinuation (13.4% vs. 11.8%). Adverse events of special interest were reported in 58.2% of patients in the tiragolumab plus atezolizumab arm and in 32.4% of patients in the placebo plus atezolizumab arm. One death due to Epstein-Barr virus (EBV) reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in this study, which was considered by the investigator to be related to the study drugs.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A14–2.6 BENEFIT–RISK ASSESSMENT

The combination of RO7247669 and tiragolumab has not yet been clinically tested. The combination of atezolizumab and tiragolumab has a favorable emergent benefit–risk profile, and early clinical experience with RO7247669 suggest a safety profile comparable to that of atezolizumab and other PD-1/PD-L1 blocking antibodies (Appendix 12). The combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) improved PFS over nivolumab alone as first-line therapy in melanoma patients in the Phase III Relativity-047 study (*Tawbi et al. 2022*), which supports the expected benefit from RO7247669 (anti–PD-1/anti–LAG-3 bispecific therapy) in combination with tiragolumab. Taking into account the potentially synergistic mechanisms of action of RO7247669 and tiragolumab, as well as their manageable and tolerable safety profiles (see Section A14–5), combination treatment with these two agents has promise as a potential therapy in solid tumors such as melanoma.

A minimum of 6 patients in Cohort 2 must complete the initial safety run-in phase. If the combination is determined to be tolerable, enrollment into the preliminary phase may be opened, and the same arm in Cohort 1 can be opened for enrollment (refer to

Sections 3.1.2–3.1.4 for details). Patients in the safety run-in phase will be enrolled and treated in a sequential manner, with at least one week between the first patient and the remaining patients.

The assessment will be based on safety data from a minimum of 6 patients who have received at least one dose of treatment (i.e., one dose of each agent) and who have completed safety follow-up assessments for at least 28 days. If ≥30% of patients experience a treatment-related Grade ≥3 adverse event, enrollment in the safety run-in phase will be stopped. There will be an evaluation of the benefit–risk profile of that treatment by the Sponsor.

After Cohort 2 safety run-in patients have completed 2 cycles of 2100 mg RO7247669 Q3W in combination with 600 mg tiragolumab Q3W in addition to the required safety follow-up of 28 days, and the safety of the combination has been assessed and deemed appropriate, the combination may be investigated in additional Cohort 2 arms. These arms will investigate administration of RO7247669 at doses lower than 2100 mg, e.g., 1200 mg and 600 mg. This will further inform safety, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of RO7247669 in combination with tiragolumab.

If the stopping criteria are not met during the safety run-in phase, enrollment in Cohort 1 will proceed.

In addition, a minimum of 6 patients in Cohort 1 in the RO7247669 *2100 mg* + Tira arm must complete a safety evaluation before additional patients can be enrolled in that arm (refer to Section 3.1.3 for details).

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.3.

A14–3 RATIONALE FOR DOSE AND SCHEDULE FOR RO7247669 *2100 mg* + TIRA ARM

A14–3.1 RATIONALE FOR RO7247669 DOSE AND SCHEDULE

RO7247669 will be administered at a fixed dose of 2100 mg every 3 weeks (Q3W) (2100 mg on Day 1 of each 21-day cycle). A fixed dosing regimen of 2100 mg Q3W was selected based on available clinical pharmacokinetic, efficacy, and safety data from Study NP41300. During the dose-escalation Part A of the study, RO7247669 was well tolerated, and no specific safety concern associated with RO7247669 was identified. No DLT up to the highest dose of 2100 mg Q2W was observed, and no MTD was identified. Anti-tumor activity, as measured by radiographic PRs, was observed starting at a dose of 600 mg Q2W. PK results for RO7247669 were dose linear within the dose

range tested in Study NP41300 and therefore predicted to be in the range of target saturation. Peripheral receptor occupancy was > 90% ~80 days after administration. Therefore, Q3W administration should result in similar receptor occupancy to Q2W on treatment. A Q3W regimen for RO7247669 is also more convenient when it is administered with tiragolumab, which is administered Q3W.

In addition, RO7247669 was well tolerated in both the dose-range finding studies and Good Laboratory Practice (GLP) monkey toxicology studies up to the highest dose evaluated (100 mg/kg). Toxicology findings were consistent with the findings in cynomolgus monkey studies of marketed CPIs.

The supporting data for the selected dose can be found in the current RO7247669 Investigator's Brochure.

A14–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle).

The fixed dose of 600 mg IV Q3W was selected on the basis of available clinical pharmacokinetic, efficacy, and safety data from the combined Phase Ia/Phase Ib Study GO30103 with single-agent tiragolumab or tiragolumab in combination with atezolizumab. In the Phase Ia portion of the study with tiragolumab as a single agent, the MTD was not reached, and no DLTs were observed during dose-escalation. As of the clinical cutoff date, anti-drug antibodies (ADAs) to tiragolumab were rare in the Phase Ia or Phase Ib portions across all dose levels. Complete occupancy of peripheral TIGIT receptors on $CD4^+$, $CD8^+$, and NK cells was observed beginning at 30 mg of tiragolumab in both the Phase Ia and Phase Ib portions of the study and remained sustained at all higher doses (unpublished Roche data on file).

Prolonged stable disease was observed in patients in the Phase Ia portion of the study at tiragolumab doses beginning at 400 mg. In the Phase Ib portion of the study with tiragolumab plus atezolizumab, the MTD was not reached. Anti-tumor activity, as measured by radiographic partial responses, was observed across doses for tiragolumab beginning at 30 mg and ranging up to 600 mg in combination with 1200 mg atezolizumab. Refer to the Tiragolumab Investigator's Brochure for additional details.

A14–4 MATERIALS AND METHODS SPECIFIC TO RO7247669 *2100 mg* + TIRA ARM

A14–4.1 TREATMENT IN RO7247669 *2100 mg* + TIRA ARM

A14–4.1.1 Formulation, Packaging, and Handling

A14–4.1.1.1 RO7247669

The RO7247669 drug product will be supplied by the Sponsor as a 50 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of RO7247669, refer to the pharmacy manual and the RO7247669 Investigator's Brochure.

A14–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor as a 60 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of tiragolumab, refer to the pharmacy manual and the Tiragolumab Investigator's Brochure.

A14–4.1.2 Dosage, Administration, and Compliance

Patients in the RO7247669 plus tiragolumab (RO7247669 + Tira *2100 mg*) arm will receive treatment as outlined in Table A14-1. Patients in Cohort 1 will receive treatment for 2 cycles (6 weeks) until surgery, or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details).

Patients in Cohort 2 will receive treatment 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 (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization (Cohort 1) or enrollment (Cohort 2).

Table A14-1 Treatment Regimen for RO7247669 *2100 mg* + Tira Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• RO7247669 2100 mg IV on Day 1 of each cycle [a] • Tiragolumab 600 mg IV on Day 1 of each cycle

Tira = tiragolumab.

[a] After the safety run-in has been completed, the Sponsor may explore lower doses (e.g., 1200 mg and 600 mg).

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.
No safety data related to overdosing of RO7247669 or tiragolumab are available to date.

A14–4.1.2.1 RO7247669

RO7247669 will be administered by IV infusion at a fixed dose of 2100 mg on Day 1 of each 21-day cycle.

Administration of RO7247669 will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8.
RO7247669 infusions will be administered per the instructions outlined in Table A14-2.

Table A14-2 Administration of First, Second, and Subsequent RO7247669 Infusions

First and Second Infusion	Subsequent Infusions
• No premedication is permitted prior to the first RO7247669 infusion. • Vital signs (respiratory rate, pulse rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • For the first infusion, RO7247669 should be infused over 60 (±10) minutes. • After the infusion of RO7247669, the patient begins a 60-minute observation period. • For the second infusion, RO7247669 should be infused over 30 (±10) minutes if the first infusion was tolerated without an IRR. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities. • 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 should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • RO77247669 should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR. • If the patient tolerated the previous infusion of RO77247669 well without infusion-associated adverse events, the observation period may be reduced to 30 minutes. • If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.

eCRF = electronic Case Report Form; IRR = infusion-related reaction.

For patients who experience a Grade ≥ 2 infusion-related reaction (IRR), premedication with paracetamol 500–1000 mg orally [PO] or IV and diphenhydramine 25–50 mg PO or IV (or an alternative histamine $H_{1/2}$ antagonist at an adequate dose) is required prior to subsequent infusions. In case of Grade 3 or 4 IRRs related to study treatment, the patient should be permanently discontinued from the study treatment.

Guidelines for medical management of IRRs for RO7247669 are provided in Section A14–5.1.2.1.

No dose modification for RO7247669 is allowed. However, based on emerging safety and efficacy data, the Sponsor may explore lower doses (e.g., 1200 mg and 600 mg). Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4.2 and Appendix 9. RO7247669 treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of

treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in Table A14-3.

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. Tiragolumab infusions will be administered per the instructions outlined in Table A14-3.

Table A14-3 Administration of First and Subsequent Tiragolumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the tiragolumab infusion. • Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF. • Tiragolumab should be infused over 60 (±15) minutes. • After the infusion of tiragolumab, the patient begins a 60-minute observation period. • Record vital signs on the eCRF every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients will be informed about the possibility of delayed postinfusion symptoms and will be instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an IRR with the first 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 and recorded on the eCRF. • Tiragolumab 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 infusion-related reaction with the previous infusion. • Patients should be observed for 30 minutes after completion of the tiragolumab infusion if the previous infusion was tolerated without an IRR, or for 60 minutes after completion of the tiragolumab infusion if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded on the eCRF every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.

eCRF = electronic Case Report Form; IRR = infusion-related reaction.

Guidelines for medical management of IRRs for tiragolumab are provided in Table A14-4.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.4.2. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A14–4.2 CONCOMITANT THERAPY FOR RO7247669 *2100 mg* + TIRA ARM

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

A14–4.2.1 Permitted Therapy for RO7247669 *2100 mg* + Tira Arm

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

- Oral contraceptives with a failure rate of $< 1\%$ per year
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section A14–4.2.4)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease (COPD) or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency. Other use of corticosteroids may be permitted at the investigator's discretion. The Medical Monitor is available to advise as needed
- Local therapy (e.g., surgery other than complete lymph node dissection [CLND] that is not considered to be related to melanoma)

A14–4.2.2 Additional Permitted Therapy for RO7247669 *2100 mg* + Tira Arm in Cohort 2

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

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with tiragolumab may be continued during palliative radiotherapy.

Treatment with RO7247669 may be continued during palliative radiotherapy with one exception: palliative radiotherapy is not permitted on days when RO7247669 is administered.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

  Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent RO7247669 and tiragolumab 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 as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; refer to Appendix 8 for details).

A14–4.2.3 Cautionary Therapy for RO7247669 *2100 mg* + Tira Arm

A14–4.2.3.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with RO7247669 and/or tiragolumab. 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 RO7247669 and/or tiragolumab therapy (refer to Appendix 9 for details).

A14–4.2.3.2 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 A14–4.2.3) may be used during the study at the discretion of the investigator.

A14–4.2.4 Prohibited Therapy for RO7247669 $2100\ mg+$Tira Arm

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

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.4), and during study treatment until surgery, or unacceptable toxicity (Cohort 1), or until disease progression is documented and the patient has discontinued study treatment (Cohort 2), with the exception of palliative radiotherapy (see Section A14–4.2.1 for details).
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with RO7247669 and/or tiragolumab, and for 4 months after the last dose of RO7247669 and/or tiragolumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with RO7247669 and/or tiragolumab.

A14–4.3 CONTRACEPTION REQUIREMENTS FOR RO7247669 $2100\ mg+$TIRA ARM

Contraception requirements for women and men in the RO7247669 $2100\ mg+$Tira arm are outlined below:

- 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 4 months after the last dose of RO7247669, and for 90 days after the last dose of tiragolumab.

  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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential who is not pregnant or a pregnant female partner, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period, for 4 months after the last dose of RO7247669, and for 90 days after the last dose of tiragolumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A14–5 ASSESSMENT OF SAFETY FOR RO7247669 *2100 mg* + TIRA ARM

A14–5.1 SAFETY PLAN FOR RO7247669 *2100 mg* + TIRA ARM

The safety plan for patients in this study is based on clinical experience with RO7247669 and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A14–5.1.1, A14–5.1.2, A14–5.1.3, and A14–5.1.4). Guidelines for the management of patients who experience specific adverse events are provided in Section A14–5.1.4 and Appendix 9.

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. Because of the potential for overlapping toxicities for RO7247669 and tiragolumab, special caution will be taken by performing a planned safety run-in for patients randomized to this arm in Cohort 2, and a planned safety evaluation phase in Cohort 1 (see Section 3.1.4).

Administration of RO7247669 and tiragolumab 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. Adverse events will be reported as described in Sections 5.2–5.6.

A14–5.1.1 Risks Associated with RO7247669

Clinical evaluation of RO7247669 is ongoing, and not all risks are known. As an antagonist of PD-1 and LAG-3, RO7247669 is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Based on the mechanism-of-action of RO7247669, the safety profile is anticipated to be similar to other CPIs. Potential risks associated with RO7247669 include the following: IRRs (including anaphylaxis), immunogenicity, and immune-mediated adverse events. Refer to Section 6 of the RO7247669 Investigator's Brochure for a detailed description of anticipated safety risks for RO7247669.

A14–5.1.1.1 Infusion-Related Reactions and Anaphylaxis

Administration of therapeutic antibodies may cause IRRs, which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion and are predominantly reported following the first infusion. The incidence and severity of IRRs typically decrease with subsequent infusions. Based on in vitro data, the risk of proinflammatory cytokine-mediated IRRs on first administration of RO7247669 as single agent is considered low.

Refer to Section A14–4.1.2 for detailed guidance on administration of RO7247669 in this study. Refer to Appendix 8 for guidance on anaphylaxis precautions and Section A14–5.1.4.3 for guidance on the management of IRRs.

A14–5.1.1.2 Immunogenicity

Administration of therapeutic antibodies may cause the formation of anti-drug antibodies, which may negatively affect the safety of the therapeutic (e.g., allergic reactions, immune complex-mediated diseases).

A14–5.1.1.3 Immune-Mediated Adverse Events

The co-stimulatory action of RO7247669, particularly given the LAG-3 modulation, might bear the risk of exaggerated immune cell activation that may result in the occurrence of

enhanced, untoward, immune-mediated adverse events and increased cytokine-release–mediated toxicities.

Toxicities from PD-1 blocking agents can involve any organ or tissue, although some immune-mediated adverse events occur much more frequently than others. The most frequently occurring immune-mediated adverse events affect skin, colon, endocrine organs, liver, and lungs. Others are very infrequent but may be very serious, even lethal, such as neurological disorders and myocarditis.

The limited data from recent early phase studies showed that anti–LAG-3therapy was generally well tolerated as a monotherapy or in combination with anti-PD-1 therapies, and consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018).

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A14–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Patients with a history of autoimmune disease will be excluded from this study. Please see Section 4.1.2 for details.

A14–5.1.2 Risks Associated with Tiragolumab

Infusion-related reactions and immune-mediated hepatitis are identified risks of tiragolumab. Lymphopenia is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 9 of the protocol and the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks of tiragolumab.

A14–5.1.2.1 Infusion-Related Reactions

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

IRRs have been reported in patients treated with tiragolumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Refer to Section A14–4.1.2 for detailed guidance on administration of tiragolumab in this study. Please see Appendix 8 for guidance on anaphylaxis precautions and Table A14-4 for guidance on the management of IRRs.

A14–5.1.2.2 Immune-Mediated Hepatitis

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors. A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

Refer to Appendix 9 for guidance on the management of immune-mediated hepatitis.

A14–5.1.2.3 Immune-Mediated Adverse Events

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

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

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

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A14–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 9.

A14–5.1.2.4 Lymphopenia

The IgG1 backbone of tiragolumab with intact Fc-effector function may lead to ADCC-mediated reduction in lymphocyte count. Lymphopenia is a potential risk with tiragolumab. Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab.

Patients with a lymphocyte count $< 0.5 \times 10^9$/L (500/μL) will be excluded from the study (see Section 4.1.1), and complete blood counts will be monitored regularly during the study (see Appendix A14–6).

A14–5.1.2.5 Embryofetal Toxicity

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

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

A14–5.1.3 Risks Associated with Combination Use of RO7247669 and Tiragolumab

The blockade of inhibitory checkpoints leads to increase adaptive T-cell immune responses via complementary targets, and the combination targeting multiple checkpoints may be associated with heightened immune-mediated toxicity relative to either agent alone. Such toxicity could manifest as a higher incidence or greater severity of autoimmune inflammation events, or potentially the development of HLH and MAS. The following adverse events are potential overlapping toxicities associated with combination use of RO7247669 plus tiragolumab: IRR and immune-mediated toxicities, (see Appendix 9 for complete list).

A14–5.1.4 Management of Patients Who Experience Specific Adverse Events in the RO7247669 *2100 mg* + Tira Arm

A14–5.1.4.1 Dose Modifications

There will be no dose modifications for RO7247669 or tiragolumab in this study. However, based on emerging safety and efficacy data, the Sponsor may explore lower doses of RO7247669 (e.g., 1200 mg and 600 mg).

A14–5.1.4.2 Treatment Interruption for Toxicities

Treatment with RO7247669 and tiragolumab may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed, if warranted.

For Cohort 1, in the neoadjuvant setting the study treatment is limited to a pre-surgery window of 6 weeks. Treatment during this period should not be interrupted unless a patient experiences toxicity. If toxicity meets criteria for interrupting/withholding RO7247669 and tiragolumab, RO7247669 and tiragolumab should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should only be considered if the benefit/risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

For Cohort 2, if RO7247669 and tiragolumab are withheld for 12 weeks or longer due to toxicity, the patient should be discontinued from RO7247669 and tiragolumab. However, RO7247669 and tiragolumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. RO7247669 and tiragolumab may be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. RO7247669 and tiragolumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) at the discretion of the investigator. The acceptable length of the extended period of time must be must be based on the investigator's benefit–risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

On the basis of the available characterization of mechanism-of-action, tiragolumab may cause adverse events similar to, but independent of, RO7247669. Tiragolumab may also exacerbate the frequency or severity of RO7247669-related adverse events or may have non-overlapping toxicities with RO7247669. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and RO7247669. If RO7247669 is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, RO7247669 should also be withheld or discontinued.

A14–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A14-4 and Appendix 9.

For cases in which management guidelines are not covered in Appendix 9, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A14-4 Guidelines for Management of Patients Who Experience Adverse Events in the RO7247669 *2100 mg* + Tira Arm

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions	
General guidance	• For anaphylaxis precautions, see Appendix 8. • For severe hypersensitivity reactions, permanently discontinue RO7247669 and tiragolumab. • For suspected CRS, see Appendix 9 for guidance on supportive care. • Determine tryptase concentration and IgE titer if clinical presentation of IRR suggests an anaphylactic or hypersensitivity reaction (hives, obstructive shortness of breath, urticaria, other histamine associated symptoms) and/or if the first IRR or CRS (≥ Grade 2) is observed at the second infusion. If tryptase and/or IgE are elevated, collect a second sample for IgE/tryptase analysis at least 48 hours after the onset of the reaction to rule out the possibility of an anaphylactic reaction.

CRS = cytokine-release syndrome; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS = macrophage activation syndrome.

Table A14-4 Guidelines for Management of Patients Who Experience Adverse Events in the RO7247669 *2100 mg* + Tira Arm (cont.)

Event	Action to Be Taken
IRRs, anaphylaxis, and hypersensitivity reactions (cont.)	
IRR to RO7247669 and/or tiragolumab Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR to RO7247669 and/or tiragolumab Grade 2	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs.
IRR to RO7247669 and/or tiragolumab, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue RO7247669 and tiragolumab and contact the Medical Monitor.
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, myositis, HLH, MAS, and systemic immune activation	• Guidelines for the management of these events are provided in Appendix 9.

CRS = cytokine-release syndrome; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS = macrophage activation syndrome.

A14–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE RO7247669 $2100\ mg+$TIRA ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the RO7247669 $2100\ mg+$Tira arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

A14–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE RO7247669 $2100\ mg+$TIRA ARM

A14–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 4 months after the last dose of RO7247669 or within 90 days after the last dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A14–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 4 months after the last dose of RO7247669 or within 90 days after the last dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on

the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A14–5.3.3 Abortions

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

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

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

A14–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

A14–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 1)

Table A14-5 Schedule of Activities for RO7247669 *2100 mg* + Tira Arm (Cohort 1)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
IMP Administration										
RO7247669 administration *(2100 mg)*	A14–4.1.2		x	x						
Tiragolumab administration			x	x						
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [d]	4.5.3		x	x	x		x	x		x
Complete physical examination								x		
Limited physical examination [d]			x	x	x		x			x
Vital signs	4.5.4 and A14–4.1.2		x	x	x		x	x		x
12-Lead ECG [d]	4.5.5		x	x				x		
TTE or MUGA scan	4.5.6							x		

Table A14-5 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 1) (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
		D –28 to D –1	Cycle 1 D1 (≤7D after randomization)	Cycle 2 D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Clinical Assessments (cont.)										
ECOG Performance Status [d]	Appendix 6		x	x	x		x	x		x
Surgery (CLND)	3.1.5, Appendix 4					x				
Tumor response assessments	4.5.7				x				As clinically indicated	
Disease status assessments	4.5.7.2				x			x [e]	x	
Concomitant medications	A14–4.2		x	x	x		x	x		
Adverse events [f]	5.3.1, 5.5.1, and 5.6		x	x	x		x [f]	x [f]	x [f]	x [f]
Clavien-Dindo assessment	4.5.8 and Appendix 5							x		x
Follow-up and anti-cancer treatment	4.6.1								x [g]	
Local Laboratory Assessments										
Hematology	4.5.9.1		x [h]	x [h]	x		x	x		x
Chemistry			x [h]	x [h]	x [i]		x	x		x

Table A14-5 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 1) (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Local Laboratory Assessments (cont.)										
Lipid panel	4.5.9.1				x			x		
Coagulation (INR and aPTT)			x [h]	x [h]	x					
TSH, free T3 (or total T3), free T4			x [h]		x		x	x		x
Cardiac enzymes			x [h]	x [h]	x [j]			x		
C-reactive protein			x [h]	x [h]	x		x	x		x
Pregnancy test			x [h]	x [h]	x		x	x		x [k]
Urinalysis			Perform as clinically indicated.					x		
Central Laboratory Assessments										
Serum autoantibody sample	4.5.9.2		Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
PK samples			Refer to Section A14–7.							
ADA samples			Refer to Section A14–7.							

Table A14-5 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 1) (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+ 1D)	Wk 6 (≤8D to surgery)	Wk 7 (± 7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Central Laboratory Assessments (cont.)										
Blood and plasma samples for biomarkers	4.5.9.2		Refer to Section A14–7.						x (only if onsite)	Refer to Section A14–7.
Pre-dose tumor biopsy				x [l]						
Resected tissue						x				
Tumor biopsy (optional)	4.5.11		Perform at the time of unacceptable toxicity, loss of clinical benefit, relapse, or at any other time if deemed clinically feasible by the investigator.							

ADA = anti-drug antibody; CLND = complete lymph node dissection; Comp. = completion; CT = computed tomography; D = day; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; M = month; MUGA = multiple-gated acquisition; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; Wk = week.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.

[c] Patients who proceed to surgery will have the surgery follow-up 6 months after surgery.

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] The disease status assessments at Week 13 should include a mandatory CT scan.

Table A14-5 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 1) (cont.)

[f] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.

[g] Patients who complete the treatment period, regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first long-term follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first long-term follow-up visit 3 months after the final dose of study treatment. Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[h] Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[i] At the pre-surgery visit, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be included in the chemistry panel.

[j] This is only applicable if elevated levels of cardiac enzymes were detected in previous assessments.

[k] If periods are missed or delayed before the 6-month follow-up visit, pregnancy testing should be repeated. This test can be performed by a local gynecologist.

[l] The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.

A14–7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 1)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to first infusion (−6 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
	30 (±10) minutes after the end of tiragolumab infusion	• Tiragolumab PK (serum)
	30 (±10) minutes after the end of RO7247669 infusion	• RO7247669 PK (serum)
Day 1 of Cycle 2	Prior to infusion (−6 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
	30 (±10) minutes after the end of RO7247669 infusion	• RO7247669 PK (serum)
Surgery CLND Week 7	Prior to surgery (−24 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
Post-surgery Week 10 [a]	At visit	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
Treatment completion/ discontinuation Week 13	At visit	• RO7247669 ADA (serum) • RO7247669 PK (serum) • Biomarkers (blood, plasma)
Long-term follow-up Every 3 months (±7 days) [b]	At visit [b]	• Biomarkers (blood, plasma)
Surgery follow-up 6 months after surgery (±7 days)	At visit	• RO7247669 ADA (serum) • RO7247669 PK (serum) • Biomarkers (blood, plasma)

ADA = anti-drug antibody; CLND = complete lymph node dissection; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Week 10 biomarker samples must be obtained ≥ 20 days post-surgery.

[b] To be collected if visit is conducted on site.

A14–8 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 2)

Table A14-6 Schedule of Activities for RO7247669 *2100 mg* + Tira Arm (Cohort 2)

Assessments/Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)						Treatment Discon. [b]	Follow-Up
			Cycle 1			Cycle 2		Cycle ≥3		
		D –28 to D –1	D1 (≤ 7D after enrollment)	D8 (±1D)	D15 (±3D)	D1 (±3D)	D8 (–1D/+2D)	D1 (±3D)		Every 3M (±7D)
IMP Administration										
RO7247669 administration *(2100 mg)*	A14–4.1.2		x			x		x		
Tiragolumab administration			x			x		x		
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [c]	4.5.3		x	x		x		x	x	
Complete physical examination									x	
Limited physical examination [c]			x	x		x		x		
Vital signs	4.5.4 and A14–4.1.2		x	x		x		x	x	
12-lead ECG [c]	4.5.5		x			x		x	x	
TTE or MUGA scan	4.5.6		Perform as clinically indicated.							

TABLE A14-6 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 2) (cont.)

Assessments/Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)							Follow-Up
			Cycle 1			Cycle 2		Cycle ≥3		
		D –28 to D –1	D1 (≤ 7D after enrollment)	D8 (±1D)	D15 (±3D)	D1 (±3D)	D8 (–1D/+2D)	D1 (±3D)	Treatment Discon. [b]	Every 3M (±7D)
Clinical Assessments (cont'd)										
ECOG Performance Status [c]	Appendix 6		x			x		x	x	
Tumor response assessments	4.5.7		x							
Concomitant medications	A14–4.2		x	x		x		x	x	
Adverse events [d]	5.3.1, 5.5.1, and 5.6		x	x		x		x [d]	x [d]	x [d]
Follow-up and anti-cancer treatment	4.6.1									x
Local Laboratory Assessments										
Hematology	4.5.9.1		x [e]	x		x [e]		x [e]	x	
Chemistry			x [e]	x		x [e]		x [e]	x	
Coagulation (INR and aPTT)			x [e]			x [e]		x [e]	x	
TSH, free T3 (or total T3), free T4			x [f]						x	
Cardiac enzymes			x [e]	x		x [e]		x [e]	x	
C-reactive protein			x [e]			x [e]		x [e]	x	

TABLE A14-6 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 2) (cont.)

Assessments/Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)						Treatment Discon. [b]	Follow-Up
			Cycle 1			Cycle 2		Cycle ≥3		
		D –28 to D –1	D1 (≤ 7D after enrollment)	D8 (±1D)	D15 (±3D)	D1 (±3D)	D8 (–1D/+2D)	D1 (±3D)		Every 3M (±7D)
Local Laboratory Assessments (cont'd)										
Pregnancy test	4.5.9.1		x [e]			x [e]		x [e]	x	x
Urinalysis			Perform as clinically indicated.							
Viral serology			Perform as clinically indicated.							
Central Laboratory Assessments										
Serum autoantibody sample	4.5.9.2		Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
ADA samples	4.5.9.2 and A14–9		x			x		x	x	
PK samples			x	x	x	x		x	x	
Blood and plasma samples for biomarkers			x	x	x	x	x	x	x	
Pre-dose tumor biopsy							x			
Tumor biopsy (optional)	4.5.11		Perform at the time of unacceptable toxicity, loss of clinical benefit, or at any other time if deemed clinically feasible by the investigator.							

TABLE A14-6 SCHEDULE OF ACTIVITIES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 2) (cont.)

ADA = anti-drug antibody; D = day; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; HBcAb = hepatitis core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IMP = investigational medicinal product; M = month; MUGA = multiple-gated acquisition; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; Wk = week.

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

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the final dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.2 for details) may be used as the treatment discontinuation visit. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[c] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[d] After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). *For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6.* The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.

[e] Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[f] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every 3 cycles thereafter (i.e., Cycles 4, 7, 10, etc.).

A14–9 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 2)

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to first infusion (–6 hr to 0 hr)	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Tiragolumab PK (serum) • Tiragolumab ADA (serum) • Biomarkers (blood, plasma)
	30 (±10) minutes after the end of tiragolumab infusion	• Tiragolumab PK (serum)
	30 (±10) minutes after the end of RO7247669 infusion	• RO7247669 PK (serum)
Day 8 of Cycle 1	At visit (±24 hr)	• RO7247669 PK (serum) • Biomarkers (blood, plasma)
Day 15 of Cycle 1	At visit (±72 hr)	• RO7247669 PK (serum) • Biomarkers (blood, plasma)
Day 1 of Cycle 2	Prior to infusion (–6 hr to 0 hr)	• Tiragolumab PK (serum) • Tiragolumab ADA (serum) • RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
	30 (±10) minutes after the end of RO7247669 infusion	• RO7247669 PK (serum)
Day 8 of Cycle 2	At visit (±24 hr)	• Biomarkers (blood, plasma)
Day 1 of Cycles 3 and 4	Prior to infusion (–6 hr to 0 hr)	• Tiragolumab PK (serum) • Tiragolumab ADA (serum) • RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
	End of RO7247669 infusion	• RO7247669 PK (serum)

ADA = anti-drug antibody; CLND = complete lymph node dissection; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

A14-9 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 *2100 mg* + TIRA ARM (COHORT 2) (cont.)

Visit	Time	Sample Type
Day 1 of Cycles 8, 12, and 16	Prior to infusion (−6 hr to 0 hr)	• Tiragolumab PK (serum) • Tiragolumab ADA (serum) • RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• RO7247669 PK (serum) • RO7247669 ADA (serum) • Biomarkers (blood, plasma)

ADA = anti-drug antibody; CLND = complete lymph node dissection; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

A14–10 REFERENCES

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Appendix 15
Study Details Specific to RO7247669 600 mg Arm

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A15–1 BACKGROUND ON RO7247669 600 mg ARM

RO7247669 is a novel, Fc-silent IgG1-based bispecific antibody (bsAb) in 1+1 format that incorporates monovalent binding to two immune checkpoint proteins: PD-1 and LAG-3. RO7247669 is designed to target dysfunctional tumor antigen-specific T-lymphocytes expressing PD-1 and LAG-3 to establish or re-establish an effective anti-tumor immune response in cancer patients. This may result in improved therapeutic responses over currently available therapies. In addition, RO7247669 is engineered to prevent binding to Fc gamma receptors, thus potentially avoiding tumor-associated macrophage resistance mechanisms. Such mechanisms have been observed with IgG4-based anti–PD-1 antibodies, such as pembrolizumab and nivolumab (Arlauckas et al. 2017). Clinical evaluation of RO7247669 is ongoing in a first-in-human, dose-finding study (NP41300) as a single agent in cancer patients with and without prior checkpoint inhibitor (CPI) exposure.

Refer to the RO7247669 Investigator's Brochure for details on nonclinical and other planned and ongoing clinical studies.

A15–2 RATIONALE FOR RO7247669 600 mg ARM

A15–2.1 TARGETING THE PD-1 AND LAG-3 ANTIGENS

Cancer immunotherapy agents, particularly immune CPIs, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, additional treatment options targeting immune checkpoints are needed because the majority of patients eventually progress after an initial response or else fail to respond to the PD-1/PD-L1 checkpoint blockade. This is believed to be due mainly to primary or secondary resistance mechanisms, to immunosuppressive activity of myeloid-derived suppressor cells, and/or to T-regulatory cells (Sharma et al. 2017).

To overcome resistance mechanisms, additional treatment options and multiple combinations with anti–PD-L1 therapy are being assessed. One potential reason for resistance to anti–PD-L1 therapy is the upregulation of alternative immune checkpoints with non-redundant regulatory functions (Sharma et al. 2017). LAG-3 is one such alternative immune checkpoint. LAG-3 is a member of the Ig superfamily that is structurally similar to CD4. LAG-3 is expressed on activated effector T cells and is constitutively expressed on T-regulatory cells and natural killer (NK) cells. The expression of both PD-1 and LAG-3 on tumor infiltrating lymphocytes (TILs) correlates with the degree of impairment of effector functions, which is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015). Hence, LAG-3 is a marker of T-cell dysfunctionality. LAG-3 also regulates T-cell functions, presumably including the function of T-regulatory cells. In chronic infections and cancer, LAG-3, together with PD-1, contributes to T-cell–acquired

dysfunctionality and to the inability of T cells to mount an effective/protective immune response upon interaction with the LAG-3 ligand, MHC-II.

The interaction of LAG-3 with MHC-II inhibits T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production (Goldberg and Drake 2011). The effect of LAG-3 expression on T-regulatory cells is controversial. An early report concluded that LAG-3 promotes T-regulatory cell-mediated immune suppression (Camisaschi et al. 2010). However, a more recent report from the same authors found that LAG-3 limits T-regulatory cell-mediated immune suppression (Zhang et al. 2017).

Expression of LAG-3 has been reported across various tumor types, including breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), melanoma, renal cell cancer (RCC), prostate cancer, and hepatocellular carcinoma (HCC). In patients with these tumor types, LAG-3 is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norstrom et al. 2016). Clinical evaluation of anti–LAG-3 agents, as single agents and in combination with other CPIs, is ongoing in several early phase studies in patients with advanced solid tumors (Long et al. 2018). Preliminary data demonstrate that anti–LAG-3 therapy is well tolerated, both as single agents and in combination with anti–PD-1 therapies, and the safety profiles are consistent with those of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). RO7247669 may therefore be a therapeutic option for patients with melanoma.

Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory immune checkpoints on the surface of effector T cells. LAG-3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG-3 enhances $CD8^+$ T-cell effector function and potentiates anti-tumor immunity in nonclinical models. Blockade of these two receptors in mice with colon, fibrosarcoma, or ovarian tumors resulted in tumor remission in approximately 80% of animals, compared with remission in 10% to 40% with blockade of either receptor using a single agent (Woo et al. 2012; Huang et al. 2015). TILs from patients with ovarian cancer showed that antigen-specific $CD8^+$ T cells co-expressing PD-1 and LAG-3 exhibited greater impairment in their ability to respond to cognate antigen stimulation compared with $CD8^+$ T cells that expressed one checkpoint molecule (Matsuzaki et al. 2010). In patients with NSCLC, overexpression of LAG-3 on TILs correlated with PD-1/PD-L1 expression and was linked to higher risk of recurrence and poor survival outcomes (He et al. 2017).

A15–2.2 CLINICAL STUDIES OF AGENTS TARGETING THE PD-1 AND LAG-3 PATHWAYS

Clinical data are available for early- and late-phase studies that evaluated the safety, tolerability, and preliminary anti-tumor activity of agents that target both the PD-1

and LAG-3 pathways. Evidence of clinical activity has been reported in some of these studies. Overall, adverse events have been manageable to date, and the safety profiles appear similar to those of single-agent CPIs.

An ongoing Phase I/IIa study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody nivolumab and the anti–LAG-3 monoclonal antibody relatlimab in patients with advanced solid tumors. Preliminary data suggest that the combination of nivolumab and relatlimab may have an increased benefit compared with single-agent anti–PD-1. In a cohort of patients who had advanced melanoma who were previously treated with anti–PD-1/PD-L1 agents, the ORR was 11.5% (n=61) with a disease control rate (DCR) of 49%. The anti–PD-1/PD-L1 treatment combination had an acceptable safety profile that was similar to the safety profile of nivolumab monotherapy (Ascierto et al. 2017).

Relativity-047 is a Phase III study evaluating the combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) versus nivolumab alone in patients with untreated advanced melanoma. This study demonstrated that nivolumab and relatlimab improved progression-free survival (PFS=10.1 months) over nivolumab (PFS=4.6 months). The incidence of Grade 3 or 4 treatment-related adverse events was 18.9% in patients that received the nivolumab and relatlimab combination and 9.7% in patients that received nivolumab alone (Tawbi et al. 2022).

An ongoing Phase I/II study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody spartalizumab and the anti–LAG-3 monoclonal antibody LAG525 in patients with advanced solid tumors. Preliminary anti-tumor activity was observed during the Phase I dose-escalation portion of the study, including durable responses in 2 of 5 patients with triple-negative breast cancer (TNBC) and in 2 of 8 patients with mesothelioma. Analyses of tumor biopsies from the TNBC cohort also showed a trend of conversion from an immune-cold to an immune-activated phenotype. Common adverse events, i.e., adverse events reported in≥10% of patients, included fatigue (18%), diarrhea (15%), and nausea (12%). The incidence of Grade 3–4 adverse events was 8% for both the combination (n=121) and monotherapy (n=119) arms (Hong et al. 2018).

An ongoing, first-in-human, dose-escalation, and dose-expansion Phase I study is evaluating the safety, tolerability, and clinical activity of the anti–PD-1/LAG-3 dual affinity re-targeting protein (DART®) bsAb MGD013 in patients with advanced solid tumors and hematologic malignancies. During the dose-escalation phase of the study, the maximum tolerated dose (MTD) was not reached, and the safety profile was consistent with anti–PD-1 monotherapy. During the dose-expansion phase, anti-tumor activity was observed in patients with TNBC (n=23; ORR, 4.3%; DCR, 39.1%), CPI-naive NSCLC (n=14; ORR, 14.3%; DCR, 64.3%), and epithelial ovarian cancer

(n=23; ORR, 8.7%; DCR, 52.2%). Expression of LAG-3 and an IFN-γ gene signature at baseline was associated with objective responses (Luke et al. 2020). Clinical studies evaluating MGD013 as monotherapy and in combination with anti–HER-2 agents are ongoing.

A15–2.2.1 Study NP41300

Study NP41300 is an ongoing, first-in-human, dose-escalation, dose-expansion Phase I study to evaluate the safety, pharmacokinetics, and therapeutic activity of the anti–PD-1/LAG-3 bsAb RO7247669 as a single agent in patients with locally advanced and/or metastatic solid tumors. Part A, the dose-escalation phase of the study, is designed to determine the MTD and/or recommended dose for expansion (RDE) of RO7247669. Part B of the study is designed to evaluate the anti-tumor activity of RO7247669 at the MTD or RDE in tumor-specific expansion cohorts.

As of the data cutoff date, 1 March 2022, RO7247669 was well tolerated in the patients enrolled in Part A of the study. No unexpected safety concern associated with RO7247669 was identified. No dose-limiting toxicities (DLTs) were observed up to the maximum dose tested (2100 mg every 2 weeks [Q2W]), and no MTD was identified. The maximum dose of 2100 mg was determined to be the recommended dose for the dose-expansion phase (Part B) of Study NP41300. As of the data cutoff of 1 March 2022, 83 patients received treatment in Part B.

As of the data cut-off date of 1 March 2022, the DCR in Part A of the study was 51.4% (18 of 35 evaluable patients), and the ORR was 17.1% (6 of 35 patients). Among the patients treated with the proposed dose of 2100 mg Q2W, 7 of 13 patients had a best response of stable disease or better (DCR=53.8%), including 4 patients with a confirmed partial response (PR; ORR=30.8%). Besides the confirmed partial responses (cPR) observed at the RDE, there were 2 cPRs at the 600 mg dose level (ORR =50.0%).

As of the data cut-off date, 1 March 2022, in Part B of the study the DCR was 48.3% (28 of 58 patients) and the ORR was 5.2% (3 of 58 patients) among patients of the study treated at the RDE of 2100 mq Q2W (Cohorts B1, B2, and B3). Within patients treated with 600 mg Q2W (cohort B5), the DCR was 40% (4 of 10 patients), and the ORR was 10% (1 of 10 patients). Among patients treated with 600 mg Q3W, the DCR was 28.6% (2 of 7 patients) and the ORR was 14.3% (1 of 7 patients).

Refer to the RO7247669 Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A15–2.3 BENEFIT–RISK ASSESSMENT

Despite limited clinical experience with RO7247669, the clinical efficacy and safety profiles of anti–PD-1/PD-L1 monoclonal antibodies are well characterized and

established. In recent years, four checkpoint inhibitors, namely pembrolizumab, nivolumab, ipilimumab, and relatlimab have been approved by the FDA for the treatment of unresectable or advanced melanoma.

The co-stimulatory action of RO7247669 on PD-1 and LAG-3 receptors may result in enhanced and/or more durable responses than either therapy modality alone. However, there may be a risk of exaggerated immune cell activation, particularly given the LAG-3 modulation of the immune response. Preliminary data from Study NP41300, and recent early phase studies of anti–LAG-3 antibodies showed that anti–LAG-3 therapy was generally well tolerated as monotherapy or in combination with anti–PD-1 therapies, and that it had a safety profile consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). The safety and efficacy of CPIs is established in the adjuvant setting, and CPIs are now being actively evaluated as neoadjuvant treatment and show promising early results (Herrscher and Robert 2020).

For the evaluation of the impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment, please refer to Section 1.3.

A15–3 RATIONALE FOR DOSE AND SCHEDULE FOR RO7247669 600 mg ARM

A15–3.1 RATIONALE FOR RO7247669 DOSE AND SCHEDULE

RO7247669 will be administered at a fixed dose of 600 mg every 3 weeks (Q3W) (600 mg on Day 1 of each 21-day cycle). A fixed dosing regimen of 600 mg Q3W was selected based on available clinical pharmacokinetic, efficacy, and safety data from Study NP41300. During the dose-escalation Part A of the study, RO7247669 was well tolerated, and no specific safety concern associated with RO7247669 was identified. No DLT up to the highest dose of 2100 mg Q2W was observed, and no MTD was identified. Anti-tumor activity, as measured by radiographic partial responses, was observed starting at a dose of 600 mg Q2W. The pharmacokinetics of RO7247669 were dose linear within the dose range tested in Study NP41300. Greater than 90% occupancy of peripheral PD-1 and LAG3 receptors on $CD8^+$ cells was observed at 50 mg of RO7247669 and was sustained at all higher doses (unpublished Roche data on file). Further modelling of intratumoral PD-1 and LAG3 target engagement using estimated target properties was performed. A dose regimen of 600 mg Q3W was selected for this study (BO43328) to ensure that the majority of participants have at least 90% PD-1 and LAG3 tumor receptor saturation by RO7247669, irrespective of intratumoral spatial heterogeneity and intersubject variability. A dose greater than 600 mg would not be expected to result in further clinical activity.

In Study NP41300, persistent anti-drug antibodies (ADAs) formed in approximately 18% of the total population and the incidence rate was not dose dependent. An impact

on exposure was observed at 50, 150 and 300 mg; therefore, 600 mg will be used in Study BO43328 to minimize the risk of a loss in exposure due to ADAs.

In addition, RO7247669 was well tolerated in both the dose range finding studies and Good Laboratory Practice (GLP) monkey toxicology studies up to the highest dose evaluated (100 mg/kg). Toxicology findings were consistent with the findings in cynomolgus monkey studies of marketed CPIs. In the current study (BO43328), the safety evaluation of the first 6 patients enrolled in the RO7247669 2100 mg arm was completed with no safety signals identified.

The supporting data for the selected dose can be found in the RO7247669 Investigator's Brochure.

A15–4 MATERIALS AND METHODS SPECIFIC TO RO7247669 600 mg ARM

A15–4.1 TREATMENT IN RO7247669 600 mg ARM

A15–4.1.1 Formulation, Packaging, and Handling

The RO7247669 drug product will be supplied by the Sponsor as a 50 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of RO7247669, refer to the pharmacy manual and the RO7247669 Investigator's Brochure.

A15–4.1.2 Dosage, Administration, and Compliance

Patients in the RO7247669 600 mg arm will receive treatment for 2 cycles (6 weeks) as outlined in Table A15-1 until surgery, or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A15-1 Treatment Regimen for RO7247669 600 mg Arm

Cycle Length	Dose, Route, and Regimen
21 days	• RO7247669 600 mg by IV infusion on Day 1 of each cycle

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.
No safety data related to overdosing of RO7247669 are available to date.

RO7247669 will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle.

Administration of RO7247669 will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. RO7247669 infusions will be administered per the instructions outlined in Table A15-2.

Table A15-2 Administration of First and Second RO7247669 Infusions

First Infusion	*Second Infusion*
• *No premedication is permitted prior to the first RO7247669 infusion.* • *Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF.* • *RO7247669 should be infused over 60 (±10) minutes.* • *After the infusion of RO7247669, the patient begins a 60-minute observation period.* • *If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.* • *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 the first 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 and recorded on the eCRF.* • *RO77247669 should be infused over 30 (±10) minutes if the first infusion was tolerated without an IRR, followed by a 30-minute observation period.* • *If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.*

eCRF=electronic Case Report Form; IRR=infusion-related reaction.

For patients who experience a Grade 2 infusion-related reaction (IRR), premedication with paracetamol 500–1000 mg orally [PO] or IV and diphenhydramine 25–50 mg PO or IV (or an alternative histamine $H_{1/2}$ antagonist at an adequate dose) is required prior to subsequent infusions. In case of Grade 3 or 4 IRRs related to study treatment, the patient should be permanently discontinued from the study treatment.

Guidelines for medical management of IRRs for RO7247669 are provided in Section A15–5.1.2.3.

No dose modification for RO7247669 is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A15–5.1.2.2.

A15–4.2 CONCOMITANT THERAPY FOR RO7247669 600 mg ARM

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

A15–4.2.1 Permitted Therapy for RO7247669 600 mg Arm

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

- *Oral contraceptives with a failure rate of<1% per year*
- *Hormone-replacement therapy*
- *Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)*
- *Vaccinations (such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section A15–4.2.3)
- *Megestrol acetate administered as an appetite stimulant*
- *Mineralocorticoids (e.g., fludrocortisone)*
- *Corticosteroids administered for chronic obstructive pulmonary disease or asthma*
- *Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency. Other use of corticosteroids may be at the investigator's discretion. The Medical Monitor is available to advise as needed.*
- *Local therapy (e.g., surgery other than complete lymph node dissection [CLND] that is not considered to be related to melanoma)*

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second RO7247669 infusion 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 as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or $H_{1/2}$-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should

be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 8).

A15–4.2.2 Cautionary Therapy for RO7247669 600 mg Arm

A15–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor (TNF)-α inhibitors may attenuate potential beneficial immunologic effects of treatment with RO7247669. 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 RO7247669 therapy (see Appendix 9 for details).

A15–4.2.2.2 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 A15–4.2.3) may be used during the study at the discretion of the investigator.

A15–4.2.3 Prohibited Therapy for RO7247669 600 mg Arm

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

- *Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until surgery or, if earlier, disease progression is documented and the patient has discontinued study treatment.*
- *Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.*
- *Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with RO7247669, and for 4 months after the final dose of RO7247669.*

- *Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with RO7247669.*

A15–4.3 CONTRACEPTION REQUIREMENTS FOR RO7247669 600 mg ARM

Contraception requirements for women and men in the RO7247669 600 mg arm are outlined below:

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

  Women must remain abstinent or use contraceptive methods with a failure rate of<1% per year during the treatment period and for 4 months after the final dose of RO7247669.

  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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential who is not pregnant or a pregnant female partner, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of<1% per year during the treatment period, for 4 months after the last dose of RO7247669 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A15–5 ASSESSMENT OF SAFETY FOR RO7247669 600 mg ARM

A15–5.1 SAFETY PLAN FOR RO7247669 600 mg ARM

The safety plan for patients in this study is based on clinical experience with RO7247669 in ongoing studies. The potential safety risks are outlined below (see Section A15–5.1.1). Guidelines for management of patients who experience specific adverse events are provided in Section A15–5.1.2 and Appendix 9.

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 study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A15–5.1.1 Risks Associated with RO7247669

Clinical evaluation of RO7247669 is ongoing, and not all risks are known. As an antagonist of PD-1 and LAG-3, RO7247669 is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Based on the mechanism-of-action of RO7247669, the safety profile is anticipated to be similar to other CPIs. Potential risks associated with RO7247669 include the following: IRRs (including anaphylaxis), immunogenicity, and immune-mediated adverse events. Refer to Section 6 of the RO7247669 Investigator's Brochure for a detailed description of anticipated safety risks for RO7247669.

A15–5.1.1.1 Infusion-Related Reactions and Anaphylaxis

Administration of therapeutic antibodies may cause IRRs, which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion and are predominantly reported following the first infusion. The incidence and severity of IRRs typically decrease with subsequent infusions. Based on in vitro data, the risk of proinflammatory cytokine-mediated IRRs on first administration of RO7247669 as a single agent is considered low.

Refer to Section A15–4.1.2 for detailed guidance on administration of RO7247669 in this study. Refer to Appendix 8 for guidance on anaphylaxis precautions and to Section A15–5.1.2.3 for guidance on the management of IRRs.

A15–5.1.1.2 Immunogenicity

Administration of therapeutic antibodies may cause the formation of anti-drug antibodies, which may negatively affect the safety of the therapeutic (e.g., allergic reactions, immune complex-mediated diseases).

A15–5.1.1.3 Immune-Mediated Adverse Events

The co-stimulatory action of RO7247669, in particular its effects on LAG-3, may lead to an exaggerated risk of immune cell activation that may result in the occurrence of enhanced, untoward, immune-mediated adverse events and increased cytokine release-mediated toxicities.

Toxicities from PD-1 blocking agents can involve any organ or tissue, although some immune-mediated adverse events occur much more frequently than others. The most frequently occurring immune-mediated adverse events affect skin, colon, endocrine organs, liver, and lungs. Others are very infrequent but may be very serious, even lethal, such as neurological disorders and myocarditis.

The limited data from recent early phase studies showed anti–LAG-3 therapy was generally well tolerated as a monotherapy or in combination with anti-PD-1 therapies, and data were consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018).

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A15–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Patients with a history of autoimmune disease will be excluded from this study. Please see Section 4.1.2 for details.

A15–5.1.2 Management of Patients Who Experience Specific Adverse Events in RO7247669 600 mg Arm

A15–5.1.2.1 Dose Modifications

There will be no dose modifications for RO7247669 in this study.

A15–5.1.2.2 Treatment Interruption for Toxicities

RO7247669 treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before RO7247669 can be resumed if warranted. In the

neoadjuvant setting, the study treatment is limited to a pre-surgery window of 6 weeks. Treatment during this period should not be interrupted, unless a patient experiences toxicity. If toxicity meets criteria for interrupting/withholding RO7247669, RO7247669 should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should only be considered if the benefit-risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

A15–5.1.2.3 Management Guidelines for Adverse Events

Guidelines for management of patients who experience specific adverse events are provided in Table A15-3.

Table A15-3 Guidelines for Management of Patients Who Experience Adverse Events in RO7247669 600 mg Arm

Event	*Action to Be Taken*
IRRs, anaphylaxis, and hypersensitivity reactions	
General guidance	• *For anaphylaxis precautions, see Appendix 8.* • *For severe hypersensitivity reactions, permanently discontinue RO7247669.* • *For suspected CRS, see Appendix 9 for guidance on supportive care.* • *Determine tryptase concentration and IgE titer if clinical presentation of IRR suggests an anaphylactic or hypersensitivity reaction (hives, obstructive shortness of breath, urticaria, other histamine associated symptoms) and/or if the first IRR or CRS (≥Grade 2) is observed at the second infusion. If tryptase and/or IgE are elevated, collect a second sample for IgE/tryptase analysis at least 48 hours after the onset of the reaction to rule out the possibility of an anaphylactic reaction.*
IRR to RO7247669, Grade 1 or 2	• *Slow infusion to≤50% or interrupt infusion.* • *Give supportive treatment. Patients should be treated with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, if they have not been administered in the last 4 hours. IV fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice.* • *Upon symptom resolution, infusion may resume (if interrupted) at 50% starting rate. The infusion must remain at the lower rate resulting in symptom resolution for the remainder of the infusion.* • *For Grade 2 IRRs, subsequent doses of RO7247669 should be administered with pre-medication, including acetaminophen/paracetamol and an antihistamine such as diphenhydramine.* • *For Grade 2 wheezing or urticaria, patient must also be pre-medicated prior to subsequent doses (as described above).* • *If symptoms recur with the same or greater severity following the slower or interrupted infusion, the infusion must be stopped immediately. No further RO7247669 will be administered for the cycle.*

CRS=cytokine-release syndrome; GI=gastrointestinal; HLH=hemophagocytic lymphohistiocytosis; IRR=infusion-related reaction; MAS=macrophage activation syndrome.

Table A15-3 Guidelines for Management of Patients Who Experience Adverse Events in RO7247669 600 mg Arm (cont.)

Event	*Action to Be Taken*
IRR to RO7247669, Grade 3–4	• *Discontinue infusion immediately.* • *Give supportive treatment.* • *Permanently discontinue study treatment.*
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, myositis, HLH, MAS, and systemic immune activation	• *Guidelines for the management of these events are provided in Appendix 9.*

CRS=cytokine-release syndrome; GI=gastrointestinal; HLH=hemophagocytic lymphohistiocytosis; IRR=infusion-related reaction; MAS=macrophage activation syndrome.

A15–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR RO7247669 600 mg ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the RO7247669 600 mg arm are as follows:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)*
- *Suspected transmission of an infectious agent by the study treatment, as defined below:*

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A15–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN RO7247669 600 mg ARM

A15–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 4 months after the final dose of RO7247669. 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to

allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A15–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 4 months after the final dose of RO7247669. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A15–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event,

recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

A15–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

A15–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR RO7247669 600 mg ARM

Table A15-4 Schedule of Activities for RO7247669 600 mg Arm

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
		D −28 to D −1	Cycle 1 D1 (≤7D after randomization)	Cycle 2 D1 (+1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
IMP Administration										
RO7247669 administration (600 mg)	A15–4.1.2		x	x						
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [d]	4.5.3		x	x	x		x	x		x
Complete physical examination								x		
Limited physical examination [d]			x	x	x		x			x
Vital signs	4.5.4 and A15–4.1.2		x	x	x		x	x		x
12-Lead ECG [d]	4.5.5		x	x				x		
TTE or MUGA scan	4.5.6							x		

TABLE A15-4 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Clinical Assessments (cont.)										
ECOG Performance Status [d]	Appendix 6		x	x	x		x	x		
Surgery (CLND)	3.1.5, Appendix 4					x				
Tumor response assessments	4.5.7				x				As clinically indicated.	
Disease status assessments	4.5.7.2				x			x [e]	x	
Concomitant medications	A15–4.2		x	x	x		x	x		
Adverse events [f]	5.3.1, 5.5.1, and 5.6		x	x	x		x [f]	x [f]	x [f]	x [f]
Clavien-Dindo assessment	4.5.8 and Appendix 5							x		x
Follow-up and anti-cancer treatment	4.6.1								x [g]	
Local Laboratory Assessments										
Hematology	4.5.9.1		x [h]	x [h]	x		x	x		x
Chemistry			x [h]	x [h]	x [i]		x	x		x

TABLE A15-4 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Local Laboratory Assessments (cont.)										
Lipid panel	4.5.9.1				x			x		
Coagulation (INR and aPTT)			x [h]	x [h]	x					
TSH, free T3 (or total T3), free T4			x [h]		x		x	x		x
Cardiac enzymes			x [h]	x [h]	x [j]			x		
C-reactive protein			x [h]	x [h]	x		x	x		x
Pregnancy test			x [h]	x [h]	x		x	x		x [k]
Urinalysis			Perform as clinically indicated.					x		
Central Laboratory Assessments										
Serum autoantibody sample	4.5.9.2		Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).							
PK samples			Refer to Section A15–7.							
ADA samples			Refer to Section A15–7.							

TABLE A15-4 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg ARM (cont.)

Assessment/ Procedure [a]	*Protocol Section*	*Screening (see Appendix 10)*	*Treatment Cycles (21-Day Cycles)*		*Pre-Surgery*	*Surgery CLND*	*Post-Surgery*	*Treatment Comp./ Discon.* [b]	*Long-Term Follow-Up*	*Surgery Follow-Up* [c]
			Cycle 1	*Cycle 2*						
		D −28 to D −1	*D1 (≤7D after randomization)*	*D1 (+1D)*	*Wk 6 (≤8D to surgery)*	*Wk 7 (±7D)*	*Wk 10 (≥20D after surgery)*	*Wk 13*	*Every 3M (±7D)*	*6M after surgery (±7D)*
Blood and plasma samples for biomarkers	*4.5.9.2*		*Refer to Section A15–7.*						*x (only if onsite)*	*Refer to Section A15–7.*
Pre-dose tumor biopsy				*x* [l]						
Resected tissue						*x*				
Tumor biopsy (optional)	*4.5.11*		*Perform at the time of unacceptable toxicity, loss of clinical benefit, relapse, or at any other time if deemed clinically feasible by the investigator.*							

ADA = anti-drug antibody; CLND = complete lymph node dissection; Comp. = completion; CT = computed tomography; D = day; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; IMP = investigational medicinal product; M = month; MUGA = multiple-gated acquisition; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TTE = transthoracic echocardiogram; Wk = week.

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

[a] *If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.*

[b] *Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.*

[c] *Patients who proceed to surgery will have the surgery follow-up 6 months after surgery.*

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] *The disease status assessments at Week 13 should include a mandatory CT scan.*

TABLE A15-4 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg ARM (cont.)

[f] *After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.*

[g] *Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first long-term follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first long-term follow-up visit 3 months after the final dose of study treatment. Information on long-term follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

[h] *Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.*

[i] *At the pre-surgery visit, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be included in the chemistry panel.*

[j] *This is only applicable if elevated levels of cardiac enzymes were detected in previous assessments.*

[k] *If periods are missed or delayed before the 6-month follow-up visit, pregnancy testing should be repeated. This test can be performed by a local gynecologist.*

[l] *The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.*

A15–7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 600 mg ARM

Visit	*Time*	*Sample Type*
Day 1 of Cycle 1	*Prior to first infusion (–6 hr to 0 hr)*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Biomarkers (blood, plasma)*
	30 (±10) minutes after the end of RO7247669 infusion	• *RO7247669 PK (serum)*
Day 1 of Cycle 2	*Prior to infusion (–6 hr to 0 hr)*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Biomarkers (blood, plasma)*
	30 (±10) minutes after the end of RO7247669 infusion	• *RO7247669 PK (serum)*
Surgery CLND Week 7	*Prior to surgery (–24 hr to 0 hr)*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Biomarkers (blood, plasma)*
Post-surgery Week 10 [a]	*At visit*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Biomarkers (blood, plasma)*
Treatment completion/ discontinuation Week 13	*At visit*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Biomarkers (blood, plasma)*
Long-term follow-up Every 3 months (±7 days) [b]	*At visit*	• *Biomarkers (blood, plasma)*
Surgery follow-up 6 months after surgery (±7 days)	*At visit*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Biomarkers (blood, plasma)*

ADA=anti-drug antibody; CLND=complete lymph node dissection; PK=pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced, or sample collection may cease altogether.

[a] *Week 10 biomarker samples must be obtained ≥20 days post-surgery.*

[b] *To be collected if visit is conducted on site.*

A15–8 REFERENCES

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Appendix 16
Study Details Specific to RO7247669 600 mg+Tira Arm

TABLE OF CONTENTS

A16–1 BACKGROUND ON RO7247669 600 mg+TIRA ARM

A16–1.1 BACKGROUND ON RO7247669

RO7247669 is a novel, Fc-silent IgG1-based bispecific antibody (bsAb) in 1+1 format that incorporates monovalent binding to two immune checkpoint proteins: PD-1 and LAG-3. RO7247669 is designed to target dysfunctional tumor antigen-specific T lymphocytes expressing PD-1 and LAG-3 to establish or re-establish an effective anti-tumor immune response in cancer patients. This may result in improved therapeutic responses over currently available therapies. In addition, RO7247669 is engineered to prevent binding to Fc gamma receptors, thus potentially avoiding tumor-associated macrophage resistance mechanisms. Such mechanisms have been observed with IgG4-based anti–PD-1 antibodies, such as pembrolizumab and nivolumab (Arlauckas et al. 2017). Clinical evaluation of RO7247669 is ongoing in a first-in-human, dose-finding study (Study NP41300), as a single agent in cancer patients with and without prior CPI exposure.

Refer to the RO7247669 Investigator's Brochure for details on nonclinical and other planned and ongoing clinical studies.

A16–1.2 BACKGROUND ON TIRAGOLUMAB

Tiragolumab is a fully human IgG1/kappa monoclonal antibody that binds TIGIT and prevents its interaction with CD155 (also known as poliovirus receptor [PVR]). Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses. This may result in improved meaningful anti-tumor activity when tiragolumab is used in combination with other cancer immunotherapies and administered with chemotherapy. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in cancer patients.

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

A16–2 RATIONALE FOR RO7247669 600 mg+TIRA ARM

A16–2.1 TARGETING THE PD-1 AND LAG-3 ANTIGENS

Cancer immunotherapy agents, particularly immune CPIs, have had a significant impact on the treatment of patients with advanced malignancies in recent years. However, despite the remarkable clinical efficacy of these therapies, additional treatment options targeting immune checkpoints are needed, because the majority of patients eventually progress after an initial response or fail to respond to the PD-1/PD-L1 checkpoint blockade. This is believed to be mainly due to primary or

secondary resistance mechanisms, immunosuppressive activity of myeloid-derived suppressor cells and/or T-regulatory cells (Sharma et al. 2017).

To overcome resistance mechanisms, additional treatment options and multiple combinations with anti–PD-L1 are being assessed. One potential reason for resistance to anti–PD-L1 therapy is the upregulation of alternative immune checkpoints with non-redundant regulatory functions (Sharma et al. 2017). LAG-3 is one such alternative immune checkpoint. Structurally similar to CD4, LAG-3 is a member of the Ig superfamily. LAG-3 is expressed on activated effector T cells and is constitutively expressed on T-regulatory cells and natural killer (NK) cells. The expression of both PD-1 and LAG-3 on tumor infiltrating lymphocytes (TILs) correlates with the degree of impairment of effector functions, which is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015). Hence, LAG-3 is a marker of T-cell dysfunctionality. LAG-3 also regulates T-cell functions, presumably including the function of T-regulatory cells. In chronic infections and cancer, LAG-3, together with PD-1, contributes to T-cell–acquired dysfunctionality and to the inability of T cells to mount an effective/protective immune response upon interaction with the LAG-3 ligand, MHC-II.

The interaction of LAG-3 with MHC-II inhibits T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production (Goldberg and Drake 2011). The effect of LAG-3 expression on T-regulatory cells is controversial. An early report concluded that LAG-3 promotes T-regulatory cell-mediated immune suppression (Camisaschi et al. 2010). However, a more recent report from the same authors found that LAG-3 limits T-regulatory cell-mediated immune suppression (Zhang et al. 2017).

Expression of LAG-3 has been reported across various tumor types, including breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), melanoma, renal cell cancer (RCC), prostate cancer, and hepatocellular carcinoma (HCC). In patients with these tumor types, LAG-3 is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norstrom et al. 2016). Clinical evaluation of anti–LAG-3 agents, as a single-agent and in combination with other CPIs, is ongoing in several early phase studies in patients with advanced solid tumors (Long et al. 2018). Preliminary data demonstrate that anti–LAG-3 therapy is well tolerated, both as a single agent and in combination with anti–PD-1 therapies, and the safety profiles were consistent with those of other CPIs (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018). RO7247669 therefore has the potential to be a therapeutic option for patients with melanoma.

Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory immune checkpoints on the surface of effector T cells. LAG-3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG-3

enhances CD8$^+$ T-cell effector function and potentiates anti-tumor immunity in nonclinical models. Blockade of these two receptors in mice with colon, fibrosarcoma, or ovarian tumors resulted in tumor remission in approximately 80% of animals compared with 10% to 40% with blockade of either receptor using a single agent (Woo et al. 2012; Huang et al. 2015). TILs from patients with ovarian cancer showed that antigen-specific CD8$^+$ T cells co-expressing PD-1 and LAG-3 exhibited greater impairment in their ability to respond to cognate antigen stimulation compared with CD8$^+$T cells that expressed one checkpoint molecule (Matsuzaki et al. 2010). In patients with NSCLC, overexpression of LAG-3 on TILs correlated with PD-1/PD-L1 expression and was linked to higher risk of recurrence and poor survival outcomes (He et al. 2017).

A16–2.2 THE TIGIT PATHWAY

TIGIT is an immune inhibitory receptor that is a member of the immunoglobulin superfamily (Yu et al. 2009). TIGIT is expressed on the surface of activated T cell and NK cell subsets and interacts with high affinity with CD155 (also known as 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 concordantly expressed with other checkpoint immune-receptors such as PD-1 on the surface of T cells, and is associated with impaired T-cell function and anti-tumor immunity (Johnston et al. 2014; Manieri et al. 2017). Activation of TIGIT on T cells and NK cells limits cellular proliferation, effector cytokine production, and killing of target tumor cells (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. It is expressed in most solid tumors, such as NSCLC, breast cancer, and melanoma, as well as in hematological tumors, such as multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). Fluorescence activated cell sorting analysis of T cells isolated from fresh tumor samples revealed that TIGIT and PD-1 are also co-expressed on tumor-infiltrating T cells (Johnston et al. 2014; Yadav et al. 2016; Yang 2016; Guillerey et al. 2018). TIGIT was expressed in 30%–80% of tumor-infiltrating CD4$^+$ T cells and in 50%–80% of tumor-infiltrating CD8$^+$ T cells (Johnston et al. 2014).

Therefore, TIGIT is a potential target for therapeutic interventions that aim to restore the immune response against the tumor. Agents that inhibit TIGIT's interaction with PVR may inhibit an important source of tumor-associated immune suppression, thereby enhancing the activity of other immune-based therapies. Nonclinical studies using genetically deficient mice and blocking antibodies have revealed a key role for TIGIT in

regulating T-cell responses in cancer. Taken together, these data support the hypothesis that anti-TIGIT therapy may reactivate anti-tumor immunity and provide clinical benefits to patients with cancer.

A16–2.3 COMBINATION TREATMENT WITH ANTI–PD-1/ ANTI–LAG-3 AND ANTI-TIGIT AGENTS

Durable clinical benefit is limited to a minority of patients treated with single-agent PD-L1/PD-1 inhibitors. Therapies targeting the mechanisms of resistance to anti-PD-L1/PD-1 therapies are needed to improve outcomes in patients with solid cancers. Resistance to PD-L1/PD-1 blockade may result in the expression of multiple co-inhibitory receptors on the surface of effector T cells including TIGIT and LAG-3. Nonclinical tumor models have shown that TIGIT selectively suppressed the effector function of chronically stimulated $CD8^+$ T cells, and that inhibiting both TIGIT and PD-L1/PD-1 resulted in superior efficacy compared with single-agent treatments (Johnston et al. 2014). Similarly, in-vivo proof-of-concept studies using different tumor mouse models have shown PD1-LAG-3 bsAbs to be superior in controlling tumor growth and promoting tumor eradication when compared with anti-PD-1 antibodies as monotherapy. Hence, targeting PD-1/LAG-3 and TIGIT with RO7247669 and tiragolumab, respectively, may enhance the efficacy of PD-L1/PD-1 blockade across different cancer types, including melanoma.

A16–2.4 CLINICAL STUDIES OF AGENTS TARGETING THE PD-1 AND LAG-3 PATHWAYS

Clinical data are available for early- and late- phase studies that evaluated the safety, tolerability, and preliminary anti-tumor activity of agents that target both the PD-1 and LAG-3 pathways. Evidence of clinical activity has been reported in some of these studies. Overall, adverse events have been manageable to date, and the safety profiles appear similar to those of single-agent CPIs.

An ongoing Phase I/IIa study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody nivolumab and the anti–LAG-3 monoclonal antibody relatlimab in patients with advanced solid tumors. Preliminary data suggest that the combination of nivolumab and relatlimab may have an increased benefit compared with single-agent anti–PD-1. In a cohort of patients who had advanced melanoma who were previously treated with anti–PD-1/PD-L1 agents, the objective response rate (ORR) was 11.5% (n=61) with a disease control rate of 49%. The anti–PD-1/PD-L1 treatment combination had an acceptable safety profile that was similar to the safety profile of nivolumab monotherapy (Ascierto et al. 2017).

Relativity-047 is a Phase III study evaluating the combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) versus nivolumab alone in patients with untreated advanced melanoma. This study demonstrated that nivolumab and relatlimab

improved progression-free survival (PFS =10.1 months) over nivolumab (PFS = 4.6 months). The incidence of Grade 3 or 4 treatment-related adverse events was 18.9% in patients that received the nivolumab and relatlimab combination and 9.7% in patients that received nivolumab alonoe (Tawbi et al. 2022).

An ongoing Phase I/II study is evaluating the safety, tolerability, and clinical activity of combination treatment with the anti–PD-1 monoclonal antibody spartalizumab and the anti–LAG-3 monoclonal antibody LAG525 in patients with advanced solid tumors. Preliminary anti-tumor activity was observed during the Phase I dose-escalation portion of the study, including durable responses in 2 of 5 patients with triple-negative breast cancer (TNBC) and in 2 of 8 patients with mesothelioma. Analyses of tumor biopsies from the TNBC cohort also showed a trend of conversion from an immune-cold to an immune-activated phenotype. Common adverse events, i.e., adverse events reported in≥10% of patients, included fatigue (18%), diarrhea (15%), and nausea (12%). The incidence of Grade 3–4 adverse events was 8% for both the combination (n=121) and monotherapy (n=119) arms (Hong et al. 2018).

An ongoing, first-in-human, dose-escalation, and dose-expansion Phase I study is evaluating the safety, tolerability, and clinical activity of the anti–PD-1/LAG-3 dual affinity re-targeting protein (DART®) bsAb MGD013 in patients with advanced solid tumors and hematologic malignancies. During the dose-escalation phase of the study, the maximum tolerated dose (MTD) was not reached, and the safety profile was consistent with anti–PD-1 monotherapy. During the dose-expansion phase, anti-tumor activity was observed in patients with TNBC (n=23; ORR, 4.3%; disease control rate [DCR], 39.1%), CPI-naive NSCLC (n=14; ORR, 14.3%; DCR, 64.3%), and epithelial ovarian cancer (n=23; ORR, 8.7%; DCR, 52.2%). Expression of LAG-3 and an IFN-γ gene signature at baseline was associated with objective responses (Luke et al. 2020). Clinical studies evaluating MGD013 as monotherapy and in combination with anti–HER-2 agents are ongoing.

A16–2.4.1 Study NP41300

Study NP41300 is an ongoing, first-in-human, dose-escalation, dose-expansion Phase I study to evaluate the safety, pharmacokinetics, and therapeutic activity of the anti–PD-1/LAG-3 bsAb RO7247669 as a single-agent in patients with locally advanced and/or metastatic solid tumors. Part A, the dose-escalation phase of the study, is designed to determine the MTD and/or recommended dose for expansion (RDE) of RO7247669. Part B of the study is designed to evaluate the anti-tumor activity of RO7247669 at the MTD or RDE in tumor-specific expansion cohorts.

As of the data cut-off date, 1 March 2022, RO7247669 was well tolerated in the patients enrolled in Part A of the study. No unexpected safety concern associated with RO7247669 was identified. No dose-limiting toxicities (DLTs) were observed up to the

maximum dose tested (2100 mg every 2 weeks [Q2W]), and no MTD was identified. The maximum dose of 2100 mg was determined to be the recommended dose for the dose-expansion phase (Part B) of Study NP41300. As of the data cutoff date, 1 March 2022, 83 patients received treatment in Part B.

As of the data cut-off date, 1 March 2022, the DCR in Part A of the study was 51.4% (18 of 35 evaluable patients), and the ORR was 17.1% (6 of 35 patients). Among the patients treated with the proposed dose of 2100 mg Q2W, 7 of 13 patients had a best response of stable disease or better (DCR=53.8%), including 4 patients with a confirmed partial response (PR, ORR=30.8%). Besides the confirmed partial responses (cPR) observed at the RDE, there were 2 cPRs at the 600 mg dose level (ORR =50.0%).

As of the data cut-off date, 1 March 2022, in Part B of the study the DCR was 48.3% (28 of 58 patients) and the ORR was 5.2% (3 of 58 patients) among patients of the study treated at the RDE of 2100 mq Q2W (Cohorts B1, B2, and B3). Within patients treated with 600 mg Q2W (Cohort B5), the DCR was 40% (4 of 10 patients), and the ORR was 10% (1 of 10 patients). Among patients treated with 600 mg Q3W, the DCR was 28.6% (2 of 7 patients) and the ORR was 14.3% (1 of 7 patients).

Refer to the RO7247669 Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A16–2.5 CLINICAL STUDIES OF TIRAGOLUMAB

Tiragolumab is currently under investigation in two ongoing clinical studies in patients with solid tumors (Studies GO30103 and GO40290) and in one clinical study in patients with hematological malignancies (Study GO41036).

A16–2.5.1 Study GO30103

Study GO30103 is a first-in-human, open-label, multicenter, global, dose-escalation/dose-expansion Phase I study. It was designed to evaluate the safety, tolerability, and pharmacokinetics of tiragolumab as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced, recurrent, or metastatic incurable tumors, including urothelial cancer, renal cell cancer, NSCLC, head and neck squamous cell carcinoma, esophageal cancer, colorectal cancer (CRC), gastric cancer, cholangiocarcinoma, and triple-negative breast cancer.

As of the clinical cutoff date of 2 December 2020, a total of 236 patients had been enrolled in Study GO30103. Forty-two patients were enrolled in the Phase Ia portion of the study to receive single-agent tiragolumab, and 217 patients were enrolled in the Phase Ib portion of the study to receive tiragolumab in combination with atezolizumab. The latter group included 23 patients who crossed over from the Phase Ia portion of the study.

The best observed response with tiragolumab monotherapy in the Phase Ia portion was prolonged stable disease in 8 of 42 patients, with some patients, including 1 patient with CRC, experiencing a decrease in tumor size.

In the Phase Ib portion, complete response was observed in 4 of 217 patients at tiragolumab dose levels of 400 mg (n=3/48) and 600 mg (n= 1/104) in combination with 1200 mg atezolizumab. Partial response was observed in 27 of 217 patients at tiragolumab dose levels of 30 mg (n=2/13), 400 mg (n=6/48), and 600 mg (n=18/104) in combination with 1200 mg atezolizumab, including two patients who crossed over from the Phase Ia portion at the 600 mg dose level. Stable disease was observed in 53 of 217 patients at tiragolumab dose levels of 2 mg (n=1/8), 8 mg (n=3/12), 30 mg (n= 2/13), 100 mg (n= 3/8), 400 mg (n=12/48), 600 mg (n=25/104), and 1200 mg (n=7/24) in combination with 1200 mg atezolizumab, including 8 patients who crossed over from the Phase Ia portion of the study (2 patients at 8 mg, 1 patient at 30 mg, 2 patients at 100 mg, and 3 patients at 400 mg).

As of 2 December 2020, safety data were available for 235 safety-evaluable patients in Study GO30103. A total of 42 patients were treated in the Phase Ia portion with tiragolumab as a single agent (2 mg to 1200 mg), while 216 patients were treated in the Phase Ib portion with tiragolumab at dose levels of 2 mg to 1200 mg in combination with atezolizumab at 1200 mg, including 23 patients who crossed over from the Phase Ia portion to the Phase Ib portion.

Tiragolumab was tolerated across all administered dose levels both as a single agent and in combination with atezolizumab. The MTD was not reached, and the maximum administered dose was 1200 mg. No DLTs or clear dose-related trends in the incidence of adverse events were observed. Grade ≥3 adverse events, regardless of attribution to the study drug(s), were reported in 16 patients (38.1%) and 113 patients (52.3%) in the Phase Ia and Phase Ib portions, respectively. There were 14 reported deaths in the Phase Ia portion of the study, including 12 deaths due to malignant neoplasm progression, 1 death due to gastrointestinal hemorrhage in the context of progressive disease, and 1 death due to hepatic failure. The death due to hepatic failure was considered by the investigator to be related to study drug. One hundred eighteen deaths were reported in the Phase Ib portion of the study. This included 111 deaths due to progressive disease (31 cases were reported as adverse events during the adverse event reporting period and coded as malignant neoplasm progression or neoplasm malignant), 2 deaths due to pulmonary embolism, 1 death due to esophageal hemorrhage, 1 death due to sepsis, 1 death due to septic shock, 1 death due to COVID-19, and 1 death due to upper airway obstruction. Treatment-related serious adverse events were reported in 1 patient in the Phase Ia portion (hepatic failure) and in 10 patients (4.6%) in the Phase Ib portion. No patient discontinued study treatment due to adverse events in the Phase Ia portion of Study GO30103. Adverse events

leading to treatment discontinuation were reported in 12 patients in the Phase Ib portion of the study, with a Grade 4 cardiac tamponade, a Grade 4 pneumonitis, and one event of Grade 2 arthralgia considered by the investigator to be related to the study drug(s). Adverse events of special interest were reported in 5 patients (11.9%) in the Phase Ia portion and 82 patients (38.0%) in the Phase Ib portion of the study.

Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile has been observed to be consistent across different solid tumor indications.

A16–2.5.2 Study GO40290

Study GO40290 is a Phase II, randomized, blinded, placebo-controlled study of tiragolumab plus atezolizumab compared with placebo plus atezolizumab in patients with previously untreated locally advanced unresectable or metastatic PD-L1–positive NSCLC (defined as tumor proportion score [TPS] ≥ 1%).

As of the primary clinical cutoff date of 30 June 2019, 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). As of the primary analysis, 47.8% of patients in the tiragolumab plus atezolizumab group versus 27.9% of patients in the placebo plus atezolizumab group were still receiving study treatment in the ITT population. In the TPS ≥50% population, 65.5% of patients in the tiragolumab plus atezolizumab group versus 24.1% of patients in the placebo plus atezolizumab group were still receiving study treatment.

In all randomized patients, the combination of tiragolumab plus atezolizumab improved the co-primary endpoints of investigator-assessed ORR and progression-free survival (PFS) compared to placebo plus atezolizumab, with median follow-up of 5.9 months. ORR for tiragolumab plus atezolizumab was 31.3% (95% CI: 19.5, 43.2) compared with placebo plus atezolizumab which was 16.2% (95% CI: 6.7, 25.7). Investigator-assessed median PFS for tiragolumab plus atezolizumab was 5.4 months (95% CI: 4.2 months, not reached) compared with placebo plus atezolizumab which was 3.6 months (95% CI: 2.7 months, 4.4 months), with a stratified hazard ratio (HR) of 0.57 (95% CI: 0.37, 0.90). Investigator-assessed PFS was improved in the tiragolumab plus atezolizumab group over the placebo plus atezolizumab group (unstratified HR=0.33; 95% CI: 0.15, 0.72; median PFS not reached vs. 3.9 months, respectively).

As of 2 December 2020, 67 safety-evaluable patients in the tiragolumab plus atezolizumab arm in Study GO40290 were treated with a median of 8 doses of tiragolumab and atezolizumab (range: 1–38) for a median of 5.0 months (range: 0.03–26.0). In the placebo plus atezolizumab arm, 68 safety-evaluable patients

were treated with a median of 5 doses of placebo and atezolizumab (range: 1–37) for a median of 2.8 months (range: 0.03–26.3).

As of 30 June 2020, in the Phase II randomized, placebo-controlled Study GO40290, a total of 135 safety-evaluable patients were administered either tiragolumab (600 mg recommended Phase II/III dose) in combination with atezolizumab or placebo in combination with atezolizumab. The safety profile of tiragolumab plus atezolizumab was similar to that of placebo plus atezolizumab- for all-grade adverse events (98.5% vs. 97.1%), Grade ≥ 3 adverse events (53.7% vs. 50.0%), serious adverse events (47.8% vs. 39.7%), and adverse events leading to treatment discontinuation (13.4% vs. 11.8%). Adverse events of special interest were reported in 58.2% of patients in the tiragolumab plus atezolizumab arm and in 32.4% of patients in the placebo plus atezolizumab arm. One death due to Epstein-Barr virus (EBV) reactivation and possible secondary hemophagocytic lymphohistiocytosis (HLH) was reported in this study, which was considered by the investigator to be related to the study drugs.

Overall, tiragolumab in combination with atezolizumab has been well tolerated, adverse events have been manageable, and the safety profile seems to be consistent as reported across different solid tumor indications.

Refer to the Tiragolumab Investigator's Brochure for additional details on all ongoing and planned clinical studies.

A16–2.6 BENEFIT—RISK ASSESSMENT

The combination of RO7247669 and tiragolumab is currently being tested in this study. The combination of atezolizumab and tiragolumab has a favorable emergent benefit–risk profile, and early clinical experience with RO7247669 suggest a safety profile comparable to that of atezolizumab and other PD-1/PD-L1 blocking antibodies (Appendix 12). The combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) improved PFS over nivolumab alone as first-line therapy in melanoma patients in the Phase III Relativity-047 study (Tawbi et al. 2022), which supports the expected benefit from RO7247669 (anti–PD-1/anti–LAG-3 bispecific therapy) in combination with tiragolumab. Taking into account the potentially synergistic mechanisms of action of RO7247669 and tiragolumab, as well as their manageable and tolerable safety profiles (see Section A16–5), combination treatment with these two agents has promise as a potential therapy in solid tumors such as melanoma.

For the evaluation of the impact of the COVID-19 pandemic on the benefit—risk assessment, please refer to Section 1.3.

A16–3 RATIONALE FOR DOSE AND SCHEDULE FOR RO7247669 600 mg+TIRA ARM

A16–3.1 RATIONALE FOR RO7247669 600 mg DOSE AND SCHEDULE

RO7247669 will be administered at a fixed dose of 600 mg every 3 weeks (Q3W) (600 mg on Day 1 of each 21-day cycle). A fixed dosing regimen of 600 mg Q3W was selected based on available clinical pharmacokinetic, efficacy, and safety data from Study NP41300. During the dose-escalation Part A of the study, RO7247669 was well tolerated, and no specific safety concern associated with RO7247669 was identified. No DLT up to the highest dose of 2100 mg Q2W was observed, and no MTD was identified. Anti-tumor activity, as measured by radiographic partial responses, was observed starting at a dose of 600 mg Q2W. The pharmacokinetics of RO7247669 were dose linear within the dose range tested in Study NP41300. Greater than 90% occupancy of peripheral PD-1 and LAG3 receptors on $CD8^+$ cells was observed at 50 mg of RO7247669 and was sustained at all higher doses (unpublished Roche data on file). Further modelling of intratumoral PD-1 and LAG3 target engagement using estimated target properties was performed. A dose regimen of 600 mg Q3W was selected for this study (BO43328) to ensure that the majority of participants have at least 90% PD-1 and LAG3 tumor receptor saturation by RO7247669, irrespective of intratumoral spatial heterogeneity and intersubject variability. A dose greater than 600 mg would not be expected to result in further clinical activity.

In study NP41300, persistent anti-drug antibodies (ADAs) formed in approximately 18% of the total population and the incidence rate was not dose dependent. An impact on exposure was observed at 50, 150 and 300 mg; therefore, 600 mg will be used in Study BO43328 to minimize the risk of a loss in exposure due to ADAs.

In addition, RO7247669 was well tolerated in both the dose-range finding studies and Good Laboratory Practice (GLP) monkey toxicology studies up to the highest dose evaluated (100 mg/kg). Toxicology findings were consistent with the findings in cynomolgus monkey studies of marketed CPIs. In the current study (BO43328), the safety evaluation of the first 6 patients enrolled in the RO7247669 2100 mg arm was completed with no safety signals identified.

The supporting data for the selected dose can be found in the current RO7247669 Investigator's Brochure.

A16–3.2 RATIONALE FOR TIRAGOLUMAB DOSE AND SCHEDULE

Tiragolumab will be administered at a fixed dose of 600 mg IV Q3W (600 mg on Day 1 of each 21-day cycle).

The fixed dose of 600 mg IV Q3W was selected on the basis of available clinical pharmacokinetic, efficacy, and safety data from the combined Phase Ia/Phase Ib Study GO30103 with single-agent tiragolumab or tiragolumab in combination with atezolizumab. In the Phase Ia portion of the study with tiragolumab as a single agent, the MTD was not reached, and no DLTs were observed during dose-escalation. As of the clinical cutoff date, anti-drug antibodies (ADAs) to tiragolumab were rare in the Phase Ia or Phase Ib portions across all dose levels. Complete occupancy of peripheral TIGIT receptors on $CD4^+$, $CD8^+$, and NK cells was observed beginning at 30 mg of tiragolumab in both the Phase Ia and Phase Ib portions of the study and remained sustained at all higher doses (unpublished Roche data on file).

Prolonged stable disease was observed in patients in the Phase Ia portion of the study at tiragolumab doses beginning at 400 mg. In the Phase Ib portion of the study with tiragolumab plus atezolizumab, the MTD was not reached. Anti-tumor activity, as measured by radiographic partial responses, was observed across doses for tiragolumab beginning at 30 mg and ranging up to 600 mg in combination with 1200 mg atezolizumab. Refer to the Tiragolumab Investigator's Brochure for additional details.

A16–4 MATERIALS AND METHODS SPECIFIC TO RO7247669 600 mg+TIRA ARM

A16–4.1 TREATMENT IN RO7247669 600 mg+TIRA ARM

A16–4.1.1 Formulation, Packaging, and Handling

A16–4.1.1.1 RO7247669

The RO7247669 drug product will be supplied by the Sponsor as a 50 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of RO7247669, refer to the pharmacy manual and the RO7247669 Investigator's Brochure.

A16–4.1.1.2 Tiragolumab

The tiragolumab drug product will be supplied by the Sponsor as a 60 mg/mL concentrate for solution for infusion.

For information on the formulation, packaging, and handling of tiragolumab, refer to the pharmacy manual and the Tiragolumab Investigator's Brochure.

A16–4.1.2 Dosage, Administration, and Compliance

Patients in the RO7247669 600 mg+Tira arm will receive treatment for 2 cycles (6 weeks) as outlined in Table A16-1 until surgery, or until unacceptable toxicity or loss of clinical benefit, whichever occurs first (see Section 3.1.2 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table A16-1 Treatment Regimen for RO7247669 600 mg+ Tira Arm

Cycle Length	*Dose, Route, and Regimen (drugs listed in order of administration)*
21 days	• *RO7247669 600 mg IV on Day 1 of each cycle* • *Tiragolumab 600 mg IV on Day 1 of each cycle*

Tira=tiragolumab.

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

Medication errors should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.
No safety data related to overdosing of RO7247669 or tiragolumab are available to date.

A16–4.1.2.1 RO7247669

RO7247669 will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle.

Administration of RO7247669 will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. RO7247669 infusions will be administered per the instructions outlined in Table A16-2.

Table A16-2 Administration of First, Second, and Subsequent RO7247669 Infusions

First and Second Infusion	*Subsequent Infusions*
• *No premedication is permitted prior to the first RO7247669 infusion.* • *Vital signs (respiratory rate, pulse rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF.* • *For the first infusion, RO7247669 should be infused over 60 (±10) minutes.* • *After the infusion of RO7247669, the patient begins a 60-minute observation period.* • *For the second infusion, RO7247669 should be infused over 30 (±10) minutes if the first infusion was tolerated without an IRR.* • *If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.* • *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 should be measured within 60 minutes prior to the infusion and recorded on the eCRF.* • *RO77247669 should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR.* • *If the patient tolerated the previous infusion of RO77247669 well without infusion-associated adverse events, the observation period may be reduced to 30 minutes.* • *If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. Record on the eCRF in case of abnormalities.*

eCRF=electronic Case Report Form; IRR=infusion-related reaction.

For patients who experience a Grade≥2 infusion-related reaction (IRR), premedication with paracetamol 500–1000 mg orally [PO] or IV and diphenhydramine 25–50 mg PO or IV (or an alternative histamine $H_{1/2}$ antagonist at an adequate dose) is required prior to subsequent infusions. In case of Grade 3 or 4 IRRs related to study treatment, the patient should be permanently discontinued from the study treatment.

Guidelines for medical management of IRRs for RO7247669 are provided in Section A16–5.1.2.1.

No dose modification for RO7247669 is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.2.2.

A16–4.1.2.2 Tiragolumab

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21-day cycle with a post-infusion observation period as described in Table A16-3.

Administration of tiragolumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. Tiragolumab infusions will be administered per the instructions outlined in Table A16-3.

Table A16-3 Administration of First and Second Tiragolumab Infusions

First Infusion	*Second Infusions*
• *No premedication is permitted prior to the tiragolumab infusion.* • *Vital signs (pulse rate, respiratory rate, pulse oximetry, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion and recorded on the eCRF.* • *Tiragolumab should be infused over 60 (±15) minutes.* • *After the infusion of tiragolumab, the patient begins a 60-minute observation period.* • *Record vital signs on the eCRF every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.* • *Patients will be informed about the possibility of delayed postinfusion symptoms and will be instructed to contact their study physician if they develop such symptoms.*	• *If the patient experienced an IRR with the first 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 and recorded on the eCRF.* • *Tiragolumab 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 infusion-related reaction with the previous infusion.* • *Patients should be observed for 30 minutes after completion of the tiragolumab infusion if the previous infusion was tolerated without an IRR, or for 60 minutes after completion of the tiragolumab infusion if the patient experienced an IRR with the previous infusion.* • *If clinically indicated, vital signs should be recorded on the eCRF every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.*

eCRF=electronic Case Report Form; IRR=infusion-related reaction.

Guidelines for medical management of IRRs for tiragolumab are provided in Table A16-4.

No dose modification for tiragolumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.4.2. Tiragolumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on the investigator's benefit—risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

A16–4.2 CONCOMITANT THERAPY FOR RO7247669 600 mg+TIRA ARM

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

A16–4.2.1 Permitted Therapy for RO7247669 600 mg+Tira Arm

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

- *Oral contraceptives with a failure rate of<1% per year*
- *Hormone-replacement therapy*
- *Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)*
- *Vaccinations (such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section A16–4.2.3)
- *Megestrol acetate administered as an appetite stimulant*
- *Mineralocorticoids (e.g., fludrocortisone)*
- *Corticosteroids administered for chronic obstructive pulmonary disease (COPD) or asthma*
- *Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency. Other use of corticosteroids may be permitted at the investigator's discretion. The Medical Monitor is available to advise as needed*
- *Local therapy (e.g., surgery other than complete lymph node dissection [CLND] that is not considered to be related to melanoma)*

A16–4.2.2 Cautionary Therapy for RO7247669 600 mg+Tira Arm

A16–4.2.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor-α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment

with RO7247669 and/or tiragolumab. 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 RO7247669 and/or tiragolumab therapy (refer to Appendix 9 for details).

A16–4.2.2.2 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 A16–4.2.2) may be used during the study at the discretion of the investigator.

A16–4.2.3 Prohibited Therapy for RO7247669 600 mg+Tira Arm

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

- *Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.4), and during study treatment until surgery, or unacceptable toxicity.*
- *Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.*
- *Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with RO7247669 and/or tiragolumab, and for 4 months after the last dose of RO7247669 and/or tiragolumab.*
- *Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with RO7247669 and/or tiragolumab.*

A16–4.3 CONTRACEPTION REQUIREMENTS FOR RO7247669 600 mg+TIRA ARM

Contraception requirements for women and men in the RO7247669 600 mg+Tira arm are outlined below:

- *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 4 months after the last dose of RO7247669, and for 90 days after the last dose of tiragolumab.

  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 acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

  With a female partner of childbearing potential who is not pregnant or a pregnant female partner, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of<1% per year during the treatment period, for 4 months after the last dose of RO7247669, and for 90 days after the last dose of tiragolumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

A16–5 ASSESSMENT OF SAFETY FOR RO7247669 600 mg+TIRA ARM

A16–5.1 SAFETY PLAN FOR RO7247669 600 mg+TIRA ARM

The safety plan for patients in this study is based on clinical experience with RO7247669 and tiragolumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A16–5.1.1, A16–5.1.2, A16–5.1.3, and A16–5.1.4). Guidelines for the management of patients who experience specific adverse events are provided in Section A16–5.1.4 and Appendix 9.

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 RO7247669 and tiragolumab 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. Adverse events will be reported as described in Sections 5.2–5.6.

A16–5.1.1 Risks Associated with RO7247669

Clinical evaluation of RO7247669 is ongoing, and not all risks are known. As an antagonist of PD-1 and LAG-3, RO7247669 is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Based on the mechanism-of-action of RO7247669, the safety profile is anticipated to be similar to other CPIs. Potential risks associated with RO7247669 include the following: IRRs (including anaphylaxis), immunogenicity, and immune-mediated adverse events. Refer to Section 6 of the RO7247669 Investigator's Brochure for a detailed description of anticipated safety risks for RO7247669.

A16–5.1.1.1 Infusion-Related Reactions and Anaphylaxis

Administration of therapeutic antibodies may cause IRRs, which may include symptoms such as fever, chills, hypotension, shortness of breath, skin rash, headache, nausea, and vomiting. Such reactions typically occur during or shortly after the infusion and are predominantly reported following the first infusion. The incidence and severity of IRRs typically decrease with subsequent infusions. Based on in vitro

data, the risk of proinflammatory cytokine-mediated IRRs on first administration of RO7247669 as single agent is considered low.

Refer to Section A16–4.1.2 for detailed guidance on administration of RO7247669 in this study. Refer to Appendix 8 for guidance on anaphylaxis precautions and Section A16–5.1.4.3 for guidance on the management of IRRs.

A16–5.1.1.2 Immunogenicity

Administration of therapeutic antibodies may cause the formation of anti-drug antibodies, which may negatively affect the safety of the therapeutic (e.g., allergic reactions, immune complex-mediated diseases).

A16–5.1.1.3 Immune-Mediated Adverse Events

The co-stimulatory action of RO7247669, particularly given the LAG-3 modulation, might bear the risk of exaggerated immune cell activation that may result in the occurrence of enhanced, untoward, immune-mediated adverse events and increased cytokine-release–mediated toxicities.

Toxicities from PD-1 blocking agents can involve any organ or tissue, although some immune-mediated adverse events occur much more frequently than others. The most frequently occurring immune-mediated adverse events affect skin, colon, endocrine organs, liver, and lungs. Others are very infrequent but may be very serious, even lethal, such as neurological disorders and myocarditis.

The limited data from recent early phase studies showed that anti–LAG-3therapy was generally well tolerated as a monotherapy or in combination with anti–PD-1 therapies, and consistent with the safety profiles of other CPIs (Ascierto et al. 2017; Hong et al. 2018).

In this study, specified immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A16–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Patients with a history of autoimmune disease will be excluded from this study. Please see Section 4.1.2 for details.

A16–5.1.2 Risks Associated with Tiragolumab

Infusion-related reactions and immune-mediated hepatitis are identified risks of tiragolumab. Lymphopenia is a potential risk with tiragolumab. Although clinical evaluation of tiragolumab is limited and not all risks are known, as an antagonist of TIGIT, tiragolumab is anticipated to enhance T-cell and NK-cell proliferation, survival, and function. Therefore, tiragolumab may increase the risk of autoimmune inflammation (also described as immune-mediated adverse events).

Refer to Appendix 9 of the protocol and the Tiragolumab Investigator's Brochure for a detailed description of anticipated safety risks of tiragolumab.

A16–5.1.2.1 Infusion-Related Reactions

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

IRRs have been reported in patients treated with tiragolumab. The majority of events were mild to moderate and manageable.

To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period. Subsequent infusions and observation times may be shortened if the preceding infusion was well tolerated. All infusions will be administered in an appropriate medical setting.

Refer to Section A16–4.1.2 for detailed guidance on administration of tiragolumab in this study. Please see Appendix 8 for guidance on anaphylaxis precautions and Table A16-4 for guidance on the management of IRRs.

A16–5.1.2.2 Immune-Mediated Hepatitis

The use of tiragolumab to block the immune inhibitory receptor TIGIT serves to increase a baseline T-cell and NK-cell immune response, especially in combination with other checkpoint inhibitors. A disruption in the functioning of immune checkpoint molecules may lead to imbalances in immunologic tolerance that results in an unchecked immune response, including immune-mediated hepatitis.

Refer to Appendix 9 for guidance on the management of immune-mediated hepatitis.

A16–5.1.2.3 Immune-Mediated Adverse Events

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

Clinical experience with therapeutics intended to enhance anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory conditions is a general risk and may therefore be considered a potential risk of tiragolumab. Such immune-mediated adverse events have been described for virtually all organ

systems and include, but are not limited to, colitis, pneumonitis, endocrinopathies, ocular toxicity, pancreatic toxicity, neurologic toxicity, cardiac toxicity, nephritis, myositis, and severe cutaneous adverse reactions.

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

In this study, immune-mediated adverse events will be considered adverse events of special interest and will be captured accordingly (see Section A16–5.2 for the list of adverse events of special interest and Section 5.4.2 for reporting instructions).

Suggested management guidelines for individual suspected immune-mediated adverse events are provided in Appendix 9.

A16–5.1.2.4 Lymphopenia

The IgG1 backbone of tiragolumab with intact Fc-effector function may lead to ADCC-mediated reduction in lymphocyte count. Lymphopenia is a potential risk with tiragolumab. Transient decreases in lymphocyte count without clinical sequelae have been observed in patients treated with tiragolumab.

Patients with a lymphocyte count $<0.5\times10^9$/L (500/μL) will be excluded from the study (see Section 4.1.1), and complete blood counts will be monitored regularly during the study (see Section A16–6).

A16–5.1.2.5 Embryofetal Toxicity

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

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

A16–5.1.3 Risks Associated with Combination Use of RO7247669 and Tiragolumab

The blockade of inhibitory checkpoints leads to increase adaptive T-cell immune responses via complementary targets, and the combination targeting multiple checkpoints may be associated with heightened immune-mediated toxicity relative to

either agent alone. Such toxicity could manifest as a higher incidence or greater severity of autoimmune inflammation events, or potentially the development of HLH and MAS. The following adverse events are potential overlapping toxicities associated with combination use of RO7247669 plus tiragolumab: IRR and immune-mediated toxicities, (see Appendix 9 for complete list).

A16–5.1.4 Management of Patients Who Experience Specific Adverse Events in the RO7247669 600 mg+Tira Arm

A16–5.1.4.1 Dose Modifications

There will be no dose modifications for RO7247669 or tiragolumab in this study.

A16–5.1.4.2 Treatment Interruption for Toxicities

Treatment with RO7247669 and tiragolumab may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before study treatment can be resumed if warranted. In the neoadjuvant setting, the study treatment is limited to a pre-surgery window of 6 weeks. Treatment during this period should not be interrupted, unless a patient experiences toxicity. If toxicity meets criteria for interrupting/withholding RO7247669 and tiragolumab, RO7247669 and tiragolumab should be interrupted/withheld. After resolution of the toxicity, subsequent treatment cycles should only be considered if the benefit-risk profile is acceptable and if the surgery can be conducted within 2 weeks of the planned date. Otherwise, subsequent treatment cycles should be omitted to allow the patient to proceed directly to surgery without further delay.

On the basis of the available characterization of mechanism-of-action, tiragolumab may cause adverse events similar to, but independent of, RO7247669. Tiragolumab may also exacerbate the frequency or severity of RO7247669-related adverse events or may have non-overlapping toxicities with RO7247669. Because these scenarios may not be distinguishable from each other in the clinical setting, adverse events should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to adverse events should be applied to both tiragolumab and RO7247669. If RO7247669 is withheld or discontinued, tiragolumab should also be withheld or discontinued. If tiragolumab is withheld or discontinued, RO7247669 should also be withheld or discontinued.

A16–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table A16-4 and Appendix 9.

For cases in which management guidelines are not covered in Appendix 9, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A16-4 Guidelines for Management of Patients Who Experience Adverse Events in the RO7247669 600 mg+Tira Arm

Event	*Action to Be Taken*
IRRs, anaphylaxis, and hypersensitivity reactions	
General guidance	• *For anaphylaxis precautions, see Appendix 8.* • *For severe hypersensitivity reactions, permanently discontinue RO7247669 and tiragolumab.* • *For suspected CRS, see Appendix 9 for guidance on supportive care.* • *Determine tryptase concentration and IgE titer if clinical presentation of IRR suggests an anaphylactic or hypersensitivity reaction (hives, obstructive shortness of breath, urticaria, other histamine associated symptoms) and/or if the first IRR or CRS (≥Grade 2) is observed at the second infusion. If tryptase and/or IgE are elevated, collect a second sample for IgE/tryptase analysis at least 48 hours after the onset of the reaction to rule out the possibility of an anaphylactic reaction.*

CRS=cytokine-release syndrome; GI=gastrointestinal; HLH=hemophagocytic lymphohistiocytosis; IRR=infusion-related reaction; MAS=macrophage activation syndrome.

Table A16-4 Guidelines for Management of Patients Who Experience Adverse Events in the RO7247669 600 mg+Tira Arm (cont.)

Event	*Action to Be Taken*
IRRs, anaphylaxis, and hypersensitivity reactions (cont.)	
IRR to RO7247669 and/or tiragolumab Grade 1	• *Reduce infusion rate to half the rate being given at the time of event onset.* • *After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate.* • *If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.*
IRR to RO7247669 and/or tiragolumab Grade 2	• *Interrupt infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids).* • *After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset.* • *For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs.*
IRR to RO7247669 and/or tiragolumab, Grade 3 or 4	• *Stop infusion.* • *Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids).* • *Permanently discontinue RO7247669 and tiragolumab and contact the Medical Monitor.*
Pulmonary, hepatic, GI, endocrine, ocular, immune-mediated myocarditis, CRS, pancreatic, dermatologic, neurologic, immune-mediated meningoencephalitis, renal, myositis, HLH, MAS, and systemic immune activation	• *Guidelines for the management of these events are provided in Appendix 9.*

CRS=cytokine-release syndrome; GI=gastrointestinal; HLH=hemophagocytic lymphohistiocytosis; IRR=infusion-related reaction; MAS=macrophage activation syndrome.

A16–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR THE RO7247669 600 mg+TIRA ARM (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 5.2.3 for reporting instructions). Adverse events of special interest for the RO7247669 600 mg+Tira arm are as follows:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)*
- *Suspected transmission of an infectious agent by the study treatment, as defined below:*

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

A16–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN THE RO7247669 600 mg+TIRA ARM

A16–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 4 months after the last dose of RO7247669 or within 90 days after the last dose of tiragolumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A16–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 4 months after the last dose of RO7247669 or within 90 days after the last dose of tiragolumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for the Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information

on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A16–5.3.3 Abortions

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

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

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

A16–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.2.2).

A16–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR RO7247669 600 mg+TIRA ARM

Table A16-5 Schedule of Activities for RO7247669 600 mg+Tira Arm

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
IMP Administration										
RO7247669 600 mg administration	A16–4.1.2		x	x						
Tiragolumab administration			x	x						
Clinical Assessments										
Molecular profile of melanoma	4.5.2		Whenever updated information becomes available							
Weight [d]	4.5.3		x	x	x		x	x		x
Complete physical examination								x		
Limited physical examination [d]			x	x	x		x			x
Vital signs	4.5.4 and A16–4.1.2		x	x	x		x	x		x
12-Lead ECG [d]	4.5.5		x	x				x		
TTE or MUGA scan	4.5.6							x		

Table A16-5 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg+TIRA ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Clinical Assessments (cont.)										
ECOG Performance Status [d]	Appendix 6		x	x	x		x	x		x
Surgery (CLND)	3.1.5, Appendix 4					x				
Tumor response assessments	4.5.7				x				As clinically indicated.	
Disease status assessments	4.5.7.2				x			x [e]	x	
Concomitant medications	A16–4.2		x	x	x		x	x		
Adverse events [f]	5.3.1, 5.5.1, and 5.6		x	x	x		x [f]	x [f]	x [f]	x [f]
Clavien-Dindo assessment	4.5.8 and Appendix 5							x		x
Follow-up and anti-cancer treatment	4.6.1								x [g]	
Local Laboratory Assessments										
Hematology	4.5.9.1		x [h]	x [h]	x		x	x		x

Table A16-5 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg+TIRA ARM (cont.)

Assessment/ Procedure [a]	*Protocol Section*	*Screening (see Appendix 10)*	*Treatment Cycles (21-Day Cycles)*		*Pre-Surgery*	*Surgery CLND*	*Post-Surgery*	*Treatment Comp./ Discon.* [b]	*Long-Term Follow-Up*	*Surgery Follow-Up* [c]
			Cycle 1	*Cycle 2*						
		D −28 to D −1	*D1 (≤7D after randomization)*	*D1 (+1D)*	*Wk 6 (≤8D to surgery)*	*Wk 7 (±7D)*	*Wk 10 (≥20D after surgery)*	*Wk 13*	*Every 3M (±7D)*	*6M after surgery (±7D)*
Local Laboratory Assessments (cont.)										
Chemistry	*4.5.9.1*		x [h]	x [h]	x [i]		x	x		x
Lipid panel					x			x		
Coagulation (INR and aPTT)			x [h]	x [h]	x					
TSH, free T3 (or total T3), free T4			x [h]		x		x	x		x
Cardiac enzymes			x [h]	x [h]	x [j]			x		
C-reactive protein			x [h]	x [h]	x		x	x		x
Pregnancy test			x [h]	x [h]	x		x	x		x [k]
Urinalysis			*Perform as clinically indicated.*					X		
Central Laboratory Assessments										
Serum autoantibody sample	*4.5.9.2*		*Perform if a patient experiences a suspected immune-mediated adverse event. Autoantibody analysis should be repeated for patients who develop signs or symptoms suggestive of autoimmune disease (e.g., lupus erythematosus).*							
PK samples			*Refer to Section A16–7.*							
ADA samples			*Refer to Section A16–7.*							

Table A16-5 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg+TIRA ARM (cont.)

Assessment/ Procedure [a]	Protocol Section	Screening (see Appendix 10)	Treatment Cycles (21-Day Cycles)		Pre-Surgery	Surgery CLND	Post-Surgery	Treatment Comp./ Discon. [b]	Long-Term Follow-Up	Surgery Follow-Up [c]
			Cycle 1	Cycle 2						
		D −28 to D −1	D1 (≤7D after randomization)	D1 (+1D)	Wk 6 (≤8D to surgery)	Wk 7 (±7D)	Wk 10 (≥20D after surgery)	Wk 13	Every 3M (±7D)	6M after surgery (±7D)
Central Laboratory Assessments (cont.)										
Blood and plasma samples for biomarkers	4.5.9.2		Refer to Section A16–7.						X (only if onsite)	Refer to Section A16–7.
Pre-dose tumor biopsy				x [1]						
Resected tissue						x				
Tumor biopsy (optional)	4.5.11		Perform at the time of unacceptable toxicity, loss of clinical benefit, relapse, or at any other time if deemed clinically feasible by the investigator.							

ADA=anti-drug antibody; CLND=complete lymph node dissection; Comp.=completion; CT=computed tomography; D=day; Discon.=discontinuation; ECOG=Eastern Cooperative Oncology Group; IMP=investigational medicinal product; M=month; MUGA=multiple-gated acquisition; PK=pharmacokinetic; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; TTE=transthoracic echocardiogram; Wk=week.

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

[a] *If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window.*

[b] *Regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will return to the clinic for a treatment completion/discontinuation visit 6 weeks after surgery and patients who do not proceed to surgery will return to the clinic for a treatment completion/discontinuation visit not more than 30 days after the final dose of study treatment.*

[c] *Patients who proceed to surgery will have the surgery follow-up 6 months after surgery.*

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] *The disease status assessments at Week 13 should include a mandatory CT scan.*

Table A16-5 SCHEDULE OF ACTIVITIES FOR RO7247669 600 mg+TIRA ARM (cont.)

[f] *After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). For details on reporting all treatment-related non-serious adverse events that lead to surgical delay, see Section 5.6. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to 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.*

[g] *Patients who complete the treatment period, regardless of whether they complete the study drug treatment period or discontinue study drug prematurely, patients who proceed to surgery will have their first long-term follow-up visit 3 months after surgery and patients who do not proceed to surgery will have their first long-term follow-up visit 3 months after the final dose of study treatment. Information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. 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 only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

[h] *Laboratory tests must be performed within 72 hours prior to dosing during the treatment period. If screening laboratory assessments were performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.*

[i] *At the pre-surgery visit, adrenocorticotropic hormone, cortisol, S100, and erythrocyte sedimentation rate will be included in the chemistry panel.*

[j] *This is only applicable if elevated levels of cardiac enzymes were detected in previous assessments.*

[k] *If periods are missed or delayed before the 6-month follow-up visit, pregnancy testing should be repeated. This test can be performed by a local gynecologist.*

[l] *The Cycle 2 Day 1 on-treatment tissue sample must be collected up to 72 hours prior to drug administration.*

A16–7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 600 mg+TIRA ARM

Visit	*Time*	*Sample Type*
Day 1 of Cycle 1	*Prior to first infusion (−6 hr to 0 hr)*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Tiragolumab PK (serum)* • *Tiragolumab ADA (serum)* • *Biomarkers (blood, plasma)*
	30 (±10) minutes after the end of tiragolumab infusion	• *Tiragolumab PK (serum)*
	30 (±10) minutes after the end of RO7247669 infusion	• *RO7247669 PK (serum)*
Day 1 of Cycle 2	*Prior to infusion (−6 hr to 0 hr)*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Tiragolumab PK (serum)* • *Tiragolumab ADA (serum)* • *Biomarkers (blood, plasma)*
	30 (±10) minutes after the end of RO7247669 infusion	• *RO7247669 PK (serum)*
Surgery CLND *Week 7*	*Prior to surgery (−24 hr to 0 hr)*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Tiragolumab PK (serum)* • *Tiragolumab ADA (serum)* • *Biomarkers (blood, plasma)*
Post-surgery *Week 10* [a]	*At visit*	• *RO7247669 PK (serum)* • *RO7247669 ADA (serum)* • *Tiragolumab PK (serum)* • *Tiragolumab ADA (serum)* • *Biomarkers (blood, plasma)*
Treatment completion/ discontinuation *Week 13*	*At visit*	• *RO7247669 ADA (serum)* • *RO7247669 PK (serum)* • *Tiragolumab PK (serum)* • *Tiragolumab ADA (serum)* • *Biomarkers (blood, plasma)*
Long-term follow-up *Every 3 months (±7 days)* [b]	*At visit* [b]	• *Biomarkers (blood, plasma)*

A16-7 SCHEDULE OF PHARMACOKINETIC, IMMUNOGENICITY, AND BIOMARKER SAMPLES FOR RO7247669 600 mg+TIRA ARM (CONT'D)

Visit	*Time*	*Sample Type*
Surgery follow-up *6 months after surgery (±7 days)*	*At visit*	• *RO7247669 ADA (serum)* • *RO7247669 PK (serum)* • *Biomarkers (blood, plasma)*

ADA = anti-drug antibody; CLND = complete lymph node dissection; PK = pharmacokinetic; Tira = tiragolumab.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] *Week 10 biomarker samples must be obtained ≥20 days post-surgery.*

[b] *To be collected if visit is conducted on site.*

A16–8 REFERENCES

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

Table A17-1 Investigational and Auxiliary Medicinal Product Designations for the European Economic Area under Clinical Trials Regulation (CTR EU No. 536/2014)

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
RO7247669	IMP (test product)	Unauthorized	Not applicable
Nivolumab	IMP (comparator)	Authorized	Yes
Ipilimumab	IMP (comparator)	Authorized	Yes
Prednisone	AxMP (rescue medication)	Authorized	Yes
Methylprednisolone	AxMP (rescue medication)	Authorized	Yes
Dexamethasone	AxMP (rescue medication)	Authorized	Yes
Diphenhydramine	AxMP (rescue medication)	Authorized	Yes
Methimazole	AxMP (rescue medication)	Authorized	Yes
Carbimazole	AxMP (rescue medication)	Authorized	Yes
Insulin	AxMP (rescue medication)	Authorized	Yes
Paracetamol	AxMP (rescue medication)	Authorized	Yes

AxMP = Auxiliary Medicinal Product; EEA = European Economic Area; IMP = investigational medicinal product.

Table A17-2 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area under CTD (Clinical Trials Directive 2001/20/EC)

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Atezolizumab (RO5541267)	IMP (test product)	Authorized	No
Tiragolumab (RO7092284)	IMP (test product)	Unauthorized	Not applicable
RO7247669	IMP (test product)	Unauthorized	Not applicable
Nivolumab	IMP (comparator)	Authorized	Yes
Ipilimumab	IMP (comparator)	Authorized	Yes
Prednisone	NIMP (rescue medication)	Authorized	Yes
Methylprednisolone	NIMP (rescue medication)	Authorized	Yes
Dexamethasone	NIMP(rescue medication)	Authorized	Yes
Diphenhydramine	NIMP(rescue medication)	Authorized	Yes
Methimazole	NIMP (rescue medication)	Authorized	Yes
Carbimazole	NIMP(rescue medication)	Authorized	Yes
Insulin	NIMP (rescue medication)	Authorized	Yes
Paracetamol	NIMP (rescue medication)	Authorized	Yes

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

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