Official Title: A Phase II, Open-Label, Multicenter, Randomized Study of the Efficacy and Safety of RO7198457 in Combination with Pembrolizumab Versus Pembrolizumab in Patients with Previously Untreated Advanced Melanoma

NCT Number: NCT03815058

Document Date: Protocol Amendment Version 5: 14-Nov-2023

PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF RO7198457 IN COMBINATION WITH PEMBROLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED MELANOMA**
PROTOCOL NUMBER:	GO40558
STUDY NAME:	IMCODE001
VERSION NUMBER:	5
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 18374 EU CT Number: 2023-507389-15-00 EUDRACT Number: 2018-001773-24
TEST PRODUCT:	RO7198457
SPONSOR NAME AND ADDRESS:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on final page.
4	11 October 2023
3 (Germany)	21 October 2019
2	27 April 2019
1	14 August 2018

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol GO40558 has been amended to correct minor errors introduced in Protocol GO40558, Version 4. Protocol GO40558, Version 4 was amended to align with the harmonized multinational Clinical Trials Regulation (CTR) guidelines and to add clarity on study conduct. This amendment supersedes Protocol GO40558 Version 3 (Germany) and Version 4. Due to the administrative nature of this amendment, cumulative changes to the protocol from Version 3 (Germany) and Version 4 along with changes specific to this amendment are included.

Changes specific to Version 5, along with a rationale for each change, are summarized below:

- Minor deletions have been made to correct errors from Protocol GO40558, Version 4 (Section 4.3.1, Appendices 2, 3, and 13).
- The email address to which the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form is sent has been updated from "SAEIntake@covance.com" to "SAEIntake@Fortrea.com" (Section 5.4.2.1).

Changes specific to Version 4, along with a rationale for each change, are summarized below:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitor has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information in Section 5.4.1 has been replaced with a sentence indicating that this information will be provided separately to sites.
- The synopsis has been simplified to align with CTR and other guidelines.
- Language has been updated to clarify the responsibilities of the investigator and the role of the Medical Monitor and Sponsor to ensure the appropriate execution of the study (Sections 3.3.13, 4.1.1, 4.1.2, 4.2, 4.3.2.1, 4.4.1–4.4.3, 4.5.7, 5.1.1.1, 5.1.4.1–5.1.4.3; Appendices 1, 2, and 7).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements (Section 4.3 and Appendix 13).
- [redacted]
- Updated the frequency of tumor assessments during follow-up to better align with standard of care (Section 4.5.5, Appendix 1, and Appendix 2).
- Language describing procedures for patient withdrawal from the study and the Research Biosample Repository has been updated to clarify that patients may withdraw verbally or in writing (Sections 4.5.13.6 and 4.6.2).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.13.6).

- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- To align with CTR requirements, text has been modified to clarify that summaries of clinical study results may be available for public access in health authority databases. And language has been modified to clarify that Roche's global policy on data sharing does not have requirements that must be met before study results can be made available (Sections 8.4 and 9.5).
- The URL for the Roche Global Policy on Sharing of Clinical Study Information has been updated (Section 9.5).
- Blood biomarker collection (PBMC-I) has been removed for patients in the Follow-Up period (Appendix 1 and Appendix 2).
- Language has been added to clarify that questionnaires can be performed at earlier timepoints in the event that other assessments associated with Day 1 are done in advance of study treatment within protocol-specified time windows (Appendix 1 and Appendix 2).
- Language has been added to allow patients who cross over from Arm A to Arm B to skip screening assessments (Parts A and B) and the Cycle 1, Day 1 (C1D1) visit [redacted]
- [redacted]

Changes specific to Version 3 (Germany), along with a rationale for each change, are summarized below:

- Sections 3.1.3 and 3.1.4 have been updated to specify that informed consent to treatment beyond disease progression or to cross over from treatment Arm A to B includes understanding and actively declining other treatment options available.
- Section 5.1.4.2 has been amended to align treatment interruption and modification guidelines for pembrolizumab (Keytruda®) with the Keytruda Summary of Product Characteristics.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF RO7198457 IN COMBINATION WITH PEMBROLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED MELANOMA**
PROTOCOL NUMBER:	GO40558
VERSION NUMBER:	5
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 18374 EU CT Number: 2023-507389-15-00 EUDRACT Number: 2018-001773-24
TEST PRODUCT:	RO7198457
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF RO7198457 IN COMBINATION WITH PEMBROLIZUMAB VERSUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED MELANOMA**
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SPONSOR:	Genentech, Inc.

PRIMARY AND SECONDARY OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and patient-reported outcomes (PROs) of RO7198457 plus pembrolizumab compared with pembrolizumab alone in patients with previously untreated advanced melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective	*Corresponding Endpoint*
• *To evaluate the efficacy of RO7198457 plus pembrolizumab compared with pembrolizumab alone*	• *Progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)*
Secondary Objectives	***Corresponding Endpoints***
• *To evaluate the efficacy of RO7198457 plus pembrolizumab compared with pembrolizumab alone*	• *Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1* • *Overall survival (OS) after randomization, defined as the time from randomization to death from any cause* • *Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, as determined by the investigator according to RECIST v1.1* • *Mean change from baseline in health-related quality of life (HRQoL) scores as assessed through use of the two-item global health status (GHS)/HRQoL subscale (Questions 29 and 30) of the European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 (EORTC QLQ-C30) at specified timepoints*
Secondary Objectives (cont.)	***Corresponding Endpoints (cont.)***
• *To evaluate the efficacy of RO7198457 plus pembrolizumab in patients who have progressed following pembrolizumab monotherapy*	• *ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ³4 weeks apart, as determined by the investigator according to RECIST v1.1, at the time of crossover*
• *To evaluate the safety of RO7198457 plus pembrolizumab compared with pembrolizumab alone*	• *Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)* • *Change from baseline in targeted vital signs* • *Change from baseline in targeted clinical laboratory test results*

OVERALL DESIGN AND STUDY POPULATION

This is a Phase II, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of RO7198457 plus pembrolizumab compared with pembrolizumab alone in patients with previously untreated advanced melanoma.

The study has an initial safety run-in stage and a randomized stage.

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

Phase:	*II*	***Population Type:***	*Adult patients*
Control Method:	*Active comparator*	***Population Diagnosis or Condition:***	*Advanced melanoma*
Interventional Model:	*Parallel group*	***Population Age:***	*Age ≥18 years*
Test Compound:	*RO7198457*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*Pembrolizumab*	***Study Intervention Assignment Method:***	*Randomized*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*Approximately 120*

STUDY TREATMENT

Patients in the safety run-in will receive at least 1 cycle (21 days) of 200 mg pembrolizumab monotherapy administered by IV infusion. Once RO7198457 is manufactured and available, patients will receive 200 mg pembrolizumab by IV infusion every 3 weeks (Q3W) and [redacted] *RO7198457 by IV infusion.*

DURATION OF PARTICIPATION

The study consists of two stages: an initial safety run-in stage and a randomized stage. Each stage will have a two-part screening period (Part A and Part B), a treatment period *of 24 months*, and post-treatment follow-up period.

COMMITTEES

Independent Committees:	*Not applicable*
Other Committees:	*Internal Monitoring Committee*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AJCC v8.0	American Joint Committee on Cancer 8th Edition
anti-HBc	antibody to hepatitis B core antigen
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
CIT	cancer immunotherapy
CL	clearance
C_{max}	maximum serum concentration observed
C_{min}	minimum serum concentration observed
CR	complete response
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte–associated protein 4
CV	coefficient of variation
DC	dendritic cell
[redacted]	[redacted]
DOR	duration of response
[redacted]	[redacted]
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life–Core 30
ESMO	European Society for Medical Oncology
FACS	fluorescence-activated cell sorting
FPI	first patient in
G-CSF	granulocyte colony-stimulating factor
GHS	global health status
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Definition
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HLA	human leukocyte antigen
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IFN(-α,-γ)	interferon(-α,-γ)
IHC	immunohistochemistry
IL(-2,-6,-12)	interleukin(-2,-6,-12)
IMC	Internal Monitoring Committee
iRECIST	immune-based therapeutics Response Evaluation Criteria in Solid Tumors
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat (population)
IWRS	interactive web-based response system
LC	liquid chromatography
LDH	lactate dehydrogenase
MAOI	monoamine oxidase inhibitor
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MS	mass spectrometry
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NK	natural killer (cell)
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCV	personalized cancer vaccine
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic

Abbreviation	Definition
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
Q3W	every 3 weeks
qRT-PCR	quantitative reverse transcription polymerase chain reaction
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
RO7198457	investigational medicinal product
SCID	severe combined immunodeficiency
SJS	Stevens-Johnson syndrome
TCR	T-cell receptor
TEN	toxic epidermal necrolysis
TIL	tumor-infiltrating lymphocyte
TNF-α	tumor necrosis factor–α
ULN	upper limit of normal
V_{ss}	volume of distribution under steady-state conditions
WES	whole exome sequencing
WGS	whole genome sequencing
WPAI	Work Productivity and Activity Impairment
WPAI:Melanoma	Work Productivity and Activity Impairment: Melanoma, Version 2.0

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA

Melanoma is a potentially deadly form of skin cancer originating from melanocytes. In 2012, there were approximately 232,000 new cases and 55,000 deaths from melanoma worldwide, with more than 100,000 new cases and 22,000 deaths in Europe (Ferlay et al. 2013). In the United States in 2018, an estimated 91,270 new diagnoses of melanoma are projected and approximately 9,320 patients are expected to die of the disease (American Cancer Society 2018). Additionally, estimates suggest a doubling of the incidence of melanoma every 10−20 years (Garbe and Leiter 2009).

The clinical outcome of patients with melanoma is highly dependent on the stage at presentation. Until recently, treatment options for metastatic melanoma were limited. Dacarbazine was considered to be the standard first-line treatment; however, outcomes were poor, with response rates of 5%–12%, median progression-free survival (PFS) of less than 2 months, and median overall survival (OS) of 6.4 to 9.1 months (Middleton et al. 2000; Bedikian et al. 2006; Chapman et al. 2011; Robert et al. 2011). Combination chemotherapy and chemotherapy combined with interferon-α (IFN)-α or interleukin-2 (IL-2), although showing improved response rates, have not resulted in improved OS (Chapman et al. 1999; Ives et al. 2007).

Immunotherapeutic agents that target co-inhibitory receptors or "immune checkpoints" that suppress T-cell activation have improved the outcomes of patients with advanced melanoma. In the Phase I KEYNOTE-001 study of pembrolizumab monotherapy in advanced melanoma, 3-year OS was 40% in all patients and 45% in treatment-naive patients (Robert et al. 2016), and 5-year OS was 34% in all patients and 41% in treatment-naive patients (Hamid et al. 2018). In the Phase III KEYNOTE-006 study (pembrolizumab vs. ipilimumab) in advanced melanoma, the 1-year OS rates ranged from 74%–58% for pembrolizumab and ipilimumab, respectively (Robert et al. 2015b). Two-year OS rates were 55%−43% (Schachter et al. 2017), and 4-year OS rates were 41%−34% (Long et al. 2018). In the CheckMate 067 trial, the median OS in the nivolumab group was 37.6 months (95% CI: 29.1, not reached), with 52% of the patients in the nivolumab group alive at 3 years, as compared with 34% of those in the ipilimumab group. At a minimum follow-up of 36 months, the median OS had not been reached in the nivolumab-plus-ipilimumab group. The survival rate at 3 years was 58% among patients in the nivolumab plus-ipilimumab group (Wolchok et al. 2017).

Despite these advances, many patients do not respond to current therapies or later succumb to their disease, highlighting the continuing unmet medical need for more efficacious treatment options.

1.2 BACKGROUND ON RO7198457

Human cancers carry numerous non-synonymous mutations, many of which are immunogenic and, therefore, targetable by cancer vaccines. Some cancers, like

melanoma, can harbor in excess of 500 non-synonymous mutations on average. Although some non-synonymous mutations may act as drivers for maintaining the oncogenic phenotype, every patient's cancer bears a highly individual mutation repertoire.

Several recent studies have shown that neoantigens may have an important role in anti-tumor immunity. High mutational burden correlates with higher tumor-infiltrating $CD8^+$ T cells (Brown et al. 2014) and cytolytic activity of natural killer (NK) and $CD8^+$ T cells (Rooney et al. 2015). Multiple studies have suggested that mutational burden and neoantigen frequency in melanoma, bladder cancer, and lung cancer correlate with improved survival in response to checkpoint inhibitors, such as anti–CTLA-4 and anti–PD-1 (van Rooij et al. 2013; Snyder et al. 2014; Rizvi et al. 2015; Van Allen et al. 2015; Rosenberg et al. 2016; Ramalingam et al. 2018). Furthermore, a comparison of the effects of PD-1 blockade in patients with mismatch repair proficient and deficient cancer shows a strong association between clinical response and mismatch repair deficiency (Le et al. 2015). Neoantigen-specific $CD4^+$ and $CD8^+$ T cells can be detected in cancer patients (Snyder et al. 2014; Linnemann et al. 2015; Rizvi et al. 2015) and the frequency of $CD8^+$ T cells against neoantigens in the tumor or the blood increases after checkpoint inhibitor treatment (Snyder et al. 2014; Rizvi et al. 2015), indicating that these T cells are the targets of checkpoint blockade. The neoantigen-specific immune-stimulating effects of a therapeutic vaccine may improve the efficacy of checkpoint blockade by expanding the tumor-specific T-cell repertoire through the priming of de novo immune response and by further expanding the preexisting immune response, which may significantly improve the response rate and durability of responses compared to either agent alone.

Most mutations are randomly induced by carcinogens, ultraviolet radiation, or DNA repair defects. As the resulting neoantigens are unique to each patient, targeting them through vaccination requires a personalized approach (Hartmaier et al. 2017). RO7198457 is a personalized cancer vaccine (PCV) classified as an iNeST (Individualized Neoantigen Specific Therapy) that is based on the immunotherapeutic targeting of the unique mutations in a given patient's tumor. Multiple key technologies have been combined to generate a controlled process that covers all steps from identification of mutations in individual clinical tumor specimens to the supply of an individually tailored RNA vaccine for use in a specific patient.

There are three critical vaccine components that determine the type and strength of the immune response: 1) the antigens, 2) the delivery platform that brings antigens to dendritic cells (DCs) for presentation to T cells, and 3) the adjuvant that provides the immunostimulatory signal to DCs that shapes the outcome of the immune response (Coffman et al. 2010). [redacted]

In myeloid DCs, the RNA is released into the cytosol and translated into a poly-neoepitopic peptide (Kreiter et al. 2010). The polypeptide contains additional sequences to enhance antigen presentation. The signal sequence (sec) from the MHCI heavy chain at the N-terminal of the polypeptide targets the nascent molecule to the endoplasmic reticulum, which has been shown to enhance MHCI presentation efficiency (Kreiter et al. 2008). The transmembrane and cytoplasmic domains of MHCI heavy chain guide the polypeptide to the endosomal/lysosomal compartments that were shown to improve MHCII presentation (Kreiter et al. 2008).

1.2.1 Summary of Nonclinical Studies Supporting RO7198457

A comprehensive nonclinical program was undertaken to demonstrate in vitro and in vivo pharmacology, pharmacodynamic (PD), pharmacokinetic (PK), and toxicology profiles of RO7198457. Nonclinical studies supporting RO7198457 utilized various representative RNA molecules from the vaccine platform in either RNA-Lipoplex or RNA applied in Ringer's solution (i.e., naked RNA) formulations using RNA encoding tumor-associated shared non-mutated antigens (termed IVAC WAREHOUSE) or unique mutated antigens (termed IVAC MUTANOME). Refer to the RO7198457 Investigator's Brochure for details on nonclinical studies.

1.2.2 Summary of RO7198457 Phase I Clinical Data

RO7198457 is currently being studied in Study GO39733, an open-label, multicenter Phase Ia/Ib trial evaluating the safety and pharmacokinetics of escalating doses of RO7198457 as a single agent (Phase Ia) and in combination with atezolizumab (Phase Ib) in patients with locally advanced or metastatic tumors. [redacted] Clinical pharmacology and efficacy information are not yet available.

1.2.2.1 Clinical Safety

As of 5 October 2018, RO7198457 has been administered in 50 safety evaluable patients in Study GO39733. [redacted]

[redacted]

[redacted]

Enrollment and analyses are ongoing in Study GO39733, and all clinical data presented in this document are preliminary. Refer to the RO7198457 Investigator's Brochure for details on clinical safety.

1.2.2.2 Clinical Efficacy

Preliminary clinical data are available on similar vaccine platforms (Kranz et al. 2016; Sahin et al. 2017). [redacted] The first in human study of RO7198457 is ongoing in patients with advanced solid tumors.

For further details, refer to the RO7198457 Investigator's Brochure for details on clinical efficacy.

1.2.2.3 Pharmacodynamic Activity of RO719845

As of 05 October 2018, preliminary PD data measuring cytokine response in peripheral blood are available for patients treated in Phase Ia portion of Study GO39733 at [redacted]

transient returns to baseline levels by 24 hours. Similar cytokine induction is observed after repeated RO719845 infusions in individual patients. These cytokine data demonstrate PD effects of RO7198457 mediated through TLR7/8 stimulation.

For further details, refer to the RO7198457 Investigator's Brochure.

1.3 COMBINATION OF A THERAPEUTIC CANCER VACCINE AND INHIBITION OF PD-L1/PD-1 PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

Clinical and nonclinical data on currently available immunotherapeutics suggest that single-agent immunotherapy is unlikely to induce complete and durable anti-tumor responses in the majority of patients. Host immunosuppression by malignant cells is mediated by multiple pathways; therefore, combination therapy regimens employing two or more targeted cancer immunotherapy (CIT) agents may be required to fully engage the anti-tumor potential of the host immune system. Therapeutic vaccines, while promising, have historically fallen short of expectations. One of the potential reasons is that cancer-specific T cells become functionally exhausted during chronic exposure to cancer cells. Conversely, no objective responses are observed in the majority of patients treated with anti–PD-L1/PD-1 antibodies. A possible explanation for this is the lack of natural infiltration of effector immune cells into the tumor microenvironment (Herbst et al. 2014).

Nonclinical studies indicate that the combination of checkpoint inhibitors and vaccines has the potential for combined effects. Experimental animal models of chronic infection and cancer demonstrate that the PD-L1/PD-1 pathway plays a critical role in shaping $CD8^+$T cells and may cooperate with therapeutic vaccination to enhance anti-tumor T-cell responses and elicit tumor regression (Ha et al. 2008). PD-1 blockade combined with therapeutic vaccination results in an increased influx of IFN-γ producing activated T cells to the tumor compared to single treatment (Allie et al. 2011; Soares et al. 2015) and resulted in increased tumor regression (Fu et al. 2014; Soares et al. 2015). In mouse models of glioblastoma multiforme, the combination of tumor-lysate−loaded DC vaccine and anti–PD-1 also resulted in longer survival benefit dependent on CD8+T cells (Antonios et al. 2016) and was more effective than monotherapy with anti–PD-1 alone (Li et al. 2009).

Early data from clinical studies suggest that the combination of checkpoint inhibitors and vaccines is well tolerated and has potential synergy. The initial combination of anti-CTLA-4 and a granulocyte-macrophage colony-stimulating factor (GM-CSF) secreting cancer vaccine (GVAX) demonstrated objective clinical responses in patients with pancreatic ductal adenocarcinoma while neither single agent was able to induce responses (Le et al. 2013). As another example, recently, a PD-1 inhibitor was combined with a peptide vaccine in resected high-risk metastatic melanoma with HMB-45, NY-ESO−1, and/or MART-1 positive resected tumors. The combination was well tolerated, demonstrated increases in tumor antigen-specific CD8+T cells, and

showed an improved relapse-free survival rate compared to stage-matched historical controls (Gibney et al. 2015). Multiple ongoing clinical trials are assessing vaccines in combination with anti–PD-L1/PD-1 inhibitors (NCT02451982, NCT03406715, NCT03164772, NCT03169738).

The combination of RO7198457 and anti–PD-1 represents an attractive strategy for potentiating anti-tumor activity and is expected to enhance both the magnitude and quality of the tumor-specific T-cell responses, which may result in increased anti-tumor activity that might be observed with RO7198457 or pembrolizumab as a single agent.

Refer to the RO7198457 Investigator's Brochure for details on nonclinical and clinical studies.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Checkpoint inhibitors are currently the standard of care for metastatic melanoma. However, the durable clinical benefit observed with agents targeting PD-L1/PD-1 across diverse malignancies, including melanoma, appears limited to a subset of patients.

Despite the advances in OS that have accompanied the development of now widely administered immunotherapies such as PD-1 therapies (nivolumab, pembrolizumab), or the combination of anti-PD1 with anti–CTLA-4 therapy (nivolumab and ipilimumab), a significant fraction of patients do not respond to treatment with checkpoint inhibitors or experience only transient disease stabilization (Robert et al. 2015a; Rosenberg et al. 2016), which demonstrates the persistent unmet need for patients with metastatic solid tumors. Although objective responses in the approximately 10%–30% of patients who respond to treatment with PD-1 inhibitors tend to be durable, these patients nonetheless remain at risk for progression. In a recent study of melanoma patients treated with PD-1 blockade, 53 out of 205 patients (26%) who had had an objective response to pembrolizumab had disease progression at a median follow-up of 21 months (Ribas et al. 2016).

While anti-PD1 and anti-PD1 plus anti–CTLA-4 combinations have significantly improved long-term outcomes in patients with melanoma the latter has come at the cost of increased treatment related toxicities. Despite these improvements, a significant proportion of patients remain at risk of disease progression and succumb to their disease. Combination therapies that address mechanisms of resistance checkpoint blockade with increasing toxicity are needed.

Resistance may occur at the level of the effector T cell, whose activity may be limited due to poor T-cell stimulation. In preclinical models, induction of antigen specific immunity combined with concomitant blockade of PD-L1/PD-1 pathways demonstrated superior efficacy over the respective single-agent inhibitors of these pathways, even in models in which single-agent vaccine had limited activity. In these studies, tumor-infiltrating T cells demonstrated increased IFN-γ expression (a hallmark of

activation and anti-tumor activity of T cells) only when PD-L1 was blocked but not with single-agent vaccine (Duraiswamy et al. 2013; Fu et al. 2014). On the basis of these studies, it is hypothesized that the combination of RO7198457 with anti–PD-L1/PD-1 may result in activation of anti-tumor immune responses leading to enhanced killing of tumor cells and improved clinical responses in cancer patients.

Clinical efficacy data for RO7198457 in combination with anti–PD-L1/PD-1 is limited. While no direct clinical benefits are known at this time, the role of neoantigen reactive T cells in endogenous therapeutic anti-tumor responses has been well characterized in patients. In addition, the available nonclinical data provide a strong rationale for investigating the potential benefit of RO7198457 in combination with anti–PD-L1/PD-1 in patients with advanced melanoma. In addition, the postulated mechanism of action of RO7198457 in combination with anti–PD-L1/PD-1 is predicted to complement and enhance immune-potentiating activity; hence, the combination of RO7198457 and anti–PD-L1/PD-1 may be associated with a higher frequency and/or greater severity of immune-related adverse events than observed with either molecule as a single agent. The potential risks with RO7198457, [redacted] may occur more frequently or in greater severity when RO7198457 is administered in combination with anti–PD-L1/PD-1. Conversely, in combination with anti–PD-L1/PD-1, RO7198457 may exacerbate anti–PD-L1/PD-1 related adverse events (see the pembrolizumab prescribing information) or may have non-overlapping toxicities with anti–PD-L1/PD-1.

This proof-of-concept Phase II study will determine clinical benefit of adding RO7198457 to a standard-of-care therapy for advanced melanoma. Comparing novel immuno-oncology therapies to historical single-agent immunotherapy regimens with a baseline level of activity possesses many challenges. Outcomes may be biased by baseline characteristics of patients leading to misinterpretation of efficacy or lack thereof. In addition, stable plateaus are more commonly seen at the tail of PFS and OS curves in patients receiving immunotherapy and may be challenging to evaluate in single-arm studies (Kirkwood et al. 2000; Maio et al. 2015; Rittmeyer et al. 2017). These plateaus represent subsets of patients with long-term benefit. Finally, there may be discordance between ORR, PFS and OS benefit when comparing immuno-oncology agents or other therapies making reliance on one single endpoint challenging. A comparison of the DC vaccine Sipuleucel-T to placebo in patients with metastatic prostate cancer identified a 22% survival benefit (hazard ratio [HR] = 0.78; 95% CI: 0.61, 0.98) while the time to disease progression was similar in the two groups (Kantoff et al. 2010). Similarly, there was no significant difference in PFS between patients with pretreated metastatic renal-cell carcinoma who received nivolumab compared to everolimus (median PFS approximately 4 months in both groups) despite an OS benefit with nivolumab over everolimus (HR for death = 0.73; 98.5% CI: 0.57, 0.93; p = 0.002) (Motzer et al. 2015). Since randomized studies with time dependent endpoints provide the most effective

approach to determining efficacy (Hoos et al. 2010; Anagnostou et al. 2017), this proof of concept study will utilize a randomized Phase II design to determine if the addition of RO7198457 to standard-of-care pembrolizumab in melanoma provides an efficacy signal. Given the unmet need in advanced melanoma, the current data support development of RO7198457 in combination with PD-L1/PD-1 blockade in this indication.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and patient-reported outcomes (PROs) of RO7198457 plus pembrolizumab compared with pembrolizumab alone in patients with previously untreated advanced melanoma. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7198457 plus pembrolizumab compared with pembrolizumab alone on the basis of the following endpoint:

- PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

2.1.2 Secondary Efficacy Objectives

A secondary efficacy objective for this study is to evaluate the efficacy of RO7198457 plus pembrolizumab compared with pembrolizumab alone on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1
- OS after randomization, defined as the time from randomization to death from any cause
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, as determined by the investigator according to RECIST v1.1
- Mean change from baseline in health-related quality of life (HRQoL) scores as assessed through use of the two-item global health status (GHS)/HRQoL subscale (Questions 29 and 30) of the European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 (EORTC QLQ-C30) at specified timepoints

Another secondary objective is to evaluate the efficacy of RO7198457 plus pembrolizumab in patients who have progressed following pembrolizumab monotherapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1, at the time of crossover

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of RO7198457 plus pembrolizumab compared with pembrolizumab alone on the basis of the following endpoints:

- PFS rate at 12 months, defined as the proportion of patients in the intent-to-treat (ITT) population who have not experienced disease progression or death from any cause as determined by the investigator according to RECIST v1.1
- PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined according to immune-based therapeutics Response Evaluation Criteria in Solid Tumors (iRECIST)
- ORR, defined as a CR or PR on two consecutive occasions $\geq$ 4 weeks apart, as determined according to iRECIST
- Change from baseline in disease and treatment-related symptoms, as assessed through use of the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) and an additional item regarding bother due to side effects
- Change from baseline on role, physical function, and on-work productivity as assessed through use of select scales of the EORTC QLQ-C30
- Change from baseline on role, physical function, and on-work productivity as assessed through use of select scales of the Work Productivity and Activity Impairment (WPAI)

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of RO7198457 plus pembrolizumab compared with pembrolizumab alone on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC OBJECTIVES

The exploratory PK objectives for this study are as follows:

- To characterize the RO7198457 PK profile on the basis of the following endpoints:
  - Plasma concentrations [redacted] at specified timepoints
  - Plasma concentrations [redacted] at specified timepoints
- To characterize the PK of pembrolizumab when given in combination with RO719847 on the basis of the following endpoint:
  - Serum concentrations of pembrolizumab at specified timepoints
- To evaluate potential relationships between drug exposure and the efficacy and safety of RO7198457 and pembrolizumab on the basis of the following endpoints:
  - Relationship between plasma concentration or PK parameters [redacted] and efficacy endpoints
  - Relationship between plasma concentration or PK parameters [redacted] and efficacy endpoints
  - Relationship between plasma concentration or PK parameters [redacted] and safety endpoints
  - Relationship between plasma concentration or PK parameters [redacted] and safety endpoints

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objectives for this study is to make a preliminary assessment of biomarkers that might act as predictors of response to RO7198457 in combination with pembrolizumab (i.e., predictive biomarkers) or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Immunogenicity of RO7198457 in combination with pembrolizumab as determined by antigen-specific T-cell responses relative to baseline
- Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy, safety, and other biomarker endpoints.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase II, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of RO7198457 plus pembrolizumab compared with pembrolizumab alone in patients with previously untreated advanced melanoma. The patient population includes patients with unresectable locally advanced (Stages IIIC and IIID) and metastatic (recurrent or de novo Stage IV) melanoma. This study will be conducted globally.

The study consists of two stages: an initial safety run-in stage and a randomized stage. Each stage will have a two-part screening period (Part A and Part B), a treatment period, and post-treatment follow-up period.

The safety run-in stage will consist of a single arm that will enroll approximately 6–12 patients. Patients in the safety run-in will receive at least 1 cycle (21 days) of 200 mg pembrolizumab monotherapy administered by IV infusion. Once RO7198457 is manufactured and available, patients will receive 200 mg pembrolizumab IV every 3 weeks (Q3W) and [redacted] RO7198457 IV as detailed in Section 4.3.2.1. Accrual in the randomized stage will not start until an Internal Monitoring Committee (IMC) has reviewed the safety data of the first 6 patients treated in the safety run-in stage (see Section 3.1.2).

The randomized stage will enroll approximately 120 patients, randomized in a 2:1 ratio, to either the experimental or control arm:

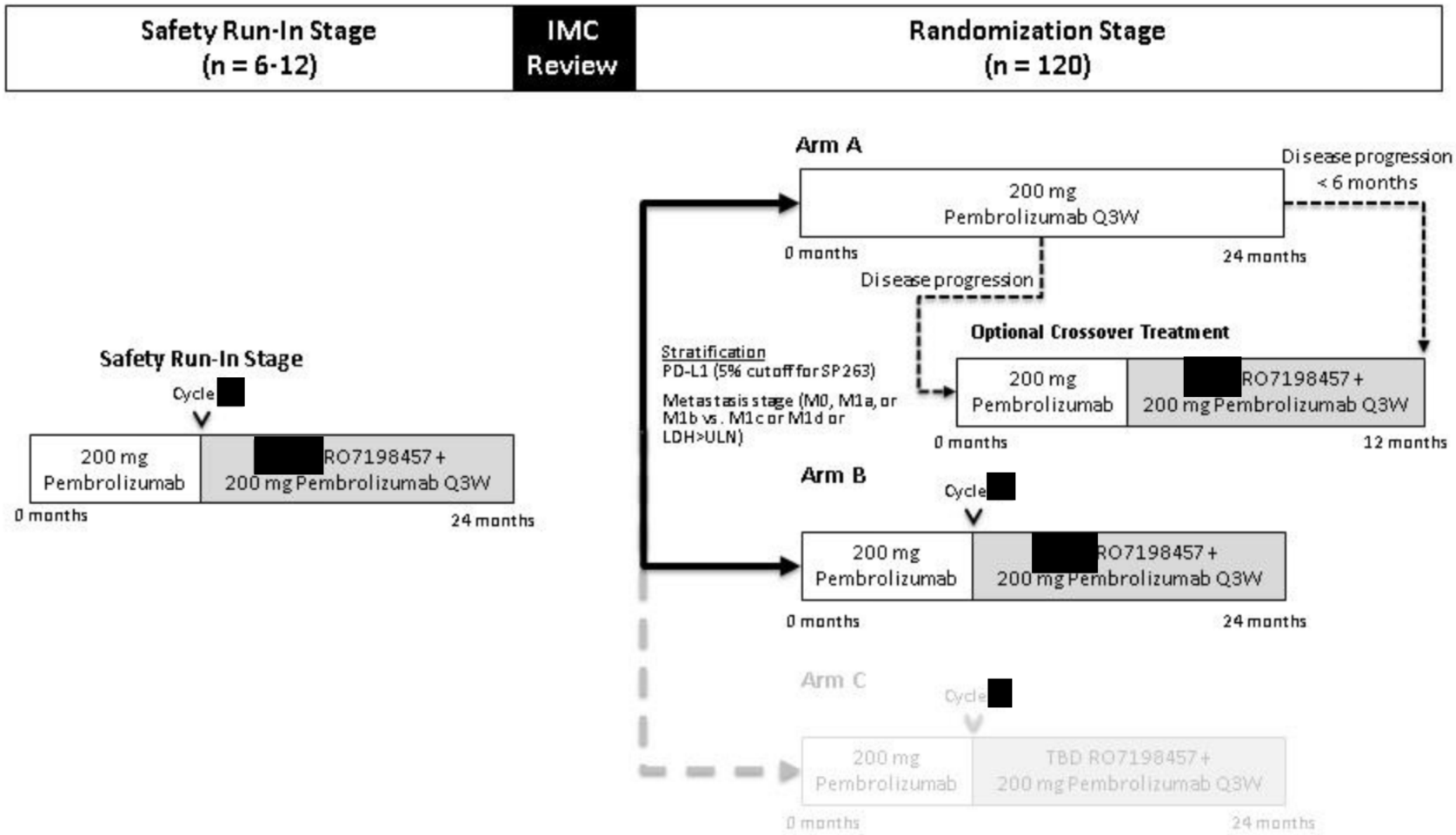
- Arm A (control): 200 mg pembrolizumab administered by IV infusion Q3W
- Arm B (experimental): at least 1 cycle of 200 mg pembrolizumab administered by IV infusion followed by 200 mg pembrolizumab IV Q3W and [redacted] RO7198457 IV as detailed in Section 4.3.2.1.

A third arm (Arm C) may be added to the study at a later time via a protocol amendment, pending the results of dose escalation in an ongoing Genentech sponsored Phase Ib study (GO39733). Patients in this arm would receive RO7198457 plus pembrolizumab with an alternative RO7198457 dose, alternative RO7198457 dosing paradigm (e.g., step-up dosing), and/or schedule of administration.

Upon confirmed disease progression (as assessed by the investigator per RECIST v1.1), patients randomized to Arm A will be given the option to cross over and receive combination treatment with RO7198457 and pembrolizumab, provided they meet eligibility criteria described in Section 4.1.3.

The study schema is presented in Figure 1.

Figure 1 Study Schema



IMC = internal monitoring committee; LDH = lactate dehydrogenase; Q3W = every 3 weeks; TBD = to be determined; ULN = upper limit of normal.
Note: In the randomized stage, patients will be randomized (2:1) to experimental treatment (Arm B) or control treatment (Arm A).

During the first part of the screening period (Part A), consenting patients will be assessed for preliminary eligibility (e.g., Eastern Cooperative Oncology Group [ECOG] Performance Status, blood chemistry, serology for HIV, hepatitis B virus [HBV], and hepatitis C virus [HCV]) and tumor tissue and a blood sample will be collected to define tumor-specific somatic mutations [redacted]

The second part of the screening period (Part B) will be a 28-day period prior to Day 1 to confirm patient eligibility.

Eligible patients in the randomized stage will be stratified by PD-L1 immunohistochemistry (IHC) status (≥5% vs. <5% or unknown) and disease stage *(based on screening Part B tumor assessment)* combined with baseline lactate dehydrogenase (LDH) level (M0, M1a, or M1b vs. M1c or M1d or LDH > upper limit of normal [ULN]) (see Section 4.2).

Patients in Arm A (pembrolizumab) will receive 200 mg of pembrolizumab monotherapy administered by IV infusion Q3W starting in Cycle 1.

Patients in the safety run-in stage and Arm B of the randomized stage ([redacted] RO7198457 plus 200 mg pembrolizumab) will receive pembrolizumab administered by IV infusion Q3W starting in Cycle 1. [redacted] Also described in this section is the timing of the subsequent doses, which are based on the timing of the first dose.

[redacted]

See Figure 2 for dosing schemas.

[redacted]

C = cycle; D = day.

Notes: Cycle = 21 days.

[redacted]

Pembrolizumab to be dosed every 3 weeks for 34 cycles (24 months).

Refer to Section 5.1.4.2 for guidance on dosing after treatment interruption.

The duration of treatment on this study will be up to 24 months for all patients as long as they are experiencing clinical benefit as assessed by the investigator in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data and clinical status. Patients may be permitted to continue treatment after RECIST v1.1 criteria for progressive disease are met (see Section 3.1.3). Patients in Arm A may have the option to cross over to combination treatment with RO7198457 plus pembrolizumab after confirmed disease progression, if crossover eligibility criteria are met (see Section 3.1.4). In addition, if a patient in Arm A completes 24 months of pembrolizumab and experiences confirmed disease progression $<$6 months after discontinuing pembrolizumab, they may have the option to receive crossover treatment with RO7198457 plus pembrolizumab (see Section 3.1.4).

Patients will undergo tumor assessments as detailed in Section 4.5.5, Appendix 1, and Appendix 2. Digital photography of cutaneous lesions, if indicated, will be performed at screening, on the same day as tumor assessment visit or at the first clinic visit following each tumor assessment (see Section 4.5.6).

Patients may be permitted to continue study treatment even if standard RECIST v1.1 criteria for progressive disease are met, provided they meet the criteria for continued treatment (see Section 3.1.3).

All patients who discontinue study treatment for reasons other than disease progression (e.g., adverse events) will continue tumor assessments per Section 4.5.5, Appendix 1 and Appendix 2.

Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 days after the last dose of study treatment. All patients will be followed for survival and subsequent anti-cancer therapy information approximately every 3 months until death, loss to follow-up, or study termination by Genentech, unless the patient requests to be withdrawn from follow-up. See Section 4.6 for details.

Primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints if needed.

In addition, patients will also be asked to complete PRO assessments at the beginning of each cycle until disease progression or treatment discontinuation, whichever occurs later (see Section 4.5.10, Appendix 1, and Appendix 2).

3.1.2 Safety Run-In Stage

Dosing of the first 2 patients in the safety run-in stage (RO7198457 plus pembrolizumab) will be separated by at least 48 hours.

Safety data from the first 6 patients in the safety run-in stage who are treated with at least 1 dose of RO7198457 will be formally reviewed by the IMC (see Section 3.1.5).

The Sponsor may enroll up to 6 additional patients in the safety run-in stage to further assess safety of the combination treatment.

Accrual in the randomized stage will not start until the IMC has reviewed the safety data of the first 6 patients treated in the safety run-in stage. On the basis of these analyses, the IMC may recommend continued enrollment into the study or may recommend changes to the conduct of the study. The Sponsor will communicate any changes to regulatory agencies and investigators for notification of the Institutional Review Boards and Ethics Committees (IRBs/ECs).

Consistent with reporting requirements for serious adverse events and adverse events of special interest (see Sections 5.2.2 and 5.2.3), the Medical Monitor must be notified of these events within 24 hours of learning of the event. This will allow for appropriate and timely communication of significant safety findings in patients in the safety run-in stage.

The Sponsor will also organize regular teleconferences with the investigators to discuss adverse events and laboratory abnormalities observed in the first 6–12 patients treated with at least 1 cycle of combination therapy in the safety run-in stage.

3.1.3 Treatment after Disease Progression

Because of the possibility of an initial increase in tumor burden caused by immune cell infiltration in the setting a T-cell response (termed pseudoprogression) with immunotherapy, patients may be permitted to continue treatment after RECIST v1.1 criteria for progressive disease are met at the investigator's discretion, in the absence of unacceptable toxicity, after discussion with the Medical Monitor, and provided that the patients meet all of the following criteria:

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

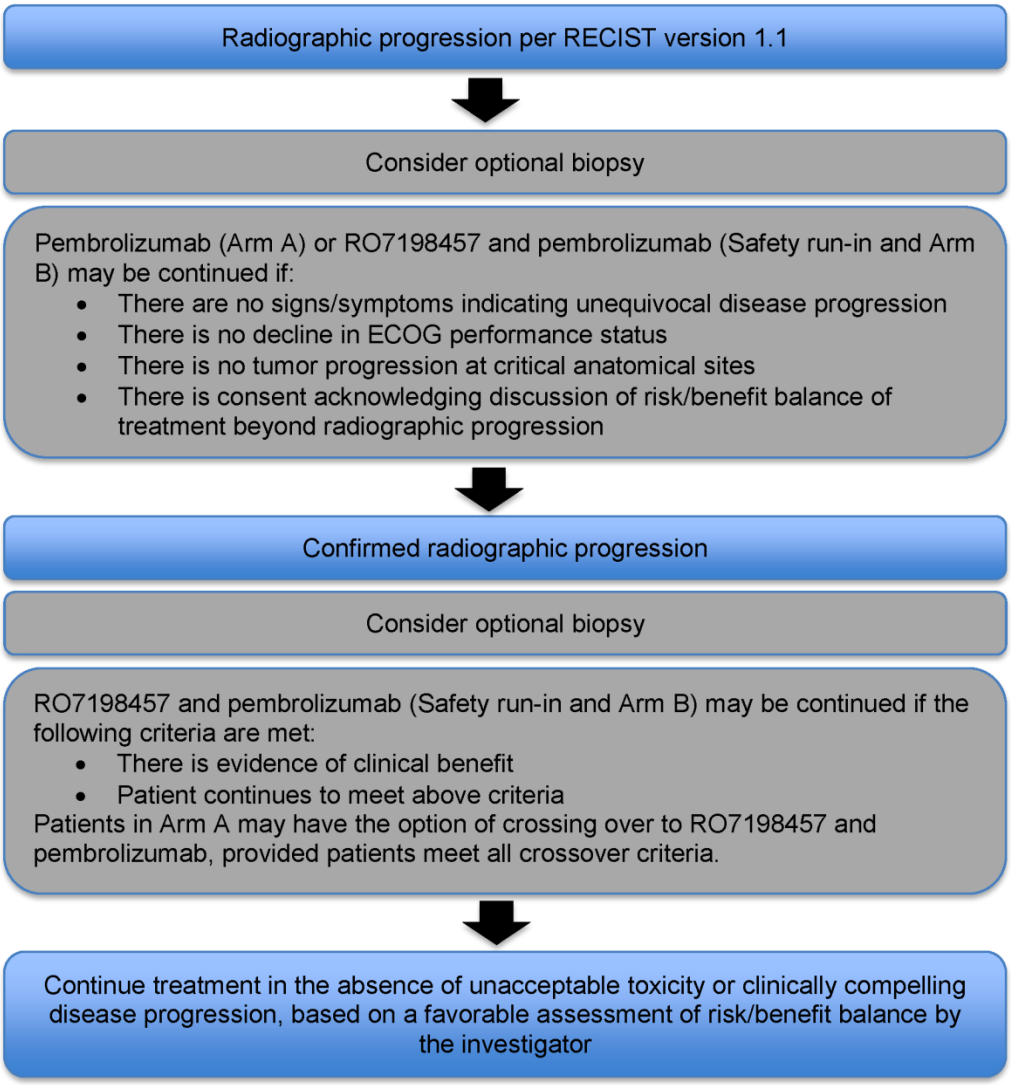
  Critical anatomical sites include the CNS, central airway, the great vessels, and other organs or tissues where compromised function secondary to tumor progression would be expected to result acutely in severe and/or irreversible disability or death.
- *Patient consent and acknowledgment of having discussed benefit–risk balance of treatment beyond radiographic progression, including options to pursue other treatments (if available)*

Patients treated on any treatment arm in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment within the current treatment arm at the discretion of the investigator (regarding patients in Arm A, refer to Section 3.1.4 for rules regarding crossover), after discussion with the Medical Monitor, if they continue to meet the criteria above and have continued clinical benefit, as evidenced by at least one of the following:

- Tumor shrinkage (at least 30% decrease in diameter from baseline) of one or more evaluable lesions
- Improvement in one or more symptoms or signs attributable to the underlying cancer (e.g., decreased requirement for narcotics for pain, decreased dyspnea associated with pleural effusion, weight gain) as assessed by the investigator.

If clinically feasible, collection of an optional tumor biopsy is requested at the time of first radiographic progression on treatment for patients being considered for treatment beyond progression to evaluate the utility of the biopsy in distinguishing pseudoprogression/tumor-immune infiltration from true disease progression and to identify possible markers of resistance or escape. These data will be analyzed for the association between changes in tumor tissue and clinical outcome.

Figure 3 Conditions for Continuing Study Treatment beyond Progression



ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: "Arm B" refers to patients who are randomized into Arm B or cross over into Arm B.

3.1.4 Crossover from Control Arm A to Experimental Treatment

Patients in Arm A (pembrolizumab only) with confirmed radiographic disease progression will be permitted to cross over to the experimental treatment (RO7198457 plus pembrolizumab) at the investigator's discretion, after discussion with the Medical Monitor, and the patient meets all of the crossover eligibility criteria in Section 4.1.3. In addition, if a patient in Arm A completes 24 months of pembrolizumab and experiences

confirmed disease progression <6 months after discontinuation of pembrolizumab, the patient may be permitted to receive crossover treatment (RO7198457 plus pembrolizumab) if crossover eligibility criteria are met (see Section 4.1.3). For patients in Arm A who experience confirmed disease progression, an optional tumor biopsy will be collected for patients with a safely accessible site of disease (see Section 4.5.7.2).

Patients must provide consent to acknowledge having had a discussion with the treating investigator of the benefit-risk balance*, including other treatment options (if available),* before beginning crossover treatment. [redacted] Refer to Appendix 2 for the schedule of assessments for crossover patients.

A radiographic tumor assessment must also be performed, unless already done to document disease progression within 6 weeks prior to starting crossover treatment. The radiographic tumor assessment at the time of disease progression/recurrence will become the new baseline for future response assessments.

Crossover treatment should begin no later than [redacted] after the last dose of prior study treatment on Study GO40558. In patients with confirmed disease progression <6 months after discontinuation of pembrolizumab therapy, crossover treatment should begin within [redacted] of confirmed progression.

Patients who cross over to the combination of RO7198457 plus pembrolizumab will continue treatment for up to 12 months as long as they are experiencing clinical benefit as assessed by the investigator. Patients with confirmed disease progression after crossing over from Arm A to Arm B may be considered for treatment beyond disease progression provided that criteria for treatment beyond disease progression are met as specified in Section 3.1.3. Patients will be evaluated for safety and efficacy according to the schedules of activity described in Appendix 2.

Genentech has the right to restrict or suspend enrollment into crossover treatment at any time. Reasons for this may include, but are not limited to, the following:

- The incidence or severity of adverse events during crossover treatment indicates a potential safety hazard to patients
- Data from ongoing studies suggest lack of equipoise
- Patient enrollment into crossover treatment is unsatisfactory
- Data recording is inaccurate or incomplete

3.1.5 Internal Monitoring Committee Reviews

The primary responsibility of the IMC is to review the available safety data and make recommendations on study conduct to ensure enhanced patient safety while patients receive study treatment. The IMC will periodically evaluate the accumulating safety data from all patients treated in this study. Following analysis of the primary endpoint of PFS, expected to occur approximately 24 months after enrollment of the first randomized patient, future safety analyses will be conducted. The IMC Chair will be a medical oncologist who is not the Medical Monitor and is not associated with the study. Other IMC members may include, but are not limited to, a safety scientist, biostatistician, and clinical pharmacologist. The IMC will operate according to a pre-specified charter and make recommendations on study conduct related to patient safety (see Section 5).

The IMC will review the safety data during the safety run-in stage as described in Section 3.1.2. During the randomization stage, safety data from the first 20 patients in Arm B treated with at least 1 cycle of RO7198457 plus pembrolizumab will be formally reviewed by an IMC. Following the initial data reviews in the safety run-in and randomization stages, the IMC will review the safety data approximately every 6 months, or more frequently if recommended by the IMC Chair or the Medical Monitor. The safety data may include, but are not limited to, demographic data, adverse event data (including serious adverse events and adverse events of special interest), study conduct data, and relevant laboratory data.

In addition, the Medical Monitor may request additional safety reports and may call for ad-hoc meetings of the IMC at any time during the study to review ongoing safety data for a benefit-risk balance.

The IMC may make recommendations regarding study conduct, including, but not limited to, the following: continuing the study as per the protocol, performing additional safety analyses, amending the study protocol, holding patient enrollment pending further safety evaluations, holding/discontinuing study treatment, or terminating the study.

The IMC may share preliminary results from these safety and interim analyses with appropriate Sponsor employees and with the investigators, as the IMC Chair deems necessary.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last data required for all study analysis are collected. [redacted]

In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decides to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study or a non-interventional study, if available.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for RO7198457 Dose and Schedule

The proposed starting dose of RO7198457 plus pembrolizumab is based on an integrated assessment of the proposed mechanism of action (i.e., generation of a T-cell response to a neoantigen), safety, and cytokine data in an ongoing study of RO7198457 plus atezolizumab (GO39733), in vivo efficacy in murine tumor models, and in vivo safety in the Good Laboratory Practice toxicology study, which included evaluation of immune activation. Refer to Section 1.2.2.1 regarding clinical safety profile of RO7198457.

[redacted] See the RO7198457 Investigator's Brochure for further details.

3.3.2 Rationale for Pembrolizumab Dose and Schedule

Pembrolizumab will be administered at the approved dose and schedule of 200 mg IV Q3W. Pembrolizumab is considered standard of care and is approved for the treatment of unresectable or metastatic melanoma (Dummer et al. 2015; NCCN 2018). Pembrolizumab (Keytruda®) is approved in the United States and the European Union, as well as other countries, for the treatment of unresectable or metastatic melanoma, metastatic non−small cell lung cancer, the first-line treatment of metastatic non−small cell lung cancer, and recurrent or metastatic head and neck squamous cell carcinoma, refractory classical Hodgkin lymphoma, advanced or metastatic urothelial carcinoma, unresectable or metastatic microsatellite instability-high, or mismatch repair deficient in solid tumors or colorectal cancer, and recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma Refer to the pembrolizumab prescribing information for a complete summary of safety information.

[redacted]

3.3.4 Rationale for Safety Run-In Stage

The safety run-in stage is designed to confirm safety of the combination of RO7198457 plus pembrolizumab. Pembrolizumab, a PD-1 inhibitor, has been approved for the treatment of melanoma patients with unresectable or metastatic melanoma.

As previously indicated, the selected starting dose of RO7198457 is currently being explored in patients with locally advanced or metastatic tumors in Study GO39733. The dose level of [redacted] has been considered safe in combination with atezolizumab, a PD-L1 inhibitor. Pembrolizumab and atezolizumab both target the same PD-1/PD-L1 pathway and have similar safety profiles. The safety run-in cohort (6–12 patients) aims to evaluate if the starting dose can be expanded in the randomization phase of the study.

3.3.5 Rationale for Patient Population

Study GO40558 will enroll patients with measurable advanced melanoma without a history of systemic therapy for locally advanced or metastatic disease. All patients on this study will receive an approved standard of care (pembrolizumab) in either arm of the study. Despite the recent advances in treatment options provided by immunotherapies, this patient population continues to have high unmet need. Early data from clinical studies suggest that the combination of checkpoint inhibitors and vaccines is well tolerated and has potential synergy. As an example, the combination of a PD-1 inhibitor and a peptide vaccine in resected high-risk metastatic melanoma with HMB-45, NY-ESO-1, and/or MART-1 positive resected tumors was well tolerated, demonstrated increases in tumor antigen-specific $CD8^+$ T cells, and showed an improved relapse-free survival rate compared with stage-matched historical controls (Gibney et al. 2015). Combining the potential neoantigen-specific immune-stimulating effects of RO7198457 with the release of immune suppression by pembrolizumab may significantly improve the response rate and durability of responses compared with that of either agent alone.

In order to ensure that the primary endpoint of PFS as well as the secondary endpoints of ORR, OS and DOR can be adequately assessed, patients must have measurable disease (per RECIST v1.1) at baseline.

Additional eligibility criteria have been incorporated that are pertinent to the safety profiles of RO7198457 and pembrolizumab (and anti−PD-L1 targeted therapies as a therapeutic class). These have been informed by the known safety profiles of each drug and supplemented by experience in Study GO39733.

3.3.6 Rationale for Control Group (Arm A)

The control arm (Arm A) will receive 200 mg of pembrolizumab monotherapy administered by IV infusion Q3W. The intent of this study is to evaluate the magnitude of benefit achievable with the combination of RO7198457 and pembrolizumab, relative to current standard of care, in treatment-naive patients with advanced melanoma. Several therapies are currently available for this indication (refer to Section 1.1). The current guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology clinical practice guidelines (Dummer et al. 2015; NCCN 2018) recommend the anti−PD-1 monotherapies pembrolizumab and nivolumab

and the combination of nivolumab with ipilimumab. The choice of treatment in clinical practice is based on evaluation of the individual patient by the treating physician.

The anti−PD-1 monotherapies pembrolizumab and nivolumab have demonstrated comparable efficacy in patients with advanced melanoma across multiple clinical trials. Efficacy has been established for survival endpoints, as well as for the correlated surrogate endpoints of PFS and ORR (median PFS for these agents in advanced melanoma is 5–6 months, with an ORR of approximately 30% [Hodi et al. 2014; Robert et al. 2015a, 2015b; Weber et al. 2015a] and OS of approximately 32 months [Hodi et al. 2016; Long et al. 2018]).

On the basis of anti−PD-1 monotherapy being a currently approved, widely used standard of care, which affords the longest established survival benefit of currently available therapies and is recommended by advisory bodies for treatment of patients with advanced melanoma, pembrolizumab is considered an appropriate comparator arm for this study.

3.3.7 Rationale for Crossover to Experimental Treatment

Patients treated with single-agent pembrolizumab (Arm A) may have the option of crossover to receive treatment with RO7198457 plus pembrolizumab.

As failure to respond to PD-L1/PD-1 axis therapies is associated with a lack of preexisting immunity (Herbst et al. 2014), induction or enhancement of immune responses against tumor neoantigens via personalized cancer vaccination is a rational approach for patients that have become resistant or refractory to pembrolizumab monotherapy (Arm A). The inclusion of study treatment crossover will address important questions regarding efficacy and tolerability of RO7198457 plus pembrolizumab following disease progression on pembrolizumab monotherapy.

To be eligible for crossover treatment, patients will need to have met appropriate criteria (see Section 4.1.3).

3.3.8 Rationale for Primary and Secondary Endpoints

PFS is established as a clinically relevant measure of treatment benefit and a correlate of OS in advanced melanoma, which in recent years has been an approvable endpoint in the setting of metastatic or unresectable melanoma for both targeted and immunotherapies (European Medicines Agency 2012). In a meta-analysis of 4416 patients with metastatic melanoma, PFS was found to be a robust surrogate for OS in dacarbazine-controlled randomized trials of metastatic melanoma. Furthermore, PFS has also been demonstrated to be predictive of OS for pembrolizumab (Robert et al. 2015a). In addition, owing to the increased number of active treatment options available and under investigation resulting in patients receiving more lines of therapy than have previously been available, OS might be confounded by the use of effective subsequent-line therapies or by mortality unrelated to cancer (Flaherty et al. 2012).

As progression events provide reliable information on the treatment effect observed and generally are not confounded by subsequent lines of therapy, PFS provides a meaningful efficacy endpoint with earlier time to evaluation (Di Leo et al. 2003). In summary, multiple drugs, including both targeted therapy and immunotherapies, have been approved in metastatic melanoma in recent years on the basis of PFS, and extensive clinical experience validates PFS as a consistent strong correlate of survival across different treatment modalities.

Metastatic melanoma is a deadly cancer that impacts patients' HRQoL (Cornish et al. 2009). Current treatment goals include improving survival, managing disease or treatment-related symptoms (insomnia, pain, and fatigue), and preserving HRQoL outcomes as feasible (Coit et al. 2016). Studies have shown that patients with advanced melanoma tend to experience a decrease in GHS and physical functioning while undergoing treatment, which can vary by therapy and presence of disease progression (Schadendorf et al. 2015; Long et al. 2016). In this study, impact of disease/treatment-related symptoms on HRQoL will be assessed using the GHS/HRQoL scale of the EORTC QLQ-C30 in order to quantify patients' experience receiving treatments. Patients will complete selected items from the EORTC library including items from the EORTC QLQ C30 and IL 12.

3.3.9 Rationale for Choice of Stratification Factors

In order to balance the distribution of prognostic factors between the treatment arms, the randomization will be stratified. In Study GO40558, the stratification factors will be PD-L1 status and disease stage at baseline/LDH (see Section 4.2). Tumor specimens will be assessed for PD-L1 expression by IHC in order to stratify patients in the treatment arms.

PD-L1 expression ($\geq$5% cutoff vs. $<$5% or unknown by SP263 PD-L1 IHC assay done in a central laboratory) has recently been recognized as a strong favorable prognostic factor in melanoma and is associated with improved outcomes for melanoma patients treated with pembrolizumab (Daud et al. 2016; Schachter et al. 2017).

Disease stage as defined by the American Joint Committee on Ca^{nc}er 8th Edition (AJCC v8.0) categorizes distant metastasis, M1 status, by both the anatomic site of distant metastatic disease as well as by the serum LDH levels (M0, M1a, or M1b vs. M1c or M1d or LDH $>$ ULN). Baseline LDH levels are recognized as strong prognostic factors in melanoma for long-term OS. Elevated LDH level is associated with poorer outcomes across multiple therapies and is reflective of other factors associated with aggressive disease, such as tumor stage and burden (Balch et al. 2009; Chapman et al. 2011; Hauschild et al. 2012; Ascierto 2013; Kelderman et al. 2014; Long et al. 2014, 2015; McArthur et al. 2014; Diem et al. 2015; Hauschild and Garbe 2015; Robert et al. 2015b; Hauschild and Schadendorf 2016).

These stratification factors were chosen because of their known or suspected potential to affect prognosis in metastatic melanoma. Prospective stratification by these factors will help to minimize potential underlying differences in the two treatment arms due to sources other than RO7198457.

[redacted]

3.3.12 Rationale for Collection of Archival or Pretreatment Fresh Tumor Biopsy for Biomarker Analysis

Tumor tissue will be analyzed for predictive biomarkers of RO7198457 plus pembrolizumab activity. These exploratory analyses will include, but are not limited to, biomarkers such as immune infiltrates, presence of stromal compartment, or CD8 expression. In addition, methods such as NGS of tumor DNA and/or RNA may be applied to evaluate the relationship between clinical benefit and candidate predictive biomarkers, such as alterations in individual disease-related genes, aggregate mutational load, or gene expression profiles. Further exploratory analyses of potential predictive and prognostic markers that are related to anti–PD-1 activity, tumor immunology, or tumor type may also be analyzed as guided by accumulating nonclinical or clinical data.

Patients who provide baseline biopsies for biomarker analysis during screening (see Section 4.5) should also provide an archival tumor specimen, if available. Comparison between the archival specimen and the freshly obtained baseline specimen may provide additional information on the optimal sample specifications for evaluation of a potential predictive biomarker for RO7198457 plus pembrolizumab.

3.3.13 Rationale for Collection of Fresh Tumor Specimens at Baseline and On-Treatment for Biomarker Analysis

One of the biomarker objectives of the study is to assess the biological activity of RO7198457 on the immune cell infiltration in the tumor. Hence, during the randomized stage of the study, a minimum of approximately 20 patients in the RO7198457 plus pembrolizumab arm (Arm B) will be required to provide a mandatory on-treatment biopsy if these can be obtained with minimal risk and discomfort and are deemed safe and on-treatment biopsies will be optional for all other patients in Arm B. To understand contribution of RO7198457 in Arm B, tumor data from the combination arm will be compared with tumor data from the pembrolizumab monotherapy Arm A. To enable this analysis, a minimum of approximately 10 patients in the pembrolizumab arm will be required to provide a mandatory on-treatment biopsy, if these can be obtained with minimal risk and discomfort and deemed safe. In addition, all patients will be asked via separate Informed Consent Forms to undergo optional on treatment biopsies, as well as biopsies at the time of progressive disease. All may undergo additional on-treatment biopsies at any other time (including progression or response) at the investigator's discretion (if deemed clinically feasible by the investigator). If the treating physician suspects that a patient will not have measurable disease at the designated time of collection due to clinical response (approximately 8–9 weeks after the first infusion of pembrolizumab in Arm A and 5–6 weeks after the first administration of RO7198457 in

Arm B, see Appendix 1 and Appendix 2), biopsy collection may be moved to an earlier time point *as indicated. The* Medical Monitor *is available to advise as needed.*

Based on the postulated mechanisms of action of RO7198457 plus pembrolizumab, several characteristics of the tumor microenvironment will be evaluated as candidate predictive biomarkers in paraffin-embedded tumor tissue including, but not limited to, the expression of PD-L1, $CD8^+$ and other biomarkers on specific cell types, and the prevalence and/or activation of immune cells. Fresh tumor tissue may also be used for antigen-specific immune monitoring using tumor-infiltrating lymphocytes (TILs). In addition, WES from tumor DNA and gene-expression profiling (RNA sequencing) may be carried out to further understand biological activity of RO7198457.

Tumor tissue post-treatment will be analyzed for changes in the immune infiltrate, immune activation markers, and changes in tumor microenvironment to define PD biomarkers of RO7198457 activity. This sample may also be used for isolating TILs and antigen-specific immune monitoring thereof. To enable such an evaluation it is important to have matched pretreatment and on-treatment biopsies from patients.

3.3.14 Rationale for Collection of Blood Samples for Biomarker Analyses

Changes in biomarkers in blood may provide evidence for biologic activity of RO7198457 and may allow for the development of a blood-based biomarker to help predict which patients may benefit from RO7198457. The mode of action of RO7198457 depends on the induction of antigen-specific T cells by antigen presenting cells that process and present RNA-encoded peptides in addition to Toll-like receptor mediated immune modulatory effects that lead to cellular activation and the induction of pro-inflammatory cytokines. Cytokine measurements in blood at baseline and potential changes upon treatment, in addition to immune monitoring assays such as ELISPOT and MHC-multimer fluorescence-activated cell sorting (FACS) staining in blood will serve as indicators of the immunogenicity and biological activity of RO7198457 plus pembrolizumab.

In addition, potential changes in number and functions of immune cells will be measured. These include, but are not limited to, the frequency of antigen-specific T cells (as measured by immune monitoring analysis) the number of T, B, and NK cells; the number, proportion, and functional status (as assessed by protein or nucleic acid analysis using methods such as FACS, T-cell receptor [TCR] sequencing, and NGS) of blood cells, including T-cell subsets, myeloid-derived suppressor cells, and other immune cells; concentrations of cytokines; and titers of antibodies against reference antigens as well as against other exploratory markers. These PD markers will be used to find potential correlation with the safety, PK, and preliminary anti-tumor activity of RO7198457 plus pembrolizumab.

3.3.15 Rationale for Optional Stool Sample Collection

Checkpoint inhibitors targeting the PD-L1/PD-1 axis have shown activity and efficacy in melanoma, but not all patients respond to treatment, suggesting that host factors, including genetics and tumor microenvironment, may play a role in determining responsiveness. The gut microbiome has been shown to be a key determinant in immune regulation in cancer, in part by influencing T-cell driven anti-tumor responses (Routy et al. 2018). For example, antibiotic treatment is associated with poor survival outcomes to anti–PD-1 therapy in preclinical melanoma models (Routy et al. 2018). Conversely, the risk of colitis with checkpoint inhibitors may be predicted based on a patient's pretreatment microbiome (Chaput et al. 2017). Thus, heterogeneity in microbiome composition across patients may be a key driver of safety events in addition to efficacy.

This study will examine whether a patient's microbiome can determine response to RO7198457 plus pembrolizumab versus pembrolizumab alone, and conversely, whether RO7198457 plus pembrolizumab can alter the microbiome to such an extent that on-treatment changes to the microbiome could be early predictors of adverse events, including colitis. Analyzing the microbiome in melanoma may provide the opportunity to discover systemic effects on distal cancers.

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

Checkpoint inhibitors may result in early radiographic progression (including the appearance of new lesions) that is followed by delayed tumor shrinkage consistent

with the time required to mobilize an effective antitumor immune response (Wolchok et al. 2009). Additionally, responding tumors may appear to initially increase in size because of the influx of immune cells (Hoos et al. 2010; Pennock et al. 2012; Hodi et al. 2018). Such unconventional "pseudoprogression" response patterns have been described in patients treated with an anti-CTLA-4 agent (Wolchok et al. 2009) and with anti–PD-L1/anti–PD-1 agents (Brahmer et al. 2012; Hamid et al. 2013; Hodi et al. 2016). Therefore, iRECIST criteria (see Appendix 5) will be used in this study to accommodate and to better characterize these different patterns of response to help understand the activity profile of RO7198457 plus pembrolizumab compared to pembrolizumab alone. The key change in iRECIST criteria, as compared to conventional RECIST criteria (see Appendix 4), is that new lesions may be incorporated in the total measurement of tumor burden rather than categorically signifying progressive disease. This study will also attempt to collect correlative clinical data at the time of apparent radiographic progression through on-treatment biopsies.

iRECIST is intended to supplement, not supplant, standard RECIST v1.1 in the investigator's integrated assessment of benefit and risk for individual patients, as depicted in Figure 3. Refer to Section 4.5.5 for tumor and response evaluations.

3.3.18 Rationale for Patient-Reported Outcome Assessments

In this study, patients will rate their symptoms associated with the disease or treatment, their functional impact and HRQoL to inform patients' experience receiving treatments. To reduce patient and site burden while maintaining scales construct validity, selected scales from the European Organisation for Research and Treatment of Cancer (EORTC) library and selected items from the PRO-CTCAE library, and a single-item assessing bother due to side effects of treatment will be collected. The WPAI will also be collected to measure impairments in work and activities due to disease/treatment-related symptoms.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 132 patients with previously untreated unresectable locally advanced or metastatic melanoma (AJCC v8.0) will be enrolled in this study at approximately 40 sites globally.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing the Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment

- Histologically confirmed metastatic (recurrent or de novo Stage IV) or unresectable locally advanced (Stage IIIC or IIID) cutaneous, acral, or mucosal melanoma, as defined by the AJCC v8.0 (Amin et al. 2017).

  The enrollment of mucosal and acral melanoma patients will be limited to approximately 10 patients total.

- ECOG Performance Status of 0 or 1 (see Appendix 6)
- Life expectancy $\geq$ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):
  - ANC $\geq$ 1,500 cells/μL (without granulocyte colony-stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1)
  - WBC count $\geq$ 2,500/μL
  - Lymphocyte count $\geq$ 500/μL
  - Platelet count $\geq$ 100,000/μL (without transfusion within 14 days prior to Cycle 1, Day 1)
  - Hemoglobin $\geq$ 9 g/dL

    Patients may be transfused or may receive erythropoietic treatment as per local standard of care.

  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - AST and ALT $\leq 3 \times$ ULN
  - ALP $\leq 2.5 \times$ ULN with the following exception:

    Patients with documented liver or bone metastases may have ALP $\leq 5 \times$ ULN.
  - Serum albumin $\geq$ 2.5 g/dL
- Measured or calculated creatinine CL $\geq$ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

  (140 – age) $\times$ (weight in kilograms) $\times$ (0.85 if female)
  72 $\times$ (serum creatinine in mg/dL)
- Measurable disease per RECIST v1.1 (see Appendix 4)

  Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion and no other target lesions are available.

  Lesions that are intended to be biopsied should not be counted as target lesions.

- Naive to prior systemic anti-cancer therapy for advanced melanoma (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies), with the following exceptions for adjuvant therapies:
  - Adjuvant treatment with anti–PD1/PD-L1 or anti-CTLA-4, if discontinued at least 6 months prior to Cycle 1, Day 1 and not meeting any of the following criteria:
    - Any history of an immune-related Grade 4 adverse event attributed to prior CIT (other than endocrinopathy managed with replacement therapy or asymptomatic elevation of serum amylase or lipase)
    - Any history of an immune-related Grade 3 adverse event attributed to prior CIT that required permanent discontinuation of the prior immunotherapeutic agent per local prescribing information, European Society for Medical Oncology (ESMO) guidelines (Haanen et al. 2017), or American Society of Clinical Oncology (ASCO) guidelines (Brahmer et al. 2018)
    - Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 except for alopecia, vitiligo, or endocrinopathy managed with replacement therapy
    - Immune-related adverse events related to prior CIT (other than endocrinopathy managed with replacement therapy or stable vitiligo) that have not resolved to baseline

      Patients treated with corticosteroids for immune-related adverse events must demonstrate absence of related symptoms or signs for ≥ 4 weeks following discontinuation of corticosteroids.
  - Adjuvant treatment with targeted therapies (e.g., BRAFi/MEKi), if discontinued at least 2 months prior to initiation of study treatment
- Confirmed availability of representative tumor specimens in formalin-fixed, paraffin-embedded blocks (preferred), or sectioned tissue (as described in the laboratory manual) with an associated pathology report. Archival tumor tissue or fresh biopsy tissue are acceptable; it must be submitted and assessed for evaluation of mutations prior to enrollment.
  - Acceptable samples may also include core-needle biopsies for deep tumor tissue (recommend a minimum of five cores), excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

  Fine-needle aspiration samples, brushings, cell pellets from effusions or ascites, and lavage samples are not acceptable.

Tumor tissue from bone metastases is difficult to evaluate for PD-L1 expression and should be avoided. However, if a bony metastatic site is the only viable source of tissue, it may be an acceptable tumor specimen. *The* Medical Monitor *is available to advise as needed*. Submitted tissue from bone metastases must not be exposed to decalcification agents that can render tissue not usable for RO7198457 manufacturing and PD-L1 testing.

If adequate tissue from distinct timepoints (such as time of initial diagnosis and time of disease recurrence) and/or multiple metastatic tumors are available, priority should be given to the tissue with the highest tumor content and lowest necrotic area (if feasible). Multiple samples may be collected for a given patient, on the basis of availability; however, the requirement for a block or sectioned tissue should be satisfied by a single biopsy or resection specimen.

Prior to signing the main study ICF, patients may sign a prescreening ICF to specifically allow the collection and testing of archival or fresh tumor specimens.

A patient with insufficient or unavailable archival tissue will not be eligible due to the need for evaluable tumor tissue to create RO7198457 unless the patient is willing to undergo a pretreatment biopsy sample collection of the tumor (refer to above for acceptable samples).

- [redacted]
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 90 days after the final dose of RO7198457 and at least 4 months after the final dose of pembrolizumab, whichever occurs later. Women must refrain from donating eggs during this same period.

  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 requirements.

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

  Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.

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 at least 28 days after the final dose of study treatment 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.

4.1.2 Exclusion Criteria

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

- Ocular/uveal melanoma
- Inability to comply with study and follow-up procedures
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the final dose of RO7198457 or 4 months after the final dose of pembrolizumab, whichever occurs later

  Women of childbearing potential (including women who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study drug (i.e., Cycle 1, Day 1).
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater, see Appendix 12), myocardial infarction within the previous 3 months, unstable arrhythmias, and/or unstable angina
- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease or current alcohol abuse
- Major surgical procedure within 28 days prior to Cycle 1, Day 1, or anticipation of need for a major surgical procedure during the course of the study
- Any other diseases, metabolic dysfunction, physical examination finding, and/or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or may render the patient at high risk from treatment complications

- Corticosteroids at dosages higher than 10 mg prednisolone (if not for physiologic substitution)
- Previous splenectomy
- Known primary immunodeficiencies, either cellular (e.g., DiGeorge syndrome, T-negative severe combined immunodeficiency [SCID]) or combined T- and B-cell immunodeficiencies (e.g., T- and B-negative SCID, Wiskott-Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency)
- Any medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of 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.
  – Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
  – No history of metastases within 10 mm of the optic apparatus (optic nerves and chiasm)
  – No ongoing requirement for corticosteroids as therapy for CNS disease
  – No stereotactic radiation within 7 days
  – No prior whole-brain radiation
  – No clinical evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  – Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to Cycle 1 Day 1, if all other criteria are met.
  – Treatment with an anticonvulsant at a stable dose is allowed.
  – No intracranial hemorrhage from CNS lesions
- History of leptomeningeal metastatic disease
- Uncontrolled tumor-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated >2 weeks prior to Cycle 1, Day 1. Patients should be recovered from the effects of radiation.

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 Cycle 1, Day 1.

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days

  Indwelling drainage catheters (e.g., PleurX®) are allowed.

- Any anti-cancer therapy, in the metastatic setting whether investigational or approved, including chemotherapy, hormonal therapy, and/or radiotherapy, prior to initiation of study treatment, with the following exceptions:
  - Herbal therapy > 1 week before Cycle 1, Day 1
  - Palliative radiotherapy for painful metastases or metastases in potentially sensitive locations (e.g., epidural space) > 2 weeks prior to Cycle 1, Day 1
  - Prior cancer vaccines (e.g., T-vec) are not allowed.
- Malignancies other than disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ)
- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca^{+2} > 12 mg/dL or corrected serum calcium ≥ ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 2 weeks prior to screening.
- History of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 7 for a more comprehensive list of autoimmune diseases) with the following exceptions:

  Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

  Patients with controlled type 1 diabetes mellitus on a stable insulin regimen may be eligible.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) may be eligible provided that they meet the following conditions:

- Rash must cover less than 10% of the body surface area.
- Disease is well controlled at baseline and only requires low potency topical steroids.
- There are no acute exacerbations of underlying condition within the last 12 months (e.g., not requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency, or oral steroids).

- Treatment with monoamine oxidase inhibitors (MAOIs) within 3 weeks prior to Cycle 1, Day 1
- Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone $\geq$ 10 mg/day, cyclophosphamide, azathioprine, methotrexate, thalidomide, and TNF-α antagonists) within 2 weeks prior to Cycle 1, Day 1

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study.

  The use of inhaled corticosteroids (e.g., fluticasone for chronic obstructive pulmonary disease) is allowed.

  The use of oral mineralocorticoids (e.g., fludrocortisone for patients with orthostatic hypotension) is allowed.

  Physiologic doses of corticosteroids for adrenal insufficiency are allowed.
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV infection
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)

  Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive IgG antibody to hepatitis B core antigen [anti-HBc]) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1 and must demonstrate no active infection.
- Active hepatitis C

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Known active or latent tuberculosis infection

  If the investigator considers a potential patient to be at an increased risk for infection with *Mycobacterium tuberculosis*, latent tuberculosis diagnostic procedures must be followed according to local practice standards during the screening period.

- Severe infections within 4 weeks prior to Cycle 1, Day 1 including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Recent infections not meeting the criteria for severe infections, including the following:
  - Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1
  - Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study

  Influenza vaccination should be given during influenza season only. Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study, and for 5 months following the last study treatment.
- Known hypersensitivity to the active substance or to any of the excipients in the vaccine
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary-cell products
- Allergy or hypersensitivity to components of the pembrolizumab formulation

4.1.3 Inclusion and Exclusion Criteria for Crossover Treatment

Patients in Arm A (pembrolizumab alone) must meet all of the following eligibility criteria to be eligible to enter the crossover treatment (RO7198457 plus pembrolizumab).

4.1.3.1 Inclusion Criteria for Crossover Treatment

- Confirmed progression of disease as assessed by investigator per RECIST v1.1 after at least one dose of pembrolizumab in Arm A

  Disease progression must be confirmed by a consecutive assessment $\geq$4 weeks from the date first documented.

  Patients who complete 24 months of pembrolizumab and experience disease progression < 6 months after discontinuing pembrolizumab may also be eligible to cross over.
- ECOG Performance Status of 0 or 1 (see Appendix 6)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods that result in a failure rate of $<$1% per year during the treatment period and for at least 90 days

after the final dose of RO7198457 and at least 4 months after the final dose of pembrolizumab, whichever occurs later. Women must refrain from donating eggs during this same period.

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 requirements.

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

Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.

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 at least 28 days after the final dose of study treatment 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.

4.1.3.2 Exclusion Criteria for Crossover Treatment

- Toxicity experienced while on study treatment in the control arm that would require permanent discontinuation of pembrolizumab or preclude treatment with the combination of RO7198457 and pembrolizumab in the Arm B portion of the study.

- Tumor progression at critical anatomical sites that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

  Critical anatomical sites include the CNS, central airway, the great vessels, and other organs or tissues where compromised function secondary to tumor progression would be expected to result acutely in severe and/or irreversible disability or death.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label trial. For the safety run-in stage, after written informed consent has been obtained and eligibility has been established, patients will be assigned to combination treatment with RO7198457 plus pembrolizumab. For the randomization phase, after written informed consent has been obtained and eligibility has been established, each patient will be randomized to one of the two treatment arms through an interactive web-based response system (IWRS). A stratified, permuted block randomization scheme will be used to obtain approximately a 2:1 ratio between the two treatment arms. Patients should receive their first dose of study treatment as soon as possible and within approximately 1 week of randomization.

Randomization will be stratified by the following criteria.

- PD-L1 status by SP263 IHC (≥5% vs. <5% or unknown)
- Disease stage (AJCC v8.0, *based on screening Part B tumor assessment*) combined with baseline LDH level (M0, M1a, or M1b vs. M1c or M1d or LDH>ULN)

These stratification factors were chosen because of their known or suspected potential to affect prognosis in metastatic melanoma. Prospective stratification by these factors will minimize differences in the two treatment arms due to sources other than RO7198457.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMPs for this study are RO7198457 and pembrolizumab. *Appendix 13 identifies all investigational and auxiliary medicinal products for this study.*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 RO7198457

RO7198457 will be supplied by the Sponsor [redacted]

[redacted]

For information on the formulation, packaging, and handling of RO7198457 see the RO7198457 pharmacy manual and/or the RO7198457 Investigator's Brochure.

4.3.1.2 Pembrolizumab

Pembrolizumab will be supplied by the Sponsor where required by local health authority regulations. For information on the formulation, packaging, and handling of pembrolizumab, see the local prescribing information for pembrolizumab.

Where pembrolizumab is supplied by the Sponsor, study drug packaging will be overseen by the Sponsor's Clinical Trial Supplies Department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labeling of pembrolizumab drug will be in accordance with the Sponsor's standards and local regulations.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Administration of RO7198457 and/or pembrolizumab will be performed in a setting with emergency medical facilities with access to a critical care unit and staff who are trained to monitor for and respond to medical emergencies. Administration instructions for first and subsequent RO7198457 infusions are presented in Table 1.

On days of scheduled study treatment infusion, RO7198457 should be administered after pembrolizumab, with an intervening observation period (as described in Section 4.3.2.1).

For details on dose preparation and administration instructions for RO7198457 refer to the RO7198457 Investigator's Brochure. For pembrolizumab dose preparation and administration instructions, refer to the local prescribing information.

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

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

[redacted]

[redacted]

[redacted]	[redacted]
• [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

[redacted]

[redacted]

4.3.2.2 Pembrolizumab

Pembrolizumab will be administered at a dose of 200 mg as an IV infusion over 30 *(±10)* minutes.

If pembrolizumab is administered in combination with RO7198457 (safety run-in stage and Arm B), refer to [redacted] for prophylactic treatment and RO7198457 administration information. [redacted]

Vital signs (pulse rate, respiratory rate, blood pressure and temperature) should be recorded within 60 minutes prior to the infusion. If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion. If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±5) minutes after the infusion.

Patients should be observed for 30 minutes after the infusion. Patients may be hospitalized overnight if required by institutional guidelines. If infusion-related adverse events (e.g., fever, chills) are not resolved to ≤Grade 1 following the outpatient observation period, patients should be admitted for overnight observation.

Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4. Guidance on study drug administration in the context of management of specific adverse events is provided in Section 5.1.4.3.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO7198457 and pembrolizumab) will be provided by the Sponsor where required by local health authority regulations.

The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Continued Access to RO7198457 and/or Pembrolizumab

The Sponsor (Genentech, a member of the Roche Group) will offer continued access to IMPs RO7198457 and/or pembrolizumab (in countries where applicable) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive IMPs RO7198457 and/or pembrolizumab after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive IMPs RO7198457 and/or pembrolizumab (in countries where applicable) after completing the study if any of the following conditions are met:

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

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following web site:

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

[redacted]

[redacted]

[redacted]

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

- [redacted]
- [redacted]

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability and will be assessed for toxicity prior to each dose of RO7198457 and/or pembrolizumab. Dosing will occur only if the clinical assessment and select local laboratory test results are acceptable. Results from local lab tests with longer turn-around times (e.g., thyroid function test, amylase/lipase) may not be required prior to dosing.

All assessments will be performed on the day of the scheduled visit date unless a time window is specified. Assessments scheduled on the days of study treatment should be performed before the infusion of study drug(s) unless otherwise noted. If the timing of a study visit coincides with a holiday, weekend, or other administrative disruption that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

Patient care kits, which consist of a thermometer and memory aid log, will be provided to patients. These are provided to help patients monitor and recall signs and symptoms that occur after leaving the clinic to relay to the study staff at their next study visit.

Collection of any non–safety-related data or patient samples may be suspended or terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary objective(s). The decision to suspend or discontinue any data collection will be communicated to sites' IRBs\ECs by means of a memorandum and will not require a protocol amendment.

4.5.1 Informed Consent Forms and Screening Log

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

This study requires documentation of consent for the following components of study participation, as applicable:

- Participation in Study GO40558

  Written informed consent for participation in the study must be documented by signing the relevant page before any study-specific screening tests or evaluations are performed.

- Acknowledgement of Treatment Continuation after Possible Disease Worsening

  This applies only to patients who continue study treatment beyond radiographic progression in the study (see Section 3.1.3).

- Acknowledgement of Treatment Crossover

  This applies only to patients randomized to Arm A who elect to cross-over to RO7198457 plus pembrolizumab (see Section 3.3.7).

In addition, a separate, specific signature will be required to document consent for either of the following:

- Screening Part A (i.e., collection and testing of archival or fresh tumor specimens and blood prior to signing of the main study Informed Consent Form). This applies to all patients in the study.
- Optional research, including the conduct of optional tumor biopsies, the collection of optional stool samples, and the storage of remaining biological samples up to 15 years or until depleted

The investigator or authorized designee will explain to each patient in the study the objectives of screening Part A or optional research. 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. Patients who decline to participate will not sign the applicable Informed Consent Forms.

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes cancer history (including, but not limited to, prior cancer therapies and/or prior CITs and procedures and tumor characteristics such as hormone receptor status or mutation status), other clinically significant diseases, surgeries, smoking history, use of alcohol and/or drugs of abuse, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

4.5.3 Physical Examinations

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

ECOG Performance Status (see Appendix 6) should be assessed per the schedules of activities in Appendix 1 and Appendix 2.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in the patient's medical record. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

As part of tumor assessments, the physical examination should also include evaluation for lymphadenopathy, splenomegaly, hepatomegaly, and cutaneous neoplasms or metastases. All patients should be monitored for symptoms of CNS metastases and such reported symptoms should be followed by a full neurological examination. A brain magnetic resonance imaging (MRI) scan or contrast-enhanced head CT scan should be conducted as clinically indicated to confirm or refute new or worsening brain involvement.

4.5.4 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. Blood oxygen saturation will be measured at baseline by pulse oximetry.

Vital signs should be measured during the infusion of pembrolizumab and during the observation period (see [redacted] and Section 4.3.2.2 for frequency of vital sign assessments) or if clinically indicated (see schedules of activities in Appendix 1 and Appendix 2).

All vital signs collected per protocol should be documented in the patient's medical record and recorded in the appropriate eCRF. For other measurements, only those vital signs that constitute an adverse event (e.g., temperature for event of fever) or a primary manifestation of an adverse event (e.g., blood pressure associated with an IRR or heart rate associated with an arrhythmia) should be recorded in the eCRF.

4.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation.

Screening and subsequent tumor assessments must include CT scans of the chest, abdomen, and pelvis (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards). Patients who have a contraindication to IV contrast may have MRI scans of the abdomen and pelvis performed in lieu of CTs and a non-contrast CT of the chest. If a CT scan for tumor assessment is performed in a positron emission tomography-CT scanner, the CT acquisition must be of full diagnostic quality and include CT contrast.

A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Patients with untreated or actively progressing CNS metastases are not eligible for the study (see Section 4.1.2). Stable brain metastases must be evaluated at each tumor assessment with the same radiographic procedure as the baseline study. Patients without brain metastases do not need brain scans for tumor assessment unless clinically warranted. Clinical disease assessments by physical examination should be performed for patients with palpable/superficial lesions (in addition to radiographic assessments). Tumor measurements for each patient should be made by the same investigator or radiologist, if feasible, using the same assessment technique or procedure throughout the study.

Further investigations, such as bone scans and CT scans of the neck or extremities, should also be performed as indicated by the underlying disease and if there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule of assessments listed above. As the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Results of standard of care tests or examinations performed prior to obtaining Informed Consent and ≤28 days prior to *Day 1 of Cycle 1* may be used for the purposes of screening rather than repeating such tests. All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

Response will be assessed on the basis of the Investigator's physical examinations and the imaging modalities detailed above, using both RECIST v1.1 and iRECIST criteria (see Appendix 4 and Appendix 5, respectively). The investigator's assessment of overall tumor response at all timepoints should only be based on RECIST v1.1. Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing the next cycle.

The timing of tumor assessments will be determined based on weeks from first study treatment (C1D1; pembrolizumab monotherapy) and will not be tied to cycle-specific visits. The purpose of having the tumor assessments independent of cycle-specific visits is so that they occur at the same interval for all patients, regardless of delays in dosing.

Tumor assessments must be obtained and documented during Screening Part B (to establish a baseline assessment prior to Cycle 1, Day 1), during Week 12, and then every 6 weeks thereafter for the first 48 weeks (i.e., during Weeks 12, 18, 24, 30, 36, 42, and 48). *"During week" is defined as the first day/Day 1 of each targeted week (e.g., 12, 18, or 24 weeks from C1D1 date) plus 6 calendar days.* After Week 48, tumor assessments will occur every 12 (±1) weeks *through Week 96* (i.e., *during* Weeks 60, 72, 84, and *96). After Week 96, follow-up tumor assessments will occur approximately every 12 weeks through Week 156 (i.e., Weeks 108, 120, 132, 144, and 156). After Week 156, follow-up tumor assessments will occur approximately every 24 weeks (i.e., Weeks 180, 204, 228, and 252);* see also Appendix 1 and Appendix 2.

Per investigator discretion, tumor assessments may also occur as clinically indicated.

If applicable, cutaneous lesions are to be obtained by digital photography and documented at each tumor assessment as described in Section 4.5.6.

After initial study treatment discontinuation (if discontinuation were for reasons other than disease progression), follow-up tumor assessments will be performed until death, disease progression, initiation of another systemic anti-cancer therapy, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will be monitored with a follow-up scan in 6 *(±1)* weeks (i.e., at the next scheduled tumor assessment when the protocol-defined scan frequency is every 6 weeks or as an unscheduled tumor assessment when the protocol-defined scan frequency is every 12 [±1] weeks), or earlier if clinically indicated. Tumor assessments should be continued every 6 weeks thereafter until two consecutive scans demonstrate stability or improvement with respect to the first scan that showed radiographic disease progression, at which point the scan frequency should revert or transition to every 12 weeks if applicable. For patients who consented to treatment beyond radiographic disease progression (see Section 3.1.3), new lesions will also be assessed according to the iRECIST criteria, and applicable measurements should be entered into the eCRF. While the Sponsor will derive overall tumor assessment as per iRECIST, investigator assessment of overall tumor response at all timepoints should be only based on RECIST v1.1.

Patients who fulfill the criteria to receive crossover treatment (see Section 3.1.4) will have *tumor* assessments during the crossover treatment period as described in Appendix 2, *footnote k.* Refer to Section 3.1.4 for guidance on duration of treatment on

Arm B after crossing over from Arm A. Patients who discontinue from crossover treatment will be asked to return to the clinic within 30 days after the final dose of RO7198457 or pembrolizumab, whichever is later, for a crossover treatment discontinuation visit. The visit at which response assessment shows disease progression on crossover treatment may be used as the early termination visit. Refer to Appendix 1 and Appendix 2 for assessments to be performed at the treatment discontinuation visit.

An independent review of the responses of all patients may be conducted, including a central review of CT and/or MRI scans, at an independent review facility. All primary imaging data used for tumor assessment may be collected by the Sponsor to enable a centralized, independent review of response endpoints. If available, a scan prior to the baseline (up to 3 months) may also be obtained to evaluate changes in tumor growth rate.

4.5.6 Photography of Cutaneous Lesions

Cutaneous lesions not evaluable by CT or MRI will be documented by color digital photography, including a ruler to estimate lesion size. Cutaneous lesions may be considered target lesions if they meet RECIST v1.1 criteria (see Appendix 4), otherwise they may be considered non-target lesions.

Photographs of cutaneous lesions will be taken at screening and on the same day as a tumor assessment visit, or at the first clinic visit following each tumor assessment (see Appendix 1 and Appendix 2). Copies of the de-identified photographs should be forwarded to for potential retrospective analysis.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

4.5.7.1 Local Laboratory Tests

The following laboratory tests will be performed at the study site's local laboratory:

- Hematology: CBC including RBC count, hemoglobin, hematocrit, platelet count, and WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, BUN or urea, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, total protein, albumin, amylase, and lipase
- Serum ferritin
- C-reactive protein
- Coagulation: PT, aPTT, and INR

- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation)

  If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.
- Urinalysis: dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) if warranted by dipstick results
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine, and free thyroxine
- Serology:
  - HBsAg, antibodies against HBsAg and hepatitis B core antigen

    HBV DNA test is to be obtained prior to Cycle 1, Day 1 if the patient has positive serology for anti-HBc.
  - Anti-HCV

    HCV RNA test is required prior to Cycle 1, Day 1 for consideration of eligibility if the patient has positive serology for anti-HCV.
  - HIV antibodies
- Tuberculosis testing (only if patient is considered at increased risk for infection with *Mycobacterium tuberculosis*): IFN-γ release assays or tuberculin skin test (according to local standard practice)

4.5.7.2 Central Laboratory Tests

The tests listed below will be performed at the central laboratory, a specialty laboratory, BioNTech, or at Genentech. Instruction manuals and supply kits will be provided by the central laboratory for these central assessments. Please refer to the central laboratory manual for additional details on biosample collection and handling instructions.

Assessments Performed on Blood Samples

- PK assays
  - EDTA-plasma samples will be obtained for measurement of RO7198457 component concentration [redacted] using liquid chromatography/mass spectrometry (LC/MS) and appropriate mRNA measurement assay
  - Serum samples will be obtained for measurement of pembrolizumab concentration using a validated assay.
- Auto-antibody testing

  Serum samples will be obtained for auto-antibody testing including, but not necessarily limited to, anti-nuclear antibody, anti–double-stranded DNA, anti-neutrophil cytoplasmic antibodies, and thyroid peroxidase antibody, to be performed based on clinical events during the study, either in individual patients or across the study population.

- Immune monitoring assays

  The following analysis will be applied on PBMCs or plasma samples for immune monitoring:

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

- Exploratory biomarker assays in blood
  - Samples will be obtained for cytokine biomarker and circulating tumor DNA evaluation as detailed in the schedule of assessments (see Appendix 3).
- NGS analysis

  Blood sample will be collected for NGS (WES, RNA sequencing, circulating tumor DNA analysis or TCR sequencing) and may be sent to one or more laboratories for analysis. NGS data and associated clinical data may be shared with researchers who are not participating in the study or may be submitted to government or other health research databases for broad sharing with other researchers to perform research on human health and disease. Study participants will not be identified by name or any other personally identifying information.

  NGS data will be analyzed in the context of this study for the identification of mutations in the tumor and explored in aggregate with other studies to better understand disease pathobiology and guide the development of new therapeutic approaches. Given the complexity and exploratory nature of these analyses, NGS data and analyses are for research purposes only and will not be shared with investigators or study participants unless required by law.

- [redacted]

Assessments Performed on Tumor Samples

The status of immune-related and tumor type-related biomarkers (including, but not limited to, the expression of PD-L1 on specific cell types and the prevalence and/or activation of infiltrating T cells) will be evaluated using methods including, but not limited to, IHC, immunofluorescence, and NGS assays in both archival and fresh tumor samples. Fresh tumor samples may also be used to generate TIL cultures for antigen-specific immune monitoring in tumors. In addition, tumor RNA and/or DNA may be purified and subject to characterization by NGS. Additional exploratory biomarkers may also be assessed if guided by clinical and nonclinical data.

- Archival tumor tissue: for all patients enrolled in the study

  If available, archival tumor tissue samples obtained outside of this study for other purposes will be collected from all patients (paraffin blocks are preferred; see laboratory manual for further details) to enable RO7198457 manufacturing and determine PD-L1 expression for stratification. Fine-needle aspirates, cell pellets from effusions or ascites, lavage samples, and bone biopsies do not satisfy the requirement for archival tissue.

  If adequate tissue from different timepoints (such as time of initial diagnosis and time of disease recurrence) and/or multiple metastatic tumors is available, priority should be given to the tissue with highest tumor content and lowest necrotic area (when feasible).

  Archival or fresh tumor tissue will be used for RO7198457 manufacturing and for testing PD-L1 expression, leftover material, if sufficient, will be used for the evaluation of potential predictive biomarkers using characterized assays for analysis of proteins, RNA and DNA.

- Fresh tumor biopsy at baseline: For patients who do not have sufficient archival tumor tissue sample, a fresh biopsy is required to enable vaccine manufacturing.

- An optional tumor tissue biopsy after investigator-assessed radiographic disease progression for patients being considered for either continuation of current treatment beyond progression or crossover from pembrolizumab monotherapy to RO7198457 plus pembrolizumab:

  An optional biopsy at time of progression will be collected if the sample collection is deemed safe and clinically feasible by the investigator and also if the scheduling can be accommodated. Tumor tissue samples consisting of core-needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions will be obtained.

  The biopsy at progression will be used for evaluation of tumor PD biomarkers and potential predictive biomarkers using characterized assays for analysis of proteins, RNA, and DNA.

- On-treatment tumor biopsies to assess tumor pharmacodynamic effects (randomized stage only):

  On treatment biopsy is mandatory for a minimum of 20 patients enrolled in Arm B and for 10 patients in Arm A. Once the required numbers of interpretable biopsies are collected, patients may provide an optional biopsy in both arms. The on-treatment biopsy should be obtained approximately 8–9 weeks after the first infusion of pembrolizumab in Arm A and 5–6 weeks after the first administration of RO7198457 in Arm B or an earlier time point *as indicated. The* Medical Monitor *is available to advise as needed.*

  Tumor tissue samples can be collected using core-needle, punch, excisional (as specified above), or forceps biopsy. Please refer to the sample specifications described below for mandatory tumor biopsies for further guidance pertinent to the chosen biopsy technique.

The mandatory and optional tumor biopsies will be used for evaluation of tumor PD biomarkers and potential predictive biomarkers using characterized assays for analysis of proteins, and NGS assays using RNA, and DNA. NGS data will be analyzed in the context of this study for the identification of mutations in the tumor and explored in aggregate with other studies to better understand disease pathobiology and guide the development of new therapeutic approaches. Given the complexity and exploratory nature of these analyses, NGS data and analyses are for research purposes only and will not be shared with investigators or study participants unless required by law.

Sample specifications: The mandatory and optional biopsies should meet the following sample requirements:

Tumor tissue samples consisting of core-needle biopsies of deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies of cutaneous, subcutaneous, or mucosal lesions will be obtained. Fine-needle aspirates, cell pellets from effusions or ascites, lavage samples, and bone biopsies are not permitted. Lesions considered for core needle biopsies should be deemed suitable for retrieval of at minimum three cores (but recommend five cores) at a given timepoint (refer to the Laboratory Manual for more details regarding biopsy requirements). The quality and quantity of tissue provided is critical for RO7198457 manufacturing and biomarker analysis. If possible, successive passes through the same lesion should be ≥ 1 cm apart.

If multiple lesions are available, it is preferable to obtain the on-treatment biopsy from the same lesion (or organ) as the pretreatment biopsy, if feasible, to avoid introduction of heterogeneity related to site of metastasis.

RECIST target lesions are not to be biopsied.

Sample Storage

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 4.5.13), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum/plasma samples collected for PK analysis may be needed for additional method development, assay validation, and characterization; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for NGS will be stored no later than 5 years after the final Clinical Study Report has been completed.
- Blood and plasma samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after 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 upon request or within 3 months of eligibility determination, whichever occurs first.

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

Data arising from sample analysis, including data on mutations, will be subject to the confidentiality standards described in Section 8.4.

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

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at screening and end of treatment visits, as outlined in the schedules of activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as clinically indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. Blood draws and other procedures should be avoided, if possible, during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability due to the effects of physiologic stress.

ECGs will be reviewed by the investigator to determine patient eligibility at screening.

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.

If at a particular postdose timepoint the mean QT interval corrected through use of Fridericia's formula (QTcF) is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled at that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate

the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.9 Cancer-Related Procedures

Collection of cancer-related medical, surgical, and radiation procedures will begin on Day 1 and be performed throughout the treatment period and during the survival follow-up period.

4.5.10 Patient-Reported Outcomes

To more fully characterize the clinical profile of RO7198457 plus pembrolizumab compared with pembrolizumab, PRO data will be obtained through use of select scales of the EORTC library, select items of the PRO-CTCAE library, an item capturing "bother" of treatment-related symptoms, and the full WPAI. The questionnaires will be translated as appropriate into the local language.

A total of 31 items from these 3 measures will be administered. Using selected scales/items from an item library instead of static questionnaires, minimize patient response burden (response fatigue), avoid concept redundancy (e.g., two scales assessing fatigue) and improve patients' compliance in rating the burden associated with their disease and treatment.

Paper PRO questionnaires scheduled for administration during a clinic visit must be completed by the patient at the investigational site at the start of the clinic visit prior to other study assessments that might bias patients' ratings of symptoms, function, and HRQoL and before administration of study treatment. Interviewer-administered assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to complete the measures on their own. Study personnel should only review all questionnaires for completeness before the patient leaves the investigational site.

4.5.10.1 EORTC Library

The EORTC library (see Appendix 9) includes single-item or multi-item symptom scales as well as GHS/HRQoL scale and five functional scales (Aaronson et al. 1993; Sprangers et al. 1996; Fitzsimmons et al. 1999). The Global GHS/HRQoL, Physical Function and Role Function scales will be collected from patients at baseline, while receiving treatment, and at time of treatment discontinuation.

The EORTC scales will be scored according to EORTC scoring manual (Fayers et al. 2001). Scale scores vary from 0 to 100 with 100 indicating a better functioning or HRQoL; a 10-point change from baseline within a treatment arm is considered clinically meaningful (Osoba et al. 1998).

PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for each measure in the ITT population.

The questionnaire is considered completed if at least one question was completed. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular timepoint.

4.5.10.2 Patient-Reported Outcomes Common Terminology Criteria for Adverse Events

The PRO-CTCAE (see Appendix 10) is an item bank reflecting to date, 78 symptomatic adverse events rated according to their severity, interference with daily function, frequency, and/or occurrence (Basch et al. 2014).

Symptomatic adverse events that are patient self-reportable were selected based on the side effects associated with CRS and immunotherapy (Weber et al. 2015b). Adverse events of which assessments rely on laboratory testing (e.g., neutropenia) that are presented as being primarily asymptomatic or with nonspecific signs and symptoms were disregarded. Adverse events that do not have an identifiable symptom equivalent in the PRO-CTCAE were also excluded. Based on the above criteria, *8* symptomatic adverse events were selected from the PRO-CTCAE item bank (i.e., chills, nausea, rash, fatigue, headache, shortness of breath, heart palpitations*, injection site reaction*); a total of *16* items. An additional item providing an overall assessment of the burden of side effects will be collected in addition to the *15* selected items of the PRO-CTCAE.

PRO-CTCAE will be completed per the schedules of activities (see Appendix 1 and Appendix 2), only when available in the local language of the investigational site.

4.5.10.3 Work Productivity and Activity Impairment: Melanoma, Version 2.0

The Work Productivity and Activity Impairment: Melanoma, Version 2.0 (WPAI:Melanoma) (see Appendix 11) evaluates effects on employment status, hours missed due to health problems, hours worked, and the degree to which health problems affect productivity and regular daily activities (Schadendorf et al. 2015). Patients who are employed will answer all the questions, while those not employed will only answer questions about their ability to do daily activities. For employed patients, work productivity impairment is expressed as percent work time missed, percent impairment while working, and percent overall work impairment. For employed and unemployed patients, the ability to perform daily activities is expressed as percent activity impairment. Higher scores indicate greater impairment and less productivity. The WPAI:Melanoma will be scored according to the WPAI scoring instructions (Reilly et al. 1993).

The WPAI will be administered specifically at Day 1 of Cycles 1, 4, and 13 and at the discontinuation visit to capture responses at patient's transition through induction to maintenance therapy.

4.5.11 Samples for Optional Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) to identify mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. The samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples 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 sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

Blood samples collected for WGS are to be stored no later than 5 years after the final Clinical Study Report has been completed.

Patient medical information associated with WGS 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 WGS 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.

4.5.12 Tumor Biopsies

Consenting patients will undergo tumor biopsies at baseline and may undergo additional on-treatment biopsies at any other time (including progression or response) at the investigator's discretion (if deemed clinically feasible by the investigator). During the randomized stage, on treatment biopsy is mandatory for a minimum of 20 patients enrolled in Arm B and for 10 patients in Arm A. Once the required numbers of interpretable biopsies are collected, patients may provide an optional biopsy in both

arms. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps 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 undergo 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 4.5.7. Refer to Section 4.5.13 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be 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 or diagnostic assays and establish the performance characteristics of these assays

4.5.13.2 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 4.5.13) will not be applicable at that site.

4.5.13.3 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 RO7198457, diseases, or drug safety:

- Leftover blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study
- Optional stool sample performed during screening and, if collected at screening, between C3D15 and C4D1 and C8D15 and C9D1

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 will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

4.5.13.4 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.

4.5.13.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.13.6 Withdrawal from the Research Biosample Repository

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

patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

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

4.5.13.7 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:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration (e.g., uncontrollable pain secondary to disease, unmanageable ascites) attributed to disease progression as determined by the investigator after an integrated assessment of all the radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to study treatment, including development of an immune-related adverse event (see Section 5.1.1.2), determined by the investigator to be unacceptable given the individual patient's potential response to therapy and the severity of the event

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study drug (see Appendix 1 and Appendix 2 for additional details).

The visit at which a response assessment shows disease progression that results in discontinuation of pembrolizumab and RO7198457 (if applicable) may be used as the treatment discontinuation visit as applicable, in which case all assessments associated with the treatment discontinuation visit should be performed at that time.

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

Patients who discontinue study treatment primarily for reasons other than disease progression will continue tumor assessments (see Section 4.5.5) if feasible, until disease progression, initiation of another systemic anti-cancer therapy, death, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first. After treatment discontinuation, information on survival follow-up and new anti-cancer therapy 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).

4.6.2 Patient Discontinuation from Study

Patient discontinuation from the study is distinguished from study treatment discontinuation (see Section 4.6.1) and occurs when the patient dies, is lost to follow-up, or withdraws consent to be followed.

Patients have the right to voluntarily withdraw from the study *(verbally or in writing)* 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 a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced

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

4.6.3 Study Discontinuation

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

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

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

RO7198457 is not approved, and clinical development is ongoing. The anticipated important safety risks for RO7198457 are outlined below. Please refer to the RO7198457 Investigator's Brochure for a complete summary of safety information.

Pembrolizumab is approved for several indications, including melanoma (see Section 3.3.2), and clinical development is ongoing. Please refer to the pembrolizumab local prescribing information for a complete summary of safety information.

The following information is based on limited data from an ongoing Phase I study of RO7198457 alone or in combination with atezolizumab, anticipated mechanism of action, results from nonclinical studies, results from ongoing clinical studies with similar RNA based vaccines and published data on similar molecules, in addition to the individual clinical safety profile of pembrolizumab that has been established to date (refer to pembrolizumab local prescribing information).

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Administration of study drug will be performed in a setting with available

emergency medical facilities with access to a critical care unit and staff who are trained to monitor for and respond to medical emergencies. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. All adverse events and serious adverse events will be recorded during the trial and for up to 90 days after the final dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurs first. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

The risks associated with RO7198457 and pembrolizumab are detailed in Sections 5.1.1 and 5.1.2, respectively.

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5.1.1.2 Immune-Related Adverse Events

Clinical experience with checkpoint inhibitors intended to enhance prevalent anti-tumor T-cell responses has demonstrated that development of autoimmune inflammatory

conditions is a general risk. Such immune-related adverse events have been described for virtually all organ systems and include, but are not limited to, colitis, hepatitis, pneumonitis, endocrinopathy, ocular toxicity, pancreatic toxicity, neurologic toxicity, myocarditis and rash.

In melanoma patients treated with non-mutated tumor antigens, cases of vitiligo were reported and may indicate an immune-mediated reaction to melanocyte-specific antigens. In contrast, such adverse events suggestive of an immune-mediated nature were not reported in trials with neoantigen vaccines which are directed against tumor mutations that arise during the process of tumorigenesis and are therefore not expressed by normal cells.

Theoretically, T cells directed against tumor–derived mutations might be cross-reactive to the respective wild-type sequence and, therefore, RO7198457 may increase the risk of autoimmune inflammation (also described as immune-related adverse events). Risk mitigation is implemented on the level of neoantigen selection. The bioinformatics workflow for creating the vaccine includes a process for excluding peptides associated with a high risk of autoimmunity. The mutation discovery, prioritization, and confirmation processes are complemented by a database that provides comprehensive information about expression levels of respective wild-type genes in healthy tissues. This information enables a personalized risk mitigation strategy by removing target candidates with an unfavorable risk profile. Mutations occurring in proteins with a possible higher auto-immunity risk in critical organs are filtered out and not considered for vaccine production.

In addition, eligibility criteria for this study are designed to exclude patient who may be at higher risk to develop immune-related adverse events.

Patients with a history of autoimmune disease (other than autoimmune thyroid disease managed with thyroid hormone replacement, controlled type 1 diabetes mellitus, certain cases of eczema, psoriasis, lichen simplex chronicus or vitiligo) and patients with a history of Grade ≥ 3 immune-related adverse events associated with prior CIT that resulted in permanent discontinuation of prior CIT or history of any Grade 4 immune-related adverse events attributed to prior CIT (other than endocrinopathy managed with replacement therapy) will be excluded from this trial (see Section 4.1.2). In addition, all immune-related adverse events related to prior CIT must have resolved completely. Patients treated with corticosteroids for immune-related adverse events from prior CIT (other than endocrinopathy managed with replacement therapy or stable vitiligo) must demonstrate the absence of related symptoms or signs for at least 4 weeks following discontinuation of corticosteroids prior to study entry (see Section 4.1.2).

Suggested management guidelines for individual suspected immune-related adverse events are provided in Section 5.1.4.3.

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5.1.2 Risks Associated with Pembrolizumab

The overall safety profile for pembrolizumab is based on data from patients treated with pembrolizumab in clinical trials, including approximately 1500 patients with melanoma. Adverse drug reactions in patients who received pembrolizumab include immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies (hypophysitis, thyroid dysfunction, and type 1 diabetes mellitus), immune-mediated nephritis and renal dysfunction, immune-mediated skin reactions (rashes, including Stevens-Johnson syndrome [SJS], and toxic epidermal necrolysis [TEN]), other immune-mediated adverse reactions (may involve any organ system), IRRs, complications of allogeneic hematopoietic stem cell transplantation after treatment with pembrolizumab, increased mortality in patients with multiple myeloma when pembrolizumab is added to a thalidomide analogue and dexamethasone, and embryo−fetal toxicity. Immune-mediated adverse reactions that occurred in less than 1% (unless otherwise indicated) of patients treated with pembrolizumab include arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials and postmarketing use. Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with pembrolizumab.

The most frequently observed adverse drug reactions in patients with melanoma who received pembrolizumab in clinical trials were fatigue, diarrhea, nausea, and rash. Please refer to the pembrolizumab local prescribing information for complete information regarding clinical safety.

5.1.3 Potential for Overlapping Toxicities with RO7198457 and Pembrolizumab

Based on nonclinical and/or clinical studies with each molecule as a single agent and experience with molecules with similar mechanisms of action, there is a potential for overlapping toxicity in patients treated with the combination of RO7198457 and pembrolizumab. Because the expected pharmacological activity of these two molecules is to increase adaptive T-cell immune responses via complementary mechanisms, the combination may be associated with heightened immune-related toxicity relative to either agent alone.

The largest clinical experience to date with the combination of complementary modulators of adaptive immunity is derived from trials of ipilimumab combined with nivolumab (Wolchok et al. 2013; Antonia et al. 2014; Hammers et al. 2014; Larkin et al. 2015). In a Phase III trial of this combination in patients with advanced melanoma, an increased frequency of treatment-related toxicities of all grades as well as Grade 3–4 events was observed for the regimen of nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W (for the initial four doses followed by ipilimumab 3 mg/kg every 2 weeks beyond Cycle 3), as compared with either single agent alone (Larkin et al. 2015). Nevertheless, most treatment-related events in this trial were qualitatively similar to those observed with ipilimumab or nivolumab as a single agent and were manageable and reversible with established treatment guidelines. Another combination with the anti–PD–L1 antibody durvalumab and the anti–CTLA–4 antibody tremelimumab in patients with NSCLC in a Phase Ib study also showed a similar manageable safety profile (Antonia et al. 2016).

On the basis of these data, it is anticipated that any potential immune-related adverse events following treatment with RO7198457 and pembrolizumab will likewise be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with immune checkpoint inhibitors to date was incorporated into the design and safety management plan (see Section 5.1.4), with the goal of reducing the risks to participating patients.

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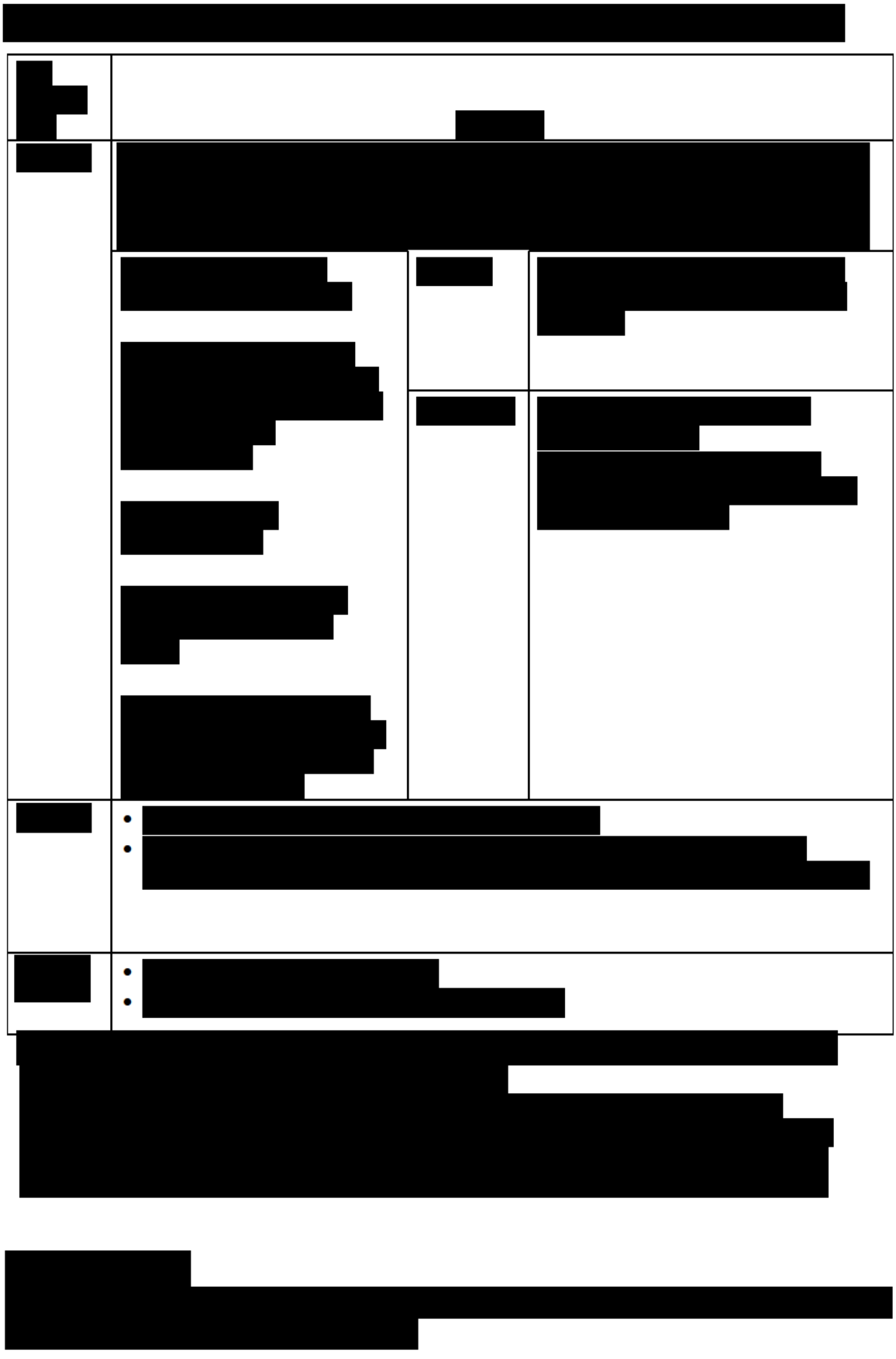

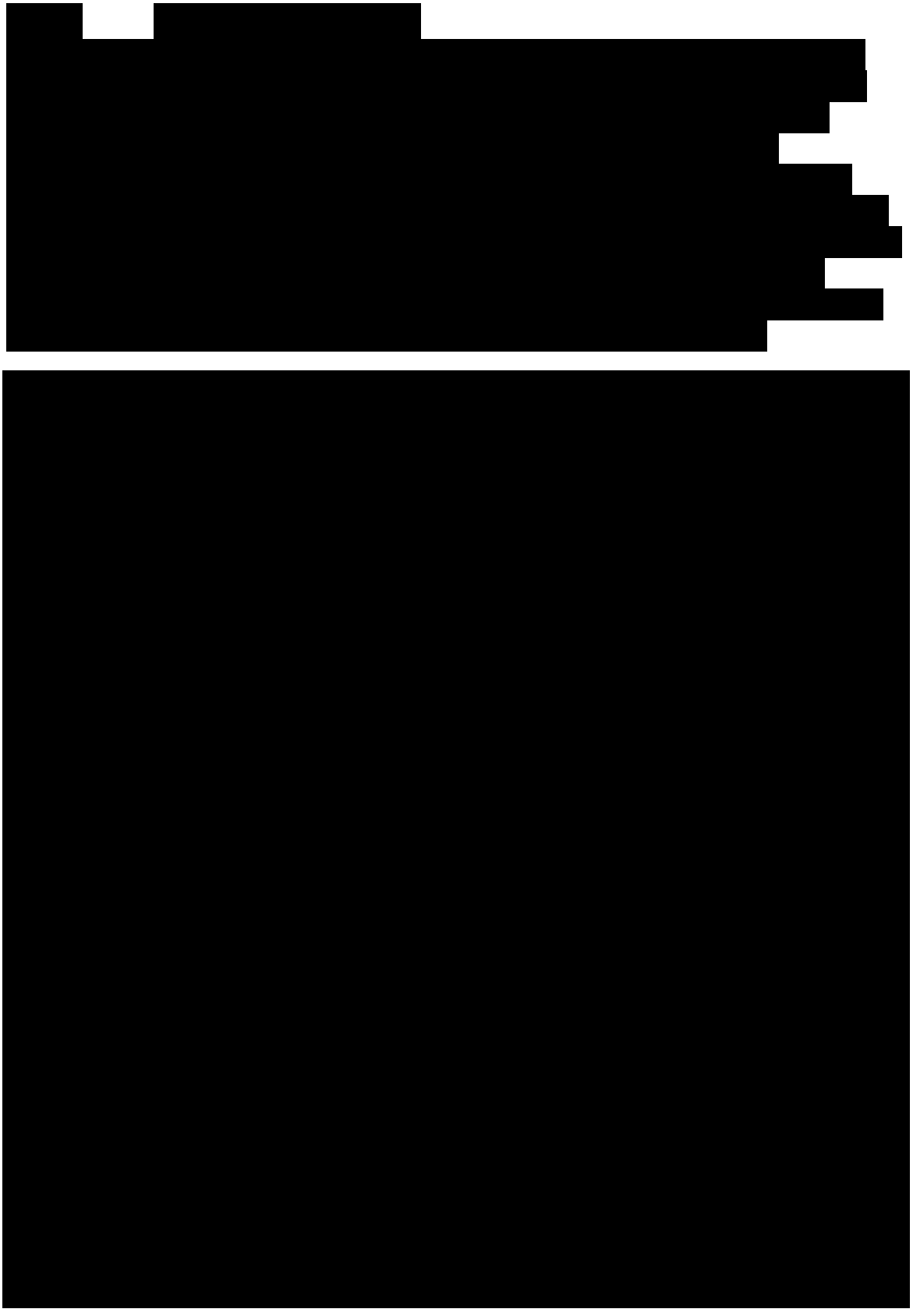

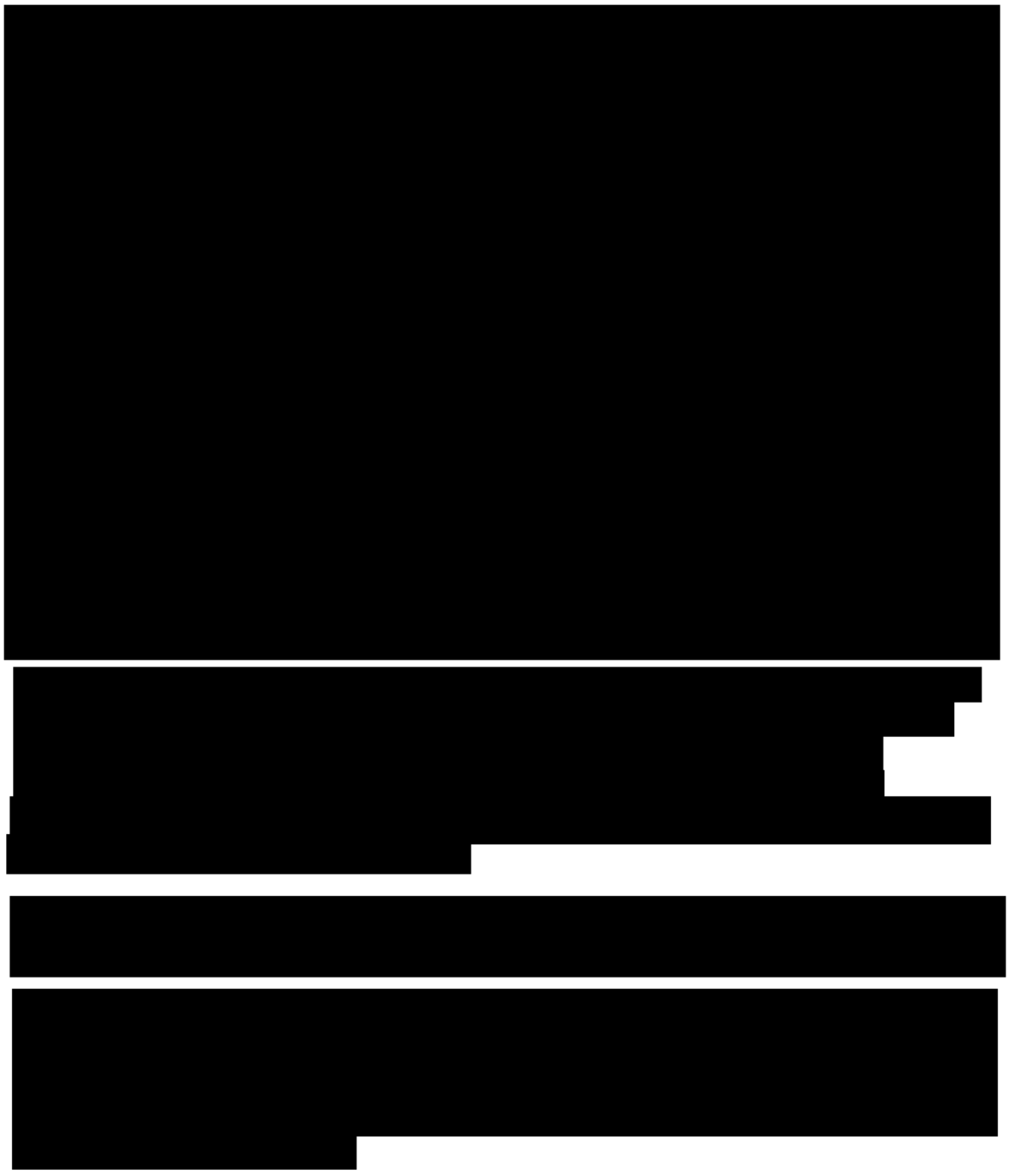

5.1.4.3 Management Guidelines for Specific Adverse Events

Events associated or possibly associated with pembrolizumab alone (Arm A) or RO7198457 plus pembrolizumab (safety run-in stage, Arm B, and crossover) should be managed according to standard medical practice. Management guidelines for systemic reactions during or after study drug infusion are discussed below and described in Table 5, Table 6, Table 7, and Table 8. For management of immune-related adverse events, investigators may also consult ASCO/ESMO guidelines (Haanen et al. 2017; Brahmer et al. 2018). Although most immune-related adverse events observed with immune modulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010; Weber et al. 2012). Discontinuation of RO7198457 and/or pembrolizumab may not have an immediate therapeutic effect, and there is no available antidote for either of these experimental agents.

The investigator should consider the benefit–risk balance for an individual patient, taking into account the totality of information as it pertains to the nature and severity of the event, as well as the degree of clinical benefit a given patient may be experiencing prior to further administration of RO7198457 and/or pembrolizumab. In some cases, for example, patients who develop a clinically manageable Grade 3 immune-related adverse event but who are otherwise experiencing clear signs of clinical benefit, such as tumor shrinkage or stable disease with significant improvement in tumor-associated symptoms, may elect to continue treatment with RO7198457 and/or pembrolizumab upon recovery from the event, under continued close supervision by the study investigator. *The* Medical Monitor *is available to advise as needed.* If, with continued treatment, the event should be seen to reoccur such that the benefit–risk balance for a given patient is deemed unfavorable, pembrolizumab (Arm A) or RO7198457 and pembrolizumab (safety run-in stage, Arm B, and crossover) should be permanently discontinued.

Single-agent pembrolizumab (Arm A) or RO7198457 and pembrolizumab (safety run-in stage, Arm B, and crossover) must be permanently discontinued in patients with life-threatening immune-related adverse events.

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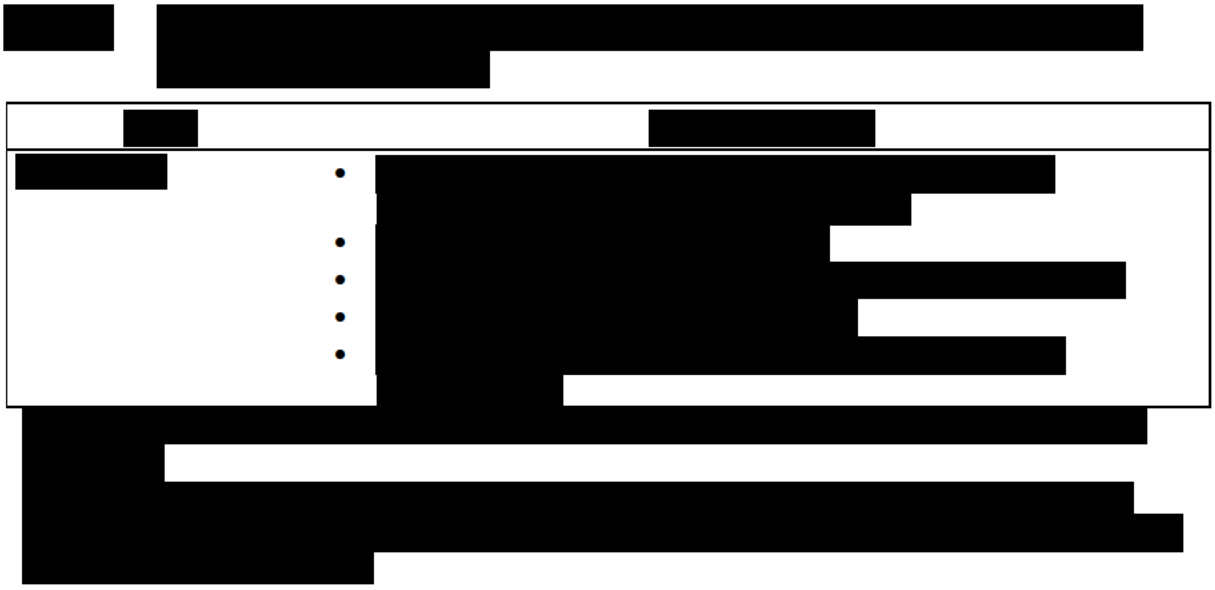

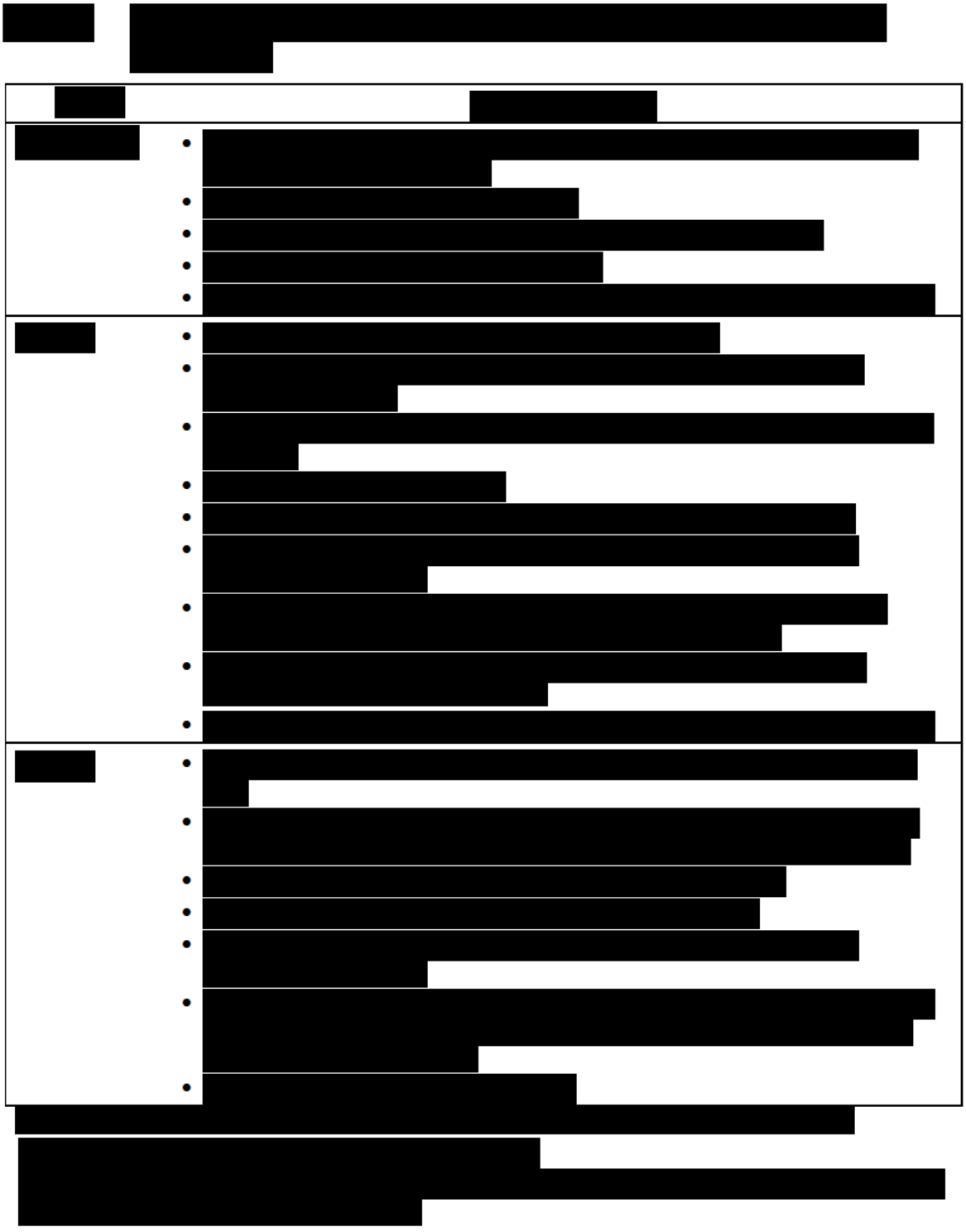

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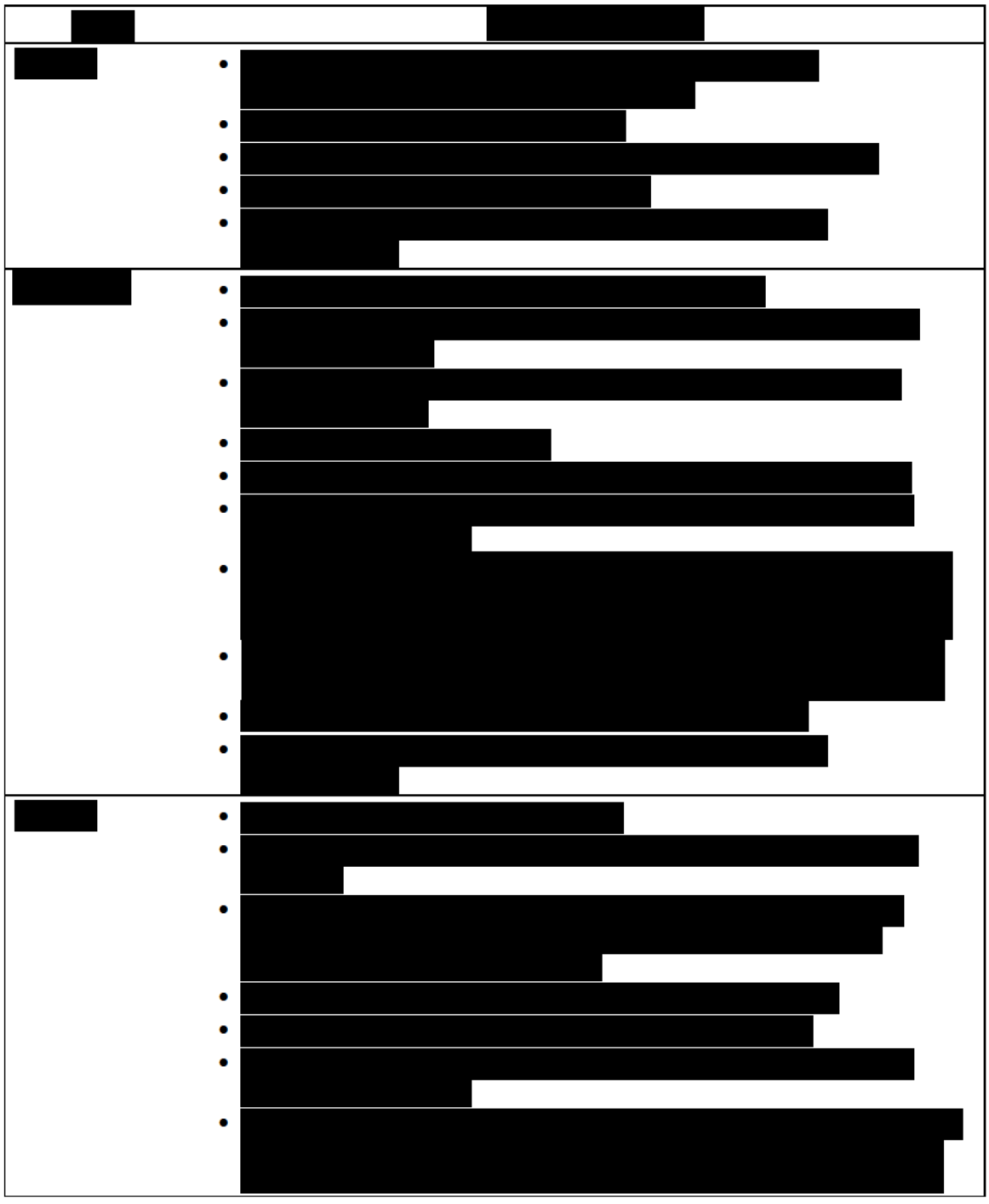

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Please refer to the pembrolizumab local prescribing information for detailed guidance on management of specific immune-related adverse events.

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- 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 drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an 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 drug, 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 the study drug is suspected.
- [redacted]
- [redacted]
- Grade ≥ 3 hypoxia or dyspnea within 24 hours of study treatment
- Grade ≥ 3 hypotension within 24 hours of study treatment
- Conditions (regardless of grade) suggestive of an immune-mediated disorder, including, but not limited to, the following:
  - Pneumonitis
  - Colitis
  - Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
  - Hepatitis, including AST or ALT $> 10 \times$ ULN
  - Systemic lupus erythematosus

  - Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
  - Nephritis
  - Ocular toxicities (e.g., uveitis, retinitis, 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., SJS, dermatitis bullous, TEN)
- Grade ≥3 AST/ALT/total bilirubin elevation—asymptomatic
- Grade ≥2 AST/ALT/total bilirubin elevation—with constitutional symptoms

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 90 days after the final dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator is not required to actively monitor patients for new events, but should report any serious adverse events that are believed to be related to treatment with RO7198457 and/or pembrolizumab in this study (see Section 5.6). Deaths should be reported as described in Section 5.3.5.8.

Ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

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 unless otherwise specified. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 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.

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

Table 10 Causal Attribution Guidance

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

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

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 Systemic Infusion Reactions During or After Study Drug Infusion

Adverse events that occur during or within 24 hours after completion of study drug administration and are judged to be related to study drug infusion(s) should be captured as a diagnosis (e.g., "flu-like symptoms," "infusion-related reaction," "cytokine release syndrome" or other adverse event term denoting the overall diagnosis) on the Adverse Event eCRF based on the most clinically-significant individual adverse event, its timing, and any required interventions.

For example, mild to moderate presentation that may include fever, chills or other constitutional symptoms, may be best described as flu-like symptoms, whereas more severe events, such as hypotension, hypoxia or signs of organ toxicity, may be signs of CRS. Events that occur during or shortly after the infusion may be referred to as "infusion-related reaction." Clinical symptoms that include dyspnea, bronchospasm, chest tightness, urticaria, angioedema, hypotension and other cardiovascular symptoms, and (pre-)syncope may be indicative of hypersensitivity, allergic reaction or anaphylaxis.

If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF. [redacted]

[redacted] Section 5.2.3 for details on adverse events of special interest, and Section 5.3 for reporting requirements.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than systemic reactions during or after study drug infusion (see Section 5.3.5.1), 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. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes 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

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of melanoma.

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").

If the death is attributed to progression of malignancy, "malignant neoplasm progression" should be recorded on the Adverse Event eCRF. The term "disease progression" should be avoided since it is not clearly linked to a patient's underlying malignancy.

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 Incurable, Advanced Malignancy

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 criteria. 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
- Hospitalization solely for coordination of care, including hospice arrangements
- Planned hospitalization required by the protocol (e.g., for study drug administration, protocol mandated observation window, insertion of access device for study drug administration, etc.)
- 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
- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For RO7198457, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7198457, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF. Special situations should be recorded as described below:

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

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

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data (e.g., EORTC QLQ-C30, PRO-CTCAE, and WPAI) by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

5.4.1 Emergency Medical Contacts

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

Once the electronic data capture (EDC) system is available, all information will need to be entered and submitted via the EDC system

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. In the event the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing

the form using the fax number or email address provided to investigators by emailing the form using the following email address: SAEIntake@*Fortrea*.com

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study drug or until initiation of subsequent 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 EDC system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and 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 >90 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of RO7198457 or 4 months after the final dose of pembrolizumab, whichever occurs later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the final dose of study treatment. 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 drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- RO7198457 Investigator's Brochure
- Pembrolizumab Summary of Product Characteristics (SmPC)

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This study will include an initial safety run-in stage followed by a randomization stage. During the safety run-in stage, 6–12 patients with metastatic melanoma will be enrolled and treated with RO7198457 and pembrolizumab. Following IMC review, enrollment will be opened for the randomization stage.

The randomization stage will enroll approximately 120 patients that will represent the ITT population for the primary PFS and secondary activity endpoints. Unless otherwise stated, summaries of study conduct, patient demographics, baseline characteristics, and secondary and exploratory endpoints will be assessed in all randomized patients and separately for patients in the safety run-in stage.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is estimation and hypothesis generation regarding the safety and efficacy of RO7198457 plus pembrolizumab relative to pembrolizumab monotherapy.

Enrollment of 120 randomized patients (approximately 80 patients in the RO7198457 plus pembrolizumab arm and 40 patients in the standard-of-care arm) is expected to occur 18 months after first patient in (FPI).

The null and alternative hypotheses with respect to PFS can be phrased in terms of the survival function $S_{PFS_a}(t)$ in Arm A (control) and $S_{PFS_b}(t)$ in Arm B (experimental):

$$H_0: S_{PFS_a}(t) = S_{PFS_b}(t) \text{ vs. } H_a: S_{PFS_a}(t) \neq S_{PFS_b}(t)$$

[redacted]

[redacted] in our PFS primary efficacy endpoint, the first efficacy endpoint tested in a hierarchical fashion. However, the totality of data, including safety and sensitivity analyses while accounting for non-proportional hazards as stated in Section 6.4.1 will be important for evaluating clinical benefit.

Point and interval estimates for the primary endpoint of PFS HR and key secondary endpoint of improvement in ORR (i.e., Δ ORR) in the RO7198457 plus pembrolizumab arm relative to the pembrolizumab arm will be obtained.

To control for Type 1 error, two pre-specified interim analyses and one primary analysis will be conducted with a Haybittle-Peto alpha spending approach (Haybittle 1971; Peto et al. 1976). Testing will be performed in a hierarchical fashion testing PFS followed by secondary endpoints. Each interim analysis will be conducted at the two-sided significance level of 0.001. The final analysis will be conducted at the two-sided significance level of 5%. If PFS is significant at the two-sided significance level of 5%, alpha will be passed down to the secondary endpoints in order of presentation below.

The study will not, however, have adequate power to detect other potentially clinically meaningful differences in PFS and Δ ORR. [redacted] improvement in ORR in the RO7198457 plus pembrolizumab arm relative to the pembrolizumab arm (assuming a 33% ORR in the pembrolizumab arm). Thus, a statistically negative outcome does not rule out a potentially clinically meaningful outcome.

Table 11 and Table 12 show the power and CIs for several possible true underlying improvements in PFS and ORR in favor of the RO7198457 plus pembrolizumab arm. The study will not have adequate power to detect other potentially clinically meaningful differences in PFS or ORR. See Table 11 below.

Table 11 Power and Confidence Intervals for Study Design for Several Possible True Underlying PFS Hazard Ratio Values

	True Underlying PFS Hazard Ratio
[redacted]	

PFS = progression-free survival.

Notes: Results are based on 80 total events from 120 total patients in a 2:1 ratio

[a] Two-sided $\alpha = 0.05$

Table 12 Power and Confidence Intervals for Study Design for Several Possible True Underlying Δ ORR Values

	True Underlying Δ ORR
[redacted]	

ORR = objective response rate.

Notes: Results are based on 120 total patients (80 and 40 patients in the treatment and control arm, respectively).

[a] Two-sided $\alpha = 0.05$

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be listed by treatment arm and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, race, weight, stage, and baseline ECOG Performance Status will be summarized by treatment arm for all randomized patients. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

6.4 EFFICACY ANALYSES

The primary analysis population includes all patients randomized (i.e., the intent-to-treat [ITT] population). Supportive per protocol analysis populations will include patients on-study at Cycle 2 receiving intended treatment (e.g., patients who received at least 2 cycles of study treatment) as well as safety run-in stage patients. The primary analysis will be PFS.

6.4.1 Primary Efficacy Endpoint of PFS

PFS is defined as the time from randomization to the date of first documented disease progression or death, whichever occurs first. Disease progression for PFS analysis will be determined on the basis of investigator assessment using RECIST v1.1. The primary PFS analysis will occur after approximately 80 events have been observed in the primary population or approximately 24 months from FPI.

Data for a patient without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the date of randomization plus 1 day if no tumor assessment was performed after the baseline visit). Data from a patient who is lost to follow-up will be included in the analysis and censored on the last date of tumor assessment that the patient was known to be progression free.

Kaplan-Meier methodology will be used to estimate the PFS curve and median PFS for each treatment arm. A stratified Cox proportional-hazards model will be used to estimate the HR and its 95% CI. The two-sided stratified log-rank test will be used to compare PFS between the two treatment arms at the two-sided significance level of 5%. Unstratified modeling approaches may be used to assess the robustness of the PFS primary endpoint results. To account for patients who may discontinue study treatment prior to first administration of RO7198457, a landmark analysis restricted to patients treated at Cycle 2 and beyond may be performed with PFS time calculated starting from Cycle 2, Day 1 on the ITT and modified subsets.

6.4.2 Secondary Efficacy Endpoints

ORR Analysis

ORR is defined as the proportion of patients who have experienced a CR or PR on two consecutive occasions $\geq$ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Objective response will be evaluated by treatment arm. Patients without postbaseline overall response assessments will be counted as non-responders. An estimate of the difference between the ORR in the two arms will be computed along with its 95% CI. The Mantel-Haenszel test will be used to compare the ORR between the two treatment arms at the two-sided significance level of 5%, if PFS analysis is significant at the 5% threshold for type I error control, stratified by the protocol-defined stratification factors. Final ORR analysis will occur at the time of primary PFS analysis.

OS Analysis

OS is defined as the time from randomization to death from any cause. Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day. A final OS analysis will be performed at approximately 40% event maturity at approximately 40 months. Statistical analyses will be performed similarly to PFS as described in 6.4.1.

Duration of Response Analysis

DOR is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1. The analysis of DOR will include only patients who achieved an objective response to study treatment. DOR will be estimated using the Kaplan-Meier methodology.

Crossover Analysis

The statistical analysis to evaluate the efficacy of patients who have progressed following pembrolizumab monotherapy and received the combination of RO7198457 plus pembrolizumab as assessed by ORR per RECIST v1.1 will be performed as described in Section 6.4.2.

Patient-Reported Outcomes Analysis

Summary statistics and longitudinal analyses will inform change from baseline in GHS/HRQoL scores at each timepoint (including baseline, end of induction, crossover for Arm A, time to first PD per RECIST v1.1, end of treatment for any cause) by treatment arm during treatment will be analyzed for all randomized patients who had a baseline and one or more postbaseline assessments. A score change of at least 10 points is considered clinically meaningful and will be used to define deterioration and improvement.

6.4.3 Exploratory Efficacy Endpoints

A 12-month PFS rate will be analyzed in the ITT. The PFS rate will be estimated using Kaplan Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from the Greenwood formula. The 95% CI for the difference in the PFS rate between the two treatment arms will be estimated using the normal approximation method.

PFS, ORR, and DOR may be further evaluated using definitions of response per iRECIST criteria (see Appendix 5) in all randomized patients.

Exploratory PRO endpoints may be evaluated to further characterize the patient experience when treated with RO7198457 plus pembrolizumab versus pembrolizumab alone. PRO scales (EORTC scales, PRO-CTCAE scale, single-item bother, and WPAI) completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for each measure in the ITT population. Summary statistics at each timepoint including proportion of patients with meaningful changes, time-to-event analyses, and longitudinal analyses as relevant will be generated to inform patients' experience in each treatment arm.

6.5 SAFETY ANALYSES

Safety analyses will be conducted in all randomized patients who received at least one dose of RO7198457 and/or pembrolizumab. Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the RO7198457 plus pembrolizumab arm in the safety analyses if the patient receives any amount of RO7198457, regardless of the initial treatment assignment at randomization.

Safety endpoints will include incidence and severity of adverse events (using NCI CTCAE v5.0), including serious adverse events and adverse events of special

interest, changes from baseline in clinically relevant vital signs, physical findings, and clinical laboratory results following the administration of RO7198457 plus pembrolizumab or solely pembrolizumab. Drug exposure will be summarized, including duration, dosage, and dose intensity. Verbatim description of adverse events will be mapped to the MedDRA thesaurus terms and graded according *to* the NCI CTCAE v5.0.

All adverse events that occur during or after the first study treatment, until 90 days after the final dose of study drug or initiation of another systemic anti-cancer therapy, whichever occurs first, will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrence of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data will be summarized by treatment arm and grade. Vital signs will also be summarized by treatment arm and visit. Deaths and causes of deaths will be summarized. Analyses of safety endpoints will be conducted at the time of the primary efficacy analysis.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with any blood sample drawn according to Appendix 3 for the purpose of PK analysis. Individual and mean plasma [redacted] concentrations (minimum serum concentration observed [C_{min}] and maximum serum concentration observed [C_{max}]) will be tabulated and summarized for each cycle for which pharmacokinetics are to be measured. Data will be pooled with data from the Phase Ia/Ib study (GO39733) using an established population PK model to estimate total AUC, total CL, V_{ss}, and terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation [%CV], median, range, geometric mean, and geometric mean CV [%CV]) by treatment arm, when appropriate and as data allow. Inter-patient variability and drug accumulation will be evaluated.

Serum pembrolizumab concentration data (C_{max} and C_{min}) will be tabulated and summarized for each cycle where collected. Descriptive statistics will include geometric mean and geometric mean CV, as appropriate. Pembrolizumab concentration data may be pooled with data from other studies using an established population PK model to estimate total AUC, as warranted by the data. Data may be compared with historical data, as these results will provide preliminary information on whether [redacted] pembrolizumab pharmacokinetics are altered by co-administration of the other agent.

6.7 BIOMARKER ANALYSES

Exploratory biomarker analyses may be performed in order to inform the disease pathobiology and provide greater understanding of the mechanism of action with response. In particular, we may perform prognostic, predictive, and PD biomarker

analyses from IHC or DNA/RNA-based assays, where applicable. Cellular immune responses, cytokines, antibody responses, and further immunological parameters as represented in the schedules of activities (see Appendix 1 and Appendix 2) will be determined once or repeatedly in the course of the study. In the latter case, changes from baseline will be tabulated.

Exploratory analysis of WGS data may additionally be conducted in the context of this study and explored in aggregate with data from other studies to increase researchers' understanding of disease pathobiology and guide the development of new therapeutic approaches. WGS is not applicable for a site that has not been granted regulatory approval for WGS sampling.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

Periodic analyses of cumulative safety data and two interim analyses of efficacy data are planned for this study. Safety interim analyses will be conducted at regular intervals by the IMC (see Section 3.1.5).

The first efficacy interim analysis will take place after either approximately 60 patients have had two scans or 25% PFS event maturity, both of which are expected to occur at approximately 16 months after FPI. The second interim analysis will occur at approximately 50% event maturity, which is expected to be around 18 months.

Outcomes from these reviews that may affect study conduct will be communicated in a timely manner to the investigators, and IRBs and/or ECs will be notified. Any changes to the study design resulting from these analyses will be addressed through a protocol amendment.

6.8.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to one additional interim efficacy analyses beyond what is specified in Section 6.8.1. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Genentech will retain study data for 25 years after the final Clinical Study Report has been completed 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. Food and Drug Administration 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 Trial Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. 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, which may include data on germline mutations, 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, *data may* be *disseminated as described in 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 by Genentech and managed by Genentech and a contract research organization (CRO). The CRO will provide clinical operations management support.

For the safety run-in stage, approximately 8 sites in the United States and Australia will participate to enroll up to 12 patients. Approximately 40 sites globally will participate to enroll approximately 120 patients in the randomized stage of the trial. Enrollment will occur through an IWRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected. An independent radiologic review facility will be used to collect and retain copies of tumor assessment scans for potential centralized review.

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 of the U.S. National Institutes, 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 more details), and redacted Clinical Study Reports and*/or* other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request.

For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following web site:

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 (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities: Arm A (Pembrolizumab)

Arm A—Screening Parts A and B and Cycles 1–12

	Screening Period [a]			Treatment Period (Initial)						
	Part A	Part B		Cycle 1	Cycle 2	Cycles 3, 5, 7	Cycles 4, 6	Cycles 9, 11	Cycles 8,10, 12	UV [b]
Day (Window)		−28	−14	1 (±2)	1 (±2)	1 (±2)	1 (±2)	1 (±3)	1 (±3)	
Signed informed consent [c]	x	x								
Review of eligibility criteria [d]	x	x								
Medical, surgical, cancer histories, demographic data [e]		x								
Tumor assessments [f, g]		x		x [h]						
Digital photography, cutaneous lesions [j]		x		x						
Concomitant medications [k]		x		x	x	x	x	x	x	x
Adverse events [l]		x		x	x	x	x	x	x	x
Vital signs [m]		x		x	x	x	x	x	x	x
ECOG Performance Status [n]	x	x		x	x	x	x	x	x	x
Weight		x		x	x	x	x	x	x	x
Height		x								
Complete physical examination [o]		x								
Limited physical examination [o]				x	x	x	x	x	x	x
12-lead ECG [p]		x								
Hematology [q]			x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities: Arm A (Pembrolizumab) (cont.)
Screening Parts A and B and Cycles 1–12

	Screening Period [a]			Treatment Period (Initial)						
	Part A	Part B		Cycle 1	Cycle 2	Cycles 3, 5, 7	Cycles 4, 6	Cycles 9, 11	Cycles 8,10, 12	UV [b]
Day (Window)		−28	−14	1 (±2)	1 (±2)	1 (±2)	1 (±2)	1 (±3)	1 (±3)	
Serum/plasma chemistry [r]	x [r]		x	x	x	x	x	x	x	
Coagulation (PT, aPTT, INR)			x							
Amylase, lipase			x		x		x		x	
Urinalysis [s]			x		x		x (C6 only)		x (C10 only)	
Pregnancy test [t]			x		x		x		x	
Serum ferritin and CRP [u]			x		x	x		x		
TSH, free T3, and free T4 [v]			x				x (C4 only)		x (C8 and C12 only)	
Autoantibody tests [w]			x							
HBV, HCV, HIV, TB serology tests [x]	x									
Cancer-related procedures [y]				x	x	x	x	x	x	
EORTC scales [z]				x	x	x	x	x	x	
PRO-CTCAE scales and single-item bother [z]				x	x	x	x	x	x	
WPAI [aa]				x			x (C4 only)			
Pembrolizumab infusion [bb]				x	x	x	x	x	x	
Serum (pembrolizumab) PK sample	See Appendix 3									

Appendix 1: Schedule of Activities: Arm A (Pembrolizumab) (cont.)
Screening Parts A and B and Cycles 1–12

	Screening Period [a]			Treatment Period (Initial)						
	Part A	Part B		Cycle 1	Cycle 2	Cycles 3, 5, 7	Cycles 4, 6	Cycles 9, 11	Cycles 8,10, 12	UV [b]
Day (Window)		−28	−14	1 (±2)	1 (±2)	1 (±2)	1 (±2)	1 (±3)	1 (±3)	
Plasma sample for biomarkers	See Appendix 3									
[redacted]										
Blood sample for WGS (optional) [ee]				x						
Stool sample for RBR (optional) [ff]			x				x (C4 only)	x (C9 only)		
Baseline tumor tissue [gg]	x									
On-treatment tumor biopsies [hh]				x						

Cycles 13–*34*, Treatment Discontinuation, and Follow-Up

	Treatment Period (Maintenance) [ii]							TX DC [jj]	FU
	Cycles 13, 21, 29	Cycles 14, 20, 22, 28, 30	Cycles 15, 23, 31	Cycles 16, 24, 32	Cycles 17, 25, 33	Cycles 18, 26, 34	Cycles 19, 27		
Days (Window)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)		
Tumor assessments [f, g]	x [h]								x [i]
Digital photography, cutaneous lesions [j]	x								x
Concomitant medications [k]	x	x	x	x	x	x	x	x	
Adverse events [l]	x	x	x	x	x	x	x	x	
Vital signs [m]	x	x	x	x	x	x	x	x	
ECOG Performance Status [n]	x	x	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	x	x	
Limited physical examination [o]	x	x	x	x	x	x	x	x	
12-lead ECG [p]								x	
Hematology [q]	x	x	x	x	x	x	x	x	
Serum/plasma chemistry [r]	x	x	x	x	x	x	x	x	
Amylase, lipase		x		x		x		x	
Urinalysis [s]		x (C14, C22, C30 only)				x		x	
Pregnancy test [t]		x		x		x		x	
Serum ferritin and CRP [u]	x				x			x	

Appendix 1: Schedule of Activities: Arm A (Pembrolizumab) (cont.)
Cycles 13–34, Treatment Discontinuation, and Follow-Up

	Treatment Period (Maintenance) [ii]							TX DC [jj]	FU
	Cycles 13, 21, 29	Cycles 14, 20, 22, 28, 30	Cycles 15, 23, 31	Cycles 16, 24, 32	Cycles 17, 25, 33	Cycles 18, 26, 34	Cycles 19, 27		
Days (Window)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)		
TSH, free T3, and free T4 [v]		x C20, C28 only		x				x	
Cancer-related procedures [y]	x	x	x	x	x	x	x	x	x
EORTC scales [z]	x	x	x	x	x	x	x	x	
PRO-CTCAE scales and single-item bother [z]	x	x	x	x	x	x	x	x	
WPAI [aa]	x C13 only							x	
Survival, anticancer therapy, and -follow-up [kk]									x
Pembrolizumab infusion [bb]	x	x	x	x	x	x	x		
Serum (pembrolizumab) PK sample	See Appendix 3								
Blood sample for biomarkers	See Appendix 3								
Blood sample (PBMC-I) for biomarkers [cc]								x	
On-treatment tumor biopsies [hh]	x								

Appendix 1: Schedule of Activities: Arm A (Pembrolizumab) (cont.)

C = cycle; CCP = cyclic citrullinated peptide; CIT = cancer immunotherapy; CRP = C-reactive protein; CT = computed tomography; D = day; [redacted]; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 and IL12 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire–Core 30 and IL12; FU = Follow-Up; HBc = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; iRECIST = immune-based therapeutics Response Evaluation Criteria in Solid Tumors; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PET = positron emission tomography; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RF = rheumatoid factor; TB = *Mycobacterium tuberculosis*; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TX DC = Treatment Discontinuation; UV = unscheduled visit; WGS = whole genome sequencing; WPAI = Work Productivity and Activity Impairment.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] During screening period Part A and after informed consent has been obtained, patients will provide tumor tissue and blood samples to allow time for vaccine manufacturing. Patients whose samples are of sufficient quality and quantity for vaccine manufacturing will sign the main consent (Participation in Study GO40558 ICF) and start the remaining procedures outlined for the screening Part B section. Time window for screening equals the number of days to Cycle 1, Day 1 (see Section 3.1).

[b] Unscheduled visits may include the assessments indicated. Additional assessments and/or procedures may be requested or performed as needed.

[c] Written informed consent is required before performing any study-specific tests or procedures (including screening evaluations) and may be obtained at any time prior to such tests or procedures.

[d] A limited review of the eligibility checklist (e.g., ECOG Performance Status, blood chemistry, serology for HIV, HBV, and HCV) may be performed during the first part of screening (Part A). The rest of the eligibility checklist will be reviewed during the second part of screening (Part B).

[e] Medical history includes cancer history (including, but not limited to, prior cancer therapies and/or prior CITs and procedures and tumor characteristics such as hormone receptor status or mutation status), other clinically significant diseases, surgeries, smoking history, use of alcohol and/or drugs of abuse, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the screening visit. Demographic information includes sex, age, and self-reported race/ethnicity.

[f] All sites of disease should be assessed and documented. If available, a scan prior to the baseline (up to 3 months) may also be obtained to evaluate changes in tumor growth rate. Baseline CT assessments should be performed within 28 days prior to the start of study treatment (Cycle 1, Day 1). Screening and subsequent tumor assessments should include CT scans (with IV contrast unless contraindicated and oral contrast per institutional standards) of the chest, abdomen, and pelvis. Patients who have a contraindication to IV contrast may have MRI scans of the abdomen and pelvis performed in lieu of CTs and a non-contrast CT of the chest. A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan (see Section 4.5.5). Bone scans and CT scan of neck or extremities should also be performed if clinically indicated. If a CT scan for tumor assessment is performed in a PET-CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. The same radiographic procedure used to define measurable lesions at baseline should be used throughout the study for each patient.

[g] Patients who continue treatment beyond radiographic disease progression (see Section 3.1.3) will be monitored with a follow-up scan in 6 (±1) weeks (i.e., at the next scheduled tumor assessment when the scan frequency is every 6 weeks or as an unscheduled tumor assessment when the scan frequency is every 12 (±1) weeks) or earlier if clinically indicated. Tumor assessments should be continued until two consecutive scans demonstrate stability or improvement with respect to the first scan that showed radiographic disease progression, at which point the scan frequency should revert or transition to at least every 12 weeks), if applicable. For patients who consented to treatment beyond progression, new lesions will also be assessed according to iRECIST (see Section 3.1.3) and applicable measurements entered into eCRF. While the Sponsor will derive overall tumor assessment as per iRECIST, investigator assessment of overall tumor response at all timepoints should be only based on RECIST v1.1 (see Section 3.1.3).

[h] The timing of tumor assessments will be based on weeks from first study treatment (C1D1; pembrolizumab monotherapy) and will not be tied to Cycle-specific visits. Tumor assessments will occur during Week 12 (based from C1D1) and every 6 weeks thereafter until Week 48 (i.e., during Weeks 12, 18, 24, 30, 36, 42, and 48). *"During week" is defined as the first day/Day 1 of each targeted week (e.g., 12, 18, or 24 weeks from C1D1 date) plus 6 calendar days.* After Week 48, tumor assessments will occur every 12 (± 1) weeks *through Week 96* (i.e., during Weeks 60, 72, 84, and 96). *After Week 96, follow-up tumor assessments will occur approximately every 12 weeks through Week 156 (i.e., Weeks 108, 120, 132, 144, and 156). After Week 156, follow-up tumor assessments will occur approximately every 24 weeks (i.e., Weeks 180, 204, 228, and 252).*

[i] Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until *Week 156, then approximately every 24 weeks until* disease progression, death, initiation of another systemic anticancer therapy, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first.

[j] Photographs of cutaneous lesions will be taken at screening and on the same day a tumor assessment is obtained or at the first clinic visit after each tumor assessment if timing is preferable to the patient and clinical site study team. See Section 4.5.6 for more details.

[k] Concomitant medications any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after RO7198457 administration and medications as a result of an adverse event) from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[l] After informed consent has been obtained but prior to initiation of study treatment, report only serious adverse events caused by a protocol-mandated intervention. After initiation of study treatment, report all adverse events until 90 days after the final dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first. Patients will be contacted at approximately 60 and 90 days after the final dose of study treatment to determine whether any new adverse events have occurred or if the patient has initiated another systemic anti-cancer therapy. After this period, the investigator is not required to actively monitor patients for adverse events but should report any serious adverse events that are believed to be related to prior study treatment. Deaths should be reported as described in Section 5.3.5.8. 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

[m] Vital signs include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. See Section 4.5.4 for more details.

[n] ECOG Performance Status, weight, limited physical examination, and local hematology and serum/plasma chemistry panels may be obtained $\leq$ 96 hours before each scheduled treatment and the treatment discontinuation visit, as applicable.

[o] Complete and limited physical examinations are defined in Section 4.5.3.

[p] Digitized, single ECGs will be performed as part of the screening assessment and at the treatment discontinuation visit. If sustained QTc prolongation ($>$ 500 ms and/or 60 ms longer than baseline value; at two consecutive readings) is noted, repeat ECG, and notify the Medical Monitor (see Section 4.5.8). Single ECG recordings may be obtained at unscheduled timepoints as clinically indicated.

[q] Hematology consists of CBC including RBC count, hemoglobin, hematocrit, platelet count, and WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells). A manual differential can be done if clinically indicated. During screening, hematology results must be obtained within 14 days prior to Cycle 1, Day 1 (see Section 4.1.1).

[r] Serum/plasma chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, BUN or urea, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, total protein, and albumin. During first part of screening (Part A), results of standard–of–care tests or examinations performed prior to obtaining informed consent may be used for assessments rather than repeating such tests. During second part of screening (Part B), serum/plasma chemistry results must be obtained within 14 days prior to Cycle 1, Day 1 (see Section 4.1.1).

[s] Urinalysis/$urine$ dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) if warranted by dipstick results.

[t] Serum pregnancy test (for women of childbearing potential, as defined in Section 4.1.1) must be performed and documented as negative within 14 days prior to Day 1. Urine or serum pregnancy tests (for women of childbearing potential only) will be performed at the specified subsequent visits. If a urine pregnancy test is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[u] Investigators may collect CRP and ferritin ad-hoc for work-up of inflammatory or immune mediated adverse events.

[v] TSH, free T3, and free T4 will be assessed during screening (Part B), on Day 1 of Cycle 4 and every 4 cycles thereafter (i.e., Day 1 of Cycles 8, 12, 16, and so on).

[w] Serum samples will be obtained for autoantibody testing including, but not necessarily limited to, anti-nuclear antibody, anti–double-stranded DNA, anti-neutrophil cytoplasmic antibodies, and thyroid peroxidase antibody, to be performed based on clinical events during the study, either in individual patients or across the study population. If inflammatory arthritis develops, CCP and RF antibody titers will also be evaluated. Additional serum collection for autoantibody testing should be performed as clinically indicated.

[x] All patients will be tested for HIV locally during screening (Part A); HIV-positive patients will be excluded from the study. Perform HBsAg, anti-HBc, and anti-HBs at local laboratory during screening (Part A). In patients who have positive serology for the anti-HBc antibody, HBV DNA should also be collected. Patients who are positive for HBc antibody are eligible only if negative for HBV DNA. Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Patients will also be tested for TB only if investigator considers patient to be at an increased risk for infection; latent TB diagnostic procedures must be followed according to local practice standards.

[y] Collection of cancer-related medical, surgical, and radiation procedures will begin on Day 1 of Cycle 1 and continue through the end of the treatment period and during the follow-up period.

[z] All PRO questionnaires *(EORTC scales and PRO-CTCAE scales)* are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patients' responses. The EORTC scales and PRO-CTCAE scales should be completed on Day 1 of each cycle and at the treatment discontinuation visit. *In the event that other assessments associated with Day 1 are done in advance of study treatment within protocol-specified time windows (e.g., per footnote n), then PRO questionnaires can also be done at that earlier timepoint.* PRO-CTCAE scales and single-item bother will be completed when available in the local language of the investigational site.

[aa] The WPAI questionnaire is required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patients' responses. The WPAI should be completed Day 1 of Cycles 1, 4, 13, and at the treatment discontinuation visit. *In the event that other assessments associated with Day 1 are done in advance of study treatment within protocol-specified time windows (e.g., per footnote n), then the WPAI questionnaire can also be done at that earlier timepoint.*

[bb] All infusions of pembrolizumab should be followed by a 30-minute observation period. See the pharmacy manual for more details.

[cc] Blood biomarker collection (PBMC-I): for immune monitoring as described see Section 4.5.7.2. Blood for baseline PBMC-I (prior to first study drug administration at C1D1) must be collected during screening Part B, between Day –28 and prior to study drug administration at Cycle 1 Day 1. PBMC-I collection at screening Part B does not have specific time windows as long as it is collected prior to the first study drug administration and patient did not receive any intervening therapy between date of collection and first study drug administration. Sites are encouraged to collect the total blood volume over two visits (e.g., collection may occur during the screening Part B visit and prior to study drug administration on C1D1). Collections should meet specified total volume in the laboratory manual. See the laboratory manual for more details. For the subsequent cycles of drug administration, blood for PBMC-I should be drawn before the infusion of any study drug. Collection at the treatment discontinuation visit should be performed for all patients.

[dd] [redacted]

[ee] Not applicable for a site that has not been granted approval for WGS.

[ff] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. For patients who have consented to collection of optional stool samples, samples will be collected at screening, C3D15–C4D1 predose, and C8D15–C9D1 predose. Samples may be collected at home.

[gg] [redacted]

[hh] During the randomization stage, on-treatment biopsy is mandatory for a minimum of 10 patients enrolled in Arm A and should be obtained approximately 8–9 weeks after the first infusion of pembrolizumab or an earlier time point *as indicated. The Medical Monitor is available to advise as needed.* Optional biopsies are requested at time of progression for patients being considered for treatment beyond progression or crossover from Arm A to combination therapy with RO7198457 plus pembrolizumab and at time of response or progression (if patient not considered for treatment beyond progression or crossover). If possible, biopsies should be taken after the tumor assessment. Acceptable samples include core-needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. See the laboratory manual for more details.

[ii] [redacted] Patients may be permitted to continue study treatment even if standard RECIST v1.1 criteria for progressive disease are met provided that they meet the criteria for continued treatment (see Sections 3.1.3 and 3.1.4). Assessments [redacted]

[jj] Patients will be asked to return to the clinic within 30 days after the last dose of study treatment for a discontinuation visit. Tumor assessment scans performed within 6 weeks prior to the treatment discontinuation visit do not need to be repeated. The visit at which a response assessment shows progressive disease resulting in treatment discontinuation may be used as the treatment discontinuation visit, in which case all assessments associated with the treatment discontinuation visit should be performed at that time.

[kk] *After study treatment completion or discontinuation, information on survival status,* new anti-cancer therapy *(including targeted therapy and immunotherapy), and cancer-related procedures* 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, *study* staff may use a public information source (e.g., county records) to obtain information about survival status *only.*

Appendix 2
Schedule of Activities: Safety Run-In, Arm B, and Crossover (RO7198457 Plus Pembrolizumab)

Safety Run-in, Arm B, and Crossover [a]—Screening Parts A and B and Cycles 1–12

	Screening [b]			Treatment Period (Initial)										
	Part A	Part B		Cycle 1	Cycle 2			Cycle 3 [c]		Cycles 4, 6	Cycles 5,7	Cycles 8, 10, 12	Cycles 9, 11	UV [d]
Day (Window)		−28	−14	1 (±2)	1 (±2)	8 (±2) [e]	15 (±2) [e]	1 (±2)	8 (±2)	1 (±2)	1 (±2)	1 (±3)	1 (±3)	
Signed informed consent [f]	x	x												
Review of eligibility criteria [g]	x	x												
Medical, surgical, cancer histories, demographic data [h]		x												
Tumor assessments [i, j]		x		x [k]										
Digital photography, cutaneous lesions [m]		x		x										
Concomitant medications [n]		x		x	x	x	x	x	x	x	x	x	x	x
Adverse events [o]		x		x	x	x	x	x	x	x	x	x	x	x
Vital signs [p]		x		x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status [q]	x	x		x	x	x	x	x	x	x	x	x	x	x
Weight		x		x	x	x	x	x	x	x	x	x	x	x
Height		x												
Complete physical examination [r]		x												
Limited physical examination [r]				x	x	x	x	x	x	x	x	x	x	x
12-lead ECG [s]		x												
Hematology [t]			x	x	x			x		x	x	x	x	

Appendix 2: Schedule of Activities: Safety Run-In, Arm B, and Crossover (RO7198457 Plus Pembrolizumab) (cont.)
Screening Parts A and B and Cycles 1–12

	Screening [b]			Treatment Period (Initial)										
	Part A	Part B		Cycle 1	Cycle 2			Cycle 3 [c]		Cycles 4, 6	Cycles 5,7	Cycles 8, 10, 12	Cycles 9, 11	UV [d]
Day (Window)		−28	−14	1 (±2)	1 (±2)	8 (±2) [e]	15 (±2) [e]	1 (±2)	8 (±2)	1 (±2)	1 (±2)	1 (±3)	1 (±3)	
Serum/plasma chemistry [u]	x [u]		x	x	x			x		x	x	x	x	
Coagulation (PT, aPTT, INR)			x											
Amylase, lipase			x		x					x		x		
Urinalysis [v]			x		x					x (C6 only)		x (C10 only)		
Pregnancy test [w]			x		x					x		x		
Serum ferritin and CRP [x]			x		x			x			x		x	
TSH, free T3, and free T4 [y]			x							x (C4 only)		x (C8, C12 only)		
Autoantibody tests [z]			x											
HBV, HCV, HIV, TB serology tests [aa]	x													
Cancer-related procedures [bb]				x	x			x		x	x	x	x	
EORTC scales [cc]				x	x			x		x	x	x	x	
PRO-CTCAE scales and single-item bother [cc]				x	x			x		x	x	x	x	

Appendix 2: Schedule of Activities: Safety Run-In, Arm B, and Crossover (RO7198457 Plus Pembrolizumab) (cont.)
Screening Parts A and B and Cycles 1–12

	Screening [b]			Treatment Period (Initial)										
	Part A	Part B		Cycle 1	Cycle 2			Cycle 3 [c]		Cycles 4, 6	Cycles 5,7	Cycles 8, 10, 12	Cycles 9, 11	UV [d]
Day (Window)		–28	–14	1 (±2)	1 (±2)	8 (±2) [e]	15 (±2) [e]	1 (±2)	8 (±2)	1 (±2)	1 (±2)	1 (±3)	1 (±3)	
WPAI [dd]				x						x (C4 only)				
Pembrolizumab infusion [ee]				x	x			x		x	x	x	x	
[redacted]														
	See Appendix 3													
	See Appendix 3													
Serum (pembrolizumab) PK sample	See Appendix 3													
Plasma sample for biomarkers	See Appendix 3													
[redacted]														
Blood sample WGS (optional) [jj]				x										
Stool sample for RBR (optional) [kk]			x							x (C4 only)			x (C9 only)	
Baseline tumor tissue [ll]	x													
On-treatment tumor biopsies [mm]				x										

Cycles 13-*34*, Treatment Discontinuation, and Follow-Up

	Treatment Period (Maintenance) [nn]								
	Cycles 13, 21, 29	Cycles 14, 20, 22, 28, 30	Cycles 15, 23, 31	Cycles 16, 24, 32	Cycles 17, 25, 33	Cycles 18, 26, 34	Cycles 19, 27	TX DC [oo]	FU
Days (Window)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)		
Tumor assessments [i, j]	x [k]								x [l]
Digital photography, cutaneous lesions [m]	x								x
Concomitant medications [n]	x	x	x	x	x	x	x	x	
Adverse events [o]	x	x	x	x	x	x	x	x	
Vital signs [p]	x	x	x	x	x	x	x	x	
ECOG Performance Status [q]	x	x	x	x	x	x	x	x	
Weight	x	x	x	x	x	x	x	x	
Limited physical examination [r]	x	x	x	x	x	x	x	x	
12-lead ECG [s]								x	
Hematology [t]	x	x	x	x	x	x	x	x	
Serum/plasma chemistry [u]	x	x	x	x	x	x	x	x	
Amylase, lipase		x		x		x		x	
Urinalysis [v]		x (C14, C22, C30 only)				x		x	
Pregnancy test [w]		x		x		x		x	
Serum ferritin and CRP [x]	x				x			x	

Appendix 2: Schedule of Activities: Safety Run-In, Arm B, and Crossover (Pembrolizumab Plus RO7198457) (cont.)
Cycles 13–34, Treatment Discontinuation, and Follow-Up

	Treatment Period (Maintenance) [nn]								
	Cycles 13, 21, 29	Cycles 14, 20, 22, 28, 30	Cycles 15, 23, 31	Cycles 16, 24, 32	Cycles 17, 25, 33	Cycles 18, 26, 34	Cycles 19, 27	TX DC [oo]	FU
Days (Window)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)		
TSH, free T3, and free T4 [y]		x (C20, C28 only)		x				x	
Cancer-related procedures [bb]	x	x	x	x	x	x	x	x	x
EORTC scales [cc]	x	x	x	x	x	x	x	x	
PRO-CTCAE scales and single-item bother [cc]	x	x	x	x	x	x	x	x	
WPAI [dd]	x (C13 only)							x	
Survival, anti-cancer therapy, and follow-up [pp]									x
Pembrolizumab infusion [ee]	x	x	x	x	x	x	x		
[redacted]									
Serum (pembrolizumab) PK sample	See Appendix 3								
Blood and plasma sample for biomarkers	See Appendix 3								
Blood sample (PBMC-I) for biomarkers [hh]		x (C14, C22 and C30)						x	
On-treatment tumor biopsies [mm]	x								

Appendix 2: Schedule of Activities: Safety Run-In, Arm B, and Crossover (Pembrolizumab Plus RO7198457) (cont.)

C = cycle; CCP = cyclic citrullinated peptide; CIT = cancer immunotherapy; CRP = C-reactive protein; CT = computed tomography; D = day; [redacted] ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30; FU = Follow-Up; HBc = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; iRECIST = immune-based therapeutics Response Evaluation Criteria in Solid Tumors; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PET = positron emission tomography; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; RF = rheumatoid factor; TB = *Mycobacterium tuberculosis*; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TX DC = Treatment Discontinuation; UV = unscheduled visit; WGS = whole genome sequencing; WPAI = Work Productivity and Activity Impairment.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Upon disease progression (as assessed by the investigator per RECIST v1.1), patients randomized to Arm A (pembrolizumab alone) will be given the option to cross over and receive combination treatment with RO7198457 and pembrolizumab, provided they continue to meet eligibility criteria described in Section 4.1.3. Patients will continue on pembrolizumab monotherapy until vaccine is available. Refer to Section 3.1.4 for guidance on duration of treatment on Arm B after crossing over from Arm A. [redacted]

[b] During the screening period (Part A and after informed consent was obtained), patients will provide tumor tissue and blood samples [redacted] (Participation in Study GO40558 ICF) and start the remaining procedures outlined for the screening Part B section. Time window for screening equals the number of days to Cycle 1, Day 1 (see Section 3.1).

[c] [redacted]

[d] Unscheduled visits may include the assessments indicated. Additional assessments and/or procedures may be requested or performed as needed.

[e] [redacted]

[f] Written informed consent is required before performing any study-specific tests or procedures (including screening evaluations) and may be obtained at any time prior to such tests or procedures.

[g] A limited review of the eligibility checklist (e.g., ECOG Performance Status, blood chemistry, serology for HIV, HBV, and HCV) may be performed during the first part of screening (Part A). The rest of the eligibility checklist will be reviewed during the second part of screening (Part B).

[h] Medical history includes cancer history (including, but not limited to, prior cancer therapies and/or prior CITs and procedures and tumor characteristics such as hormone receptor status or mutation status), other clinically significant diseases, surgeries, smoking history, use of alcohol and/or drugs of abuse, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the screening visit. Demographic information includes sex, age, and self-reported race/ethnicity.

[i] All sites of disease should be assessed and documented at this visit. Baseline CT assessments should be performed within 28 days prior to the start of study treatment (Cycle 1, Day 1). If available, a scan prior to the baseline (up to 3 months) may also be obtained to evaluate changes in tumor growth rate. Screening and subsequent tumor assessments should include CT scans (with IV contrast unless contraindicated and oral contrast per institutional standards) of the chest, abdomen, and pelvis. Patients who have a contraindication to IV contrast may have MRI scans of the abdomen and pelvis performed in lieu of CTs and a non-contrast CT of the chest. A CT or MRI scan (with IV contrast unless contraindicated) of the head must be performed at screening to assess CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan (see Section 4.5.5). Bone scans and CT scan of neck or extremities should also be performed if clinically indicated. If a CT scan for tumor assessment is performed in a PET-CT scanner, the CT acquisition must be consistent with standards of a full-contrast CT scan. The same radiographic procedure used to define measurable lesions at baseline should be used throughout the study for each patient.

[j] Patients who continue treatment beyond radiographic disease progression (see Section 3.1.3) will be monitored with a follow-up scan in 6 (± 1) weeks (i.e., at the next scheduled tumor assessment when the scan frequency is every 6 weeks or as an unscheduled tumor assessment when the scan frequency is every 12 [±1] weeks) or earlier if clinically indicated. Tumor assessments should be continued until two consecutive scans demonstrate stability or improvement with respect to the first scan that showed radiographic disease progression, at which point the scan frequency should revert or transition to at least every 12 weeks), if applicable. For patients who consented to treatment beyond progression, new lesions will also be assessed according to iRECIST (see Section 3.1.3) and applicable measurements entered into eCRF. While the Sponsor will derive overall tumor assessment as per iRECIST, investigator assessment of overall tumor response at all timepoints should be only based on RECIST v1.1 (see Section 3.1.3).

[k] The timing of tumor assessments will be based on weeks from first study treatment (C1D1; pembrolizumab monotherapy) and will not be tied to Cycle-specific visits. Tumor assessments will occur during Week 12 (based from C1D1) and every 6 weeks thereafter until Week 48 (i.e., during Weeks 12, 18, 24, 30, 36, 42, and 48). *"During week" is defined as the first day/Day 1 of each targeted week (e.g., 12, 18, or 24 weeks from C1D1 date) plus 6 calendar days.* After Week 48, tumor assessments will occur every 12 (±1) weeks *through Week 96* (i.e., during Weeks 60, 72, 84, and 96). *After Week 96, follow-up tumor assessments will occur approximately every 12 weeks through Week 156 (i.e., Weeks 108, 120, 132, 144, and 156). After Week 156, follow-up tumor assessments will occur approximately every 24 weeks (i.e., Weeks 180, 204, 228, and 252).*

[l] Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments approximately every 12 weeks until *Week 156, then approximately every 24 weeks until* disease progression, death, initiation of another systemic anticancer therapy, loss-to-follow-up, withdrawal of consent, or study termination, whichever occurs first.

[m] Photographs of cutaneous lesions will be taken at screening and on the same day a tumor assessment is obtained or at the first clinic visit after each tumor assessment if timing is preferable to the patient and clinical site study team. See Section 4.5.6 for more details.

[n] Concomitant medications any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after RO7198457 administration and medications as a result of an adverse event) from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[o] After informed consent has been obtained but prior to initiation of study treatment, report only serious adverse events caused by a protocol-mandated intervention. After initiation of study treatment, report all adverse events until 90 days after the final dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first. Patients will be contacted at approximately 60 and 90 days after the final dose of study treatment to determine whether any new adverse events have occurred or if the patient has initiated another systemic anti-cancer therapy. After this period, the investigator is not required to actively monitor patients for adverse events but should report any serious adverse events that are believed to be related to prior study treatment. Deaths should be reported as described in Section 5.3.5.8. 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.

[p] Vital signs include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position. See Section 4.5.4 for more details.

[q] ECOG Performance Status, weight, limited physical examination, and local hematology and serum/plasma chemistry panels may be obtained $\leq$ 96 hours before each scheduled treatment and the treatment discontinuation visit, as applicable.

[r] Complete and limited physical examinations are defined in Section 4.5.3.

[s] Digitized, single ECGs will be performed as part of the screening assessment and at the treatment discontinuation visit. If sustained QTc prolongation ($>$ 500 ms and/or 60 ms longer than baseline value; at two consecutive readings) is noted, repeat ECG, and notify the Medical Monitor (see Section 4.5.8). Single ECG recordings may be obtained at unscheduled timepoints as clinically indicated.

[t] Hematology consists of CBC including RBC count, hemoglobin, hematocrit, platelet count, and WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells). A manual differential can be done if clinically indicated. During screening, hematology results must be obtained within 14 days prior to Cycle 1, Day 1 (see Section 4.1.1).

[u] Serum/plasma chemistry includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, BUN or urea, creatinine, glucose, calcium, magnesium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, total protein, and albumin. During first part of screening (Part A), results of standard-of-care tests or examinations performed prior to obtaining informed consent may be used for assessments rather than repeating such tests. During second part of screening (Part B), serum/plasma chemistry results must be obtained within 14 days prior to Cycle 1, Day 1 (see Section 4.1.1).

[v] Urinalysis/*urine* dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) if warranted by dipstick results.

[w] Serum pregnancy test (for women of childbearing potential, as defined in Section 4.1.1) must be performed and documented as negative within 14 days prior to Day 1. Urine or serum pregnancy tests (for women of childbearing potential only) will be performed at the specified subsequent visits. If a urine pregnancy test is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[x] Investigators may collect CRP and ferritin ad-hoc for work-up of inflammatory or immune mediated adverse events.

[y] TSH, free T3, and free T4 will be assessed during screening (Part B), on Day 1 of Cycle 4 and every 4 cycles thereafter (i.e., Day 1 of Cycles 8, 12, 16, etc.).

[z] Serum samples will be obtained for autoantibody testing including, but not necessarily limited to, anti-nuclear antibody, anti–double-stranded DNA, anti-neutrophil cytoplasmic antibodies, and thyroid peroxidase antibody, to be performed based on clinical events during the study, either in individual patients or across the study population. If inflammatory arthritis develops, CCP and RF antibody titers will also be evaluated. Additional serum collection for autoantibody testing should be performed as clinically indicated.

[aa] All patients will be tested for HIV locally during screening (Part A); HIV-positive patients will be excluded from the study. Perform HBsAg, anti-HBc, and anti-HBs at local laboratory during screening (Part A). In patients who have positive serology for the anti-HBc antibody, HBV DNA should also be collected. Patients who are positive for HBc antibody are eligible only if negative for HBV DNA. Patients who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Patients will also be tested for TB only if investigator considers patient to be at an increased risk for infection; latent TB diagnostic procedures must be followed according to local practice standards.

[bb] Collection of cancer-related medical, surgical, and radiation procedures will begin on Day 1 of Cycle 1 and continue through the end of the treatment period and during the follow-up period.

[cc] All PRO questionnaires *(EORTC scales and PRO-CTCAE scales)* are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patients' responses. The EORTC scales and PRO-CTCAE scales and single-item bother should be completed on Day 1 of each cycle and at the treatment discontinuation visit. *In the event that other assessments associated with Day 1 are done in advance of study treatment within protocol-specified time windows (e.g., per footnote q), then PRO questionnaires can also be done at that earlier timepoint.* PRO-CTCAE questionnaires will be completed when available in the local language of the investigational site.

[dd] The WPAI questionnaire is required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patients' responses. The WPAI should be completed Day 1 of Cycles 1, 4, 13, and at the treatment discontinuation visit. *In the event that other assessments associated with Day 1 are done in advance of study treatment within protocol-specified time windows (e.g., per footnote q), then the WPAI questionnaire can also be done at that earlier timepoint.*

[ee] Pembrolizumab will be administered prior to RO7198457 as described in Section 4.3.2.2. All infusions of pembrolizumab should be followed by a 30-minute observation period. See the pharmacy manual for more details.

[ff] [redacted]

[gg]

[hh] Blood biomarker collection (PBMC-I): for immune monitoring as described see Section 4.5.7.2. Blood for baseline PBMC-I (prior to first study drug administration at C1D1) must be collected during screening Part B, between Day –28 and prior to study drug administration at Cycle 1 Day 1. PBMC-I collection at screening Part B does not have specific time windows as long as it is collected prior to the first study drug administration and patient did not receive any intervening therapy between date of collection and first study drug administration. Sites are encouraged to collect the total blood volume over two visits (e.g., collection may occur during the screening Part B visit and prior to study drug administration on C1D1). Collections should meet specified total volume in the laboratory manual. See the laboratory manual for more details. For the subsequent cycle of drug administration, blood for PBMC-I should be drawn before the infusion of any study drug. [redacted]

[redacted] Collection at the treatment discontinuation visit should be performed for all patients.

[ii] [redacted]

[jj] Not applicable for a site that has not been granted approval for WGS.

[kk] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. For patients who have consented to collection of optional stool samples, samples will be collected at screening, C3D15–C4D1 predose, and C8D15-C9D1 predose. Samples may be collected at home.

[ll] [redacted]

[mm] During the randomization stage, on-treatment biopsy is mandatory for a minimum of 20 patients enrolled in Arm B and should be obtained approximately 5–6 weeks after the first administration of RO7198457 in Arm B [redacted] or an earlier time point *as indicated. The* Medical Monitor *is available to advise as needed.* The sponsor requests optional biopsies be taken at time of progression for patients being considered for treatment beyond progression or crossover from Arm A to combination therapy with RO7198457 plus pembrolizumab. Optional biopsies may be taken at time of response or progression (if patient not considered for treatment beyond progression or crossover). If possible, biopsies should be taken after the tumor assessment. Acceptable samples include core-needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. See the laboratory manual for more details. Biopsies are not required for the safety run-in stage.

[nn] Maintenance treatment will consist of pembrolizumab treatment every 21 days [redacted]. Patients may be permitted to continue study treatment even if standard RECIST v1.1 criteria for progressive disease are met provided that they meet the criteria for continued treatment (see Section 3.1.3). [redacted]

[oo] Patients will be asked to return to the clinic within 30 days after the last dose of study treatment for a discontinuation visit. Tumor assessment scans performed within 6 weeks prior to the treatment discontinuation visit do not need to be repeated. The visit at which a response assessment shows progressive disease resulting in treatment discontinuation may be used as the treatment discontinuation visit, in which case all assessments associated with the treatment discontinuation visit should be performed at that time.

[pp] *After study treatment completion or discontinuation, information on survival status,* new anti-cancer therapy *(including targeted therapy and immunotherapy), and cancer-related procedures* 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, *study* staff may use a public information source (e.g., county records) to obtain information about survival status *only*.

Appendix 3
Schedule of Pharmacokinetic and Biomarker Samples

		Treatment Period								TX DC	FU
		Initial							Maintenance [a]		
Cycle	Cycle 1	Cycle 2			Cycle 3 [b]		Cycle 4	Cycles 5, 6, 7	Cycles 13, 21, 29		
Days (window)	1 (± 2)	1 (±2)	8 (±2) [c]	15 (±2) [c]	1 (±2)	8 (±2)	1 (±2)	1 (±2)	1 (±3)		
[redacted]											
Serum pembrolizumab PK sample [e, f]	Pre-dose, and 30 (±5) min after pembro infusion	Pre-dose					Pre-dose				2 months post EOT (±1 week) [f]
Plasma Biomarker (Cytokines) (safety run-in, Arm B, and crossover only) [g, h]	Pre-dose, 4–6 hr post-dose		Pre-dose, 4–6 hr post-dose	Pre-dose, 4–6 hr post-dose	Pre-dose, 4–6 hr post-dose	Pre-dose, 4–6 hr post-dose	Pre-dose, 4–6 hr post-dose	C5, C6, C7: pre-dose, 4–6 hr post-dose	Pre-dose, 4–6 hr post-dose		
Blood Biomarker (ctDNA)	Pre-dose							C7D1 only (pre-dose)	C13D1 only (pre-dose)		

Appendix 3: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples (cont.)

C = cycle; [redacted] OT = end of treatment; FU = Follow-Up; hr = hours; min = minutes; mos = months; [redacted] PK = pharmacokinetic; TX DC = treatment discontinuation.

[redacted]

[a] [redacted]

[b] [redacted]

[c] [redacted]

[d] [redacted]

[e] Pre-dose pembrolizumab PK collections are to be collected just prior to infusion of pembrolizumab. Post-dose collections are to be collected after infusion of pembrolizumab is completed. On the days that pembrolizumab is given on the same day as RO7198457, post-dose collections are to be collected 30 (±5) min after infusion of pembrolizumab is completed and before starting infusion of RO7198457 RNA-A.

[f] *Serum pembrolizumab* PK collection will be collected at 2 months post end of treatment *unless pembrolizumab is administered as a new anti-cancer therapy.*

[g] At C1D1 (pembrolizumab monotherapy), plasma cytokines sample will be collected prior to pembrolizumab administration and 4–6 hours after infusion of pembrolizumab. For the subsequent cycles, a plasma cytokines sample will only be collected on the days of RO7198457 infusion, regardless of the pembrolizumab cycle and day. Pre-dose sample will be collected prior to infusion of any study drug. Post-dose collections are to be collected 4–6 hours after infusion of RO7198457 RNA-B is completed. NOTE: Pre-and postdose plasma for biomarker cytokines do not need to be drawn if RO7198457 is not available for dosing, except on C1D1.

[h] Ad hoc plasma cytokine levels may be drawn once daily in patients experiencing Grade ≥2 cytokine release syndrome, infusion-related reaction, or flu-like symptoms.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

a. Measurable Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imagining (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), 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 masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] 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.

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

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of 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.

b. Method of Assessment

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

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

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 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 non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

<u>TUMOR RESPONSE EVALUATION</u>

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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

measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION 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 in instances where 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 recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

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

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

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, 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").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

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

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

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 nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) 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 measure 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 BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. 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 maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although 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 protocol.

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

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

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

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, 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 disease in the face of SD or PR of target disease will therefore be extremely rare.

e. 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, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: 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 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.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. 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 only a subset of lesion measurements are made at an assessment, 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 lesion(s) 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

c. Best Overall Response: All Timepoints

The best overall response is determined once all data for the patient is known, and is interpreted as in Table 3. Complete or partial responses may be claimed if the criteria for each are met at a subsequent timepoint ≥ 4 weeks later.

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

d. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

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

objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

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.

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST)

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. These include modified RECIST v1.1 for immune-based therapeutics (iRECIST; Seymour et al. 2017), which was developed by the RECIST working group in an effort to create a common set of criteria that the cancer immunotherapy 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 3.3.17.

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 4) 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 1. Once a lesion has been categorized as a target, non-target, or new lesion, it will remain classified as such.

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.

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.

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 $<$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 pathological 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 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 = modified RECIST v1.1 for immune-based therapeutics; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.

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).

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 6
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 7
Pre-Existing Autoimmune Diseases

Patients with a convincing history of any 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). *The* Medical Monitor *is available to advise on* any uncertainty over autoimmune exclusions.

Examples of Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Epidermolysis bullosa acquisita	Opsoclonus myoclonus syndrome
Addison disease	Gestational pemphigoid	Optic neuritis
Ankylosing spondylitis	Giant-cell arteritis	Ord thyroiditis
Antiphospholipid antibody syndrome	Goodpasture syndrome	Pemphigus
Aplastic anemia	Graves disease	Pernicious anemia
Autoimmune hemolytic anemia	Guillain-Barré syndrome	Polyarteritis nodosa
Autoimmune hepatitis	Hashimoto thyroiditis	Polyarthritis
Autoimmune hypoparathyroidism	IgA nephropathy	Polyglandular autoimmune syndrome
Autoimmune hypophysitis	Inflammatory bowel disease	Primary biliary cirrhosis
Autoimmune myocarditis	Interstitial cystitis	Psoriasis
Autoimmune oophoritis	Kawasaki's disease	Reiter syndrome
Autoimmune orchitis	Lambert-Eaton myasthenia syndrome	Rheumatoid arthritis
Autoimmune thrombocytopenic purpura	Lupus erythematosus	Sarcoidosis
Behcet disease	Lyme disease - chronic	Scleroderma
Bullous pemphigoid	Meniere syndrome	Sjögren syndrome
Chronic inflammatory demyelinating polyneuropathy	Mooren ulcer	Stiff-Person syndrome
Churg-Strauss syndrome	Morphea	Takayasu arteritis
Crohn's disease	Multiple sclerosis	Ulcerative colitis
Dermatomyositis	Myasthenia gravis	Vogt-Koyanagi-Harada disease
Diabetes mellitus Type 1	Neuromyotonia	Wegener's granulomatosis
Dysautonomia		

Appendix 8
Anaphylaxis Precautions

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

REQUIRED EQUIPMENT AND MEDICATION

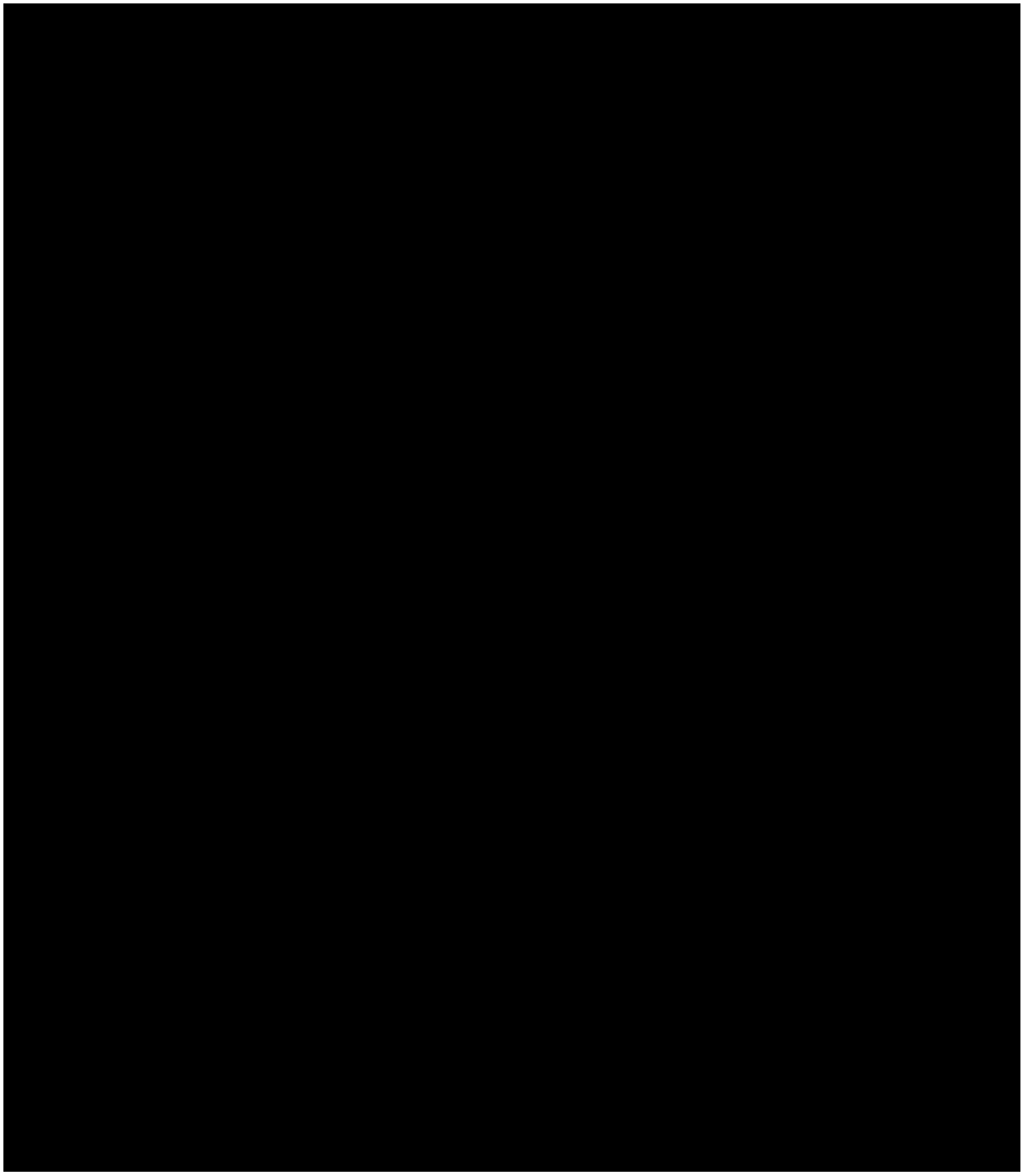
The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

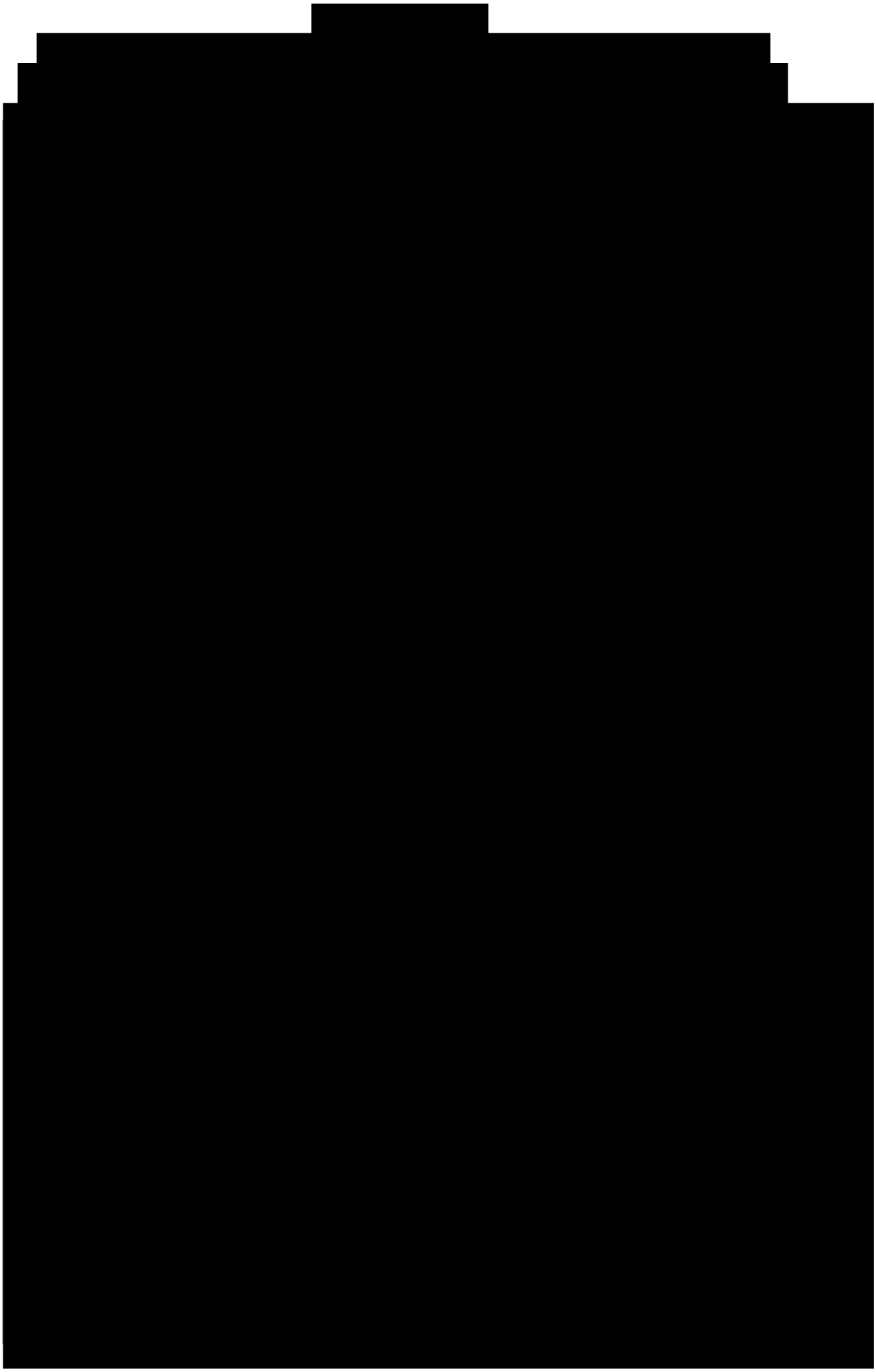
- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion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

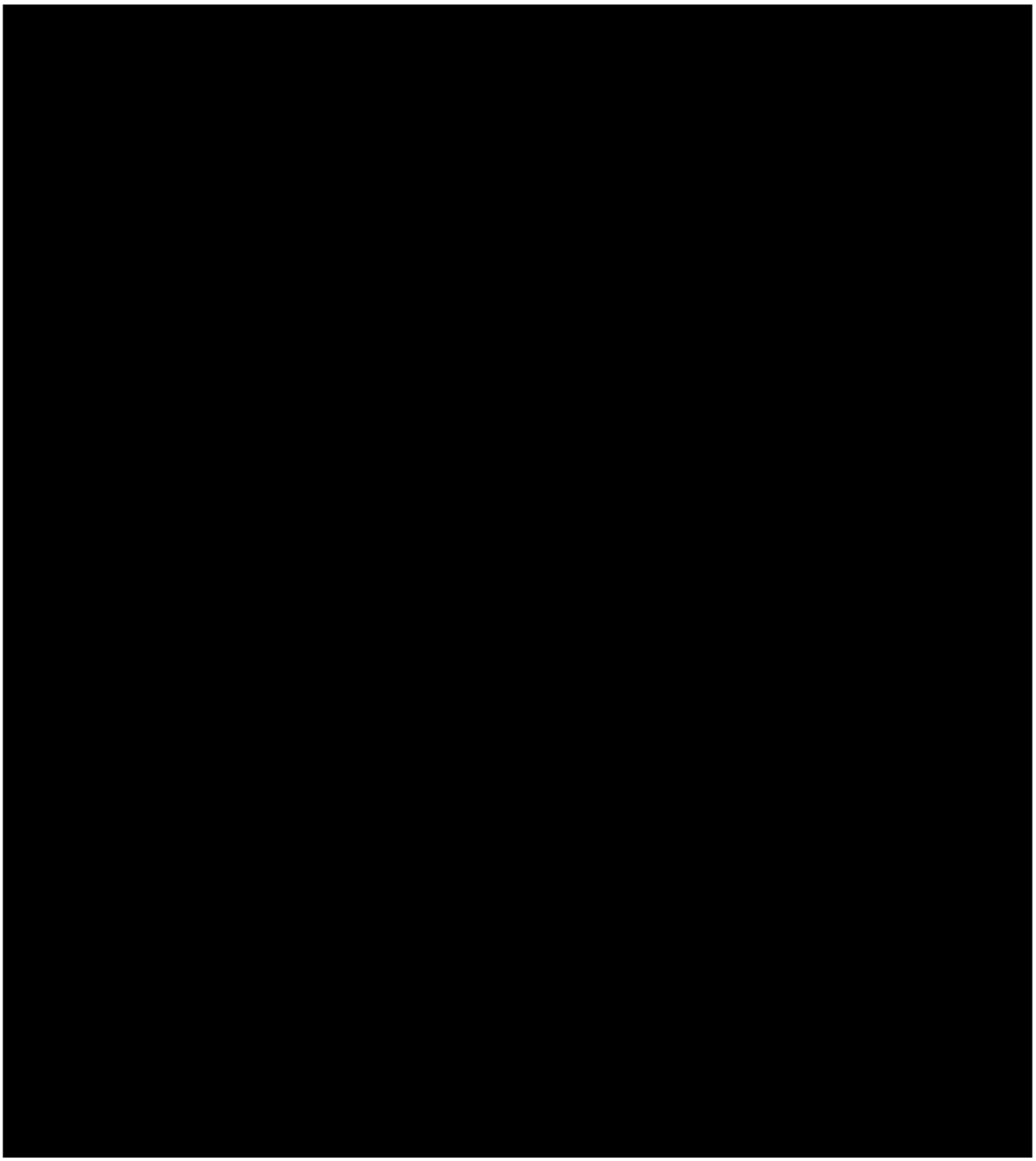
PROCEDURES

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

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







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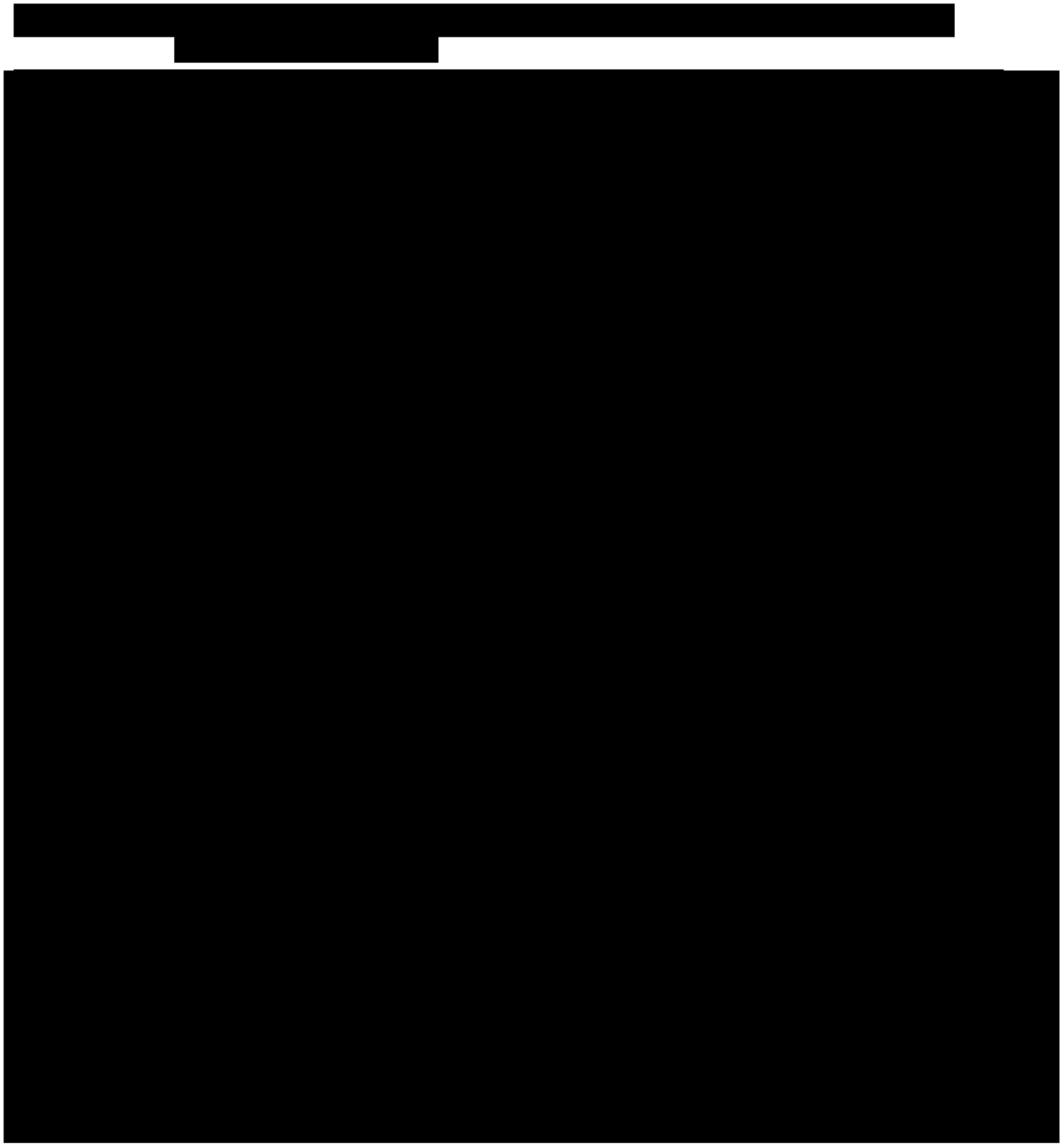

Appendix 12
New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 13
Investigational and Auxiliary Medicinal Product Designations (for Use in European Economic Area)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
RO7198457	*IMP (test product)*	*Unauthorized*	*Not applicable*
Pembrolizumab	*IMP (test product)* [a]	*Authorized*	*No* [b]

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

[a] *Pembrolizumab is considered to be an IMP test product as well as an IMP comparator.*

[b] *Pembrolizumab is not approved in combination with RO7198457.*

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