Clinical Study Protocol IMCgp100-202

A Phase II Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared with Investigator's Choice in HLA-A*0201 Positive Patients with Previously Untreated Advanced Uveal Melanoma

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[redacted]

[redacted]

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This study will be conducted in compliance with the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

PROTOCOL VERSION HISTORY

Version	Title	Date
1.0	Original Protocol	12 Jan 2017
2.0	Amendment 1	28 Mar 2017
3.0	Amendment 2	11 Apr 2017
3.0 FR	Local FR	20 Jun 2017
4.0	Amendment 3	20 Dec 2018
5.0	Amendment 4	31 Mar 2020

AMENDMENT 4

Amendment Rationale

This amendment is being implemented primarily to remove the sample size re-estimation planned to occur at 55 events, to increase the overall power of the study for the primary endpoint of overall survival, to permit patients to switch between formulations of IMCgp100, and to incorporate a number of administrative changes meant to clarify study conduct.

A summary of the key changes is as follows:

Key Changes to the Protocol

1. Given the limited information that would have been available at the time of the sample size re-estimation, this is being removed from the protocol. Instead, the target sample size will be increased to N = 369 with implementation of this amendment based on new assumptions (summarized below) and without a formal sample size re-estimation. The new sample size is based on the following assumptions: a) a 2:1 randomization ratio of tebentafusp versus Investigator's Choice; b) 250 events (deaths) are needed in the randomized trial to provide 89% power to detect a difference in survival distributions that can be characterized by a 0.645 hazard ratio for overall survival (OS); c) assuming OS is exponentially distributed, this translates to a median OS of 18.6 months in the tebentafusp treated arm and 12 months in the Investigator's Choice arm; and d) considering a uniform recruitment time of about 33 months and a 10% annual drop-out rate, 369 patients need to be randomized in a 2:1 ratio to the 2 arms in order to observe 250 events after approximately 51 months as follows:

    - 246 patients to the tebentafusp arm
    - 123 patients to the Investigator's Choice arm

2. Added an additional primary objective: comparison of OS among patients randomized to the tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomized to the Investigator's Choice monotherapy with the appropriate statistical considerations as detailed in Section 9.3 of the protocol.

3. Inclusion criterion #4 (Protocol Section 5.2) was modified to better reflect standard-of-care treatment for patients with oligometastic disease. Although liver metastases are most frequently the first site of metastatic disease, limited metastatic disease may occur outside the liver. Therefore, the inclusion criterion was clarified to allow prior surgical resection of oligometastatic disease outside the liver.

4. To allow for greater operational flexibility, while maintaining safe conduct of the study, patients currently enrolled and receiving tebentafusp at a given site will be allowed to switch to the alternative formulation after receiving at least 2 months of tebentafusp

therapy. Whenever such a change is implemented at a site, all patients, participating in this study and receiving tebentafusp at a given site, should be switched over to the same formulation (ie, minimize situations where multiple patients in this study at a given site are receiving 2 different formulations of tebentafusp).

5. Patients currently enrolled and receiving pembrolizumab on Investigator's Choice arm may switch from weight-based to flat dosing where locally approved. Additional clarifications were made regarding prior adjuvant/neoadjuvant therapy for localized disease, and Investigator's Choice options based upon prior therapy received.

6. Exclusion criterion #1 (Protocol Section 5.3) was updated to redefine the out-of-range value for absolute lymphocyte count from $< 1.0 \times 10^9$/L to $< 0.5 \times 10^9$/L. The rationale for the update is that emerging data suggest no adverse impact on treatment in either arms.

7. Wording around the mandatory hold of antihypertensive drugs 24 hours before and after the tebentafusp administration during at least the first 3 weeks of treatment has been adjusted to allow for greater flexibility by the treating investigators to adjust the medications safely based on the clinical context.

8. Determination of tumor response by immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) was removed from the protocol as it was not part of any primary or secondary endpoint. Management of patients beyond progression was defined without using irRECIST.

9. Clarified lactate dehydrogenase stratification in regards to the primary analysis of OS in Section 9.3.3.

10. Hypotension and cytokine release syndrome management guidelines have been adjusted to allow the earlier use of steroids and/or tocilizumab in the setting of either prolonged Grade 2 events (ie, hypotension) despite the initial interventions or in response to initial onset of Grade 3 or 4 events.

11. Removed the option to conduct an ECG sub-study at select sites which was originally added via Amendment 3. Instead, now all participating sites may be asked to provide ECGs already being collected as part of the current study to a central ECG vendor for storage. At the Sponsor's discretion, the centrally collected ECGs may undergo interpretation by qualified reviewer(s) at the centeral ECG vendor to validate the machine-calculated ECG data.

12. Additional editorial changes to clarify study conduct, including the impact of prior adjuvant/neoadjuvant anti-PD1 therapy on subsequent Investigator's Choice, were also made to the protocol.

VERSION 3.0 FRENCH LOCAL AMENDMENT 1

Amendment Rationale

This amendment updates the exclusion criterion to exclude patients who would not be able to receive the Investigator's Choice comparator. For the Investigator's Choice treatment, the investigator selects from the 3 choices of dacarbazine, ipilimumab, and pembrolizumab in advance of the patient's randomization and considering the applicable labelling. Thus, as per the summary of product characteristics for dacarbazine, patients with leukopenia or thrombocytopenia or those concomitantly receiving the yellow fever vaccine would not have dacarbazine selected as the Investigator's Choice. This will be emphasized in the site training and is clarified with this amendment. Specifically, patients with contraindication to all the designated comparator arm drugs will be excluded from the study. A patient may have a contraindication to 1 or 2 of the choices if he/she is a candidate for dosing with at least 1 Investigator's Choice and meets all other study eligibility criteria.

Changes to the Protocol

1. Update to protocol synopsis and Section 5.3 to exclude patient with contraindication to dacarbazine, ipilimumab, and pembrolizumab.

2. Administrative update to the Sponsor emergency contacts on page 1.

AMENDMENT 3

Amendment Rationale

This amendment is done to introduce a new formulation of IMCgp100 (0.2 mg/mL) for use in clinical development. The 0.2 mg/mL formulation is intended to be the commercial formulation and will allow for a simpler dose preparation method and improved storage. Introduction of the new formulation will be controlled through the Interactive Response Technology. Patients currently enrolled and receiving IMCgp100 will not be switched to the new formulation. Introduction of the 0.2 mg/mL formulation will provide safety and efficacy on the commercial formulation.

This amendment also provides clarifications to the recommended toxicity management and dose modification guidance for IMCgp100 based on the Investigator Notification letter for hypotension and cytokine release syndrome (CRS) dated 12 October 2017. This letter followed the report of an event of grade 4 hypotension with CRS in a patient participating in an IMCgp100 protocol. Guidance updates include management of hypotension and CRS events with early implementation of intravenous (IV) fluid therapy, supportive measures, and immunosuppression.

Events of "CRS" and "hypotension" are included in the Reference Safety Information for IMCgp100 as expected events per the current Investigator's Brochure. Although both events of hypotension and CRS are expected per the current IMCgp100 Investigator's Brochure, these events observed, as noted above, are considered by the Sponsor to be medically important events with updated hypotension and CRS guidance warranted in the IMCgp100 development program.

As of 12 August 2018, CRS with IMCgp100 treatment was reported in the IMCgp100-102 study in approximately 6% of patients with approximately 2% of these cases grade ≥ 3. Management with supportive therapies for treatment of symptoms of CRS are recommended and high-dose IV corticosteroid therapy should be considered as an early intervention in the setting of acute CRS.

Management of hypotension is recommended with IV fluid therapy in the setting of grade 1 or grade 2 events. In the case of grade 3 or grade 4 hypotension that is refractory to fluid therapy, IV corticosteroid therapy should be considered. Patients with hypotension should be carefully monitored for the development of associated symptoms of CRS and the need for aggressive immunosuppression in patients with suspected CRS should be assessed.

The single-agent dosing regimen for IMCgp100 is updated in this amendment based on data from a Phase 1 study identifying an escalated dose and regimen (IMCgp100-102). The protocol is updated to reflect the Statistical Analysis Plan. In addition, a change to the analysis method for estimating the hazard ratio for overall survival (OS) (from stratified log rank to Cox proportional) has been introduced.

In the Investigator's Choice arm, the dosing of pembrolizumab was updated to be consistent with approved dosing for treatment of advanced melanoma. Specifically, a fixed dose of 200 mg pembrolizumab administered intravenously (IV) is allowed where locally approved, and in regions where fixed dosing is not approved, the weight-based dosing of pembrolizumab was updated to institute a maximum dose of 200 mg administered IV to be consistent with the fixed dosing regimen.

The exclusion criteria were updated to ensure that appropriate patients are included in the study. Specifically, the exclusion criterion is added to exclude a patient who has a contraindication to all of the alternatives for Investigator's Choice. Patients who are institutionalized due to official or judicial order are excluded from the study. Patients who are related to the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study are excluded from the study. Finally, the minimum acceptable absolute lymphocyte count was increased to be consistent across the IMCgp100 clinical trials.

Based on a review of pharmacokinetic (PK) and biomarker data collected to date in the IMCgp100 program, the 1-hour post-dose serum blood sample at Cycle 1 Day 1 (C1D1), C1D8, and C1D15 are being removed. Pharmacokinetic and anti-drug antibody sampling time points after 3 months of treatment have been refined.

To allow a better understanding of the cytokine response with treatment, all cytokine assessments, including those done in the event of a suspected CRS will be assessed centrally. The local cytokine assessment has been removed and replaced by additional, as needed pharmacodynamic assessment of cytokines.

A sub-study at select sites will be added via a separate protocol to evaluate electrocardiograms (ECGs), pharmacokinetics, and biomarkers. In this sub-study, sites will provide ECGs to a central ECG vendor for interpretation by a qualified physician and additional PK and biomarker samples will be taken. Intensive PK sampling after the first doses of IMCgp100 will be performed to better characterize the PK profile and assess the exposure-response relationship for ECG parameters (ie, QT interval corrected by Fridericia's formula) and pharmacodynamic biomarkers.

This global protocol amendment incorporates Version 3 French Local Amendment 1.

Additional changes have been made to clarify existing protocol requirements as listed below.

Changes to the Protocol

1. The single-agent dosing and regimen for IMCgp100 is updated based on data from Phase 1 study IMCgp100-102.
2. The guidance on dose modifications and follow-up for toxicities is updated to include additional guidance on management of events of hypotension and CRS, including a CRS grading scale to provide clarification of toxicity management.

3. The table of Recommended Dose Modifications of IMCgp100 by Toxicity Grade for Study Modifications is revised to provide more detailed guidance on management of hypotension and CRS events.
4. Prohibited concomitant therapies are updated to include additional guidance on permitted treatments for hypotension and CRS.
5. Requirements for reporting of immune-related adverse events (AEs) are updated to include events of hypotension and CRS.
6. The guidelines for management of immune-related AEs are revised to include events of hypotension and CRS.
7. Changes to the statistical section including removal of per-protocol set analysis, correction to progression free survival definition in relation to subsequent therapy, removal of confirmation of response and clarification of analyses of objective response rate (ORR), addition of secondary endpoints to the multiple testing strategy and clarification of definition of exploratory efficacy endpoints.
8. Clarification that survival calls will be made in the 2 weeks following the date of the data cutoff for each OS analysis. Death dates may be found by checking publicly available death registries.
9. Clarification that objective responses do not need to be confirmed 4 weeks later in order to qualify as an objective response in this randomized study.
10. Update to prohibited medications to allow treatment with denosumab, tocilizumab, or bisphosphonates during the study if required.
11. The 0.2 mg/mL formulation of IMCgp100 is described.
12. Clarified the Disease Progression Follow-Up period: To include all patients who discontinue for reasons other than death, progressive disease (PD) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 or modified immune-related RECIST, lost to follow-up, withdrawal of consent, or study termination.
13. Clarification of requirements for hospitalization: As defined in the protocol, patients are required to have an overnight, inpatient hospitalization for the first 3 doses of IMCgp100. The amendment clarifies that "inpatient hospitalization" refers to a facility with fully functional resuscitation facilities, 24-hour monitoring, and physician availability (Section 6.2.3).
14. Clarification of vital signs monitoring required for IMCgp100 dosing time points (Section 7.3.3.2, Table 7.3).
15. Exclusion criteria is updated clarifying that a patient may have a contraindication to 1 or 2 of the investigator choices if he/she is a candidate for dosing with at least 1 Investigator's Choice and meets all other study eligibility criteria. Patients who are institutionalized due to official or judicial order are excluded. Additionally, patients who are related to the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study are excluded.
16. Reference is added to the sub-study that will be introduced via a separate protocol at select sites to evaluate ECGs, pharmacokinetics, and biomarkers. In this sub-study, sites will provide ECGs to a central ECG vendor for interpretation by a qualified physician and additional PK and biomarker samples will be taken.

Institutional Review Board/Independent Ethics Committee

A copy of this amended protocol will be sent to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Health Authorities. The changes described in this amended protocol require IRB or IEC approval. Changes herein affect the informed consent, and sites are required to update and submit for approval a revised informed consent that takes into account the changes described in this amended protocol. The revised informed consent form will replace the previous informed consent form.

AMENDMENT 2

Amendment Rationale

This amendment updates the nomenclature of the recommended Phase II dose (RP2D) of IMCgp100 utilizing the intra-patient escalation from 75 mcg to 68 mcg. No changes are made in the dose preparation guidance, thus there is no change in the actual dose administered. Recent information described below indicates that the actual dose administered and defined as the RP2D in the Phase I study (IMCgp100-102) is 68 mcg.

Individual doses of IMCgp100 are prepared from a concentrated, frozen stock solution (0.5 mg/mL) by a 2-step dilution procedure in the drug preparation guidelines, requiring dilution of approximately 2500-fold to accurately achieve the microgram doses. The dilution procedure is described in the Pharmacy Handling Instructions, provided for each dose level administered, eg, 20 mcg, 30 mcg. The dilution procedure utilizes 2 saline infusion bags, the first is the dilution bag (a labelled 50 mL bag), and the second is the actual infusion bag (100 mL).

The protocol-specified doses in study IMCgp100-102 were intentionally determined before the study began to represent the maximum theoretical dose that could be prepared and administered based on the labelled fill volumes of the dilution bags (range of 54–64 mL). The Pharmacy Handling Instructions are authored using the lowest potential dilution bag volumes as the start volume and thus, the highest initial concentrations of IMCgp100 at dilution step 1 to calculate doses. Setting the protocol-specified dose based on the maximum theoretical dose ensured that no patients received actual doses with IMCgp100 quantities above the protocol-specified dose. However, newly available empirical data demonstrate that although there is a labelled range of bag volumes (54–64 mL per packaging), there exists a narrow distribution of the actual fill volumes at the first dilution step (generally 57–59 mL). Thus, the doses actually prepared and administered in the Phase I study (IMCgp100-102) were accurate and represented a lower point estimate than stated in the protocol.

Based on the 2-step dilution procedure used to prepare IMCgp100 doses and considering the conservative approach to the variance in the fill range for the primary dilution bag, the protocol-specified doses for the higher dose cohorts in the IMCgp100-102 trial and the final RP2D were over-estimates of the actual administered dose. Based on the available empirical evidence of dilution bag fill volumes (dilution step 1), it is important to correct the over-estimate of the actual dose administered from 75 mcg to 68 mcg. The 68 mcg dose level is the most accurate within the range produced by the dilution procedure and is the RP2D. Based on the limited impact at the lower doses (20 mcg and 30 mcg doses) no change in these protocol-specified doses is warranted.

Changes to the Protocol

1. Updated throughout the protocol that the target IMCgp100 dose from Cycle 1 Day 15 and beyond is 68 mcg

2. Changed the dose levels investigated in study IMCgp100-102 in Section 1.4 to reflect the actual doses administered rather than the maximum theoretical dose

Institutional Review Board/Independent Ethics Committee

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AMENDMENT 1

Amendment Rationale

This amendment will implement changes and provide additional detail to the Study Statistical Methods (Section 9). These changes detail how the p-value and hazard ratio for the primary endpoint of overall survival will be calculated, explain how the false positive rate will be controlled for the secondary efficacy endpoints, and provide clarification of stratification factors to be used for randomization and in the statistical analysis.

Additional safety enhancements are also introduced in this amendment. These include 3 additional exclusion criteria for patients with history of specific autoimmune diseases including interstitial lung disease, pneumonitis, and inflammatory bowel disease to limit the risk of immune-related adverse events associated with study treatment. Further detail is provided regarding the rationale for excluding patients receiving corticosteroid or immunosuppressive treatment.

Changes to the Protocol

1. Detailed the statistical methods for the primary analysis of overall survival (Section 9.3.3)

2. Removed extent of liver metastatic disease as a prespecified covariate (Synopsis and Section 9.3) Added a multiple testing strategy to provide strong control of the type I error rate (Section 9.7)

3. Added exclusion criteria for patients with autoimmunity including pneumonitis, interstitial lung disease, and inflammatory bowel disease (Synopsis and Section 5.3)

4. Explained that corticosteroids are exclusionary as they may interfere with the mechanism of action of study drug (Section 5.3 and 6.6.3 "Prohibited Concomitant Medications")

5. Clarified Section 6.10 that safety follow-up will be at least 90 days for consistency with Section 6.11

6. Corrected typographic errors and inserted minor clarifications throughout to improve readability and content presentation

Institutional Review Board/Independent Ethics Committee

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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SIGNATURES

Sponsor Signature

I have read the protocol and confirm that the protocol follows the current Good Clinical Practice guidelines.

Approved By:

[redacted]

Principal Investigator Signature

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to the tripartite International Council for Harmonisation guideline E6(R2): Guideline for Clinical Practice and all the ethical and regulatory considerations stated.

Signed By:

_____ _____

Principal Investigator Date (DD MMM YYYY)

_____

Print Name

_____

Institution Name

PROTOCOL SYNOPSIS

Study Number	IMCgp100-202
Title	A Phase II randomized, open-label, multi-center study of the safety and efficacy of IMCgp100 compared with Investigator's Choice in HLA-A*0201 positive patients with previously untreated advanced uveal melanoma
Brief Title	Safety and efficacy of IMCgp100 versus Investigator's Choice in advanced uveal melanoma
Sponsor and Clinical Phase	Immunocore, Ltd. Phase II
Study Drugs	tebentafusp (IMCgp100) Investigator's Choice: Dacarbazine, ipilimumab, or pembrolizumab
Study Type	Interventional
Study Purpose and Rationale	This is a randomized, open-label, Phase II clinical study of tebentafusp versus Investigator's Choice (dacarbazine, ipilimumab, or pembrolizumab) in human leukocyte antigen-A*0201 positive (HLA-A*0201 positive) patients with previously untreated advanced uveal melanoma (UM). Two Phase I studies were conducted with tebentafusp to support the rationale for this Phase II study: the first-in-human (FIH) Phase I study of weekly dosing in patients with advanced melanoma (IMCgp100-01), and the Phase I study of the intra-patient escalation regimen in patients with advanced UM (IMCgp100-102). In the IMCgp100-01 FIH study, 2 key observations were made: (1) immune-related toxicities of T cell redirection (fever, rash, and hypotension) were observed and were generally limited to the first 2 weeks of dosing; and (2) preliminary anti-tumor activity in the setting of advanced UM was observed at doses higher than the identified recommended Phase II dose (RP2D) with confirmed and durable partial responses (identified RP2D once weekly [QW] is 50 mcg). In a retrospective review of the tumor response data from these Phase I cohorts, objective responses, including durable partial responses, in UM patients with higher degrees of tumor burden were generally noted at the higher absolute doses administered (approximately 48–81 mcg absolute doses). Such initial starting doses could not be achieved in the FIH Phase I study, due to the immune-related toxicity of tebentafusp in the initial weekly dose escalation trial observed at the first and/or second dose (Cycle 1 Day 1 [C1D1] and/or Cycle 1 Day 8 [C1D8]). All dose limiting toxicities in the weekly dose escalation study were seen at the first or second dose. To avoid the immune-related toxicity observed in the first 2 doses, a modified dosing regimen was implemented in the FIH Phase I study (IMCgp100-01, the intra-patient escalation regimen) where patients received the flat dose of 20 mcg at C1D1 and 30 mcg flat dose at C1D8 (where the infrequent occurrences of immune toxicity associated with hypotension were noted). Following this at C1D15 and beyond, patients received the previously identified RP2D-QW of 50 mcg. All patients treated with this regimen in the FIH Phase I study (n=7 total; 6 patients with UM) tolerated it well.

	Based on these observations in the FIH Phase I study (IMCgp100-01), a second Phase I study of the intra-patient escalation regimen was conducted in patients with advanced UM (IMCgp100-102). In this study, patients received low, fixed doses of tebentafusp at C1D1 (20 mcg) and C1D8 (30 mcg) in the first 2 weeks of dosing, where the majority of immune-related toxicities related to profound T cell redirection have been observed. At C1D15, a dose escalation of tebentafusp was conducted with the goal of increasing the overall exposure to tebentafusp in the setting with limited immune-related toxicity associated with T cell redirection. The dose identified for Phase II testing in the intra-patient dose escalation regimen (the recommended Phase II dose of the intra-patient dose escalation regimen) is 68 mcg, administered QW at C1D15 and beyond, following the low, fixed doses of 20 mcg at C1D1 and 30 mcg at C1D8 in all patients. This randomized Phase II study is designed to evaluate the safety and efficacy of tebentafusp compared with Investigator's Choice (dacarbazine, ipilimumab, or pembrolizumab) in patients with advanced UM treated in the first-line setting with no prior systemic or liver-directed therapy administered in the advanced setting (prior surgical resection of liver metastases is acceptable). Comparison of the tebentafusp efficacy results in this Phase II study will be made with the concurrently randomized Investigator's Choice arm. The primary endpoint is overall survival (OS), defined as the time from randomization until the date of death by any cause.
Primary Objectives	The dual primary objectives are: 1) To compare the OS in all patients randomized to the tebentafusp monotherapy versus all patients randomized to the Investigator's Choice monotherapy 2) To compare the OS in all patients randomized to the tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomized to the Investigator's Choice monotherapy Both objectives relate to HLA-A*0201 positive patients with advanced UM with no prior treatment in the metastatic setting.
Secondary Objectives	The secondary objectives of the study are: • To characterize the safety and tolerability of tebentafusp in the intra-patient dose escalation regimen relative to Investigator's Choice • To characterize the PK profile of single-agent tebentafusp in the intra-patient dose escalation regimen • To assess the anti-tumor efficacy of tebentafusp versus Investigator's Choice with the parameters of progression free survival (PFS), best overall response, duration of response (DOR), time to response, and disease control rate (DCR) using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 • To evaluate the treatment and disease impact to health-related quality of life (HRQoL) in patients treated with tebentafusp versus patients treated with Investigator's Choice. HRQoL will be assessed using the following 2 established patient-reported outcome instruments:

	○ The EuroQoL-5 Dimensions – 5-levels (EQ-5D,5L) of disease severity scale to enable an assessment of health status compared to population norms ○ The European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire-Core 30 (QLQ-C30) to provide an insight into domains of cancer-specific patient health • To evaluate the incidence of anti-tebentafusp antibody formation following multiple infusions of tebentafusp in the intra-patient dose escalation regimen
Study Design	This is an open-label, randomized, multi-center Phase II study of tebentafusp versus Investigator's Choice (dacarbazine, ipilimumab, or pembrolizumab) in adult (> 18 years) HLA-A*0201 positive patients with advanced UM previously untreated in advanced or metastatic setting. In this study, tebentafusp is administered on a weekly basis with an intra-patient escalation dosing regimen compared with limited Investigator's Choice at the approved doses of these agents. Patients enrolled in the study will be randomized in a 2:1 ratio (tebentafusp:Investigator's Choice) and stratified by lactate dehydrogenase status to receive either tebentafusp (Arm 1) in the intra-patient escalation dosing regimen or Investigator's Choice (Arm 2) at the approved dose every 3 weeks of a 21-day cycle. **Arm 1 (Tebentafusp):** All patients randomized to Arm 1 will receive tebentafusp by intravenous (IV) infusion following the intra-patient escalation regimen. On C1D1, patients receive 20 mcg (flat dose); on C1D8, patients receive 30 mcg (flat dose); and beginning with C1D15, patients will receive the escalated dose of 68 mcg. Due to the anticipated cytokine release-associated toxicity with tebentafusp, patients will be monitored overnight as an inpatient following the weekly doses at C1D1, C1D8, and C1D15. **Arm 2 (Investigator's Choice):** All patients randomized to Arm 2 will receive Investigator's Choice of 1 of 3 options: dacarbazine in the standard dosing regimen in UM of 1000 mg/m^2 given on Day 1 of each 21-day cycle; ipilimumab in the approved dosing regimen for unresectable or metastatic melanoma of 3 mg/kg given on Day 1 of each 21-day cycle for a maximum of 4 doses; or pembrolizumab in the dosing regimen of 2 mg/kg up to a maximum of 200 mg or 200 mg administered intravenously where approved locally given on Day 1 of each 21-day cycle. The preferred Investigator's Choice agent will be selected prior to randomization. No overnight monitoring will be required in Arm 2. Treatment with tebentafusp or Investigator's Choice option, will be administered as described until the patient experiences either unacceptable toxicity or progressive disease per RECIST v1.1 as outlined below: • Patients randomized to Arm 2 receiving dacarbazine will discontinue treatment at the time of disease progression by RECIST v1.1 assessment. • Patients receiving tebentafusp, pembrolizumab, or ipilimumab experiencing disease progression per RECIST v1.1. For patients who continue tebentafusp, ipilimumab, or pembrolizumab therapy beyond initial RECIST v1.1 PD, further PD warranting treatment discontinuation is defined as **ANY** one of the following observed at least 4 weeks after the initial PD assessment per RECIST v1.1: 1)

	an additional ≥ 20% increase in tumor burden (sum of diameters of both target and new measurable lesions) accompanied by an absolute increase of ≥ 5 mm; 2) unequivocal PD of non-target lesions; or 3) new non-measurable lesions.
Population Under Study	The trial will enroll HLA-A*0201 positive patients with a diagnosis of advanced UM, defined as histologically confirmed diagnosis of UM and metastatic, stage IV disease at study entry. Patients are eligible if they have received no prior systemic therapy or local (ie, liver-directed) therapy administered in the metastatic or advanced setting. Neoadjuvant and/or adjuvant therapy are acceptable, provided these treatments are administered in the setting of local ocular disease with a curative intent. Patients may not be re-treated with an Investigator's Choice therapy that was administered as adjuvant or neoadjuvant treatment.
Inclusion Criteria	1. Male or female patients age ≥ 18 years of age at the time of informed consent 2. Ability to provide and understand written informed consent prior to any study procedures 3. Histologically or cytologically confirmed metastatic UM 4. Must meet the following criteria related to prior treatment: • No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy • No prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization • Prior surgical resection of oligometastatic disease is allowed • Prior neoadjuvant or adjuvant therapy is allowed provided administered in the curative setting in patients with localized disease. Patients may not be re-treated with an Investigator's Choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who have received nivolumab as prior adjuvant/neoadjuvant treatment should not receive pembrolizumab as Investigator's Choice therapy. 5. HLA-A*0201 positive by central assay 6. Life expectancy of > 3 months as estimated by the investigator 7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 at Screening 8. Patients have measurable disease or non-measurable disease according to RECIST v1.1 9. All other relevant medical conditions must be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug
Exclusion Criteria	1. Patient with any out-of-range laboratory values defined as: • Serum creatinine > 1.5 × upper limit of normal (ULN) and/or creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 50 mL/minute

	• Total bilirubin > 1.5 × ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN • Alanine aminotransferase > 3 × ULN • Aspartate aminotransferase > 3 × ULN • Absolute neutrophil count < 1.0 × 10^9/L • Absolute lymphocyte count < 0.5 × 10^9/L • Platelet count < 75 × 10^9/L • Hemoglobin < 8 g/dL 2. History of severe hypersensitivity reactions (eg, anaphylaxis) to other biologic drugs or monoclonal antibodies 3. Clinically significant cardiac disease or impaired cardiac function, including any of the following: • Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia currently requiring medical treatment • QT interval corrected by Fridericia's formula (QTcF) > 470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome. NOTE: If the initial automated QTcF is > 470 msec at screening, for the purpose of determining eligibility, the mean QTcF, based on at least 3 ECGs obtained over a brief time interval (ie, within 30 minutes), should be manually determined by a medically qualified person. • Acute myocardial infarction or unstable angina pectoris < 6 months prior to Screening 4. Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to study Day 1. Patients with brain metastases are eligible if lesions have been treated with localized therapy and there is no evidence of PD for at least 4 weeks by magnetic resonance imaging (MRI) prior to the first dose of study drug 5. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy at least 1 week prior to the first dose of study drug 6. Known history of human immunodeficiency virus infection (HIV). Testing for HIV status is not necessary unless clinically indicated 7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection 8. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any

	malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type 9. Any medical condition that would, in the investigator's or Sponsor's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results 10. Patients receiving systemic steroid therapy or any other systemic immunosuppressive medication at any dose level, as these may interfere with the mechanism of action of study treatment. Local steroid therapies (eg, otic, ophthalmic, intra-articular, or inhaled medications) are acceptable 11. History of adrenal insufficiency 12. History of interstitial lung disease 13. History of pneumonitis that required corticosteroid treatment or current pneumonitis 14. History of colitis or inflammatory bowel disease 15. Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumor biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary) 16. Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass 17. Use of hematopoietic colony-stimulating growth factors (eg, G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to start of study drug. An erythroid-stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is not red blood cell transfusion dependent 18. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation) 19. Women of childbearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during study treatment (defined in Section 6.7), and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Highly effective methods of contraception are described in Section 6.7 20. Male patients must be surgically sterile or use double barrier contraception methods from enrollment through treatment and for 6 months following administration of the last dose of study drug 21. Patients who are in an institution due to official or judicial order. 22. Patients who are the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study.

	23. Contraindication for treatment with Investigator's Choice alternatives (dacarbazine, ipilimumab and pembrolizumab) as per applicable labelling. Patient may have a contraindication to 1 or 2 of the choices if he/she is a candidate for dosing with at least 1 Investigator's Choice and meets all other study eligibility criteria.
Efficacy Assessments	Radiologic assessments should be performed as scheduled every 12 weeks (Section 7.3.1), using a reference to C1D1 and should NOT follow delays incurred in the treatment period. Tumor response will be determined locally by site according to RECIST v1.1 A blinded independent central review assessment may be conducted in support of the local read for assessment of efficacy. Guidelines for the assessments by RECIST v1.1 are presented in Appendix 2. Local investigator's review of the imaging studies will be used for efficacy assessment and treatment decision making (study discontinuation due to progressive disease as per RECIST v1.1).
Safety Assessments	Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, pregnancy, ECG, cytokine testing, as well as collecting of the adverse events (AEs) at every visit. All data (including efficacy and safety data) will be reviewed centrally by the independent data monitoring committee.
Other Assessments	• Patient-reported outcomes will be assessed using: (1) the general health status EQ-5D,5L questionnaire and (2) the HRQoL instrument EORTC QLQ-C30 • Serum PK parameters and immunogenicity in tebentafusp Arm 1 only • Pharmacodynamic assessment on pre- and post-treatment newly obtained tumor samples • Treatment and health-related medical resource utilization
Sample Size	The sample size of the trial is planned at 369 patients with advanced UM randomized in a 2:1 ratio to tebentafusp (n = 246) or Investigator's Choice (n = 123). The total number of planned death events for the intent-to-treat analysis of OS is 250.
Statistical Considerations	The primary endpoint is OS, date of death in relation to study randomization. The primary analysis of OS in all randomized patients and in the Rash Analysis Set will be conducted using a 2-sided log-rank test stratified by LDH status (LDH above ULN versus LDH below or equal to ULN; measured centrally). Secondary endpoints: • Progression free survival • Best overall response

	• Safety and tolerability: Incidence and severity of AEs and SAEs; changes in safety laboratory parameters, vital signs, and electrocardiogram (QTcF); dose interruptions, reductions, discontinuations, and dose intensity of all administered agents • Serum PK parameters (eg, C_{max}, C_{min}, C_{trough}) • Other measures of tumor response over time as determined by RECIST v1.1, including DOR, time to response, and DCR (defined as CR or PR, or SD ≥ 24 weeks) • EQ-5D,5L, and EORTC QLQ-C30 change from Baseline over time and between treatment strategies • Assessments of anti-tebentafusp antibody formation Exploratory endpoints: • Correlation of the expression of T cell infiltration, expression of glycoprotein 100 (gp100), human leukocyte antigen-DR, programmed death-ligand 1, tumoral lymphocyte activation status, and myeloid-derived suppressor cell infiltration and other immune markers evaluated in tumor biopsies with anti-tumor activity • Changes in serum cytokine, chemokines (eg, C-X-C motif chemokine ligands, CXCL9 and CXCL10, hepatocyte growth factor, interleukin 1 receptor alpha, and monocyte chemoattractant protein-1), or other analytes in response to treatment • Duration of treatment and response for patients treated beyond RECIST v1.1 PD • PFS2, defined as time from randomization to the subsequent PD following the initial RECIST v1.1 PD, or death • Hospitalizations, concomitant medication use, medical procedures, and other measures of healthcare utilization
Keywords	Uveal melanoma, tebentafusp, dacarbazine, ipilimumab, pembrolizumab

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
°C	Degrees Celsius
4QD-Q3W	Daily × 4 days dosing repeated every 3 weeks
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
Akt	Protein kinase B
anti-CD3	Anti-cluster of differentiation 3
BICR	Blinded independent central review
BOR	Best overall response
C#D#	Cycle # Day #
CD#	Cluster of differentiation #
CI	Confidence interval
C_{max}	Maximum observed concentration observed over the dosing interval
C_{min}	Minumum observed concentration observed over the dosing interval
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRS	**Cytokine release syndrome**
CT	Computed tomography
CTL	Cytotoxic T lymphocyte
CTLA4	Cytotoxic T lymphocyte antigen - 4
C_{trough}	Drug concentration at X days after dosing
CXCL#	C-X-C motif chemokine ligand #
DCO	Data cutoff
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EQ-5D, 5L	EuroQoL-5 Dimensions – 5-levels
FIH	First-in-human
FoxP3	Forkhead box P3
GNA11	Heterotrimeric G protein alpha subunit 11
GNAQ	Heterotrimeric G protein alpha subunit q
gp100	Glycoprotein 100
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-A*0201	Human leukocyte antigen-A*0201 (allele genotype)
HLA-A*0206	Human leukocyte antigen-A*0206 (allele genotype)
HLA-A2	Human leukocyte antigen-A2 (serotype)

Abbreviation	Definition of Term
HLA-DR	Human leukocyte antigen-DR isotype
HR	Hazard ratio
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFNγ	Interferon-gamma
IHC	Immunohistochemistry
IL-#	Interleukin-#
IMCgp100	77 kDa bi-specific protein
IRB	Institutional Review Board
IRC	Independent radiology committee
irRC	Immune-related response criteria
IRT	Interactive Response Technology
ITT	Intent to treat
IV	Intravenous(ly)
kg	Kilogram
LAG-3	Lymphocyte activation gene-3
LDH	Lactate dehydrogenase
m	Meter
mcg	Microgram
MCP-1	Monocyte chemoattractant protein-1
MEK	Mitogen-activated protein kinase/extracellular signal-regulated kinase
mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
Q3W	Every 3 weeks
QD	Once daily
QLQ-C30	Quality of life Questionnaire-Core 30
QTcF	QT interval corrected by Fridericia's formula
QW	Once weekly
RAS	Rash Analysis Set
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II dose

Abbreviation	Definition of Term
RP2D-IE	Recommended Phase II dose intra-patient escalation regimen
RP2D-QW	Recommended Phase II dose weekly
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TIL	Tumor-infiltrating lymphocyte
T_{max}	Time of maximum concentration
TMTB	Total measured tumor burden
TNFα	Tumor necrosis factor-alpha
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UM	Uveal melanoma

1 BACKGROUND

1.1 Uveal Melanoma: Overview of Disease Setting

Melanoma arises from pigment containing cells (melanocytes) present in the skin, eye, and mucus membranes. Melanoma most frequently occurs in the skin; however, ocular melanoma arises from pigmented cells in the eye. The primary cause of melanoma is thought to be radiation-induced DNA damage from ultraviolet light exposure. Melanoma is the most deadly of skin cancers. Globally, in 2012, melanoma occurred in 232,000 people and resulted in 55,000 deaths (Cancer Research UK). Cutaneous and uveal melanoma (UM) is more common in men than women. UM is a rare type of melanoma where the incidence has ranged from 5.3 to 10.9 cases per million (Singh, 2011). Despite its rare incidence rate (representing approximately 3% of melanoma cases, approximately 4000 cases globally per year), UM is the most frequent primary intraocular malignancy of the adult eye (85%) (Patel, 2011; Maio, 2013). UM is an extremely malignant neoplasm that affects the vascular layers of the eye (iris, ciliary body, and choroid; Maio, 2013). The majority of UM cases in the United States occur in the Caucasian population (Andreoli, 2015). UM is biologically distinct from cutaneous melanoma with differences in the mutational landscape, where BRAF and NRAS mutations dominate the landscape in cutaneous melanoma and mutations in guanine nucleotide binding protein (G protein) coupled receptors heterotrimeric G protein alpha subunit q (*GNAQ*) and heterotrimeric G protein alpha subunit 11 (*GNA11*) dominate in UM (Shoushtari, 2014). In addition, the mode of spread of disease is distinct between the 2 disease settings, with hematogenous spread of uveal versus lymphatic spread in cutaneous, leading to the different patterns of metastatic disease with primary liver metastases in UM, and contrasted with visceral, bone, and brain metastases predominant in cutaneous melanoma (Dunavoelgyi, 2011; Yu, 2014).

Local therapy approaches in UM generally rely on radiation and surgical enucleation; however, despite adequate local therapy, UM metastases are very common and develop in 50% of patients with the liver being the predominant metastatic site (>90% with hepatic metastases; Carvajal, 2014). UM has also been shown to spread to the lungs, bones, and skin (Carvajal, 2014; Maio, 2013). The American Joint Committee on Cancer Tumor-Node-Metastasis staging system is used for UM (Edge, 2010) and represents 1 aspect of the estimated prognosis. Molecular markers such as monosomy 3 and newer expression profiling methods (Field, 2014) are used to guide prognosis and risk of metastasis in addition to classic histology such as the presence of spindle versus epithelioid (Campbell, 1998). Once patients have developed metastatic disease (metastatic UM), the prognosis and outcomes are very poor with a median survival of less than 12 months, and for those with liver metastases, the median survival is approximately 6 months (Singh, 2011). Despite much investigation of metastatic UM in the clinic, to date, no systemic therapy has improved survival and no effective therapy has been achieved (Maio, 2013; Carvajal, 2014; Luke, 2013; Zimmer, 2015).

UM has a poor response to cytotoxic chemotherapy and radiotherapy, and therapies for cutaneous melanoma have had little impact in the treatment of UM (eg, BRAF inhibitors, due to the absence of the target mutation in UM; Buder, 2013). UM has been characterized by specific

driver mutations in G protein, *GNAQ* or *GNA11*, leading to the downstream activation of multiple signaling nodes, including mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK), phosphatidylinositol 3-kinase/protein kinase B (Akt), protein kinase C, and Yes-associated protein (Shoushtari, 2014; Yu, 2014). Treatments for metastatic UM can be divided into (1) liver-directed treatments; such as surgical resection, ablation, radiation, and hepatic arterial chemo-infusion; and (2) systemic treatments; such as chemotherapy (anti-neoplastic drugs used alone or in combinations), immunotherapy (interferon, interleukin-2 [IL-2], programmed death-1 [PD-1] inhibition, and ipilimumab), anti-angiogenetic drugs, and recently the targeted agents such as MEK and Akt inhibitors. The targeted agents are applied based on the high percentage of patients' tumors harboring *GNAQ* or *GNA11* mutations; however, these therapies have not been as effective as other targeted agents in the BRAF mutation subset (Buder, 2013). A randomized study of the MEK inhibitor selumetinib administered in combination with dacarbazine showed an objective response rate (ORR) by blinded independent central review (BICR) 3.1%, and progression free survival (PFS) was not significantly improved when compared to dacarbazine monotherapy (2.8 v. 1.8 months) (Carvajal, 2017).

Recent evidence suggests that immunotherapy for UM has similar efficacy to cytotoxic therapy, where the estimates of the response rate of dacarbazine and other single-agent chemotherapy agents are between 0–5% (Carvajal, 2014; Augsberger, 2009; Buder, 2013). Response rates with ipilimumab in this setting are approximately 0–8% across multiple studies (Maio, 2013; Luke, 2013; Zimmer, 2015; Carvajal, 2014). Similarly, response rates in UM with PD-1 or programmed death-ligand 1 (PD-L1) targeting antibodies are also approximately 5% (Algazi, 2016; Karydis, 2016). The response to new immunotherapy approaches in the uveal subset is significantly diminished compared to that for cutaneous melanoma, possibly due to the low mutational burden of UM compared to that of cutaneous melanoma (Furney, 2014). The tumor microenvironment of UM is characterized by a uniquely suppressive environment with the presence of M2 macrophages and immature myeloid cells along with strong forkhead box P3 (FoxP3) expression and cluster of differentiation 8 positive (CD8+) T cells (Bronkhorst, 2012). Both phenotypes are associated with a distinctly immune suppressive environment and this immune infiltrate is associated with monosomy 3 in UM and poor prognosis (Maat, 2008; Bronkhorst, 2011). The suppressive environment and lack of activity of checkpoint inhibition suggests that mobilization of activated T cells with a tumor-specific focus may have anti-tumor activity in this disease setting. With the wide and strong expression of glycoprotein 100 (gp100) in UM, the application of a redirected T cell approach to gp100 in this setting may have enhanced anti-tumor activity (van Dinten, 2005), and preliminary evidence from the first-in-human (FIH) trial with tebentafusp supports this hypothesis (Middleton, 2016; Shoushtari, 2016). Furthermore, with the immunologically privileged site of UM, immunotherapy represents a promising treatment approach for this devastating and life-threatening condition (Buder, 2013; Woodman, 2012).

1.2 Overview of Tebentafusp

Tebentafusp is a 77 kDa bi-specific protein with targeting and effector moieties which is manufactured in *Escherichia coli* (Figure 1-1). The targeting portion of tebentafusp (the T cell receptor) functions to bind to the gp100 antigen as presented by major histocompatibility complex

Class I on the surface of melanoma cells. The targeted gp100 peptide is presented by a subset of the population that express a specific variant (serotype) of the major histocompatibility complex Class I complex known as human leukocyte antigen-A2 (HLA-A2). This variant is carried by approximately 50% of the population in North American and Western European Populations (Middleton, 2003).

The effector function (anti-cluster of differentiation 3 [anti-CD3]) works by binding and activating T cells via cluster of differentiation 3 (CD3). These T cells can be tumor-specific cells which are already resident in the tumor (tumor-infiltrating lymphocytes [TILs]) but circulating polyclonal T cells may also be activated as they traffic through the tumor as part of the normal blood supply. CD4+ and CD8+ T cells are both activated by tebentafusp triggering cytolytic activity associated with release of immune mediators potentially resulting in a cascade of anti-tumor immune effector mechanisms. T cell proliferation studies on CD8 T cell subtypes have shown that effector memory, central memory, and naïve cells all respond to tebentafusp stimulation as well as CD4+ T cells. Memory T cell activation following exposure to tebentafusp is rapid (pharmacodynamic effects seen within hours of exposure), although naïve cell activation can be delayed in comparison to the activation of effector cells.

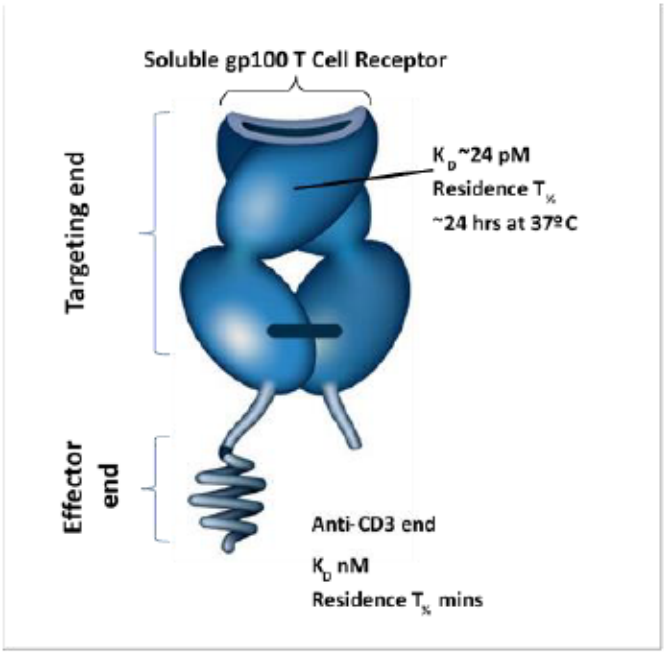

Figure 1-1 Tebentafusp Structure

CD3 = cluster of differentiation 3; K_D = dissociation constant; $T_{1/2}$ = terminal binding half-life

Tebentafusp is a biologic with dual effector and targeting ends. The targeting end is an affinity-enhanced soluble T cell receptor recognizing the gp100 antigen and the effector end is an anti-CD binding domain.

1.3 Non-clinical Experience with Tebentafusp

1.3.1 Preclinical Pharmacology Summary

Tebentafusp has been shown to induce the full repertoire of cytotoxic T lymphocyte (CTL) activation events in a dose-dependent manner in vitro when combined with target melanoma cells. This activation is evident at concentrations as low as 1 picomolar, and activity is maximal at a concentration of 1 nanomolar irrespective of whether isolated CD8 or peripheral blood mononuclear cells (PBMC) are used as the effector cells. Furthermore, maximal killing effects may require up to a few days exposure with cancer cells. The activation of CD4 T cells has also been demonstrated at similar concentrations and with similar kinetics. Such activation would be expected to augment the CTL-mediated immune response through the recruitment of other inflammatory cells.

Using PBMCs from melanoma patients, tebentafusp has been shown to augment an already present anti-tumoral response. Finally, the tumor-infiltrating T cells that would be the first line of attack in a clinical situation would be expected to be outnumbered by melanoma targets; therefore, a single T cell is capable of serial killing in vitro. These data demonstrate that tebentafusp is a potent tumor-killing agent.

HLA-A2 represents a serotype or a group of related alleles. Tebentafusp has been shown to have the capacity to bind to the various alleles of the HLA-A2 serotype (eg, HLA-A*0201, HLA-A*0206), with the longest residence time against the HLA-A*0201 allele. Using in vitro methods, the ability of tebentafusp to mediate killing of an HLA-A*0206 cell line (the HLA-A*0206, gp100 positive UM cell line 92-1) was tested for response, with little anti-tumor activity demonstrated in these in vitro assays. In contrast, when the HLA-A*0201 allele was introduced into this cell line via transfection (in addition to the native HLA-A*0206 allele), tebentafusp-mediated killing and cytokine release were restored to a similar degree as is observed with native HLA-A*0201 cell lines (eg, MEL624; Figure 1-2), suggesting that optimal cell killing is induced when tebentafusp interacts with the HLA-A*0201 allele.

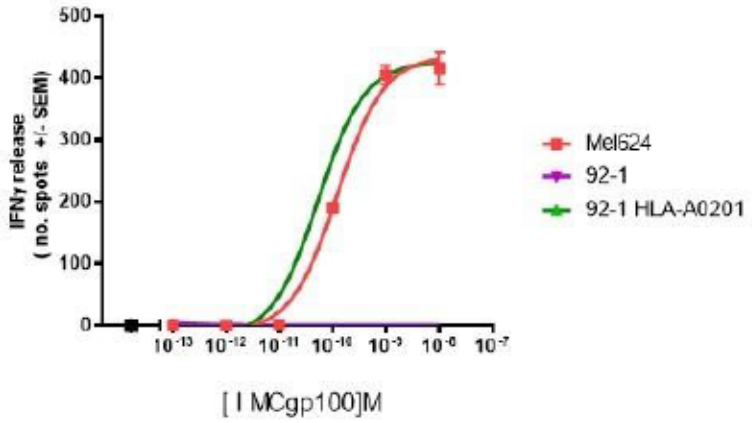

Figure 1-2 ImCgp100 Redirects Peripheral Blood Mononuclear Cell Response Against Ocular Melanoma Cell Line 92-1 (HLA-A*0206) when HLA-A*0201 is Introduced via Lentivirus Transduction

HLA-A*0201 = human leukocyte antigen-A*0201; IFNγ = interferon-gamma; PBMC = peripheral blood mononuclear cell; SEM = standard error of the mean

Ocular melanoma cell line 92-1 expressing HLA-A*0206 subtype is unable to induce PBMC response when compared to cutaneous melanoma line Mel624 (HLA-A*0201 positive). Ectopic expression of HLA-A*0201 in 92-1 ocular melanoma restores tebentafusp driven T cells responsiveness. Cutaneous melanoma cell line Mel624 (HLA-A*0201 and gp100 positive) (red), ocular melanoma cell line 92-1 (HLA-A0206 and gp100 positive) (violet) wild type and transduced with lentivirus expressing HLA-A*0201 molecule (green) have been incubated at 37°C, 5% CO_2 with PBMC (Donor RPL022) at an effector:target ratio of 1:1 in the presence of tebentafusp at the concentrations indicated in the graph. A series of controls are also indicated. IFNγ-producing cells were enumerated by IFNγ enzyme-linked immunospot assay.

1.3.2 Non-clinical Toxicology Summary

Both the gp100-specific soluble T cell receptor and the CD3 targeting ends of tebentafusp have been demonstrated to have high specificity for the human HLA-A2-gp100 peptide complex and human CD3. Therefore, binding and activation of tebentafusp cannot be demonstrated in non-human primates, which show a relatively high degree of sequence homology to human CD3. In addition, both the T cell receptor targeting end and CD3 activation arm do not interact at any level in any other species. Given the limitations in binding of tebentafusp and activation of any T cell subsets in any standard toxicology species, there is no relevant toxicology species in which tebentafusp can be tested.

Tissue cross-reactivity studies with tebentafusp and published gp100 immunohistochemistry (IHC) demonstrate gp100 expression in human melanocytes, and expression levels have been demonstrated directly in the retina, melanocytes, the substantia nigra, and the thymus (Takase, 2005; Wagner, 1997). Other tissues that are known to contain melanocytes, but to our knowledge have not been directly tested for gp100 expression, include the iris, the inner ear, and the choroid plexus of the brain.

In the absence of a relevant toxicology species, tebentafusp was investigated for potential cross-reactivity to normal tissues other than target melanoma tissue in vitro. Tebentafusp could redirect T cell activity to normal cells that are known to express gp100; however, higher concentrations of tebentafusp were required to elicit an effect in these normal tissue cells indicating that there may be a therapeutic window between a dose of drug required to effect melanoma cells and that which may cause potential organ-specific toxicity. These assays were also used to determine a minimal anticipated biological effect level, and the starting dose for the first tebentafusp dose escalation study. Other assays designed to assess unexpected reactivity of both the T cell receptor and the anti-CD3 were entirely negative.

1.4 Clinical Program and Safety Summary

Tebentafusp is being studied in 2 ongoing Phase I studies in melanoma: a FIH, open-label, dose escalation study (IMCgp100-01) and an intra-patient dose escalation study of UM patients (IMCgp100-102). In addition, a combination study in cutaneous melanoma with inhibition of PD-L1 and cytotoxic T lymphocyte antigen-4 (CTLA4) pathways is ongoing (IMCgp100-201).

1.4.1 First-in-human Dose Escalation Study (IMCgp100-01)

In this Phase I, FIH study of tebentafusp alone, patients with advanced melanoma were enrolled into 2 distinct dose escalation cohorts: a once weekly (QW) dosing regimen cohort (Arm 1), and a once daily (QD) dosing regimen cohort (Arm 2) in which patients received daily × 4 days dosing repeated every 3 weeks (4QD-Q3W). The study was designed to identify the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of tebentafusp in each of the 2 repeat dosing regimens: either weekly dosing (the RP2D-QW) or daily dosing × 4 days (the RP2D-4QD).

1.4.1.1 Weekly Dosing Regimen — Arm 1

Identification of the MTD and RP2D

The dose escalation in the Phase I QW dosing regimen arm (Arm 1) included dose levels from 5 ng/kg up to 900 ng/kg, and the MTD for this dosing regimen was identified at 600 ng/kg QW (Middleton, 2015). The data presented here are from a data cutoff of 12 August 2016 (N=66 patients, QW regimen only). The RP2D-QW was initially identified as a flat dose of 50 mcg administered intravenously (IV) on a weekly basis, starting with Cycle 1 Day 1 (C1D1), based on the range of absolute doses administered at the MTD of 600 ng/kg (n=5 patients, ranging from 34–66 mcg QW, median dose of 54 mcg); however, a review of the safety and pharmacokinetic (PK) data for the QW regimen suggested that the higher absolute doses administered and higher drug exposures of tebentafusp were associated with more severe toxicities.

During Arm 1, dose limiting toxicities (DLT) of grade 3 or 4 hypotension were observed in 4 patients treated across cohorts: 405 ng/kg (1 of 6), 600 ng/kg (1 of 6), and 900 ng/kg (2 of 6). The DLT events all occurred at the first (n=3) or second (n=1) doses and within 24 hours after the doses were administered. Hypotension in these 4 cases was managed with IV fluids (normal saline and colloid infusions) alone. None of the patients required inotropic support for blood

pressure and all were treated with IV corticosteroid therapy. All cases of grade 3 or 4 hypotension resolved within 2 days. In addition, in a cohort of patients with UM, severe immune-related infusion toxicity was observed with the first or second dose at C1D1 or Cycle 1 Day 8 (C1D8). Patients experiencing infusion-related toxicity have presented with pyrexia, facial edema, mild-to-moderate rash (grade 1 or 2), and moderate-to-severe (grade 2 or 3) hypotension.

Other toxicities were generally mild to moderate in severity (grade 1 or 2). The most common related adverse events (AEs) (any grade) observed across all dose levels (N=66 patients) included rash (45 patients, 68%), pruritus (42 patients, 64%), pyrexia (34 patients, 52%), and periorbital edema (30 patients, 46%). The most common causally related severe AEs (grade ≥ 3) were rash (10 patients, 15%), lymphopenia (9 patients, 14%), and hypotension (6 patients, 9%). In general, cases of grade 3 rash were managed with antihistamine therapy; however, occasional symptomatic patients required IV corticosteroid therapy. Rash typically resolved within 72 hours after dosing.

The RP2D-QW was subsequently adjusted to reduce the doses administered in the first 2 weeks due to the observation of severe hypotension at the 50 mcg starting dose. An expansion cohort of patients was enrolled to assess this intra-patient escalation regimen: 20 mcg at C1D1, 30 mcg at C1D8, and 50 mcg at Cycle 1 Day 15 (C1D15) and beyond. Seven patients (n=6 UM) were treated with this regimen with no severe toxicity.

Preliminary efficacy has been observed in the FIH Phase I study of tebentafusp (IMCgp100-01 study). Of the 66 patients (n=50 non-UM; n=16 UM) treated with QW dosing, a total of 54 patients were considered evaluable for efficacy, defined as patients treated at ≥ 270 ng/kg (in dose escalation cohorts; starting median absolute dose of 16 mcg) or the RP2D-QW with at least 1 follow-up scan or discontinued prior to the first scan. In this cohort, the best objective response was partial response (PR) in 5 patients (n=3 UM and n=2 cutaneous melanoma, including patients refractory to checkpoint antagonists), 17 patients with stable disease (SD), and 25 with progressive disease (PD); 2 patients discontinued prior to their first scan. Of the patients with SD, 5 had minor responses (≤ -10% target sum of the longest diameter; 3 cutaneous melanoma, 2 UM).

In this FIH Phase I trial (IMCgp100-01), data showed that patients frequently experience rash, as a consequence of on-target activity against gp100 melanocytes, and lymphocyte trafficking from the periphery into tissues, which in some cases leads to hypotension. Based on preclinical binding data, demonstrating that all HLA-A2 serotype alleles bind to tebentafusp, the IMCgp100-01 FIH trial was designed to allow enrollment of patients expressing any of the alleles of the HLA-A2 serotype. Two patients expressing the HLA-A*0206 molecule were treated at the RP2D cohort with weekly dosing. One patient with UM experienced grade 1 rash (unrelated to tebentafusp) and grade 1 hypotension, and this patient then was notable for PD at the first on-treatment tumor assessment at 8 weeks. In 1 patient with cutaneous melanoma, no rash or hypotension were observed associated with the first doses and, similarly, this patient was noted to have PD at the first on-treatment assessment at 8 weeks. In both non-HLA-A*0201 patients treated at the RP2D, no evidence of lymphocyte trafficking was observed (with minimal changes noted in the peripheral

lymphocyte count immediately following dosing with tebentafusp), suggesting the more transient binding of tebentafusp to the peptide-HLA-A*0206 molecule may lead to inferior clinical activity. Given the preliminary preclinical and clinical evidence in UM, this study will enroll only HLA-A*0201 positive patients.

1.4.1.2 Daily Dosing Regimen — Arm 2

The dose escalation in the Phase I QD regimen (Arm 2) was completed, and no DLTs were observed in the Arm 2 dose escalation (n=15 patients across 5 dose levels ranging from 10 mcg to 50 mcg). Based on the lack of observations of DLT in these cohorts, an MTD in Arm 2 was not determined, and the initial RP2D-QD (RP2D of the daily dosing regimen) was identified as the 50 mcg 4QD-Q3W dose. Preliminary data from this arm suggest that, in general, the safety profile of the QD regimen appears similar to that observed with the QW regimen. However, limited anti-tumor activity has been observed in this cohort with only 1 PR. No further development is currently planned for the daily dosing regimen.

1.4.2 Intra-patient Dose Escalation Study in Uveal Melanoma (IMCgp100-102)

IMCgp100-102 is the Phase I dose escalation study of the intra-patient escalation regimen initiated in the FIH study. The study design was based on the observations of immune-related infusion toxicity in the FIH study, and the amelioration of these events with the intra-patient escalation regimen, as well as the response data in UM at doses higher than the RP2D (PR observed at 65–85 mcg absolute doses). In this study, cohorts of patients are treated with the low, fixed dosing at C1D1 (20 mcg) and C1D8 (30 mcg) followed by a dose escalation at C1D15. In the dose escalation portion of this study, which was completed 18 October 2016, 19 patients were treated across 4 dose level cohorts defined by the dose administered at C1D15 and beyond. The 4 dose levels tested were 54 mcg QW, 64 mcg QW, 73 mcg QW, and 68 mcg QW. Three DLTs of transaminase elevation (with or without a concurrent rise in total bilirubin) were observed in this study in 2 cohorts. The first DLT (grade 3 transaminase elevation with concurrent mild increase in bilirubin) was observed in 1 of 6 patients in the 64 mcg QW cohort. Following this evaluation of 64 mcg, the dose was escalated to 73 mcg QW. At the dose level of 73 mcg QW, 2 DLT (of grade 3 or 4 transaminase elevations) were observed among 4 patients treated at this dose level. This dose level was deemed as not tolerated and the cohort of 68 mcg was enrolled. Six patients were treated at 68 mcg QW with no DLTs reported and no significant elevations of hepatic transaminases. As the highest dose level tested with a DLT rate < 33% with 6 patients treated, 68 mcg was identified as the MTD. This study continues to enroll in the RP2D expansion cohort at the dose of 68 mcg in the intra-patient escalation regimen (RP2D-IE).

1.4.2.1 Definition of the Recommended Phase II Dose and Dilution Procedure

Individual doses of tebentafusp are prepared from a concentrated, frozen stock solution (0.5 mg/mL) by a 2-step dilution procedure in the drug preparation guidelines, requiring dilution of approximately 2500-fold to accurately achieve the microgram doses. The dilution procedure is described in the Pharmacy Handling Instructions, provided for each dose level administered, eg,

20 mcg, 30 mcg. The dilution procedure utilizes 2 saline infusion bags, the first is the dilution bag (a labelled 50 mL bag) and the second is the actual infusion bag (100 mL).

The protocol-specified doses in study IMCgp100-102 were intentionally determined before the study began to represent the maximum theoretical dose that could be prepared and administered based on the labelled fill volumes of the dilution bags (range of 54–64 mL). The Pharmacy Handling Instructions are authored using the lowest potential dilution bag volumes as the start volume and thus, the highest initial concentrations of tebentafusp at dilution step 1 to calculate doses. Setting the protocol-specified dose based on the maximum theoretical dose ensured that no patients received actual doses with tebentafusp quantities above the protocol-specified dose. Empirical data gathered during the dose escalation of the IMCgp100-102 study demonstrate that although there is a labelled range of bag volumes (54–64 mL per packaging), there exists a narrow distribution of the actual fill volumes at the first dilution step (generally 57–59 mL). Thus, the doses actually prepared and administered in the Phase I study (IMCgp100-102) were accurate and represented a lower point estimate than stated in the protocol.

Based on the 2-step dilution procedure used to prepare tebentafusp doses and considering the conservative approach to the variance in the fill range for the primary dilution bag, the protocol-specified doses for the higher dose cohorts in the IMCgp100-102 trial and the final RP2D were initially over-estimates of the actual administered dose. Based on the available empirical evidence of dilution bag fill volumes (dilution step 1), it is important to correct the over-estimate of the actual dose administered from 75 mcg to 68 mcg. The 68 mcg dose level is the most accurate within the range produced by the dilution procedure and is the RP2D. Based on the limited impact at the lower doses (20 mcg and 30 mcg doses), no change in these protocol-specified doses was warranted.

1.4.3 Tebentafusp Combination with Checkpoint Inhibition Study in Cutaneous Melanoma (IMCgp100-201)

Paired tumor samples obtained in patients with cutaneous melanoma in the FIH Phase I trial (IMCgp100-01) demonstrate a rapid and persistent influx of CD3+ T cells into the tumor within 1-2 days after the first dose of tebentafusp. This rapid influx is followed by the appearance of multiple checkpoint molecules in the T cells such as PD-L1 and lymphocyte activation gene-3 (LAG-3) along with FoxP3 (see Section 1.4.4). With the accumulation of negative influences in the tumor microenvironment routinely in patients treated with tebentafusp, it is hypothesized that combining T cell redirection with tebentafusp with checkpoint inhibition may lead to deeper and more sustained tumor responses, even in patients resistant to checkpoint inhibition. The IMCgp100-201 study is a randomized, open-label Phase Ib/II study of more frequent or escalating doses of tebentafusp as a monotherapy and 3 separate combinations: (1) tebentafusp with PD-L1 inhibition (durvalumab), (2) tebentafusp with CTLA4 inhibition (tremelimumab); and (3) the triple combination of tebentafusp with both durvalumab and tremelimumab. This study continues to enroll.

1.4.4 Pharmacokinetic and Pharmacodynamic Studies

1.4.4.1 Preliminary Tebentafusp Pharmacokinetics

PK data were assessed across the dose escalation cohorts of the weekly dosing regimen from dose levels ranging from 45 ng/kg to 900 ng/kg with the MTD identified as 600 ng/kg. Preliminary PK analysis of the Phase 1 studies (IMCgp100-01 and IMCgp100-102) indicated that maximal concentration was reached rapidly after the IV administration of tebentafusp. The elimination of tebentafusp was rapid following the IV infusion, with the majority of the administrated dose eliminated in the first 24 hours. The half-life of tebentafusp in serum was approximately 6–8 hours, suggesting that the drug is unlikely to accumulate with QW dosing. Despite the relatively short half-life in serum, clinical pharmacodynamic data of lymphocyte infiltration in the skin and tumor following dosing suggest multiple compartments may play a role in the distribution of tebentafusp, with pharmacodynamic activity observed at 1–2 days following dosing.

The preliminary assessment of PK from the clinical PK studies demonstrate that at the dose of 50 micrograms (mcg), the maximum observed concentration (C_{max}) was approximately 7800 pg/mL. The measured/observed C_{max} at this dose is only approximately 78% of theoretical C_{max} (approximately 10,000 pg/mL, assuming 5 L volume of distribution). The time of maximum concentration (T_{max}) ranged from a few minutes following administration to 1 hour. In general, nearly dose proportional exposures were observed as measured by C_{max} and the area under the curve. The rapid "clearance" of tebentafusp is likely attributed to target binding, where some of the preliminary evidence from both clinical PK and pharmacodynamic studies, as well as animal biodistribution studies demonstrate the potential that longer retention in sites of antigen expression (ie, tumor and skin) may occur despite the apparent rapid clearance in the peripheral circulation.

For detailed information regarding PK data of tebentafusp, refer to the most recent version of the tebentafusp Investigator's Brochure.

1.4.4.2 Tebentafusp Pharmacodynamic Studies

Cytokine analyses in the peripheral circulation combined with clinical findings in patients treated with weekly dosing in the FIH IMCgp100-01 study revealed rare cases of severe systemic cytokine release syndrome (CRS) with strong elevations of interleukin-6 (IL-6) and interleukin-10 (IL-10) post-first dose (Middleton, 2016). Rather, many patients had shown drug-induced, modest levels of 1 or more inflammatory cytokines (eg, IL-6, interferon-gamma [IFNγ], and tumor necrosis factor-alpha [TNFα]) as a consequence of on-target skin or tumor activity with consequential cytokine permeating into the periphery. The greatest increases observed in the periphery were in the levels of tissue chemoattractant chemokines (eg, C-X-C motif chemokine ligands, CXCL9 and CXCL10) that parallel the transient drop in peripheral circulating lymphocytes generally resolving by 48 hours after dosing and reaching pre-dose levels by Day 8.

Paired tumor tissue studies have demonstrated a strong influx of CD3+ lymphocytes immediately (within 48 hours) following the first dose of tebentafusp and expression of markers of cell death, such as cleaved caspase 3, suggesting that these CD3+ T cells infiltrating the tumor may have activity. Over the course of the first 4–6 weeks of treatment, studies have shown a distinct and

escalating expression of negative immune-modulatory molecules on the surface of these lymphocytes such as PD-L1, LAG-3, and FoxP3 (Middleton, 2015; Middleton, 2016).

2 RATIONALE

2.1 Study Rationale and Purpose

This is a randomized, open-label, Phase II clinical study of tebentafusp versus Investigator's Choice in HLA-A*0201 positive patients with previously untreated advanced UM. Two Phase I studies with tebentafusp that support the rationale for this Phase II study: (1) the FIH, Phase I study of weekly dosing in patients with advanced melanoma (IMCgp100-01), and (2) the Phase I study of the intra-patient escalation regimen in patients with advanced UM (IMCgp100-102). Please refer to Section 1.4 for the full summary of the clinical development of tebentafusp.

In the IMCgp100-01 FIH study, 2 key observations were made: (1) immune-related toxicities of T cell redirection (fever, rash, and hypotension) were observed and were generally limited to the first 2 weeks of dosing; and (2) preliminary anti-tumor activity in the setting of advanced UM was observed at doses higher than the identified RP2D with confirmed and durable PRs (identified RP2D-QW is 50 mcg). In a retrospective review of the tumor response data from these Phase I cohorts, objective responses in patients with higher degrees of tumor burden were generally noted at the higher absolute doses administered (approximately 48–81 mcg absolute doses). Such initial starting doses could not be achieved in the FIH Phase I study, due to the immune-related toxicity of tebentafusp in the initial weekly dose escalation trial at the first and/or second dose (C1D1 and/or C1D8). All DLTs in the weekly dose escalation study were observed at the first or second dose (Middleton, 2015; Middleton, 2016). To avoid the immune-related toxicity observed in the first 2 doses, a modified dosing regimen was implemented in the FIH Phase I study (IMCgp100-01, the intra-patient escalation regimen) where patients received the flat dose of 20 mcg at C1D1 and 30 mcg flat dose at C1D8 (where the infrequent occurrences of immune toxicity associated with hypotension were noted). Following this at C1D15 and beyond, patients received the previously identified RP2D-QW (weekly dosing) of 50 mcg. All patients treated with this regimen in the FIH Phase I study (n=7 total; 6 patients with UM) tolerated it well.

Based on these observations in the FIH Phase I study (IMCgp100-01), a second Phase I study of the intra-patient escalation regimen was conducted in patients with advanced UM (IMCgp100-102). In this study, patients received low, fixed doses of tebentafusp at C1D1 (20 mcg) and C1D8 (30 mcg) in the first 2 weeks of dosing, where the majority of immune-related toxicities related to profound T cell redirection have been observed. At C1D15, a dose escalation of tebentafusp was conducted with the goal of increasing the overall exposure to tebentafusp in the setting with limited immune-related toxicity associated with T cell redirection. The dose identified for Phase II testing in the RP2D-IE is 68 mcg, administered QW at C1D15 and beyond, following the low, fixed doses of 20 mcg at C1D1 and 30 mcg at C1D8 in all patients (see Section 1.4.2 for details of the identification study).

This randomized Phase II study is designed to evaluate the safety and efficacy of tebentafusp compared with Investigator's Choice in patients with advanced UM treated in the first-line setting with no prior systemic or liver-directed therapy administered in the advanced setting. Comparison of the tebentafusp safety and efficacy results in this Phase II study will be made with the Investigator's Choice arm as described in Section 9.

2.2 Rationale for Dose and Regimen Selection

2.2.1 Rationale for Tebentafusp Dose and Regimen

Several key observations in the FIH Phase I study of tebentafusp (IMCgp100-01) led to the intra-patient escalation regimen. First, the identified RP2D of the weekly dosing regimen at 50 mcg led to severe toxicity at the first or second dose in a cohort of patients with UM in the expansion cohort. The basis for the enhanced toxicity is the high expression level of the gp100 antigen in UM, profound lymphocyte trafficking into skin and tumor, as well as the extent of disease in these patients. From this observation, the intra-patient escalation regimen was tested with a low fixed dose at C1D1 (20 mcg) and C1D8 (30 mcg) followed by resumption of dosing at the RP2D of 50 mcg at C1D15 and beyond. This regimen was well tolerated in a subsequent cohort of patients with UM (n=6) and cutaneous (n=1) melanoma. A review of the efficacy data from this FIH Phase I study revealed that patients with more extensive disease had demonstrated PRs generally at doses higher than at the defined RP2D of 50 mcg, and specifically in UM the PR were observed at doses of 48–81 mcg. The Phase I of the intra-patient escalation regimen was initiated (IMCgp100-102) to avoid the infusion-related toxicity at Weeks 1 and 2 and to increase the exposure of tebentafusp closer to those doses where PR were observed in UM.

Emerging preclinical data (Section 1.3.1) suggest that the residence time of tebentafusp to the HLA-A*0201 allele is considerably longer resulting in enhanced effects compared to non-HLA-A*0201 alleles. This is borne out in the clinical data (Section 1.4.1), where patients expressing non-HLA-A*0201 alleles appear to have fewer T cell-mediated toxicities and no clinical responses have been observed. Given these preclinical and clinical data, enrollment is limited to patients expressing the HLA-A*0201 allele.

In study IMCgp100-102, patients with advanced UM were treated with the intra-patient escalation regimen (20 mcg at C1D1 and 30 mcg at C1D8) and the dose escalated at C1D15 and beyond. Following a conservative dose escalation (Cohort 1 at 54 mcg, Cohort 2 at 64 mcg, and escalating in increments of approximately 10 mcg). The dose level of 73 mcg was not tolerated due to elevations in hepatic transaminases with concurrent low-grade increase in bilirubin in 2 of the 4 treated patients. These events were reversible without administration of corticosteroids and all patients experiencing DLT remained on treatment. After dose reduction to 68 mcg, 6 patients were treated with no DLTs observed and no significant elevations of hepatic transaminases. A dose of 68 mcg was identified as the MTD, and was selected as the dose level identified for further study in the intra-patient escalation regimen (RP2D-IE). All patients in the current Phase II study randomized to Arm 1 (tebentafusp) will receive this regimen with low, fixed doses at C1D1 and C1D8 followed by the escalated dose of 68 mcg at C1D15 and beyond.

2.2.2 Rationale for the Investigator's Choice as Comparator

The group of agents approved for use in cutaneous melanoma, including immunotherapy with checkpoint inhibition and chemotherapy, have a limited role in the treatment of advanced UM where no agents are approved and no effective therapies have demonstrated a gain in survival

(Ramaiya, 2007; Augsberger, 2009; Khattak, 2013). Although immunotherapy with ipilimumab or PD-1 inhibition (nivolumab and pembrolizumab) have demonstrated strong survival benefits in patients with metastatic cutaneous melanoma, the early efficacy signals in UM appear limited with response rates reported as being similar to that of single-agent chemotherapy, approximately 0-5% (Buder, 2013; Maio, 2013; Luke, 2013; Carvajal, 2014; Ramaiya, 2007). A substantial therapeutic impact on overall survival (OS), with either class of agent (immunotherapy or chemotherapy) has yet to be demonstrated in clinical studies in advanced UM. Due to the similar clinical efficacy with chemotherapy and immunotherapy (eg, CTLA4 inhibition with ipilimumab or PD-1 inhibition with pembrolizumab) in the setting of advanced UM, the comparator of choice for this randomized study with tebentafusp is an Investigator's Choice treatment arm with 3 options (dacarbazine, ipilimumab, or pembrolizumab) at the approved doses for treatment of metastatic melanoma.

2.3 Rationale for Randomized Study Design

This is a Phase II study comparing the anti-tumor activity of tebentafusp to Investigator's Choice in patients with advanced UM. The primary endpoint of the study is OS. It is critical to note that no therapy has proven a survival benefit in the setting of advanced UM. The goal of the study is to demonstrate a survival benefit over standard-of-care chemotherapy or immunotherapy in this disease setting. Additionally, surrogate endpoints of ORR and PFS have been shown in other tumor types to underestimate the OS benefit of immunotherapeutic agents including both checkpoint inhibitors and vaccines (Borghaei, 2015; Motzer, 2015; Herbst, 2016). An unbalanced randomization ratio of 2:1 will be implemented. The randomization in this study is intended to prevent bias in the choice of treatment assignment. Given the distinct toxicity patterns at the first infusion of the agents being studied (tebentafusp versus Investigator's Choice), the open-label design was chosen because the treatment assignment cannot be blinded.

2.4 Rationale of Protocol-Defined Rash as Part of the Primary Objective

Among the most frequent adverse reactions observed with tebentafusp are skin toxicities, most commonly rash and pruritus. Typically, rashes are mild-to-moderate in severity and abate without systemic steroid intervention in most cases. Skin toxicity is likely related to the tebentafusp mechanism of action (induction of anti-gp100 T-cell responses) given that melanocytes are known to express gp100.

An interim analysis of Study IMCgp100-102 demonstrated that a rash, an early and on-target pharmacodynamic biomarker, is strongly associated with a clinical benefit across all efficacy endpoints including tumor shrinkage and PFS (both per an independent radiology committee [IRC]) and OS. These new data confirmed that the association between a rash and tebentafusp activity, originally observed in a predominantly cutaneous melanoma (CM) population (Study IMCgp100-01), can now be extended to the uveal melanoma subtype, UM (Study IMCgp100-102).

These results show:

1. The UM population in Study IMCgp100-102 represents a clinical unmet need, since all available options have been exhausted (including immune checkpoint inhibitors which have never shown an OS benefit);
2. The 1-year OS rate (95% CI) in Study IMCgp100-102 of 61% (48%, 71%) compares favorably to the historical OS rate of 43% (40%, 47%) in the recent Princess Margaret Uveal Melanoma Meta-Analysis (PUMMA) study (Khoja, 2019). Although IMCgp100-102 is a single-arm trial, there has been no change in the OS for UM over 4 decades (regardless of therapy), and the baseline covariates of IMCgp100-102 were similar or worse than the meta-analysis by Khoja et al (2019). Furthermore, a rash is unlikely to be a good prognostic variable since the majority of these patients cannot have a good prognostic phenotype given all of the known baseline covariates were similar to or worse than PUMMA. If a rash was a good prognostic marker, then the rash-negative patients would have worse survival than the PUMMA population which is not the case (see #4 below);
3. There is a strong association between all efficacy endpoints (tumor shrinkage and PFS per the IRC and OS) and the on-target and expected AE of a rash, consistent with mechanism of action (Immunocore data on file). A rash appears on the same day of or within the following few days after dosing, thus limiting the potential for immortal-time bias;
4. A multivariate analysis confirmed that a rash has a very strong association with OS (p=0.0006) and is independent of other key baseline covariates (Immunocore data on file). The estimated 1-year OS rate in patients with a rash was 77% compared to 35% in patients without a rash and ~40% in the meta-analysis; and
5. The strong association between the efficacy and an early onset rash has been observed in 2 independent trials that enrolled 2 distinct melanoma populations (predominately CM in Study IMCgp100-01 and purely UM in Study IMCgp100-102).

In summary, tebentafusp monotherapy is active in previously treated UM and an on-target biomarker (rash) observed on the same day of or within the following few days after dosing can predict which UM patients are likely to have tumor shrinkage and longer PFS and OS. We aim to confirm these analyses and associations in the randomized Study IMCgp100-202 based on one of the dual primary objectives. Specifically, we propose to compare the OS among patients randomized to the tebentafusp monotherapy who develop a rash within the first week of treatment (i.e., a subgroup who may potentially benefit the most from tebentafusp) versus all patients randomized to the Investigator's Choice monotherapy. This will be in addition to the other primary objective to compare the OS in all patients randomized to the tebentafusp monotherapy versus all patients randomized to the Investigator's Choice monotherapy (ITT Popluation).

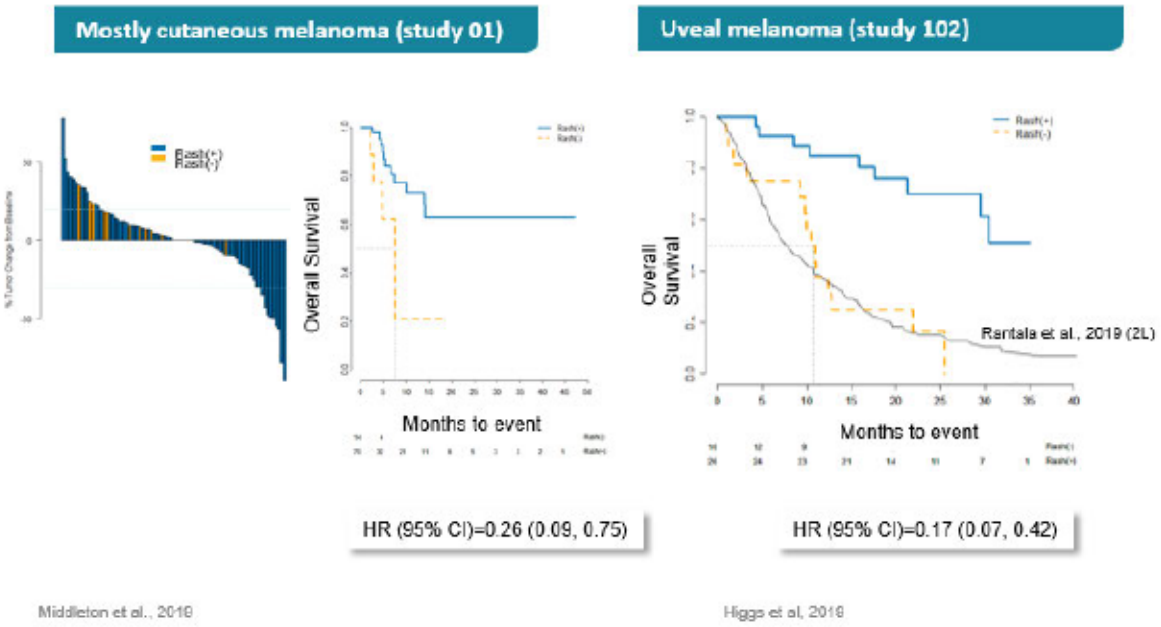

Figure 2-1 Rash Associated with Efficacy

2.5 Rationale for Stratification Factor

Recent evidence suggests that the lactate dehydrogenase (LDH) level at the time of diagnosis has a significant impact on prognosis in metastatic UM. In the PUMMA study, a multivariate analysis of potential prognostic factors identified LDH above the upper limit of normal (ULN) as associated with shortened OS (multivariate hazard ratio [HR] = 1.88, $p < 0.0001$) (Nicholas, 2016; Khoja, 2019). Similar findings were obtained in an independent UM dataset, confirming that an LDH level above the ULN is associated with shortened OS (multivariate HR = 1.6; p=0.014; Valpione, 2015).

With the strong prognostic factors of LDH level, and the interim analyses proposed in the trial, stratified randomization will protect imbalance in the 2 arms for overall prognosis. Randomization into this study will be stratified by LDH level, with the 2 strata of LDH above or below the ULN (measured centrally). Given the size of the trial and early planned interim analyses, this stratification is aimed to protect type I error by balancing the enrollment of patients with a poorer prognosis across the arms.

2.6 Rationale for Treatment Beyond Initial Disease Progression in Select Settings

There is accumulating evidence in the field of immune-oncology that some patients treated with immunotherapy agents, such as tebentafusp, may develop initial PD of the tumor, as evidenced on computed tomography (CT) or magnetic resonance imaging (MRI), before demonstrating meaningful clinical benefit from the treatment with disease stabilization or subsequent objective

response after the initial PD is noted (Hodi, 2016). Such cases were noted in the Phase I development of tebentafusp (Middleton, 2015; Middleton, 2016). In light of these data, patients receiving tebentafusp, ipilimumab, or pembrolizumab who demonstrate initial PD by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 may be able to continue treatment beyond the initial PD. See Section 6.11.1 for details regarding criteria for treatment with tebentafusp beyond initial PD by RECIST v1.1.

2.7 Overall Benefit-risk Assessment

A significant degree of unmet need exists in the setting of advanced UM. Compared to standard treatments utilized in cutaneous melanoma, no treatments have consistently demonstrated a survival benefit in clinical studies, including dacarbazine and immunotherapy with checkpoint inhibition (eg, ipilimumab or pembrolizumab included as Investigator's Choice comparators). Tebentafusp has an acceptable tolerability profile, with generally mild-to-moderate toxicity beyond the first 2 doses where manageable immune-based toxicities have been observed (Middleton, 2016). This study is designed to minimize potential risks through intensive patient monitoring and frequent safety assessments based upon available early phase clinical safety data for tebentafusp. The preliminary, robust clinical activity of tebentafusp in the setting of advanced UM, combined with the lack of any therapies demonstrating a survival benefit in this indication supports the further development of tebentafusp in patients with previously untreated, advanced UM.

3 STUDY DESIGN

3.1 Description of Study Design

This is an open-label, randomized, multi-center Phase II study of tebentafusp versus Investigator's Choice (dacarbazine, ipilimumab, or pembrolizumab) in adult (>18 years) HLA-A*0201 positive patients with advanced UM previously untreated in the advanced or metastatic setting. Prior adjuvant or neoadjuvant therapy is allowed, provided all prior therapy is administered in the localized, curative setting. Patients will be randomized 2:1 (tebentafusp:Investigator's Choice) and randomization stratified by LDH status (based on central laboratory assessment performed during the screening period) to receive either tebentafusp administered in the intra-patient escalation dosing regimen or Investigator's Choice (Figure 3-1). One cycle of treatment in this study is defined as 3 weeks (21-day cycles). Patients will be treated with one of the following regimens:

- **Arm 1 (tebentafusp):** All patients randomized to Arm 1 will receive tebentafusp following the intra-patient escalation regimen. On C1D1, patients receive 20 mcg (flat dose); on C1D8, patients receive 30 mcg (flat dose); and beginning with C1D15, patients will receive the escalated dose of 68 mcg. Due to the possible cytokine release-associated toxicity with tebentafusp, patients will be monitored overnight as an inpatient following the weekly doses at C1D1, C1D8, and C1D15

- **Arm 2 (Investigator's Choice):** All patients randomized to Arm 2 will receive Investigator's Choice of 1 of 3 options: dacarbazine in the standard dosing regimen in UM of 1000 mg/m^2 given on Day 1 of each 21-day cycle; ipilimumab in the approved dosing regimen for unresectable or metastatic melanoma of 3 mg/kg given on Day 1 of each 21-day cycle for a maximum of 4 doses; or pembrolizumab in the dosing regimen of 2 mg/kg, up to a maximum of 200 mg or 200 mg fixed dose administered IV where approved locally given on Day 1 of each 21-day cycle. The preferred Investigator's Choice agent will be selected prior to randomization. No overnight monitoring will be required in Arm 2.

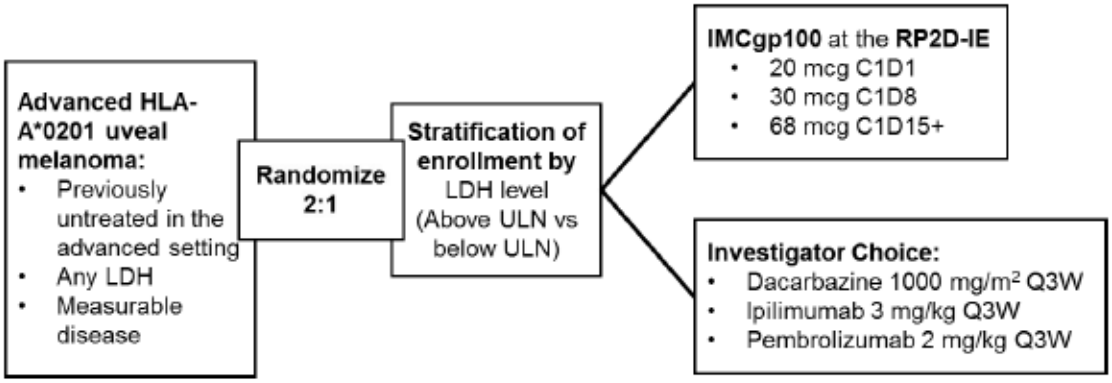

Figure 3-1 Study Design

C#D# = Cycle # Day #; HLA-A*0201 = human leukocyte antigen-A*0201 (allele genotype); LDH = lactate dehydrogenase; RP2D-IE = recommended Phase II dose intra-patient escalation regimen; Q3W = every 3 weeks; ULN = upper limit of normal.

3.1.1 Intra-patient Escalation Regimen of Tebentafusp

Tebentafusp will be administered according to the intra-patient escalation regimen as defined by the Phase I study (IMCgp100-102 in patients with advanced UM, please refer to Section 1.4.2 for a description of the study and results; see Section 2.2.1). The intra-patient escalation occurs at the third weekly dose on C1D15. According to this regimen, all patients in the trial will receive 2 weekly doses of tebentafusp at a dose level below the MTD (20 mcg at Day 1 and 30 mcg at Day 8) and then an escalated dose is administered at C1D15 and beyond. The dose at C1D15 and beyond will remain fixed at 68 mcg (RP2D-IE) and will only change in the setting of a dose adjustment for toxicity. The goal of this dosing regimen is to increase exposure to tebentafusp at the time beyond the initial observation of T cell-mediated toxicity, generally limited to the first 2 weeks of dosing at C1D1 and C1D8. For details of the intra-patient dose escalation regimen schematic, see Figure 3-2.

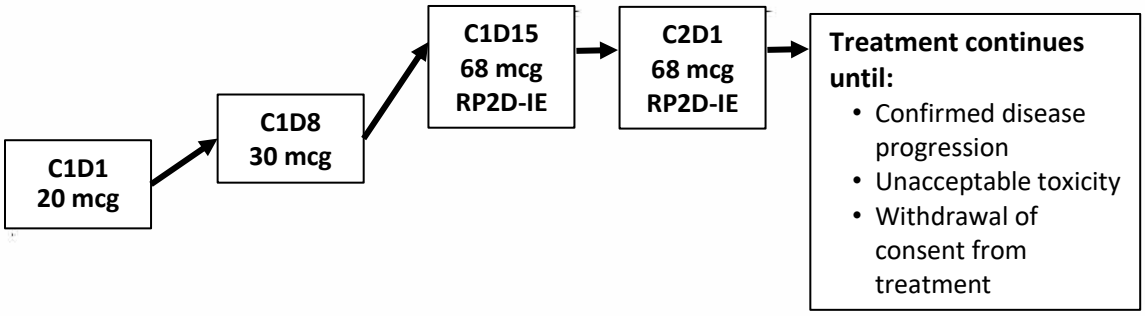

Figure 3-2 Intra-patient Escalation Regimen of Tebentafusp

C#D# = Cycle # Day #; RP2D-IE = recommended Phase II dose intra-patient escalation regimen.

Patients treated with the intra-patient escalation regimen receive low, fixed doses at C1D1 and C1D8 to minimize the risk of severe immune-related toxicity, and beginning with C1D15 patients receive the escalated fixed dose to enhance exposure to tebentafusp. The dose will not change beyond C1D15 except for dose adjustments for toxicity.

3.1.2 Replacement of Patients

No replacement of patients enrolled via Interactive Response Technology (IRT) will be done in this study regardless of treatment status.

3.2 Patient Population

The trial will enroll HLA-A*0201 positive patients with a diagnosis of advanced UM, defined as histologically confirmed diagnosis of UM and metastatic, stage IV disease at study entry. Patients are eligible if there is no prior systemic therapy or local (ie, liver-directed) therapy administered in the metastatic or advanced setting. Neoadjuvant and/or adjuvant therapy are acceptable, provided these treatments are administered in the setting of local ocular disease with a curative intent. Patients may not be re-treated with an Investigator's Choice therapy that was administered as adjuvant or neoadjuvant treatment.

3.3 Definition of Study Periods

This study will consist of 4 periods: Pre-screening, Screening, Treatment, and the Follow-up periods.

The **pre-screening period** will begin once a patient has signed the Pre-screening informed consent form (ICF) and concludes with the HLA testing results, indicating HLA-A*0201 positive or negative for HLA-A*0201. Testing for the HLA status will be completed centrally. Local testing for the HLA-A2 status is not acceptable for study enrollment. The central blood test will determine whether the patient is HLA-A*0201 positive (eligible) or HLA-A*0201 negative (not eligible). Patients will either be designated as pre-screening failure (negative test result or if positive and

the patient chooses not to enter the study), or eligible for the study and the patient can proceed and sign the Main Study ICF.

The **screening period** will begin once a patient has signed the Main Study ICF and concludes with either a screen failure decision or initiation of study dosing on C1D1. Patients should sign the Main Study ICF once the HLA status is known via central laboratory testing (see pre-screening period above). Patients who have prior positive HLA-A*0201 results (eg, per local testing) may proceed with signing the Main Study ICF and initiating Screening while completing confirmatory central HLA testing. Patients may not be randomized or treated until required confirmation of HLA-laboratory testing. During the screening period, patients are evaluated against the study inclusion and exclusion criteria (see Section 5) and all screening procedures and observations are performed including assessments of the health-related quality of life (HRQoL) outcomes in the study. The screening window for all procedures will be 21 days, other than imaging studies, which will have a 28-day window. Patients will be enrolled via the IRT. Patients who fail to meet the inclusion or the exclusion criteria may be rescreened if clinically appropriate.

If a patient is rescreened, pre-screening (HLA determination) will not be repeated (provided previously determined centrally).

The **treatment period** will begin with the first treatment in the first cycle with C1D1. For the purpose of treatment scheduling, in this study a cycle consists of 21 days or 3 weeks. The treatment period consists of the time from C1D1 until the end of study treatment. Study treatment will be continued until the patient develops unequivocal PD, develops unacceptable treatment-related toxicity, or withdraws consent for further treatment or additional protocol-specified reasons occur for discontinuation of study treatment (see Section 6.11). As soon as a patient discontinues study treatment, an end of treatment (EOT) visit should be scheduled, unless the EOT assessments described in Table 7-1 can be completed at the time it was determined to discontinue study treatment.

The **Follow-Up Periods** include:

- The **90-day Safety Follow-up Period** consists of the time from the last dose of study medication for a period of 90 days. Safety observations during this 90-day Follow-up Period are outlined in Section 7.2.4.1 and Table 7-1 include reporting of all AEs and all serious adverse events (SAEs) in the same manner as the treatment period.

- The **Disease Progression Follow-up Period** is defined for all patients who discontinue for reasons other than death, PD per RECIST v1.1 or further PD warranting treatment discontinuation, as outlined below, lost to follow-up, withdrawal of consent, or study termination.

    - All patients who discontinue treatment for reasons other than PD per RECIST v1.1 will be followed with imaging until evidence of PD per RECIST v1.1 or until the start of alternate anti-neoplastic therapy (see Section 7.2.4.2).

- For patients who consent to and continue treatment beyond initial PD per RECIST v1.1, imaging should continue until permanent treatment discontinuation.
- If patients choose not to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient has had PD.
- Patients who discontinue treatment for reasons of PD by RECIST v1.1 or further PD warranting treatment discontinuation will not enter the Disease Progression Follow-up Period.

- Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period. The **Survival Follow-up Period** will initiate after either the 90-day Follow-up Period (in patients who have discontinued for PD) or after the Disease Progression Follow-up Period (for patients discontinuing study treatment prior to PD) and continue until death. As possible, all patients will be followed for survival until the end of the study is reached. Follow-up assessments as noted for HRQoL and subsequent cancer therapy and response will be collected.

3.4 End of Treatment and Post-treatment Follow-up

In this study, OS is the primary endpoint of the study. Post-treatment study follow-up is of critical importance and is essential for preserving both patient safety, as well as the integrity of the study. Patients who discontinue study treatment for any reason must continue to be followed for collection of the final outcome measure of survival as required and in conjunction with the study assessments (Section 7.1) or the conclusion of the study.

3.4.1 Treatment Discontinuation

In all patients in this study, tebentafusp or Investigator's Choice will be administered IV according to the defined regimen (please refer to Section 6.1 for treatment schedules). Treatment with tebentafusp, dacarbazine, and pembrolizumab will be administered as described until the patient experiences unacceptable toxicity or PD per RECIST v1.1. Patients will receive ipilimumab for a maximum of 4 doses unless unacceptable toxicity or PD occurs prior to completion of the 4 doses of treatment. Each patient's disease will be assessed for efficacy using RECIST v1.1. Patients randomized to Arm 2 (Investigator's Choice) receiving dacarbazine will discontinue treatment at the time of PD by RECIST v1.1 assessment. Patients who continue treatment beyond PD by RECIST v1.1 must sign an additional informed consent and must end treatment if any of the reasons in Section 6.11.1 are met. See Section 6.11 for a full listing of reasons for discontinuation of study treatment.

Please refer to Section 7.3.1 for details regarding imaging assessment of PD for purposes of treatment discontinuation.

3.4.2 Study Discontinuation

Patients who discontinue study treatment will move into follow-up (see follow-up periods above). Patients who discontinue after randomization without receiving any study treatment will be followed for the OS endpoint only (Survival Follow-up period). All patients will be followed for the OS endpoint until: (1) death, (2) lost to follow-up, or (3) withdrawal of consent to survival follow-up. Patients who are lost to follow-up should have all reasonable efforts made to locate the patient and report ongoing status. If after all attempts have been made to contact the patient, then the last known date of alive status as determined by the investigator should be documented in the patient's medical record and reported in the electronic case report form (eCRF).

Details of anti-cancer therapies administered beyond this study treatment will be collected in the Survival Follow-up Period.

The details of the criteria for discontinuation from the study are discussed in Section 6.11.

Note: Survival calls will be made in the 2 weeks following the date of data cutoff (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and/or local treating oncologist, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.5 Definition of End of Study

The end of the study will be the last visit of the last patient undergoing the study. All patients will have completed follow-up for OS by the final DCO. Following the primary analysis, additional survival follow-up may continue for up to 3 additional years.

An individual patient may end participation in the study for reasons of death, lost to follow-up, or withdrawal of consent or the study end is reached (as described above) or the study is terminated early by the Sponsor.

3.6 Early Study Termination

The study can be terminated at any time for any reason by the Sponsor, including, but not limited to, new scientific evidence resulting in an unfavorable risk:benefit ratio and upon request of any regulatory body. Should this be necessary, any ongoing patient should be seen as soon as possible for the EOT visit and the assessments should be performed as described in Table 7-1 for the EOT visit. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. Under guidance of the Sponsor, the investigator will be responsible for informing the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) of the termination of the trial.

3.7 Post-study Access to Therapy

At the end of the study as defined in Section 3.5 and Section 3.6, patients who continue to demonstrate clinical benefit with tebentafusp may be eligible to continue to receive study treatment up to a maximum of 2 years from their first dose via one of the following mechanisms: (1) a rollover study (if available and the patient is eligible); (2) commercial supply (if approved and available in the given country); or (3) another mechanism at the discretion of the Sponsor.

4 STUDY OBJECTIVES AND ENDPOINTS

Table 4-1 Objectives and Related Endpoints

Objective	Endpoint
Primary	
The dual primary objectives are: 1) To compare the OS in all patients randomized to the tebentafusp monotherapy versus all patients randomized to the Investigator's Choice monotherapy 2) To compare the OS in all patients randomized to the tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomized to the Investigator's Choice monotherapy Both objectives relate to HLA-A*0201 positive patients with advanced UM with no prior treatment in the metastatic setting.	OS, defined as the time from randomization until death by any cause
Secondary	
To characterize the safety and tolerability of single-agent tebentafusp in the intra-patient dose escalation regimen relative to Investigator's Choice	Safety and tolerability: Incidence and severity of AEs and SAEs; changes in safety laboratory parameters, vital signs, and electrocardiogram (QTcF); dose interruptions, reductions, discontinuations, and dose intensity of all administered agents
To characterize the PK profile of single-agent tebentafusp in the intra-patient dose escalation regimen	Serum PK parameters (eg, C_{max}, C_{min}, C_{trough})
To assess the anti-tumor efficacy of tebentafusp versus Investigator's Choice with the parameters of PFS, BOR, DOR, time to response, and DCR using RECIST v1.1	• PFS • BOR • DOR • Time to response DCR (defined as CR or PR, or SD ≥ 24 weeks)
To evaluate the treatment and disease impact to HRQoL in patients treated with tebentafusp versus patients treated with Investigator's Choice. HRQoL will be assessed by the EQ-5D,5L and the EORTC QLQ-C30	EQ-5D,5L and EORTC QLQ-C30 change from Baseline over time and between treatment strategies
To evaluate the incidence of anti-tebentafusp antibody formation following multiple infusions of tebentafusp in the intra-patient dose escalation regimen	Assessments of anti-tebentafusp antibody formation

Table 4-1 Objectives and Related Endpoints

Objective	Endpoint
Exploratory	
To assess potential predictors of efficacy of tebentafusp	Correlation of the expression of T cell infiltration, expression of gp100, HLA-DR, PD-L1, tumoral lymphocyte activation status, and myeloid-derived suppressor cell infiltration and other immune markers evaluated in tumor biopsies with anti-tumor activity
To assess potential pharmacodynamic changes in peripheral cytokine levels observed with tebentafusp and Investigator's Choice	Changes in serum cytokine, chemokines (eg, CXCL9, CXCL10, HGF, IL-1Rα, and MCP-1), or other analytes in response to treatment
To assess potential clinical benefit after an initial assessment of progressive disease based on RECIST v1.1	Duration of treatment and response for patients treated beyond RECIST v1.1 PD
To assess time to PFS2 for tebentafusp and Investigator's Choice	PFS2, defined as the time from the date of randomization to the subsequent PD following the initial RECIST v1.1 PD, or death
To assess health- and treatment-related medical resource utilization associated with the advanced UM disease pathway	Hospitalizations, concomitant medication use, medical procedures, and other measures of healthcare utilization

AE = adverse event; BOR = best overall response; C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; CR = complete response; Ctrough = drug concentration at X days after dosing; CXCL# = C-X-C motif chemokine ligand #; DCR = disease control rate; DOR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D,5L = EuroQoL-5 Dimensions – 5-levels of disease severity scale; gp100 = glycoprotein 100; HGF = hepatocyte growth factor; HLA-A*0201 = human leukocyte antigen-A*0201; HLA-DR = human leukocyte antigen-DR isotype; HRQoL= health-related quality of life; IL-1Rα = interleukin 1 receptor alpha; MCP-1 = monocyte chemoattractant protein-1; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression free survival; PFS2 = second disease progression; PK = pharmacokinetic; PR = partial response; QLQ-C30 = Quality of life Questionnaire-Core 30; QTcF = QT interval corrected by Fridericia's formula; RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; SD = stable disease; UM = uveal melanoma.

5 POPULATION SELECTION CRITERIA

5.1 Patient Population

This study will be conducted in patients with metastatic UM with no prior systemic therapy and no local (eg, liver-directed) therapy in the metastatic and advanced settings (first-line metastatic patients). Prior adjuvant or neoadjuvant therapy is permitted if administered in the curative setting in patients with localized disease. Given the mechanism of action of tebentafusp, the study is limited to patients with the HLA-A*0201 positive subtype.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion Criteria

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Male or female patients age ≥ 18 years of age at the time of informed consent
2. Ability to provide and understand written informed consent prior to any study procedures
3. Histologically or cytologically confirmed metastatic UM
4. Must meet the following criteria related to prior treatment:
    - No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy
    - No prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization
    - Prior surgical resection of oligometastatic disease is allowed
    - Prior neoadjuvant or adjuvant therapy is allowed provided administered in the curative setting in patients with localized disease. Patients may not be re-treated with an Investigator's Choice therapy that was administered as adjuvant or neo-adjuvant treatment. Additionally, patients who have received nivolumab as prior adjuvant/neoadjuvant treatment should not receive pembrolizumab as Investigator's Choice therapy.
5. HLA-A*0201 positive by central assay
6. Life expectancy of > 3 months as estimated by the investigator
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 at Screening

8. Patients have measurable disease or non-measurable disease according to RECIST v.1.1

9. All other relevant medical conditions must be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug

5.3 Exclusion Criteria

Patients eligible for this study must not meet any of the following criteria:

1. Patient with any out-of-range laboratory values defined as:

   - Serum creatinine > 1.5 × ULN and/or creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 50 mL/minute
   - Total bilirubin > 1.5 × ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN
   - Alanine aminotransferase > 3 × ULN
   - Aspartate aminotransferase > 3 × ULN
   - Absolute neutrophil count < 1.0×10^9/L
   - Absolute lymphocyte count < 0.5×10^9/L
   - Platelet count < 75×10^9/L
   - Hemoglobin < 8 g/dL

2. History of severe hypersensitivity reactions (eg, anaphylaxis) to other biologic drugs or monoclonal antibodies

3. Clinically significant cardiac disease or impaired cardiac function, including any of the following:

   - Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association grade ≥ 2), uncontrolled hypertension, or clinically significant arrhythmia currently requiring medical treatment
   - QTcF > 470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome. NOTE: If the initial automated QTcF interval is > 470 msec at screening, for the purpose of determining eligibility, the mean QTcF, based on at least 3 ECGs obtained over a brief time interval (ie, within 30 minutes), should be manually determined by a medically qualified person.

- Acute myocardial infarction or unstable angina pectoris < 6 months prior to Screening

4. Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to study Day 1. Patients with brain metastases are eligible if lesions have been treated with localized therapy and there is no evidence of progression for at least 4 weeks by MRI prior to the first dose of study drug

5. Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy at least 1 week prior to the first dose of study drug

6. Known history of human immunodeficiency virus (HIV) infection. Testing for HIV status is not necessary unless clinically indicated

7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection

8. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type

9. Any medical condition that would, in the investigator's or Sponsor's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results

10. Patients receiving systemic steroid therapy or any other immunosuppressive medication at any dose level, as these may interfere with the mechanism of action of study treatment. Local steroid therapies (eg, otic, ophthalmic, intra-articular or inhaled medications) are acceptable

11. History of adrenal insufficiency

12. History of interstitial lung disease

13. History of pneumonitis that required corticosteroid treatment or current pneumonitis

14. History of colitis or inflammatory bowel disease

15. Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumor biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary)

16. Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass

17. Use of hematopoietic colony-stimulating growth factors (eg, G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to start of study drug. An erythroid-stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is not red blood cell transfusion dependent

18. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation)

19. Women of childbearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during study treatment (defined in Section 6.7), and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Highly effective methods of contraception are described in Section 6.7.

20. Male patients must be surgically sterile or use double barrier contraception methods from enrollment through treatment and for 6 months following administration of the last dose of study drug

21. Patients who are in an institution due to official or judicial order.

22. Patients who are related to the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study.

23. Contraindication for treatment with Investigator's Choice alternatives (dacarbazine, ipilimumab and pembrolizumab) as per applicable labelling. Patient may have a contraindication to 1 or 2 of the choices if he/she is a candidate for dosing with at least 1 Investigator's Choice and meets all other study eligibility criteria.

6 STUDY TREATMENTS AND ADMINISTRATION

6.1 Treatment Schedules

For this study, the investigational study drug refers to tebentafusp. Investigational study drug will be supplied by the Sponsor, Immunocore. Investigator's Choice study drug may be obtained by the investigational sites in certain countries as local commercial product, which may be available as a different potency/package size than listed in Table 6-1, if local regulations allow this. Locally sourced marketed product utilized for this study should be stored in accordance with the package insert, summary of product characteristics (SPC), or equivalent document.

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the dosage administration record in the eCRF.

Table 6-1 Dose and Treatment Schedule

Study Treatments	Pharmaceutical Form and Route of Administration	Potency and Packaging	Dose	Frequency and/or Regimen
Tebentafusp	Concentrate for solution for infusion (single use vials)	0.5 mg/mL or 0.2 mg/mL	20 mcg C1D1; 30 mcg C1D8; 68 mcg C1D15 and subsequent doses	Every week: Days 1, 8, and 15 of 21-day cycle
Dacarbazine[a]	Powder for intravenous infusion	200 mg/vial 1000 mg/vial	1000 mg/m^2 administered intravenous	Every 3 weeks: Day 1 of every 21-day cycle
Ipilimumab (YERVOY)[a]	Liquid for intravenous infusion	5 mg/mL solution supplied in: 50 mg/10 mL vial 200 mg/40 mL vial	3 mg/kg administered intravenous	Every 3 weeks for a total of 4 doses: Day 1 of every 21-day cycle
Pembrolizumab (KEYTRUDA)[a]	Lyophilized powder	Lyophilized powder: 50 mg/vial Liquid concentrate: 100 mg/4 mL vial	2 mg/kg up to a maximum of 200 mg administered intravenously Or 200 mg fixed dose administered intravenously where approved locally[b]	Every 3 weeks: Day 1 of every 21-day cycle

a. May be obtained by the investigational sites in certain countries as local commercial product, which may be available as a different potency/package size than listed above, if local regulations allow this.
b. Patients enrolled and receiving pembrolizumab on Investigator's Choice arm may switch from weight-based to flat dosing where locally approved.

For all study medication administration and protocol-specified inpatient hospitalizations, a physician must be present at the site or immediately available to respond to emergencies during all administrations of all study medications. Critical care and resuscitation facilities should be immediately available.

6.2 Tebentafusp Preparation and Administration

Tebentafusp is available in 2 formulations which have different concentrations as follows: 0.5 mg/mL and 0.2 mg/mL. Following dilution, the target dose of tebentafusp delivered is approximately the same regardless of which formulation is used.

Each vial is designed for a single use only and is not to be used to treat more than 1 patient for more than 1 dose.

6.2.1 Tebentafusp 0.5 mg/mL Drug Product

Tebentafusp 0.5 mg/mL drug product will be provided as a sterile, frozen solution in glass vials.

6.2.2 Tebentafusp 0.2 mg/mL Drug Product

Tebentafusp 0.2 mg/mL drug product will be provided as a sterile, refrigerated solution in glass vials.

Patients will begin treatment on either the 0.5 mg/mL or 0.2 mg/mL formulation. After receiving at least 2 months of tebentafusp therapy, patients at a given site may be allowed to switch to the alternative formulation if it is available at the study site. Whenever such a change is implemented at a site, all patients participating in this study and receiving tebentafusp at a given site should switch over to the same formulation (ie, minimize the situation where multiple patients in this study at a given site are receiving 2 different formulations of tebentafusp).

Dispensing, Dose Preparation, and Administration (both formulations)

Full drug accountability for tebentafusp is required in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice guidelines. Additional details including receipt of study products, storage, and management of temperature excursions are provided in the Study Pharmacy Manual.

Both formulations will be supplied as concentrate for solution for infusion and require dilution prior to administration. However, the dose preparation method is different for each formulation and so caution MUST be exercised when dispensing and preparing doses. The target duration of administration of tebentafusp will be 15–20 minutes. Detailed dose preparation and administration instructions are provided in the Study Pharmacy Manual and/or on the relevant Pharmacy Handling Instructions.

6.3 Tebentafusp Intra-patient Escalation Regimen

Patients randomized to Arm 1 will receive treatment with single-agent tebentafusp on C1D1 and C1D8 at 20 mcg and 30 mcg per week, respectively. The majority of moderate-to-severe toxicity associated with tebentafusp in the FIH study was observed at these 2 dose time points and included hypotension, rash, pruritus, fever, and chills (please refer to Section 1.4 for a full discussion of the safety data with tebentafusp). After this initial dosing period, beginning at C1D15 and beyond, patients will receive the escalated dose of 68 mcg identified in study IMCgp100-102. This escalated dose administered at C1D15 will be the dose used for the remainder of the treatment period unless dose reduction is implemented for toxicity. Beginning with C1D8, tebentafusp will be administered on the scheduled day (± 2 days), and consecutive infusions of tebentafusp must be administered at least 5 days apart.

In this intra-patient escalation regimen, all patients will require overnight hospitalization and a minimum of pre-dose and Q4-hour vital signs monitoring after the first administration of tebentafusp (C1D1), after the second administration (C1D8), and after the escalated dose of tebentafusp on C1D15 is administered. For the first 3 administrations of tebentafusp, patients should be monitored for at least 16 hours after dosing. "Inpatient hospitalization" refers to a facility with fully functional resuscitation facilities, 24-hour monitoring, and physician availability. See Section 7.3.3.2 for additional details on vital signs monitoring.

Inpatient monitoring at C2D1 will be determined by the toxicity observed in the C1D1–C1D15 doses as follows:

1. If the escalated dose at C1D15, administered as an inpatient, does not raise safety concerns (and the patient does not experience an adverse reaction involving hypotension of grade ≥ 2), the subsequent dose at C2D1 and all subsequent doses can be administered on an outpatient basis.

2. If the patient experiences hypotension requiring any medical intervention (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade ≥ 2) at C1D15, then the C2D1 dose should be administered with inpatient monitoring, similar to C1D1–C1D15. If the patient does not experience hypotension requiring medical intervention at the C2D1 dose administered as an inpatient, then all subsequent doses can be administered on an outpatient basis.

3. Hospitalization at other days (eg, Cycle 2 and beyond) is determined at the discretion of the principal investigator based on the patient's history and tolerance for the initial doses of the study medication with the exception of patients experiencing a treatment delay (please refer to bullet 4 below).

4. Patients experiencing a break or delay in treatment for any reason of more than 2 weeks AND with a history of a grade 3 or 4 event of hypotension with tebentafusp dosing during the first weeks of treatment will be monitored as an inpatient for the dose subsequent to

the break in dosing, regardless of the timing of the break in dosing, with vital signs monitored at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.

Antihypertensive drugs are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies and ImmTACs, the investigators should consider reducing or not administering antihypertensives for 24 hours before and after the tebentafusp administration during at least the first 3 weeks of treatment. Appropriate management of patients, especially those with more severe hypertension, receiving medications that may cause rebound hypertension when abruptly discontinued or those who are on multiple blood pressure medications should be discussed with a cardiology consultant and the Sponsor's Medical Monitor.

In addition, due to the risk of hypotension, IV fluids may be administered prior to tebentafusp administration and, if given, IV fluids will be recorded as a concomitant medication in the eCRF. The administration of IV fluids should be guided by clinical evaluation and the volume status of the patient. Pruritus is a common AE with tebentafusp, so premedication with an antihistamine may be considered. See Table 6-3 for further recommendations regarding treatment of skin toxicity. If a patient experiences an infusion reaction, he/she may receive premedication on subsequent dosing days after consultation with the Sponsor's Medical Monitor. Pre-medications should include, but are not limited to, paracetamol/acetaminophen and an antihistamine. Corticosteroid premedication should be avoided; corticosteroids should only be considered if the paracetamol/acetaminophen and antihistamine combination is not effective and only after consultation with the Sponsor's Medical Monitor.

Acute allergic reactions should be treated as needed using institutional guidelines. In the event of anaphylactic/anaphylactoid reactions, any therapy necessary to restore normal cardiopulmonary status should be implemented immediately. Such acute allergic reactions will be reported to the Sponsor in an expedited manner. These should be designated as reportable as an SAE, regardless of hospitalization, as medically important events. Please refer to the SAE reporting section (Section 8.4) for details. The individual symptoms of the infusion-related reaction should be captured in order to best characterize the study drug infusion reactions, unless the investigator considers another category, such as "allergic reaction" or "anaphylaxis," more appropriate in a specific situation.

6.4 Dacarbazine Preparation and Administration

Dacarbazine should be stored in accordance with the labelled storage conditions and package insert, or equivalent document. The preparation of dacarbazine should always be conducted in accordance with the most recent SPC or equivalent document.

6.5 Ipilimumab Preparation and Administration

Ipilimumab should be stored in accordance with the labelled storage conditions and package insert, or equivalent document. The preparation of ipilimumab should always be conducted in accordance with the most recent SPC or equivalent document.

6.6 Pembrolizumab Preparation and Administration

Pembrolizumab should be stored in accordance with the labelled storage conditions and package insert or equivalent document. The preparation of pembrolizumab should always be conducted in accordance with the most recent SPC or equivalent document.

6.7 Concomitant Therapy

6.7.1 Permitted Concomitant Therapy

Concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed in general. Examples include anti-diarrheal medications, antiemetics, or electrolyte supplementation.

Patients must be told to notify the investigational site staff about any new medications, herbal remedies, or dietary supplements that he or she takes after the start of the study treatment, regardless of treatment duration. All concomitant medications and significant non-drug therapies (including physical therapy, herbal or natural medications, and blood transfusions) administered during the study must be listed on the concomitant medications page in the eCRF.

IV hydration required to manage toxicity associated with any of the study medications (eg, hypotension) should be recorded on the concomitant medications page in the eCRF. IV hydration prior to administration of study medications should be recorded in the eCRF.

Required inactivated vaccinations (ie, influenza vaccine) may be administered per investigator discretion. Inactivated (non-live) vaccine(s) should **NOT** be administered during first 4 weeks of tebentafusp therapy or administered within 24 hours before or after tebentafusp dosing. Vaccine(s) administered during the study should be recorded on the concomitant medications page in the eCRF.

6.7.2 Permitted Concomitant Therapy Requiring Caution

Treatment with hematopoietic colony-stimulating growth factors (eg, G-CSF, GM-CSF, M-CSF, or erythroid-stimulating agents) may not be initiated during the first cycle in Arm 1 (tebentafusp). The use of colony-stimulating growth factors for management of cytopenias in Arm 2 (Investigator's Choice) is acceptable and at the discretion of the treating investigator. If a patient requires an erythropoiesis-stimulating agent prior to enrollment (beginning at least 2 weeks before start of study treatment), they may continue at the same dose.

Anti-coagulant therapy is permitted if the patients are already at stable doses of warfarin or stable doses of low molecular weight heparin for > 2 weeks at time of first dose. Low molecular weight heparin can be started during the overnight observations, if discussed and approved by the Sponsor's Medical Monitor in advance. The international normalized ratio should be monitored as clinically indicated per investigator's discretion. Ongoing anti-coagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of tebentafusp and monoclonal antibodies, treatment with anti-hypertensive therapy should be held for 24 hours before and 24 hours after tebentafusp in the first 6 weeks of treatment, and thereafter, at the discretion of the principal investigator in patients randomized to Arm 1 (tebentafusp) unless discussed and agreed with the Sponsor's Medical Monitor. Anti-hypertensive therapy is at the discretion of the treating investigator in patients randomized to Arm 2 (Investigator's Choice). Medications administered as supportive care of bony metastases, including bisphosphates and denosumab, may be administered during study therapy.

Treatment with palliative radiotherapy to tumor locations to alleviate pain is acceptable during the course of the study provided that: (1) with bony lesions, no new bone lesions are noted (representing clinically significant PD; Section 6.11.1) and (2) only non-target lesions are radiated. Radiation of target lesions is not permitted while receiving study treatment.

6.7.3 Prohibited Concomitant Therapy

While on study treatment, patients may not receive other additional investigational study drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. As described above (Section 6.7.2), palliative radiotherapy or surgery is allowed and bisphosphonates may be given for bone metastases. Additionally, no other therapeutic monoclonal antibodies, except for denosumab and tocilizumab if required for patient care, and no immunosuppressive medication may be administered while on this study, unless prescribed to manage toxicity as recommended in Table 6-3. While systemic corticosteroid therapy will interfere with the mechanism of action of the study medications, its use is recommended in some settings. Live or attenuated vaccines are prohibitied from 28 days prior to the first dose until 30 days after the final dose of the study drug.

Patients with adrenal insufficiency or patients receiving systemic steroid therapy or any other immunosuppressive medication at any dose level at Screening are excluded. Patients receiving corticosteroids may not be able to mount an appropriate physiologic cortisol response in the event of an infusion reaction with initial tebentafusp dosing. Corticosteroids and other immunosuppressives may interfere with the mechanism of action of the study drugs. The use of systemic corticosteroid therapy is permitted/recommended in the following settings: (1) infusion reactions and (2) immune-mediated toxicities and toxicity management (eg, hypotension and CRS) as directed in Table 6-3 (eg, hypotension not resolving with fluid support alone). Of note,

patients with a pre-existing history of adrenal insufficiency are excluded from study participation, (see Section 5.3).

Any additional uses of systemic corticosteroid therapy during the study should be discussed with the Sponsor's Medical Monitor.

6.8 Contraception

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, can be included in the study provided they are using highly effective methods of contraception during dosing and for 6 months after the last dose of tebentafusp or Investigator's Choice.

Highly effective contraception methods include the following:

- Total abstinence from sexual relations for the duration of the treatment when applicable to the lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, this applies only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

- Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

- The combination of any 2 of the following methods when both are used simultaneously:

    - Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device or intrauterine system
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) when used with spermicidal foam, gel, film, cream, or used of a spermicidal vaginal suppository

In case of use of oral contraception, women should have been stable on the same oral contraceptive pill for a minimum of 3 months before beginning treatment on this study.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms), or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to study treatment. In the case of

oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

6.9 Patient Numbering and Treatment Assignment

6.9.1 Patient Numbering

Each patient is identified in the study by a number that is assigned when the patient is first enrolled for Screening. The patient number is retained as the primary identifier for the patient throughout participation in the trial. The patient number consists of the center number assigned by the Sponsor and a sequential patient number suffix so that each patient is numbered uniquely across the entire database. Patient numbers will be assigned by the Sponsor at the time of Screening.

6.9.2 Treatment Randomization

Prior to randomization, the investigator will be asked within the IRT system to specify up front which of the Investigator's Choice treatments (dacarbazine, ipilimumab, or pembrolizumab) they will choose for the patient, should the patient be randomized to Arm 2.

Patients will be assigned to 1 of the 2 randomized treatment arms, Arm 1 (tebentafusp) and Arm 2 (Investigator's Choice) in a ratio of 2:1 (refer to Section 3.1 for details of treatment arms). The treatment assignment to the randomized Arms 1 and 2 is determined by the IRT. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization treatments, linked to Arms 1 and 2. The medication numbers will not be linked to treatments arms, since this is an open-label study.

Randomization to 1 of the 2 randomized treatment arms will be stratified by LDH levels. The 2 strata that will be used are: (1) baseline LDH below or equal to the ULN, and (2) baseline LDH above the ULN. LDH levels utilized for stratification will be assessed centrally during the screening period.

Prior to dosing, all patients who meet all inclusion/exclusion criteria will be randomized via IRT to either Arm 1 or Arm 2. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will link the patient to a treatment arm and will specify a unique medication number for the study treatment to be dispensed to the patient. If the patient fails to be started on treatment for any reason, the IRT must be notified.

6.9.3 Packaging and Labelling of Study Drug(s)

Further instructions regarding the packaging and labelling are provided in the Study Pharmacy Manual.

6.9.4 Study Drug Compliance and Accountability

Tebentafusp, dacarbazine, ipilimumab, or pembrolizumab will be administered to the patient by the trained study site staff at the study sites. Compliance with the prescribed regimen will be assured by administration of the study treatment under the supervision of the investigator or his/her designee.

The principal investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment according to local institutional drug accountability processes. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. At study close-out, and, as appropriate during the course of the study, following appropriate drug accountability procedures, each site can destroy used and unused study treatment per local institutional practice at the study site or at a third party vendor as appropriate and agreed with Sponsor.

6.9.5 Drug Supply, Storage, and Disposal

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, study drug supply should be recorded and stored according to the instructions specified on the drug labels.

All tebentafusp supply remaining at the end of the study, following appropriate drug accountability procedures at each site can be destroyed per local institutional practice at the study site or at a third party vendor as appropriate and agreed with Sponsor.

All destruction of study medications must be documented appropriately.

6.10 Management and Follow-up of Toxicity

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value must be followed up at least once a week (or more if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, for at least 90 days after treatment discontinuation or until resolution or stabilization of the event, whichever comes later. Appropriate clinical experts should be consulted as deemed necessary for any AEs observed in the course of the trial.

6.10.1 Tebentafusp Adverse Reactions

The main toxicities observed with tebentafusp are immune-related adverse reactions (eg, fever, hypotension, rash, and pruritus) and are generally associated with cytokine or chemokine release primarily observed after the first 2 to 3 weekly doses of tebentafusp (C1D1, C1D8, and C1D15). In the case of a toxicity suspected to be related to a CRS, the immunologic assessments outlined in Section 7.3.3.4.6 should be performed. In case of a rash or other related skin toxicity (eg, pruritus), photographs and a skin punch biopsy, as outlined in Section 7.3.3.6, should be considered.

Guidelines for management of AEs and dose modifications are presented in Table 6-3. Institutional protocols for management of immune-related AEs should be implemented in cases of immune-related AEs and will take precedence over guidance in Table 6-3. All patients must be followed up for the occurrence of AEs and SAEs for 90 days following the last dose of tebentafusp.

Doses not administered due to treatment-related toxicity are omitted, and treatment should resume with the next scheduled dose according to the Schedule of Events (Section 7.2.1). Required assessments, including but not limited to efficacy assessments and patient-reported outcomes, will be performed according to the Schedule of Events if treatment is held for toxicity.

6.10.1.1 Hypotension

Cases of severe hypotension have been observed across the tebentafusp clinical trials. Initial therapy for low-grade hypotension is aggressive IV fluid (crystalloid or colloid) therapy. In cases of hypotension where blood pressures are not immediately responding to fluid management, IV corticosteroid therapy should be considered. Cases of hypotension not complicated by additional symptoms associated with CRS (eg, nausea, vomiting, malaise, and fever) have been observed with tebentafusp. Retrospective analyses of peripheral cytokines in the IMCgp100-102 study have suggested that mild-to-moderate elevations in IL-6 after the first dose of tebentafusp may be associated with more severe presentations of hypotension. Intervention with early IV corticosteroid in cases of hypotension without initial response to fluid therapy is warranted as described in Table 6-3.

6.10.1.2 Cytokine Release Syndrome

Severe CRS has occurred with tebentafusp administration. Analysis of data from the completed study IMCgp100-01 demonstrated that increases in body temperature, which is a hallmark sign of CRS, developed within approximately 3 to 4 hours following tebentafusp administration. Additional observed toxicities included hypotension (severe in some patients), facial and general edema, and chills. Other commonly reported symptoms, which were typically mild to moderate, included headache, fatigue, nausea, and vomiting. CRS typically resolved within 3 days and most commonly occurred after the first dose with decreased frequency and severity after subsequent doses. Grading of CRS is based on the modified grading system (Table 6-2). Aggressive management and early intervention with immunosuppression therapy (eg, high-dose corticosteroids) are warranted in cases of suspected CRS, as described in Table 6-2.

Table 6-2 describes updated grading for events of CRS.

Table 6-2 Cytokine Release Syndrome Grading Scale[a]

Grade	Symptoms
1	Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, and malaise)

2	Symptoms require and respond to moderate intervention: • Oxygen requirement < 40% • Hypotension responsive to fluids or 1 low-dose vasopressor • Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention • Oxygen requirement > 40% • Hypotension requiring high-dose or multiple vasopressors • Grade 3 organ toxicity • Grade 4 transaminitis
4	Life-threatening symptoms • Requirement for ventilator support • Grade 4 organ toxicity (excluding transaminitis)
5	Death

a. Lee, 2014

Table 6-3 Recommended Dose Modifications of Tebentafusp by Toxicity Grade for Study Medications

Worst Toxicity NCI CTCAE v4.03 Grade	Recommended Dose Modifications
Skin Toxicity	
Pruritus	
Grade 1	Continue dosing. If symptomatic, consider systemic antihistamine regimen (see grade 2 guidance below).
Grade 2	Treat according to institutional practice and/or implement guidance below. Use systemic management and/or local skin management as indicated by symptoms. **Anti-pruritic regimen:** 1. **Systemic antihistamine regimen** recommended as first-line management of pruritus. Non-sedating, long-acting antihistamine (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (eg, evening dosing) consider diphenhydramine 25 mg oral or intravenous. The use of sedating antihistamines should be minimized in patients with co-morbid pulmonary pathology including pulmonary metastases or underlying inflammatory airways disease, such as chronic obstructive pulmonary disease or asthma. 2. **Topical corticosteroid regimens** Preparation of recommended regimens:

	• For face and/or intertriginous areas (including genitalia), recommend alclometasone 0.05% or hydrocortisone 2.5% creams • For other body areas (ie, trunk and extremities), recommend clobetasol or betamethasone 0.05% creams. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation. Prophylaxis for subsequent doses is generally not required after grade 2 pruritus, but a non-sedating antihistamine may be considered.
Grade 3	Hold all doses of tebentafusp until returned to NCI CTCAE grade ≤ 1. Manage pruritus according to institutional protocol and guidance below. **Management:** Treat according to institutional practice, which generally includes an anti-pruritic regimen (see grade 2 management above). In addition, corticosteroid treatment (oral or intravenous) can be considered for pruritus that does not respond to antihistamine therapy (recommend oral prednisone 20–40 mg or a single dose of 25 mg hydrocortisone intravenous or the equivalent for refractory pruritus). For recommended systemic or topical regimens, refer to grade 2 management above). **Prophylaxis:** In patients experiencing grade 3 pruritus, administration of a non-sedating antihistamine prophylaxis dose is recommended for the subsequent dose of tebentafusp, approximately 1–2 hours prior to the tebentafusp dose being administered (eg, cetirizine 10 mg or equivalent). Prophylaxis with corticosteroid can be considered if pruritus recurs at a similar or worse severity despite antihistamine prophylaxis (recommend oral prednisone 20–40 mg or a single dose of 25 mg hydrocortisone intravenous or the equivalent). If steroid prophylaxis is used, the steroid dose should be titrated to the minimum effective dose and ultimately discontinued if possible.
Rash/Photosensitivity	
Grade 1	Continue dosing. If symptomatic, consider systemic antihistamine regimen according to management guidance for pruritus (above).
Grade 2	Hold all doses of study tebentafusp until returned to NCI CTCAE grade ≤ 1. Use local skin management and systemic antihistamine regimen as indicated for symptoms. With observation of bullous formation or blistering rashes, consider dermatology consultation to rule out other causes (eg, bullous pemphigoid). Oral or topical corticosteroids can be used for bullous formations or blistering. If bullous formation or blistering recur, consult Sponsor's Medical Monitor for guidance. **Antihistamine (anti-pruritic) regimen:** 1. **Systemic antihistamine regimen** recommended as first-line management of pruritus.

	• Non-sedating, long-acting antihistamine (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (eg, evening dosing), consider diphenhydramine 25 mg oral or intravenous. The use of sedating antihistamines should be minimized in patients with co-morbid pulmonary pathology including pulmonary metastases or underlying inflammatory airway disease, such as chronic obstructive pulmonary disease or asthma. • Use of oral corticosteroid dosing for shorter time frames (eg, 3 days or fewer) may not require tapering dosing **2. Topical corticosteroid regimens** Preparation of recommended regimens: • For face and/or intertriginous areas (including genitalia), recommend alclometasone 0.05% or hydrocortisone 2.5% creams • For other body areas (ie, trunk and extremities), recommend clobetasol or betamethasone 0.05% creams. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation.
Grade 3	Hold all doses of tebentafusp until returned to NCI CTCAE grade ≤ 1. **Management:** Treat according to institutional practice, which generally includes an anti-pruritic regimen (see grade 2 management above). In addition, corticosteroid treatment (oral or topical) can be considered for symptomatic rash that does not respond to anti-pruritic regimen. For topical regimens, refer to grade 2 management above. Oral or topical corticosteroids can be used for bullous formations or blistering. If bullous formation or blistering recur, consult Sponsor's Medical Monitor for guidance. **Dose adjustments:** If grade 3 rash observed with tebentafusp resolves to NCI CTCAE grade ≤ 1 within 7 days, restart at the same dose level. If grade 3 rash resolves to NCI CTCAE grade ≤ 1 in 7–21 days, restart with 1 dose-level reduction in tebentafusp[a].
Grade 4	Any grade 4 rash regardless of presentation, permanently discontinue tebentafusp. Manage according to institutional practice, consultation with a dermatologist is recommended.

Hypotension	
Grade 1 Mild, asymptomatic decrease[b]: eg, < 15 mmHg systolic blood pressure	Increase frequency of vital signs assessments to every 2 hours. Consider maintenance intravenous fluids if mild decrease in blood pressure (eg, systolic blood pressure < 110 mmHg or decrease in systolic blood pressure of approximately less than 15 mmHg). Admit for inpatient monitoring (unless already hospitalized per protocol). Consider associated symptoms present and consider diagnosis of cytokine release syndrome (see below). Administer bolus intravenous fluids at a rate of approximately 1 L crystalloid per hour. If hypotension does not resolve with intravenous fluid therapy, consider intravenous corticosteroid therapy (eg, methylprednisolone 2 mg/kg initial dose or equivalent). Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum phosphorus or magnesium electrolyte levels.
Grade 2 Moderate, asymptomatic decrease[b]: eg, ≥ 15 mmHg but < 35 mmHg systolic blood pressure	Increase frequency of vital signs assessments to every 2 hours, or more frequently as medically necessary. Monitor fluid balance status with careful attention to clinical volume status, as assessed by degree of peripheral edema or rales on pulmonary examination. Administer bolus intravenous fluids at a rate of approximately 1 L crystalloid per hour. If the patient is asymptomatic and non-orthostatic after infusion of 2–3 L administered over 2–3 hours, consider transition to maintenance intravenous fluids until resolved. If hypotension is not rapidly resolved (ie, within 2–3 hours of onset) with intravenous crystalloid therapy, intravenous corticosteroid therapy of methylprednisolone 2 mg/kg initial dose or equivalent and/or tocilizumab 8 mg/kg IV(not to exceed 800 mg/infusion) per institutional guidelines should be administered until symptoms (eg, hypotension) resolve. Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels.
Grade 3 Moderate, symptomatic decrease[b]: eg, ≥ 15 mmHg and orthostasis	Increase frequency of vital signs assessments to every 2 hours, or more frequently as medically necessary. Administer bolus intravenous fluids at a rate of approximately 1 L crystalloid per hour. If the patient has symptomatic orthostatic hypotension after infusion of 2–3 L administered over 2–3 hours, corticosteroids, such as IV methylprednisolone 2 mg/kg or equivalent and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines should be administered until symptoms (eg, hypotension) resolve. Initiate vasopressor therapy as required to maintain blood pressure. Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels. If appropriate, consider additional measures according to the institutional cytokine release protocol (also see management of Infusion-related Reactions/Cytokine Release Syndrome below).

	If resolved within 48 hours of onset, no change in dosing is necessary. If repeat hypotension occurs, consult with the Sponsor's Medical Monitor prior to subsequent dosing. Please refer to guidance for continued inpatient monitoring to determine need for continued inpatient monitoring (Section 6.2). Consider the diagnosis of cytokine release syndrome and management (below).
Grade 4 Severe, symptomatic decrease[b]: eg, ≥ 35 mmHg systolic and symptomatic when supine or mean arterial pressure[c] ≤ 55 mmHg	Immediately administer high-dose corticosteroid therapy of methylprednisolone 2 mg/kg initial dose or equivalent and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines. Maximize vasopressor therapy and fluid management. Administer bolus intravenous fluids (1 L crystalloid as rapidly as feasible) and consider escalation to higher level of care ie, intensive care unit). Consider maximal immunosuppression with high-dose intravenous corticosteroid therapy **and** consider additional measures (eg, anti-IL6, tocilizumab if not already implemented) as required. If appropriate, aggressive fluid therapy as indicated and described above; consider additional measures according to prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels. Monitor vital signs every hour until resolved. Consider additional measures according to the institutional cytokine release protocol (also see management of Infusion-related Reactions/Cytokine Release Syndrome below). Tebentafusp must be dose reduced or discontinued. The Sponsor's Medical Monitor should be consulted for discussion of individual case management.
Infusion-related Reactions/Anaphylaxis (occurring during infusion)	
Grade 1	Administer medications for symptomatic relief as needed. Infusion interruption may be considered until resolution of the event (up to 4 hours). The infusion rate of the study medication may be decreased by 50%. If resolved with decreased rate of infusion, any subsequent infusions can be administered at the reduced rate.
Grade 2	Stop infusion and keep intravenous line open. Treat according to institutional practice. Provide all supportive measures as indicated. Provide supplemental oxygen and fluids, as needed. Monitor vital signs (eg, blood pressure, pulse, and temperature) until resolution. Administer medications for symptomatic relief as needed. Antihistamines, acetaminophen (paracetamol), or corticosteroids may be administered, as needed at the discretion of the investigator. Restart infusion only once infusion reaction resolves (within 4 hours of initial start of infusion), ensuring there is minimum observation period of 1 hour from stop of initial infusion to restart at reduced rate. Administer oral premedication (eg, 1000 mg of acetaminophen or paracetamol, 50–100 mg diphenhydramine hydrochloride or alternative antihistamine) 60 minutes prior to restarting the infusion, accounting for prior doses/time given for management of initial reaction. Restart infusion at 50% of previous rate under continuous observation. If the adverse event recurs at the reinitiated slow rate of infusion, and despite oral premedication, then permanently discontinue the patient from study treatment.

Grade 3 or 4	Discontinue infusion immediately, and permanently discontinue patient from study treatment. Grade 3 infusion-related reactions that improve by at least 1 grade within 6 hours of onset with medical management will not require permanent discontinuation. If treatment is continued, all guidance provided for the management of grade 2 reactions must be followed. Manage severe infusion-related reactions per institutional standards. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (eg, blood pressure, pulse, respiration, and temperature) until resolution.
Infusion-related Reactions (occurring after infusion)/Cytokine Release Syndrome (refer to modified grading system provided in Table 6-2)	
Grade 1 Symptoms are not life-threatening and require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, and malaise)	Admit for inpatient monitoring (unless already hospitalized per protocols) and manage according to individual symptoms. Assess for potential infection and treat fever and neutropenia. Treat symptomatically as indicated, including antihistamines, antipyretics, and/or analgesics as needed. Initiate bolus and/or maintenance intravenous fluids and carefully monitor fluid balance. Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels. Vigilantly monitor for escalation to grade 2 cytokine release syndrome with frequent vital signs (eg, every-hour vital signs). Strongly consider early, high-dose corticosteroid therapy with changes in vital signs (see grade 2 below).
Grade 2 Symptoms require and respond to moderate intervention. Hypotension: responds to fluids or a single low-dose vasopressor Hypoxia: requires <40% FiO_2	Management as above (grade 1) and include the following measures: • Increase monitoring with continuous cardiac and pulse oximetry monitoring and continue or increase vital sign monitoring (eg, every hour vital signs. • To manage hypotension, administer bolus intravenous fluids (recommended rate of approximately 1 L per hour). • If not rapidly resolved (ie, within 2–3 hours of onset) with fluids, high-dose IV corticosteroid therapy, eg, methylprednisolone 2 mg/kg initial dose or equivalent and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines should be administered until symptoms (eg, hypotension) resolve. • Consider prophylactic electrolyte supplementation for patients receiving intravenous fluids with low-normal serum electrolyte levels. • Manage respiratory distress and oxygen requirement with supplemental oxygen and additional respiratory support as needed.
Grade 3 Symptoms require and respond to aggressive intervention Hypotension: requires high-dose or multiple	Management as above (grade 2) and include the following measures: • Maximize immunosuppression with continued high-dose intravenous corticosteroid (eg, methylprednisolone 2 mg/kg/day or equivalent) and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines • Consider adding further immunosuppression measures or additional interventions according to the institutional cytokine release protocol (eg, anti-IL6, tocilizumab if not already implemented)

vasopressors Hypoxia: requires ≥40% FiO_2 Grade 4 transaminitis	• Continue to manage symptoms and vigilantly monitor for escalation **Next dose:** Patient may restart tebentafusp if symptoms resolve and only after discussion and written approval of Sponsor's Medical Monitor.
Grade 4 Life-threatening symptoms Hypoxia: Requirement for ventilator support (excluding transaminitis)	Management as above (grade 3) and include the following measures. • Additional immunosuppression recommended (eg, anti-interleukin-6, tocilizumab if not already implemented) with continued high-dose intravenous corticosteroid therapy as described above (eg, methylprednisolone 2 mg/kg/day or equivalent) • If appropriate, consider additional measures according to the institutional cytokine release protocol Permanently discontinue all study medications.
Hepatic Function Abnormalities	
Grade 2	Regular monitoring of liver function tests until improving or resolved. Evaluate concurrent medications for agents that may prolong or exacerbate laboratory abnormalities. Consider IV corticosteroid therapy (eg, hydrocortisone 100 mg or the equivalent) if not improving within 72 hours.
Grade 3	Hold all doses of tebentafusp until returned to NCI CTCAE grade ≤ 1. Regular monitoring of liver function tests until improving or resolved. Consider IV corticosteroid therapy (eg, hydrocortisone 100 mg or the equivalent). Dosing may resume after discussion with the Sponsor's Medical Monitor once all laboratory abnormalities returned to NCI CTCAE grade ≤ 1.
Grade 4	Hold all doses of tebentafusp until returned to NCI CTCAE grade ≤ 1. Regular monitoring of liver function tests until improving or resolved. Promptly consider IV corticosteroid therapy (eg, hydrocortisone 100 mg or the equivalent) if not resolving within 24 hours. Consider hepatology consult and additional abdominal imaging. Dosing may resume after discussion with the Sponsor's Medical Monitor and once all laboratory abnormalities returned to NCI CTCAE grade ≤ 1.
Vomiting	
Grade 2	Antiemetic therapy as per institutional standard. IV fluid support and other supportive measures for additional adverse events as needed.
Grade 3 or 4	Consider holding all doses of tebentafusp until returned to NCI CTCAE grade ≤ 1. Antiemetic therapy as per institutional standard. Intravenous fluid support and other supportive measures for additional adverse events.
Other Adverse Events	
In patients experiencing adverse events (not meeting the specific criteria above) of grade ≥ 3, study drugs should be omitted until resolved to grade ≤ 1, unless discussed and agreed with Sponsor's Medical Monitor. Treat according to institutional practice and for immune-related adverse event of grade ≥ 3, treatment with corticosteroids should be considered. Consult Sponsor's Medical Monitor for further guidance as needed.	

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

a. Dose reductions of tebentafusp for toxicity is as follows: from a starting dose tebentafusp dose of 68 mcg, the dose will be reduced to 54 mcg for any toxicity requiring dose reduction. The dose may be reduced further to 50 mcg for recurrent toxicity. Patients who require more than 2 dose reductions of tebentafusp should discontinue treatment. All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it may be increased to the initial dose level if there is no recurrence of toxicity with subsequent doses of tebentafusp.

b. The absolute systolic blood pressure change is provided as guidance for management, and must be interpreted in the clinical context of the patient. Patients with baseline hypertension may not require intervention for mild or moderate decreases in systolic blood pressure.

c. Mean arterial pressure = 1/3 (systolic blood pressure – diastolic blood pressure) + diastolic blood pressure.

d. Distinction is made for the purposes of management recommendations between anaphylaxis type reactions occurring immediately during the infusion of tebentafusp and delayed infusion-related reactions presenting several hours following completion of the tebentafusp infusion.

6.10.2 Dacarbazine Adverse Reactions

Adverse reactions with dacarbazine have been observed. Gastrointestinal adverse reactions are the most common. Symptoms of anorexia, nausea, and vomiting are the most frequently noted of all toxic reactions. Over 90% of patients are affected with the initial few doses. The vomiting lasts 1–12 hours and is incompletely and unpredictably palliated with phenobarbital and/or prochlorperazine. Recommended antiemetic regimens are described below. Rarely, intractable nausea and vomiting have necessitated discontinuance of therapy with Dacarbazine for Injection. Rarely, dacarbazine has caused diarrhea. Some helpful suggestions include restricting the patient's oral intake of food for 4–6 hours prior to treatment. The rapid toleration of these symptoms suggests that a CNS mechanism may be involved, and usually these symptoms subside after the first 1 or 2 days.

There are a number of minor toxicities that are infrequently noted. Patients have experienced an influenza-like syndrome of fever to 39°C, myalgia, and malaise. These symptoms occur usually after large single doses, may last for several days, and may occur with successive treatments. Alopecia has been noted as has facial flushing and facial paresthesia. There have been few reports of significant liver or renal function test abnormalities in man. However, these abnormalities have been observed more frequently in animal studies. Erythematous and urticarial rashes have been observed infrequently after administration of dacarbazine. Rarely, photosensitivity reactions may occur.

If the start of a subsequent dacarbazine treatment cycle is delayed by more than 21 days due to treatment-related toxicity, the default position is that then the patient must be discontinued from the treatment.

6.10.2.1 Dacarbazine Antiemetic Regimens

Antiemetic pre-medications should be administered prior to dosing of dacarbazine. The following antiemetic pre-medications are recommended, unless institutional standard is different. Antiemetic regimens should be administered per local standards: H2 receptor blockers (eg, ranitidine), 5-HT3 antagonists (eg, palonosetron and ondansetron), metoclopramide, and substance P antagonists (eg, aprepitant). Steroids should not be administered unless a patient continues to have symptoms despite the use of the acceptable antiemetics mentioned above.

6.10.3 Ipilimumab Adverse Reactions

Immune-related adverse reactions have been observed with ipilimumab, including severe and fatal events. Immune-related AEs may involve any organ system, but the most common severe AEs are immune-mediated enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and ocular manifestations. The majority of these events occurred during ipilimumab treatment, but events have been reported weeks or months after treatment discontinuation. Refer to the ipilimumab (YERVOY) prescribing information for more detailed information and management guidance. Recommended dose modifications are provided in Table 6-4. In the event of toxicity, doses of ipilimumab may be delayed, but all treatment must be administered within 16 weeks of the first dose.

Additional AEs have been observed in clinical trials of ipilimumab in patients with unresectable or metastatic melanoma. AEs of any grade, regardless of causality observed in at least 5% more of patients treated with ipilimumab than with control agent included: fatigue (41%), diarrhea (32%), colitis (8%), pruritus (31%), and rash (29%).

Table 6-4 Recomended Treatment Modifications for Immune-mediated Adverse Reactions of Ipilimumab (also refer to locally approved prescribing information)

Target/Organ System	Adverse Reaction (NCI CTCAE v4.03)	Treatment Modification
Endocrine (including hypophysitis, adrenal insufficiency, hyper- or hypothyroidism)	Symptomatic endocrinopathy	Withhold ipilimumab Resume ipilimumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1) and who are receiving less than 7.5 mg prednisone or equivalent per day
	Symptomatic reactions lasting 6 weeks or longer Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day	Permanently discontinue ipilimumab

Table 6-4 Recomended Treatment Modifications for Immune-mediated Adverse Reactions of Ipilimumab (also refer to locally approved prescribing information)

Target/Organ System	Adverse Reaction (NCI CTCAE v4.03)	Treatment Modification
Ophthalmologic	Grade 2 through 4 reactions: • Not improving to Grade 1 within 2 weeks while receiving topical therapy or • Requiring systemic treatment	Permanently discontinue ipilimumab
All Other	Grade 2	Withhold ipilimumab Resume ipilimumab in patients with complete or partial resolution of adverse reactions (grade ≤1) and who are receiving less than 7.5 mg prednisone or equivalent per day
	Grade 2 reactions lasting 6 weeks or longer Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day Grade 3 or 4	Permanently discontinue ipilimumab

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

6.10.4 Pembrolizumab Adverse Reactions

Immune-related adverse reactions have been observed with pembrolizumab. Immune-related AEs may involve any organ system, but the most common severe AEs are immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. The majority of these events occurred during pembrolizumab treatment, but events have been reported weeks or months after treatment discontinuation. Infusion-related reactions have also been observed. Refer to the pembrolizumab (KEYTRUDA) prescribing information for more detailed information and management guidance. Recommended dose modifications are provided in Table 6-5.

Additional AEs have been observed in clinical trials of pembrolizumab in patients with unresectable or metastatic melanoma. AEs of any grade, regardless of causality observed in at least 10% of patients treated with pembrolizumab and observed at a higher incidence than with control agent included: fatigue (28%), rash (29%), vitiligo (13%), arthralgia (18%), back pain (12%), cough (17%), dyspnea (11%), decreased appetite (16%), and headache (14%).

Table 6-5 Recommended Treatment Modification for Immune-mediated and Other Adverse Reactions of Pembrolizumab (also refer to locally approved prescribing information)

Target/Organ System	Adverse Reaction (NCI CTCAE v4.03)	Treatment Modification
Pneumonitis	Grade 2	Withhold pembrolizumab Resume pembrolizumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1)
	Grade 3 or 4 Recurrent grade 2 pneumonitis	Permanently discontinue pembrolizumab
Colitis	Grade 2 or 3	Withhold pembrolizumab Resume pembrolizumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1)
Endocrine (including hypophysitis, type 1 diabetes mellitus, thyroid disorders)	Grade 2 hypophysitis Grade 3 hyperthyroidism Other grade 3 or 4 events (unless specified below as criteria for discontinuation)	Withhold pembrolizumab Resume pembrolizumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1)
	Grade 3 or 4 hypophysitis Grade 4 hyperthyroidism Grade 3 or 4 hyperglycemia due to type 1 diabetes mellitus	Permanently discontinue pembrolizumab
Nephritis	Grade 2	Withhold pembrolizumab Resume pembrolizumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1)
	Grade 3 or 4 Recurrent grade 2 nephritis	Permanently discontinue pembrolizumab
Hepatitis	Aspartate aminotransferase or alanine transaminase greater than 3 and up to 5 times the upper limit of normal Total bilirubin greater than 1.5 and up to 3 times the upper limit of normal	Withhold pembrolizumab Resume pembrolizumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1)
	Aspartate aminotransferase or alanine transaminase greater than 5 times upper limit of normal or total bilirubin greater than 3 times the upper limit of normal	Permanently discontinue pembrolizumab

Table 6-5 Recommended Treatment Modification for Immune-mediated and Other Adverse Reactions of Pembrolizumab (also refer to locally approved prescribing information)

Target/Organ System	Adverse Reaction (NCI CTCAE v4.03)	Treatment Modification
	For patients with liver metastasis who begin treatment with grade 2 aspartate aminotransferase or alanine transaminase, if aspartate aminotransferase or alanine transaminase increases by greater than or equal to 50% relative to Baseline and lasts for at least 1 week	
All Other	Any other treatment-related grade 3	Withhold pembrolizumab Resume pembrolizumab in patients with complete or partial resolution of adverse reactions (grade ≤ 1)
	Grade 3 or 4 infusion-related reaction Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks Persistent grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to grade ≤ 1 within 12 weeks Any grade 3 treatment-related adverse reaction that recurs	Permanently discontinue pembrolizumab

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

6.11 Treatment Discontinuation

Study treatment must be discontinued for the following reasons:

- Patients must discontinue study treatment once PD is identified based on RECIST v1.1 unless criteria for treatment beyond initial PD is met (see Section 6.11.1)
- If continuing treatment beyond initial PD, then patients must discontinue study treatment once further PD warranting treatment discontinuation is met (see Section 6.11.1)
- For patients receiving ipilimumab, completion of the 4 planned doses

- Initiation of alternative anti-cancer therapy including another investigational agent
- Unacceptable toxicity as defined in Table 6-3 or any AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing
- Withdrawal of consent from further treatment with investigational product by the patient or the investigator or patient is lost to follow-up
- Patient is determined to have met 1 or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation AND continuing to receive investigational product might constitute a safety risk. Patients who fall into this category and for whom continuation of treatment is not thought to pose a safety risk, in the opinion of the investigator, may continue to receive study treatment after discussion with the Sponsor's Medical Monitor
- Pregnancy or intent to become pregnant

At the time patients discontinue study treatment, the EOT visit should be scheduled in the appropriate window of 14 days after the last dose was administered. At this visit, all of the assessments listed for the EOT visit will be performed (see Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that date of visit may become the EOT visit rather than having the patient return for an additional visit (safety follow-up will still continue for the full 90-day observation period, see Section 7.2 for details of assessments required). An EOT phase disposition eCRF page should be completed at the EOT visit, giving the date and reason for stopping the study treatment. End of treatment/premature withdrawal visit is not considered as the end of the study. Patients should still be followed for the survival endpoint and, if the patient does not have PD, imaging data should continue to be collected to capture PD based on RECIST v1.1.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7 and Table 7-1. If they fail to return for these assessments for unknown reasons, every effort (eg, telephone, email, and registered letter) should be made to contact them. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the study disposition eCRF page.

6.11.1 Criteria for Treatment Beyond Initial RECIST v1.1 Disease Progression

Clinical evidence suggests that a minority of patients treated with immunotherapies, including tebentafusp, will derive clinical benefit after an initial assessment of PD. For patients in the tebentafusp Arm and in Arm 2 receiving pembrolizumab or ipilimumab, if initial PD based on RECIST v1.1 occurs, treatment may continue according to the protocol-specified regimen provided **ALL** of the following criteria continue to be met:

- Absence of signs or symptoms indicating clinically significant PD
- No decline in ECOG performance status
- No impending threat to vital organs/critical anatomical sites (eg, spinal cord compression, liver function decline) requiring urgent alternative medical intervention or where continuation of study therapy would prevent institution of such intervention
- Absence of any of the investigational product discontinuation criteria (Section 6.11)

Patients are not required to continue treatment beyond initial RECIST v1.1 PD. Both the patient and the investigator must agree continuing treatment would be in the patient's best interest. Patients continuing treatment beyond the protocol-specified RECIST v1.1 PD must provide separate consent to continue treatment after an initial assessment of PD. In addition, instances where RECIST v1.1 PD is equivocal or warrants follow-up confirmation, in the judgment of the investigator, prior to continuing study treatment, consent should be obtained at the time of initial suspicion of PD with appropriate discussion of the risk:benefit of continuing study treatment with the patient.

Patients assigned to tebentafusp, ipilimumab, or pembrolizumab who are treated beyond initial RECIST v1.1 PD must permanently discontinue study treatment if they experience further progression warranting treatment discontinuation. Further progression warranting treatment discontinuation is defined as **ANY** one of the following observed at least 4 weeks after the initial PD assessment per RECIST v1.1: 1) an additional ≥ 20% increase in tumor burden (sum of diameters of both target and new measurable lesions) accompanied by an absolute increase of ≥ 5 mm; 2) unequivocal PD of non-target lesions; or 3) new non-measurable lesions.

Treatment and assessments after an initial assessment of PD will continue to follow the treatment regimen as defined in Table 6-1 (Section 6.1). Imaging data will continue to be obtained until further progression warranting treatment discontinuation (as defined above) or criteria for discontinuation of study treatment following RECIST v1.1 PD are met.

6.12 Study Discontinuation

Patient must be withdrawn from the trial for the following reasons:

- Patient dies.
- Patient is lost to follow-up.
- Patient withdraws consent for any further participation including further survival follow-up.
- The end of study is reached (please refer to Section 3.5 and Section 3.6).

If none of these conditions are met, patients should continue to be followed for survival status.

7 STUDY SCHEDULE AND ASSESSMENTS

7.1 Screening Procedures and Assessments

All of the assessments required as part of the study are indicated in Table 7-1 organized by visit date, with assessments required indicated with an "X" at the specific visits when they should be performed. All assessments listed as "Screening" must be performed within 21 days before C1D1. The only exception to the screening period of 21 days are the baseline radiological evaluations, which must be performed within 28 days of C1D1. Assessments required on C1D1 that are performed as part of the screening evaluations and within 72 hours prior to the first dose of study treatment do not need to be repeated on C1D1. Laboratory and radiological assessments performed as part of standard of care prior to signing the informed consent may be used if performed within the screening time window (21 days for laboratory assessments and 28 days for radiological assessments).

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase														Follow-up Phase		
Procedure	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3[a]			Later Cycles[a]	EOT	90-day Safety Follow-up	Disease Progression Follow-up	Survival Follow-up
Day of Cycle		-21 to -1	1	2	8	9	15	16	1	8	15	1	8	15	1–21				
Informed consent	7.1.1	X																	
Demography	7.1.1.2	X																	
Inclusion/exclusion criteria	5.2/5.3	X																	
Medical history	7.1.1.2	X																	
Diagnosis and extent of cancer	7.1.1.2	X																	
Prior anti-cancer therapy	7.1.1.2	X																	
Prior/concomitant medications	7.1.1.2	X	Continuously assessed																
Physical examination[q]	7.3.3.1	X	X		A		A		X	A	A	X	A	A	X	X			
Height	7.3.3.3	X																	
Weight	7.3.3.3	X							X			X			X	X			
Vital signs[b]	7.3.3.2	X	X	A	A	A	A	A	X	A	A	X	A	A	X	X			
ECOG performance status[c]	7.3.3.7		X									X			X	X			

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase													Follow-up Phase		
Procedure	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3[a]			Later Cycles[a]	EOT	90-day Safety Follow-up	Disease Progression Follow-up	Survival Follow-up
Day of Cycle		-21 to -1	1	2	8	9	15	16	1	8	15	1	8	15	1–21				
Hematology panel[d]	7.3.3.4.1 Table 7-4	X	X	A	A	A	A	A	X	A	A	X	A	A	X	X			
Chemistry panel[e]	7.3.3.4.2 Table 7-4	X	X	A	A	A	A	A	X	A	A	X	A	A	X	X			
Coagulation	7.3.3.4.3 Table 7-4	X														X			
Urinalysis	7.3.3.4.4 Table 7-4	X														X			
Thyroid function	7.3.3.4.5 Table 7-4	X	Thyroid function studies to be completed on Day 1 of every odd-numbered cycle at Cycle 3 and beyond, as well as at EOT																
Skin punch biopsy (optional)[f]	7.3.3.6		In case of increased skin toxicity in any patient at C1D15 or thereafter (optional)																
Pregnancy test[g]	7.3.3.4.7	X	Arm 1: Pregnancy testing required every 4 weeks and at EOT in all WOCBP Arm 2: Pregnancy testing required every 6 weeks and at EOT in all WOCBP																

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase													Follow-up Phase		
Procedure	**Protocol Section**	**Screening**	**Cycle 1**						**Cycle 2**			**Cycle 3[a]**			**Later Cycles[a]**	**EOT**	**90-day Safety Follow-up**	**Disease Progression Follow-up**	**Survival Follow-up**
Day of Cycle		**-21 to -1**	**1**	**2**	**8**	**9**	**15**	**16**	**1**	**8**	**15**	**1**	**8**	**15**	**1–21**				
Patient-reported outcomes[r]	7.3.2		PRO assessments (EQ-5D,5L questionnaire and EORTC QLQ-C30) will be administered to all patients at C1D1, on D1 of every other cycle to C5D1, every fourth cycle thereafter, beginning with C9D1, and EOT															Both EQ-5D,5L and EORTC QLQ- C30 every 12 weeks	EQ-5D,5L every 12 weeks
Anti-neoplastic therapies since treatment discontinuation	7.2.4																X	X	X
Pharmacodynamic biomarkers[h]	7.4.3.3	X	Refer to Table 7-8 for biomarker assay specifics Additional samples to be taken in case of suspected cytokine release syndrome																
Tumor evaluation as per imaging studies using RECIST v1.1 [l]	7.3.1 Table 7-2	X -28 to -1	Every 12 weeks from C1D1 and should NOT follow delays incurred in the treatment period After EOT, during PD follow-up, continuation of every 12 weeks from C1D1 until PD per RECIST v1.1 or lost to follow-up																
12-lead ECG	7.3.3.5 Table 7-5	X	Arm 1 only: Refer to ECG schedule Table 7-5																
Adverse events	8		Continuously assessed																

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase													Follow-up Phase		
Procedure	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3[a]			Later Cycles[a]	EOT	90-day Safety Follow-up	Disease Progression Follow-up	Survival Follow-up
Day of Cycle		-21 to -1	1	2	8	9	15	16	1	8	15	1	8	15	1–21				
Collection of archival tumor sample[j]	7.4.3 Table 7-8	X																	
Collection of newly obtained tumor sample[k]	7.4.3 Table 7-8	X																	
Collection of new tumor sample in the setting of progression[l]	7.4.3 Table 7-8																	X	
Arm 1: Tebentafusp administration[m]	6.1 Table 6-1		Tebentafusp given intravenously **every week with C1D15 intra-patient escalation**[m]																
Arm 2: Investigator's Choice administration[m]	6.1 Table 6-1		Dacarbazine, ipilimumab, or pembrolizumab administered intravenously every 3 weeks on Day 1 of every cycle[m]																
PK sampling[n]	7.3.3.8 Table 7-7		Arm 1 only: PK sampling to be scheduled according to Table 7-7																
Immunogenicity sampling[n]	7.3.3.8		Arm 1 only: Immunogenicity sampling to be scheduled according to Table 7-7																

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase													Follow-up Phase		
Procedure	Protocol Section	Screening	Cycle 1						Cycle 2			Cycle 3[a]			Later Cycles[a]	EOT	90-day Safety Follow-up	Disease Progression Follow-up	Survival Follow-up
Day of Cycle		-21 to -1	1	2	8	9	15	16	1	8	15	1	8	15	1–21				
	Table 7-7																		
HLA-A*0201 determination[b]	7.1.1.3	X																	
Central laboratory LDH determination	7.1.1	X																	
Survival contact	7.2.4.3																		X[b]

A = performed in patients randomized to tebentafusp (Arm 1) only; C#D# = Cycle # Day #; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; EQ-5D, 5L = EuroQoL-5 Dimensions – 5-levels ; HLA-A*0201 = human leukocyte antigen-A*0201; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcomes; QLQ-C30 = Quality of life Questionnaire-Core 30; RECIST = Response Evaluation Criteria in Solid Tumors; WOCBP = women of childbearing potential; X = performed in all patients.

FOOTNOTES:

a. Cycles 4 and greater will follow the same schedule of assessments as outlined for Cycle 3 with the exception of tumor imaging, thyroid function testing, pregnancy testing, and ECG assessments, which will follow the noted schedule and PK/immunogenicity and pharmacodynamic assessments which will follow the schedules in Table 7-6 and Table 7-8, respectively.

b. For patients randomized to tebentafusp, inpatient hospitalization and frequent vital signs (at a minimum of every 4 hours [± 30 min] or more frequently according to institutional standards) are required at C1D1, C1D8, and C1D15. Inpatient monitoring at Cycle 2 Day 1 and beyond will be determined based on the toxicity observed in the individual patient in C1D1-C1D15. Patients experiencing a grade 2 or greater hypotension event at C1D15 must be observed as an inpatient for the subsequent C2D1 dose. Please refer to Section 6.2.1 and Section 7.3.3.2 for details of inpatient hospitalizations and vital signs monitoring.

c. ECOG performance status will be determined on Day 1 of every odd-numbered cycle and at EOT.

d. Hematology panel should be obtained at Screening and up to 24 hours before every dose of study treatment. In addition, the hematology panel is obtained the day following the first 3 doses of tebentafusp (Arm 1 only), on C1D2, C1D9, and C1D16. Hematology panel is performed at EOT visit as well.

e. Chemistry panel should be obtained at Screening and up to 24 hours before every dose of study treatment. In addition, the chemistry panel is obtained the day following the first 3 doses of tebentafusp (Arm 1 only; C1D2, C1D9, and C1D16) and at EOT.

f. Skin punch biopsy should be obtained in patients with a grade ≥ 3 rash, bullous rash of any grade, or worsened rash on C1D15 or beyond as compared to the rash experienced on tebentafusp dosing days on C1D1 or C1D8. This skin biopsy is optional.

g. Pregnancy testing is required only in all WOCBP. At Screening, a serum pregnancy test must be performed within 72 hours before the first dose in all WOCBP. During the study, a serum or urine pregnancy test must be performed every 4 weeks. Patients randomized to Arm 2 (Investigator's Choice) must have pregnancy testing completed on Day 1 every 6 weeks or every other cycle, ie, Cycle 1, Cycle 3, Cycle 5, etc. At EOT, a serum or urine pregnancy test must also be performed in all WOCBP.

h. For all biomarker sampling timing and instructions, please refer to Table 7-8.

i. Radiologic assessments should be performed in all patients as scheduled every 12 weeks as indicated (see Table 7-2), using a reference to C1D1 and should NOT follow delays incurred in the treatment period. Radiologic assessments at each time point will include a CT or MRI of the chest, abdomen, and pelvis and additional imaging, ie, brain MRI, as warranted. See Table 7-2 for details.

j. A tumor biopsy sample is required from all patients, prior to randomization, which can be an archival tumor biopsy or a newly obtained biopsy during Screening, unless not medically feasible (this setting where no tissue sample can be obtained should be discussed with the Sponsor's Medical Monitor, ie, if an archival sample is not available and the patient cannot undergo a biopsy at Screening). Fine-needle aspirate or cytology specimens are not adequate and may not be submitted in lieu of a tumor biopsy.

k. Collection of a new tumor biopsy at Screening is **optional** unless an archival tumor sample is not available.

l. A biopsy obtained at the time of disease progression in the setting of treatment resistance is **optional** in all patients and should be taken from a progressing lesion.

m. Patients in Arm 1 (tebentafusp): Please refer to Section 6.2 for details of **weekly** tebentafusp administration and **intra-patient dose escalation regimen (at C1D15;** Section 6.3**)** used in this study. Beginning with C1D8, tebentafusp will be administered on the scheduled day (± 2 days), and consecutive infusions of tebentafusp must be administered at least 5 days apart. Patients in Arm 2 (Investigator's Choice): Please refer to Section 6.1 (Table 6-1) for details of treatment regimen.

n. PK and immunogenicity sampling should be performed as indicated in Table 7-7.

o. For all patients, HLA status will be determined during the pre-screening period by central assay. Patients should not sign the Main Study Informed Consent Form and enter Screening until the results of the central assay in Pre-Screening is known as HLA-A*0201 positive. Patients who rescreen for the trial need not return to the pre-screen period once HLA results are known.

p. Survival Follow-up should be completed every 12 weeks until death or until the end of the study is reached. Survival calls will also be made in the 2 weeks following the date of data cutoff for the analysis.

q. At screening and C1D1, prior to dosing, a complete physical examination will be completed. From C1D8 onwards, a short physical examination will be performed. Starting with C4D1, patients on both Arm 1 and Arm 2 will have short physical examination performed only on day 1 of the cycle and at EOT. For any patient experiencing skin toxicity during the first 3 weeks of study treatment in Arm A, a subset of selected sites may be asked to take color photographs to document the onset, progression, and resolution of the skin toxicity.

r. To reduce potential bias, patient-reported outcome assessments should be performed before dosing and laboratory or radiology results are provided to the patient during the study visit.

7.1.1 Screening Assessments

The study IRB/IEC-approved ICF must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations performed as part of standard of care within the screening window (28 days for radiological assessments, 21 days for all other assessments).

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments required at Baseline will be performed. For details of all screening assessments, refer to Table 7-1. Screening assessments must be repeated if performed outside of the specified screening window. Patients may rescreen after abnormal laboratory results or symptoms are corrected or treated after consultation with the Sponsor.

For all patients, LDH levels will be determined during the screening period by central laboratory. Radiologic assessments required at Screening include CT or MRI of the chest, abdomen, and pelvis. Brain MRI is required only if there is clinical suspicion of brain metastasis at Screening or for baseline evaluation of uveal/primary disease, as warranted.

7.1.1.1 Information to be Collected on Screening Failures

A patient who signed the Main Study ICF, but was not randomized for any reason, will be considered a screen failure. If patients are found not eligible after signing the Main Study ICF, they will be considered screening failures and data will be handled in the same manner.

The demographic information, informed consent, and limited screening pages (with reason for screen fail) must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced an SAE during Screening, which would be reported in the usual manner via the eCRF AE page (see Section 8.4).

7.1.1.2 Patient Demographics and Other Baseline Characteristics

Data to be collected will include general patient demographics, relevant medical history, and current medical conditions, diagnosis and extent of cancer, details of prior anti-cancer treatments, *GNAQ/GNA11* mutation status (if known), prior/concomitant medications, prior procedures, significant non-drug therapies, and any other assessments that are done for determining eligibility for inclusion in the study. Prior anti-neoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate prior anti-neoplastic therapy eCRF page during Screening.

7.1.1.3 Human Leukocyte Antigen Status Determination

For all patients, HLA status will be determined during Pre-screening by central assay. Patients should not sign the Main Study ICF and enter Screening until the results of the central assay in Pre-Screening is known as HLA-A*0201 positive. Patients who have prior positive HLA-A*0201

results (eg, per local testing) may proceed with signing the Main Study ICF and initiating Screening while completing the confirmatory central HLA testing. Patients may not be randomized or treated until required confirmation of HLA-A*0201 positive status is obtained via central assay.

7.2 Treatment, Treatment Discontinuation, and Follow-up Phases

7.2.1 Schedule of Events Windows

During the course of the study visits, tests and/or procedures should occur on schedule whenever possible. A visit window of ± 2 days is allowed for all visits where tebentafusp administration is scheduled. Visits where Investigator's Choice is being dosed will not have a visit window. Dosing of Investigator's Choice medications should be in line with the package insert, SPC, or equivalent document. For all other visits, a visit window of ± 7 days is allowed, unless otherwise indicated in the protocol. If the study drug infusions are delayed or otherwise moved from the scheduled day, all study assessments will be moved with the delayed study drug infusions. The only exception to moving study assessments with treatment are the radiological and patient-reported outcome assessments, which must be performed ± 7 days of the scheduled date of the assessment (unless otherwise indicated in the protocol) taking as reference C1D1. The protocol-specified radiologic assessments should be performed as scheduled every 12 weeks as indicated in the protocol (reference to C1D1) and should not follow delays incurred in the treatment period for the accurate assessment of PFS and duration of response endpoints. Radiologic assessments should not move if delays in treatment are incurred. In addition, radiological assessments should continue as per protocol schedule until PD by RECIST v1.1 or further PD warranting treatment discontinuation (refer to Section 6.11.1).

7.2.2 Treatment Period

For the purposes of scheduling procedures and evaluations, a treatment cycle is defined as 3 weeks (21 days). Please refer to Table 7-1 for details of the timing of required assessments and visit windows. Patients will be treated until they experience unacceptable toxicity, PD, and/or treatment is discontinued at the discretion of the investigator or the patient, as described in Section 6.11.

Patients receiving tebentafusp, pembrolizumab, or ipilimumab who have radiologic evidence of PD by RECIST v1.1 but have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment after re-consent (Section 6.11.1). Patients who continue on treatment after PD should discontinue study treatment once they have further PD warranting treatment discontinuation (refer to Section 6.11.1 or are no longer deriving benefit as assessed by the investigator.

7.2.3 Discontinuation of Study Treatment and End of Treatment Visit

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment and withdraw consent for treatment, the

investigator should make every effort to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. Other reasons for discontinuation of study treatment are outlined in Section 6.11. Patients who withdraw consent for treatment should still be followed for safety, survival status, subsequent cancer therapy, and quality of life, unless they have withdrawn consent to further follow-up. In addition, patients who end treatment and have not yet progressed should continue to have imaging assessments as per the Disease Progression Follow-up Period (Section 7.2.4.2) until evidence of confirmed PD by RECIST v1.1 (unless they withdraw consent for further follow-up).

Patients will be considered withdrawn from therapy if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. The investigator should discontinue study treatment for a given patient if, on balance, the investigator believes that continuation would be detrimental to the patient's well-being.

7.2.4 Follow-up Periods

7.2.4.1 90-day Safety Follow-up Period

All patients must have safety evaluations 90 days after the last dose of study treatment. Information related to all AEs (including concomitant medications taken for ongoing AEs) will be collected for 90 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly or as clinically indicated until resolution or stabilization.

Details of any anti-neoplastic therapies received following discontinuation of study drug will be collected during this follow-up period.

7.2.4.2 Disease Progression Follow-up Period

The **Disease Progression Follow-up Period** is defined for all patients who discontinue treatment for reasons other than death, PD per RECIST v1.1 or further PD warranting treatment discontinuation (refer to Section 6.11.1), lost to follow-up, withdrawal of consent, or study termination.

- All patients who discontinue treatment for reasons other than PD per RECIST v1.1 will be followed with imaging until evidence of PD per RECIST v1.1 or until the start of alternate anti- neoplastic therapy.
- For patients who consent to and continue treatment beyond initial PD per RECIST v1.1, imaging should continue until permanent treatment discontinuation as per the Treatment Period (Section 7.2.2).
- If patients choose not to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient has had PD.

- Patients who discontinue treatment for reasons of PD by either RECIST v1.1 or further PD warranting treatment discontinuation will not enter the Disease Progression Follow-up Period.
- Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

7.2.4.3 Survival Follow-up Period

Upon completion of the 90-day Follow-up or Disease Progression Follow-up, patients will be followed for survival and EuroQoL-5 Dimensions – 5-levels (EQ-5D,5L) every 12 weeks (can be done by telephone call) will be recorded until death or until the end of the study is reached, unless they withdraw consent or are lost to follow-up. Survival calls will be made in the 2 weeks following the date of DCO for the analysis as outlined in Section 3.4.2.

Anti-neoplastic therapies since discontinuation of study drug will be collected during this follow-up period.

7.2.4.4 Lost to Follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family, patient's general physician, local treating oncologist, and checking publicly available death registries and hospital records as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, eg, dates of telephone calls, registered letters - a patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate eCRF.

7.3 Details of All Assessment Types

7.3.1 Efficacy Assessments

Radiologic assessments should be performed as scheduled every 12 weeks as indicated in this section below (see Table 7-2), using a reference to C1D1 and should NOT follow delays incurred in the treatment period.

Tumor response will be determined according to RECIST v1.1 (Appendix 2).

Investigator assessment data will be used for the analysis and reporting of response and other tumor-related endpoints according to RECIST v1.1 for efficacy endpoints of the study. Scan images will be collected and BICR may be performed if required for supportive purposes per Sponsor discretion.

At Screening, all patients will undergo CT or MRI with IV contrast of the chest, abdomen, and pelvis. The same imaging modality utilized at screening (CT or MRI) should be used for all

subsequent assessments for selected target and non-target lesions. If a patient is intolerant of iodine-based contrast agents, contract-enhanced MRI is recommended. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound may not be used to measure sites of disease. See Table 7-2 for further details.

Tumor assessments will be performed at the following time points:

- Screening
- Every 12 weeks (± 1 week) from C1D1 until PD per RECIST v1.1 or patient withdrawal. After EOT, during PD follow-up, every 12 weeks until PD per RECIST v1.1, or lost to follow-up or withdrawal of consent.
- At EOT, if a scan is already scheduled to occur within 7 days of the EOT. Note, if a patient discontinues treatment, but remains in Disease Progression Follow-up, then imaging should continue as per the original study plan and will not be needed at the EOT visit

Disease progression follow-up should be performed as described in Section 7.2.4.

Table 7-2 Disease Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI with contrast enhancement (chest, abdomen, pelvis)	Mandatory	Mandatory, every 12 weeks from C1D1 until PD per RECIST v1.1, treatment discontinuation or patient withdrawal/lost to follow-up The same imaging modality should be used throughout the study (CT or MRI)
Brain MRI with contrast	Required only if clinical suspicion of brain metastasis at Screening or for baseline evaluation of uveal/primary disease as warranted	If disease was detected at Baseline, if clinically indicated, or for follow-up evaluation of uveal/primary disease as warranted

C#D# = Cycle # Day #; CT = computed tomography; EOT = end of treatment; irPD = immune-related progressive disease; MRI = magnetic resonance imaging; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors.

7.3.2 Patient-reported Outcomes Assessments

General health status of all patients will be assessed using the EQ-5D,5L questionnaire. The EQ-5D, 5L is an instrument to measure self-reported overall health status in patients. There are 5 health dimensions reported in the EQ-5D, 5L: mobility, self-care, daily activities, pain, and

anxiety. The EQ-5D, 5L uses a visual analog scale and the data collected with the EQ-5D, 5L is generally used in cost effectiveness analyses. This outcome measure will be conducted in all patients at C1D1, at Day 1 of every other cycle through C5D1, then every fourth cycle thereafter beginning with C9D1 until EOT. This assessment should be performed prior to study treatment when assessed at a visit when treatment is planned. Patients entering the Disease Progression Follow-up Phase will continue this assessment at 12-week intervals. Thereafter, during the survival follow-up phase, EQ-5D, 5L assessments (only) will be continued to be taken every 12 weeks to inform post-progression health status. During the survival follow-up phase, EQ-5D, 5L assessments may be collected by site study staff via telephone interview. Patients who do not complete a baseline EQ-5D, 5L will not complete the questionnaire at later visits. These data are needed to inform a health economic evaluation of treatment strategies.

HRQoL will be assessed in all patients using the European Organization for Research and Treatment of Cancer Quality of life Questionnaire-Core 30 (EORTC QLQ-C30). The EORTC QLQ-C30 is one of the most commonly used quality of life instruments in melanoma clinical development studies. This is a 30-question instrument measuring functional scales (physical, cognitive, emotional, social functioning with global quality of life assessment), as well as 9 symptom scales. This outcome measure will be conducted in all patients at C1D1, C3D1, and C5D1, then every fourth cycle thereafter beginning with C9D1 until EOT. This assessment will be performed prior to study treatment when assessed at a visit when treatment is planned. To reduce potential bias, this assessment should be performed before laboratory or radiology results are provided to the patient during the study visit. Using C1D1 as a reference, assessments should NOT follow delays incurred in the treatment period. Patients entering the PD follow-up period will continue this assessment at 12-week intervals, but this assessment will not be performed during survival follow-up. Patients who do not complete a baseline EORTC QLQ-C30 will not complete the questionnaire at any later visits. If the patient does not complete the questionnaire due to a technical issue with the device, it will not be considered a protocol deviation.

7.3.2.1 Independent Central Review

All on-study images acquired for tumor and treatment effect assessments will be submitted to an imaging contract research organization (CRO) for collection and storage. If required for supportive purposes per Sponsor discretion, the collected images may undergo a BICR. A Central Imaging Manual will be provided to all investigative sites detailing the procedures for de-identification and submission of imaging studies for central review. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows), will be provided to the imaging CRO. Further details of the image transfer procedures and processes will be included in the Study Imaging Manual.

Given that all images initially will only be collected and stored at the imaging CRO, all patient management decisions will be based upon local assessment of imaging studies at the site.

7.3.3 Safety Assessments

Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, pregnancy, ECG, cytokine testing, and AEs at every visit. For details on AE collection and reporting, refer to Section 8.

7.3.3.1 Physical Examination

Physical examination will be performed according to Table 7-1.

At Screening and C1D1, prior to tebentafusp infusion, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed.

From C1D8 onwards, a short physical examination will be performed. A short physical examination will include the examination of general appearance, vital signs (temperature, blood pressure, respiratory rate, and pulse) and body sites as directed by symptoms.

Significant findings that were present prior to the signature of the informed consent must be included on the medical history eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the AE eCRF page.

7.3.3.2 Vital Signs

Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) must be performed before dosing, and after the tebentafusp administration as indicated in Table 7-1 and Table 7-3 and as per institutional standards.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the investigator if medically indicated and will be recorded as unscheduled assessment.

See Section 6.2.3 for additional details on inpatient hospitalizations.

Table 7-3 Tebentafusp Post-dose Vital Signs Monitoring

C1D1, C1D8, C1D15 *Inpatient monitoring required for all dosings*	Vital signs monitored per institutional standards at a minimum of every 4 hours. Patients should be monitored for at least 16 hours after dosing. Patients experiencing grade 2 or greater hypotension at C1D15 require inpatient monitoring for the subsequent/next C2D1 dose. Those experiencing grade 3 or 4 hypotension at C1D1, C1D8, or C1D15 require hourly vital signs monitoring for a minimum of 8 hours after dosing for any doses administered as an outpatient through C3D1.
C2D1 *Inpatient monitoring required for exception noted*	Patients experiencing a grade 2 or greater hypotension at C1D15 must be observed as an inpatient for C2D1 dose, with vital signs performed at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.
C2D1 through C2D15 *Monitoring requirements for exceptions noted*	Patients experiencing grade 3 or 4 hypotension at C1D1, C1D8, or C1D15 require hourly vital signs monitoring for minimum of 8 hours after dosing for any doses administered as an outpatient through C3D1. If patients experienced grade ≥2 hypotension at C1D15, they must be monitored as an inpatient for C2D1, as noted above.
C2 and later cycles-Days 1, 8, and 15 *Outpatient monitoring*	For patients without grade 2 or greater hypotension at C1D15 or grade 3 or 4 hypotension at C1D1, C1D8, or C1D15, outpatient vital signs must be monitored in clinic for minimum of 1 hour after infusion with at least 2 post-dose vital signs measurements performed. For patients who have received outpatient treatment with tebentafusp for at least 3 months without an interruption greater than 2 weeks, outpatient monitoring in clinic may be decreased to minimum of 30 minutes after dosing.
Treatment breaks/delays	Patients with break or delay in treatment for > 2 weeks AND with history of a grade 3 or 4 event of hypotension with tebentafusp dosing during the first weeks of treatment will be monitored as an inpatient for the dose subsequent to the break in dosing, with vital signs performed at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.

C#D# = Cycle# Day#

7.3.3.3 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured as indicated in Table 7-1.

7.3.3.4 Laboratory Studies

All laboratory parameters assessed for safety purposes will be evaluated locally. Refer to Table 7-4 for a summary of the parameters to be evaluated according to Table 7-1. On dosing days of tebentafusp, samples for these parameters will be collected prior to the infusion of tebentafusp.

More frequent evaluations may be performed at the investigator's discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

The Sponsor or the designated CRO will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the Sponsor or the CRO must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-4 Local Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology	Hemoglobin, platelets, white blood cells with differential (eosinophils, lymphocytes, neutrophils)
Chemistry	Albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, calcium, chloride, creatinine, glucose magnesium, phosphate, potassium, sodium, total bilirubin (also measure direct and indirect bilirubin if total bilirubin is grade > 1), blood urea nitrogen or urea, amylase, and lipase, lactate dehydrogenase
Coagulation	Prothrombin time or international normalized ratio, activated partial thromboplastin time
Urinalysis	Macroscopic panel (dipstick) (bilirubin, blood glucose, ketones, pH, protein, specific gravity, white blood cells)
Thyroid	Thyroid stimulating hormone (reflexive thyroid hormone if abnormal)

7.3.3.4.1 Hematology

Hematology panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.3.3.4.2 Clinical Chemistry

Clinical chemistry panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1. For the purposes of stratification within the study randomization procedure, LDH measurements will be taken during Screening by a central laboratory. LDH measurements will also be taken by the local laboratory during both Screening and treatment for safety assessment.

Note: Serum calcium will be measured and recorded in the eCRF. For purposes of eligibility assessment and AE grading, calcium will be corrected for abnormal albumin measurements.

7.3.3.4.3 Coagulation

Coagulation panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.3.3.4.4 Urinalysis

Urinalysis panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.3.3.4.5 Thyroid Function

Thyroid function will be assessed by measuring levels of thyroid stimulating hormone (TSH). Abnormal TSH will require reflexive thyroxine (T4) assessments to determine the cause of the abnormality. TSH will be performed as per the assessment schedule in Table 7-1.

7.3.3.4.6 Cytokine Analysis Panel

The cytokine panel outlined in Table 7-8 will be performed on an as-needed basis in the case of a patient who has an AE suspected to include CRS. This assessment is in addition to the pharmacodynamic cytokine panels.

This assessment will be performed and sent to the central laboratory at the following time points:

- Within 5 hours after the occurrence of the AE
- 1 week (± 1 day) after the occurrence of the AE

7.3.3.4.7 Pregnancy and Assessment of Fertility

Pregnancy tests will be performed for women of childbearing potential.

Arm 1: At Screening, a serum pregnancy test must be performed within 72 hours before the first dose. During treatment, a serum or urine pregnancy test must be performed every 4 weeks. At EOT, a serum or urine pregnancy test must also be performed.

Arm 2: At Screening, every 6 weeks during treatment, and EOT.

7.3.3.5 Cardiac Assessments

A standard 12-lead ECG will be performed in patients receiving tebentafusp as per the assessment schedule in Table 7-1 and Table 7-5. An ECG will be performed in all patients during Screening. Blood samples scheduled at the same time point should be taken after the ECGs are completed. ECGs will be performed in triplicate during Screening for eligibility determination, and all subsequent ECGs can be single assessments. All participating sites may be asked to provide all ECG data collected as part of the current study to a central ECG vendor for storage. At the

Sponsor's discretion, the centrally collected ECGs may undergo interpretation by qualified reviewer(s) at the centeral ECG vendor to validate the machine-calculated ECG data. All clinical decision making (as well as eCRF reporting) will be based on Investigator/site interpretation of any observed ECG abnormalities.

Clinically significant abnormalities present at Screening should be reported on the medical history eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF page.

Table 7-5 12-lead Electrocardiogram Collection Plan

Cycle	Day	Time
Screening	-21 to -1	Anytime
1	1	Pre-dose
1	1	1 hour after dosing[b]
1	8	Pre-dose
1	8	1 hour after dosing[b]
2	1	Pre-dose
2	1	1 hour after dosing[b]
3	1	Pre-dose
3	1	1 hour after dosing[b]
5	1	Pre-dose
5	1	1 hour after dosing[b]
EOT	–	Anytime
Unscheduled[a]	–	As clinically indicated based on symptoms and/or examination

ECG = electrocardiogram; EOT = end of treatment.

a. An unscheduled pharmacokinetic sample should be collected just after an ECG is performed due to any unexpected cardiac signal.

b. ECGs should be collected between the end of infusion and 1 hour after dosing.

NOTE: When ECGs are scheduled at the same time as blood draws, the ECG should be done prior to the blood draw.

7.3.3.6 Skin Punch Biopsy

An OPTIONAL skin punch biopsy will be taken in patients experiencing a grade ≥ 3 rash, bullous rash of any grade, or worsened rash on C1D15 or beyond. A rash that worsens is defined as an increase in grade or increased in symptoms associated with the rash (eg, pruritus) compared to skin toxicity observed on tebentafusp dosing days, C1D1, or C1D8. Skin biopsies will be assessed for immune infiltrate characteristics, gp100 expression, and other markers of immune activation (eg, HLA-DR, PD-L1) to determine the immune activation status in the skin and potentially the mechanisms of skin toxicity.

7.3.3.7 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be determined as indicated in Table 7-6 and should be determined on Day 1 of all odd-numbered cycles (eg, C1D1, C3D1, C5D1) and at EOT.

Table 7-6 Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

7.3.3.8 Pharmacokinetics and Immunogenicity Assessments

The sparse PK and anti-drug antibody (ADA) blood sampling should be obtained according to Table 7-7 in Arm 1 (tebentafusp) only. PK and ADA sampling is not required in patients randomized to Arm 2 (Investigator's Choice). Details are also described in the Laboratory Manual for the handling, labelling, and shipping of the PK and ADA blood samples. It is essential that the actual time and date of collection of each blood sample be recorded in the patient's eCRF. PK samples at the end of infusion time point should be collected after the infusion completes and after the line is flushed and within 15 minutes of the completion time of the tebentafusp infusion. PK samples on C1D2 and C1D16 at the last post-infusion time point should be collected anytime in the 12- to 24-hour window after the completion of the tebentafusp infusion. The time that the sample was collected must be reported with the sample.

Blood samples for the determination of tebentafusp concentration time profiles in serum will be obtained throughout the study. The volume of blood to be collected per sample should be 2 mL to provide approximately 1 mL of serum split into 2 aliquots of 0.5 mL each.

Blood samples to assess the formation of any tebentafusp anti-drug antibodies will be obtained throughout the study.

Table 7-7 Pharmacokinetic and Immunogenicity Assessments

Day of Treatment	Pharmacokinetic Sample Timing[a]	Anti-drug Antibody Sample Timing[b]
C1D1	Pre-dose	Pre-dose
C1D1	End of infusion	
C1D2	12–24 hours post-end of infusion[c]	
C1D8	Pre-dose	Pre-dose
C1D8	End of infusion	
C1D9	12–24 hours post-end of infusion[c]	
C1D15	Pre-dose	
C1D15	End of infusion	
C1D16	12–24 hours post-end of infusion[c]	
C2D1	Pre-dose	Pre-dose
C2D1	End of infusion	
C3D1	Pre-dose	Pre-dose
C3D1	End of infusion	
CXD1[d]	Pre-dose	Pre-dose
CXD1[d]	End of infusion	
End of treatment	At visit	At visit

C#D# = Cycle# Day#; eCRF = electronic case report form.

a. Pharmacokinetic samples have the following time windows: pre-dose (within 3 hours), end of infusion (within 15 minutes).

b. Anti-drug antibody samples will be taken within 3 hours of pre-dose at C1D1, C1D8, C2D1, C3 and then every third cycle (eg, C9, C12).

c. The 12–24 hours post-end of infusion pharmacokinetic sample should be obtained in the ±1 hour timeframe just prior to discharge from inpatient observation. The time of sample must be recorded in the eCRF.

d. "CX" will refer to Cycle 6 and then every third cycle (eg, C9, C12).

7.4 Biomarker Studies

7.4.1 Rationale for Biomarker Studies

Both baseline (predictive) and on-treatment (pharmacodynamic) biomarker studies are designed to understand the biology that is predictive of an optimal response to tebentafusp to assist in selecting patients for future trials. Both sets of biomarkers, as well as markers studied in the setting of disease resistance, may contribute to the design of future studies in this disease setting.

Biomarker analyses will be used to investigate the pharmacodynamic effect of treatment with tebentafusp to determine how changes in the markers may relate to exposure and clinical

outcomes. Potential predictive markers will be studied to identify patients with optimal responses to tebentafusp.

Pharmacodynamic changes with tebentafusp treatment in the activation status of lymphocyte populations can be determined by cytokine sampling over time. Effector and regulatory lymphocyte populations may be analyzed within the tumor (TIL) via IHC or other phenotyping methods.

7.4.2 Tissue Collection Plan (Tumor and Serum)

The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s). Detailed instructions for the collecting, handling, and shipping of tumor samples are outlined in the IMCgp100-202 Laboratory Manual.

Table 7-8 Biomarker Sample Collection Plan

Sample Type	Visit/Time Point	Volume	Suggested Markers	Purpose
Tumor Samples				
Archival tumor sample from diagnosis (if available)[a]	Screening/Baseline	Archival tumor sample from diagnosis (if available)[1]	IHC: gp100, CD3, CD8, PD-L1, HLA-DR	Exploratory predictive markers
Newly obtained tumor biopsy at Screening/ pre-dose[a]	Screening/Baseline	Newly obtained formalin fixed tumor biopsy sample in ethanol (3–6 passes)	IHC: gp100, CD3, CD8, PD-L1, HLA-DR	Exploratory predictive markers
Newly obtained biopsy at **disease progression**[b]	Biopsy taken at the time of disease progression **Optional** in all cohorts	Newly obtained formalin fixed tumor biopsy in ethanol (3–6 passes)	IHC: gp100, CD3, CD8, PD-L1, HLA-DR (other immune-related markers, see below for details).	Mechanisms of tebentafusp drug resistance

Table 7-8 Biomarker Sample Collection Plan

Sample Type	Visit/Time Point	Volume	Suggested Markers	Purpose
Blood and Plasma Samples				
Serum[c]	Screening C1D1 Pre-dose C1D2 12–24 hours post-end of infusion C1D8 Pre-dose C1D9 12–24 hour post-end of infusion C1D15 Pre-dose C1D16 12–24 hour post-end of infusion C3D1 Pre-dose In case of suspected cytokine release, collect samples within 5 hours and at 1 week following adverse event	3 cc in red-top tube	Cytokine panel (HGF, IL-1Rα IL-2, IL-6, IL-10, IFNγ, MCP-1, TNFα, CXCL9, CXCL10, and CXCL11)	Pharmacodynamic effect (On-treatment)

C#D# = Cycle# Day#; CD# = cluster of differentiation #; CXCL# = C-X-C motif chemokine ligand #; gp100 = glycoprotein 100; HGF = hepatocyte growth factor; HLA-DR = human leukocyte antigen-DR isotype; IFNγ = interferon-gamma; IHC = immunohistochemistry; IL-# = interleukin-#; IL-1Rα = interleukin 1 receptor-alpha; MCP-1 = monocyte chemoattractant protein-1; PD-L1 = programmed death-ligand 1; TNFα = tumor necrosis factor-alpha.

a. A tumor biopsy sample is required from all patients, prior to randomization, which can be either or both of the following: (1) an archival tumor biopsy and/or (2) a newly obtained biopsy during Screening. (Fine-needle aspirate or cytology specimens are not adequate for this assessment. Only procedures with limited risk should be considered for fresh tumor biopsies.

b. Biopsy in the setting of treatment resistance is **optional** in all patients. This biopsy should be taken from a progressing lesion.

c. Serum biomarkers will be collected in patients as follows: Screening (all patients; within 21 days of first study treatment); Pre-dose (Arm A patients **ONLY**; within 24 hours of start of infusion); 12–24 hours post-dose (Arm A patients **ONLY**; should be obtained in the ±1 hour timeframe just prior to discharge from inpatient observation). Where possible, pharmacodynamic blood draws should be coordinated with pharmacokinetic blood draws in the post-dose time period.

7.4.3 Tumor and Serum Collections

7.4.3.1 Tumor and Serum Collection Parameters

Submission of a pre-treatment tumor sample is MANDATORY. This sample can be from an archived tumor biopsy or, if not available, a fresh tumor biopsy can be taken. A newly obtained tumor biopsy taken in the setting of resistance (biopsy of a progressing lesion at the time of PD)

is optional in all patients. Only non-significant risk procedures should be performed for accessing tumor tissue in patients enrolled in the trial. Refer to Table 7-8 for details.

7.4.3.2 Exploratory Biology and Predictive Markers

A tumor sample is required from all patients during Screening as described above. This can be an archival tumor sample (slides or the tumor block can be submitted, blocks will be returned) or a newly obtained tumor biopsy. Tumor samples at Screening will be used for studies of predictive patient-selection markers. Expression and localization of biomarkers including but not limited to gp100, PD-L1, HLA-DR, CTLA4, CD3, CD8, and TIL counts may be measured by IHC or using additional techniques deemed suitable. See Table 7-8 for details of assessments for patient selection in tumor tissues. Other immune pathway biomarkers or immunologic tumor markers may also be analyzed from this sample, depending on sample availability, resources, and patient's outcomes and as new scientific evidence becomes available.

7.4.3.3 Pharmacodynamic Markers

7.4.3.3.1 Pharmacodynamic Assessments in Blood

For pharmacodynamic assessments in blood and plasma, collection of pre- and on-treatment samples as indicated in Table 7-8 will allow the assessment of target immune cell and pathway modulation in the peripheral blood by soluble marker profiles (eg, cytokines). Collection of blood samples is mandatory for patients randomized to tebentafusp (Arm 1). Additional markers or methods may be utilized if indicated by new findings from the literature as well as from the Sponsor's internal data.

7.4.3.4 Understanding Resistance to Tebentafusp

Sampling of tumors in the setting of PD following immune-targeted therapy can provide powerful evidence for resistance mechanisms that can be attacked in the next line of therapy or next phase of development. In this study, tumor samples from Baseline and at PD will be compared to determine dynamic changes in the tumor that may represent resistance mechanisms. Assays will include all those immune-related markers tested in the screening/baseline biopsy. Tumor biopsy sampling at the time of PD is optional in all patients.

8 ADVERSE EVENTS AND SAFETY REPORTING

8.1 Assessment of Safety

All patients who receive any treatment with tebentafusp or Investigator's Choice will be considered evaluable for safety. All AEs, regardless of study drug relationship, will be collected up to the 90-day Safety Follow-up Period.

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and are mandated by regulatory agencies worldwide. The Sponsor and CRO have established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of all safety information. All clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Individual AEs should be evaluated by the investigator and should be reported to the CRO/Sponsor for evaluation. This includes the evaluation of the event's seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the AE. The CRO/Sponsor is required to maintain detailed records of all AEs reported by the investigator(s) and to perform an evaluation with respect to seriousness, causality, and expectedness. On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor should submit detailed records of all AEs which are reported by the relevant investigators. Case report processing concerns the evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

8.1.1 Definitions

Definitions of AEs, adverse drug reactions, SAEs, unexpected adverse drug reactions, suspected unexpected serious adverse reactions (SUSARs), and AEs of special interest (AESIs) are presented below.

AE: An AE is defined as the appearance of (or worsening of pre-existing) an undesirable sign, symptom, or medical condition that occurs after the patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication.

Adverse drug reaction: An adverse drug reaction is an unwanted or harmful reaction which occurs after administration of a drug or drugs and is suspected or known to be due to the drug. Adverse drug reactions have traditionally been categorized as pharmacologic (predicted based on the pharmacology of the drug) or idiosyncratic (not predicted based on pharmacology).

SAE: An SAE is any AE that is defined as one of the following:

1. Is fatal or life-threatening
2. Results in persistent or significant disability or incapacity
3. Constitutes a congenital anomaly/birth defect
4. Is medically significant, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
5. Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
6. Death due to PD of malignancy should not be reported as an SAE, if documented by use of appropriate method (eg, as per RECIST v1.1). Any AE that occurred as a result of the PD should be reported in the appropriate manner

Unexpected adverse drug reaction: An adverse drug reaction that is not consistent with applicable product information or summary characteristics of the study drug.

SUSAR: A SUSAR is an adverse reaction meeting serious criteria (above), the nature or severity of which is not consistent with the reference safety information for the investigational study drug(s).

AESI: An AESI (serious or non-serious) is an AE with scientific and/or medical concern specific to the Sponsor's program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Refer to the tebentafusp Investigator's Brochure for details of the AESI.

8.2 Criteria for Expectedness

The concept of expectedness refers to events that may or may not have previously been observed and documented and are not necessarily the known pharmacological properties of the medicine. An AE will be unexpected for purposes of regulatory reporting unless it is mentioned in the appropriate reference safety information within the current Investigator's Brochure for the

investigational study drug, even if it is a medical occurrence expected for the disease being treated.

8.3 Assessment of Causality

8.3.1 Causality Assessment Required for All Adverse Events

The investigator decides whether he or she interprets the observed AE as either related to the disease, the study medication, the study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terms are defined:

1. **Related**: a direct cause and effect relationship between the study treatment and the AE is likely
2. **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
3. **Unrelated**: without question, the AE is definitely not associated with the study treatment

All "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.4 Adverse Event Reporting

8.4.1 Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as serious are subject to expedited reporting. Expedited reporting of cases will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. Additionally, any safety information from other observations that could change the risk-benefit evaluation of the product will be communicated in an expedited manner to the regulatory authorities and all investigators by the Sponsor.

The CRO will be responsible for the processing and reporting of SAEs. AEs will be coded by using the Medical Dictionary for Regulatory Activities.

Minimum criteria for a valid adverse drug reaction case have been established by ICH and individual regulatory agencies and are listed as the following:

- An identifiable reporter
- An identifiable patient
- A reaction/event
- A suspected medicinal product

Other safety issues that also qualify for expedited reporting by the Sponsor are those that would materially alter the current risk-benefit assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial). Although these events will not be reported as SUSARs, they might require other action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and all IEC of safety issues which might materially alter the risk-benefit assessment of the investigational agents.

8.4.2 Standards for Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as SUSARs are subject to expedited reporting. Additionally, any safety information from other observations that could change the risk-benefit evaluation of the product should be promptly communicated to the regulatory authorities. Any other SUSARs associated with the investigational product should be reported as soon as the Sponsor becomes aware of them and this includes SUSARs which occur in another trial conducted by the same Sponsor, are identified by spontaneous reports or a publication, or are transmitted to the Sponsor by another regulatory authority.

8.4.3 Reporting of Out-of-range Laboratory Test Results as Adverse Events

Out-of-range laboratory test results should be reported as AEs (not as abnormal laboratory values, ie, report as anemia, not low hemoglobin) if, in the opinion of the principal investigator, they are clinically significant. Abnormal laboratory results that are not considered to be clinically significant will not be reported as AEs. The significance of abnormal laboratory results should be documented in the study records.

8.4.4 Reporting Guidelines for Other Observations

Other safety issues that also qualify for expedited reporting where they might materially alter the current risk-benefit assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial), for instance include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- A SUSAR that occurs after the patient has completed a clinical trial and is reported by the investigator to the Sponsor

Events which occur during the trial and are relevant in terms of patient safety, but which do not fall within the definition of SUSAR (and thus are not subject to the reporting requirements for SUSARs) are:

- An SAE which could be associated with the trial procedures and which could modify the conduct of the trial

- A significant hazard to the patient population such as lack of efficacy of an investigational medicinal product
- A major safety finding from a newly completed animal study (such as carcinogenicity)
- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal product in another country by the same Sponsor
- Safety recommendations of the Independent Data Monitoring Committee (IDMC)

Although these events/observations will not be reported as SUSARs, they might require another action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and the IECs of safety issues which might materially alter the risk-benefit assessment of the investigational medicinal product.

Expedited reporting is not usually required for reactions that are serious but expected, or for non-serious adverse reactions whether expected or not. It is usually also inappropriate to report events that are considered unrelated to the investigational medicinal product.

8.4.5 Pregnancy Reporting

Pregnancy will be reported through the Pregnancy Reporting Form (paper), as well as in the eCRF as an AE. The Pregnancy Reporting Form (paper) should be completed and reported as indicated to the CRO pharmacovigilance team within 24 hours of being made aware of the event. Women who become pregnant during the study will be withdrawn from treatment at the earliest opportunity. The investigator shall report all pregnancies immediately to the CRO. The CRO will then notify the Sponsor within 1 business day of being informed of the event. Following withdrawal from the study, every attempt will be made to follow the patient and any resulting offspring for up to 6 weeks postpartum, unless otherwise medically indicated. Abortion, stillbirth, or any malformation/disease in the offspring must be reported as an SAE.

For men participating in the study who report the pregnancy of a partner, the investigator will ask to collect information about the results of the pregnancy/birth using the Pregnant Partner Forms. The partner may be asked to sign a consent form giving permission for information to be collected. This health information will become part of the research study records. It will be shared with the Sponsor.

8.5 Investigator's Responsibilities

The investigator is responsible for the collection of AE data. All AEs should be recorded in the eCRF. The investigator shall report all SAEs within 24 hours of being made aware of the event to the CRO pharmacovigilance via the SAE Report Form. All SAEs that occur between obtaining the patient's informed consent and 90 days after the last dose of study drug must be reported.

SAE data will also be entered into the clinical database by completing as much information as possible and checking "Yes" when prompted whether the event is classified as an SAE on the AEs eCRF page.

The SAE Report Form must be completed, signed by the investigator, and submitted via email to pv@klserv.com within 24 hours of identifying an SAE. The following information will be included the report:

- Patient identification (patient number and date of birth)
- Trial number
- Study therapy (dose, route, form, regime, start date, end date)
- Concomitant medication (including dose, route, form, regime, start date where available)
- Nature of SAE (overall diagnosis where available or alternatively signs and symptoms)
- Date and time of occurrence
- Any associated factors (concomitant disease or medication)
- Proposed relationship to study therapy
- Outcome
- Identity of the reporter
- Action in relation to study (withdrawn from treatment, suspended, none)

The investigators or co-investigators are required to sign the SAE Report Form within 24 hours of awareness of the event, even if the required information is incomplete or if the investigators are awaiting laboratory or diagnostic reports. Investigators may be asked for additional information for any reported SAE. An SAE follow-up report with attached documents (if necessary) should be forwarded by email to the CRO pharmacovigilance team as soon as the additional information is available. The study number IMCgp100-202 must be in the title of any email for study identification purposes.

8.6 Sponsor and Clinical Research Organization's Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the investigational study drugs being studied. The Sponsor and CRO are responsible for ensuring that expedited reports are made to all concerned investigators, to the IEC where required, and to all regulatory authorities of all adverse drug reactions that are both serious and unexpected, or findings that could adversely affect the health of patients, impact on the conduct of the trial, or alter the competent authority's authorization to continue the trial in accordance with local applicable regulations.

9 STATISTICAL METHODS AND DATA ANALYSES

9.1 General Principles

Data will be summarized using descriptive statistics. Categorical data will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, minimum, and maximum will be presented. Additional details of data reporting will be outlined in the Statistical Analysis Plan (SAP).

The following rules will be followed for reporting results unless stated otherwise:

- Screen failure patients are those who signed the informed consent but are never randomized. For these patients, the eCRF data collected will not be included in most analyses
- Baseline is defined as the last assessment prior to the first dose of treatment received (ie, C1D1 pre-dose)

9.2 Analysis Sets

9.2.1 Intent to Treat Analysis Set

The intent to treat (ITT) set comprises all patients assigned to treatment analyzed by the treatment assignment whether or not the patient received the assigned treatment. All patients randomized in the study will be analyzed in the ITT set. The ITT set will be used for all demography, baseline characteristics, and efficacy data summaries and analyses.

9.2.2 Rash Analysis Set

The rash analysis set (RAS) comprises all patients randomized to the tebentafusp monotherapy who develop a rash within the first week of treatment (and prior to the second dose) and all patients randomized to the Investigator's Choice monotherapy regardless of a rash. If the RAS analysis described in Section 9.3.3 crosses the pre-specified stopping boundaries (see Section 9.7), then this analysis set will also be used for demography, baseline characteristics, efficacy, and safety data summaries and analyses. The AE preferred terms that define the RAS will be detailed in the SAP.

9.2.3 Safety Analysis Set

The safety set includes all patients who have received at least 1 full or partial dose of tebentafusp or Investigator's Choice. Patients will be classified in this set according to the initial treatment received. The safety set will be used for the safety summaries of the study.

9.3 Primary Analysis

9.3.1 Primary Objective

There are 2 primary objectives in this study. The first primary objective of the trial is to compare the OS in all patients randomized to the tebentafusp monotherapy versus all patients randomized to the Investigator's Choice monotherapy. The second primary objective will be to compare the OS in all patients randomized to the tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomized to the Investigator's Choice monotherapy.

9.3.2 Variables

The primary variable (OS) is the time to death from the date of randomization. For patients without documentation of death, OS will be censored at the last date the patient was known to be alive and will be followed continuously while patients are treated on trial and every 3 months in the follow-up phase.

9.3.3 Primary Analyses of Overall Survival

There are 2 analyses of the primary endpoint of OS, relating to the 2 objectives of the study. The overall study 2-sided α-level of 5% will be split between these objectives.

The first primary analysis of OS in the RAS will be conducted using a 2-sided log-rank test stratified by the LDH status (LDH above the ULN versus LDH below or equal to the ULN; measured centrally) for generation of the p-value. Ten percent of the study's overall Type I error rate will be allocated to this analysis ($\alpha = 0.5\%$).

The secondary primary analysis of OS in all randomized patients will be conducted using a 2-sided log-rank test stratified by LDH status (LDH above the ULN versus LDH below or equal to the ULN; measured centrally) for generation of the p-value. Ninety percent of the study's overall Type I error rate will be allocated to this analysis ($\alpha = 4.5\%$). However, if the first interim OS analysis in the RAS group crosses the pre-specified stopping boundary (see Section 9.7), then the α from that analysis will be carried over to this ITT analysis and the overall α-level for that analysis will therefore be 5%. Otherwise, an overvall α-level of 4.5% will be applied to the ITT OS analyses.

For both analyses, the HR will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties, together with the associated profile likelihood 95% CIs for the HR. Kaplan-Meier plots of OS will be presented by treatment group. Median OS with 95% CIs will be presented. In addition, landmark survival estimates at 1 year with corresponding 95% CIs will also be presented using Kaplan-Meier methodology. Kaplan-Meier survival estimates may also be presented for other time points of interest.

For both analyses, exploratory analyses to assess the impact of other potentially prognostic factors such as extent of liver metastases (defined as largest hepatic metastatic lesion ≥ 44.5

mm) will be performed using a Cox-proportional hazards model (ties=Efron) that contains the treatment term, factor, and treatment-by-factor interaction term. The treatment effect HRs for each treatment comparison along with their CIs will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis). Further details will be described in the SAP.

9.4 Secondary Efficacy Analyses

9.4.1 Efficacy

PFS

PFS is defined as the time from randomization to the date of first documented PD (per RECIST v1.1 by investigator assessment) or death due to any cause, whichever occurs first, regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to PD. Patients who have not progressed or died at the time of the analysis will be censored at the time of the last evaluable tumor assessment. Patients with 2 or more missed tumor assessments will be censored at the time of the last tumor assessment prior to the missed assessments.

The analysis of PFS will follow the ITT analysis of OS in a hierarchical manner. PFS will not be formally tested unless the null hypothesis for the OS endpoint is rejected, using the α level that is used for the ITT OS analysis (see Section 9.3.3). The PFS analysis will include all randomized patients and will be conducted using a 2-sided log-rank test stratified by LDH status (LDH above the ULN versus LDH below or equal to the ULN; measured centrally) for generation of the p-value. Formal testing of PFS in the RAS will not be conducted. The HR will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties, together with the associated profile likelihood 95% CIs for the HR.

Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of PFS will be provided, including median PFS for each treatment and landmark estimates at specific time points with corresponding CIs.

If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 planned radiological assessment visits of Baseline (ie, within 26 weeks).

The PFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of PD will be determined based on the earliest of the dates of the component that triggered the PD.

- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

ORR and BOR

ORR is defined as the number of randomized patients with at least 1 visit response of complete response (CR) or PR (ie, the best overall response [BOR]) divided by the number of randomized patients as a percentage for each treatment arm in the ITT set. The BOR is defined as the best response designation up until PD or last evaluable assessment in the absence of PD. Any CRs or PRs that occur after a further anti-cancer therapy was received will not be included in the numerator for the ORR calculation by RECIST v1.1.

The analysis of ORR will follow the ITT analyses for OS and PFS in a hierarchical manner. ORR will not be formally tested unless the null hypotheses for OS and PFS are rejected. ORR will not be formally tested in the RAS.

The ORR will be compared between treatments using logistic regression models adjusting for the covariate LDH status (LDH above the ULN versus LDH below or equal to the ULN; measured centrally). The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI. The p-value will be based on a test statistic that is calculated as twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariate defined above. The test statistic is chi-squared distributed with 1 degree of freedom.

A summary of BOR and ORR will also be presented by treatment group.

DCR

Disease control rate (DCR) is defined as the proportion of patients with a BOR of CR or PR, or SD recorded at least 24 weeks (± 1 week) after randomization of study drug and prior to any PD event. Objective responses do not require confirmation. The estimated DCR and associated 95% CI for the true DCR will be determined by treatment Arm. DCR will be compared between the arms using logistic regression, as described for ORR.

HRQoL

The HRQoL assessments will be measured in all patients at specified time points and changes from baseline assessments will be assessed between the 2 treatment groups of tebentafusp and Investigator's Choice.

More detail on HRQoL endpoints will be provided in the SAP.

Immunogenicity

Immunogenicity assessment in the study will investigate the presence of an immune response to tebentafusp and potential clinical impact. Confirmed ADA subsequent to administration of tebentafusp will be evaluated for clinical impact based on integrated analysis of immunological, PK, pharmacodynamic, and clinical efficacy and safety data.

9.4.2 Safety

9.4.2.1 Analysis Set and Grouping for the Analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into 3 mutually exclusive segments:

1. Pre-treatment period: from the day the patient signs the informed consent to the day before first dose of study medication

2. On-treatment period: from the day of first dose of study medication to 90 days after the last dose of study medication

3. Post-treatment period: starting at Day 91 after last dose of study medication

9.4.2.2 Adverse Events

Summary tables for AEs include only AEs that are new or worsened during the on-treatment period (treatment-emergent AEs). However, all safety data (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent AEs will be summarized by system organ class and/or preferred term, severity (based on NCI CTCAE v4.03 grades), type of AE, relation to study treatment by treatment group. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group.

9.4.2.3 Laboratory Abnormalities

For laboratory tests covered by the NCI CTCAE v4.03, the study team will grade laboratory data accordingly. For laboratory tests covered by NCI CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Laboratory data will be summarized either based on absolute or change from baseline values or based on NCI CTCAE grades or normal/low/high classifications. Shift tables and/or shift plots or plots representing data over time may be produced. Further detail on laboratory outputs will be provided in the SAP.

9.4.2.4 Other Safety Variables

Vital signs data will be summarized either based on absolute or change from baseline values or based on pre-defined shift criteria. Shift tables, shift plots, and/or plots representing data over time may be produced. Further detail on vital signs outputs will be provided in the SAP.

ECG data will be summarized based on changes in corrected QT interval values. Other ECG parameters may also be summarized. ECG assessment will also be classified as normal, abnormal not clinically significant, and abnormal clinically significant, and shift tables may be produced.

9.4.2.5 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized.

9.4.2.6 Pharmacokinetics

The PK parameters that will be assessed are presented in Table 9-1.

Table 9-1 Pharmacokinetic Parameters to be Analyzed

C_{max}	The maximum drug concentration observed over the dosing interval
C_{min}	The minimum drug concentration observed over the dosing interval
C_{trough}	The drug concentration at X days after dosing

The safety set will be used in all PK data analysis and PK summary statistics.

Pharmacokinetic Analyses

Descriptive statistics of all PK parameters for tebentafusp will include the arithmetic and geometric mean, median, standard deviation, and coefficient of variation, geometric coefficient of variation, minimum, and maximum. Zero concentrations will not be included in the geometric mean calculation. Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as 0 in summary statistics and reported as is in data listings. Any missing PK parameter data will not be imputed.

Further analyses may be conducted using population PK approaches. In addition, a model-based approach may be used to explore the potential relationship between efficacy, safety, and/or biomarker endpoints and tebentafusp concentration and/or exposure metrics. All analyses will be reported either in the clinical study report or a stand-alone report.

9.5 Exploratory Analyses

9.5.1 Efficacy

Time to second PD will be summarized based on Kaplan-Meier methodology according to PD dates provided by the investigator. The clinical benefit of treatment beyond initial PD will be summarized as the number (%) of patients continuing treatment beyond initial RECIST v1.1 PD, duration of treatment beyond initial RECIST v1.1 PD.

Further details on exploratory efficacy endpoints and analyses will be defined in the SAP or a separate biomarker analysis plan.

9.5.2 Biomarkers

9.5.2.1 Potential Predictor of Efficacy

The expression level of gp100 and PD-L1 at Screening/Baseline will be listed and summarized.

9.5.2.2 Pharmacodynamic Markers

Pharmacodynamic markers will be assessed in blood/serum at Screening/Baseline and on-treatment. Assessments at Screening/Baseline and on-treatment and change from Baseline will be listed by patient and summarized (when sample size is sufficient) using descriptive statistics.

Any additional exploratory analyses on biomarkers will be detailed in the SAP.

9.6 Sample Size Calculation

9.6.1 ITT Analysis

OS is the primary endpoint for this study. Assuming a 2:1 randomization ratio of tebentafusp versus Investigator's Choice, 250 events (deaths) are needed in the randomized trial to provide 89% power to detect a difference in survival distributions that can be characterized by a 0.645 HR for OS with a 2-sided significance level of 0.045. Assuming OS is exponentially distributed, this may translate to a median OS of 18.6 months in the tebentafusp treated arm and 12 months in the Investigator's Choice arm.

Considering a uniform recruitment time of about 33 months and a 10% annual drop-out rate, 369 patients need to be randomized in a 2:1 ratio to the 2 arms in order to observe 250 events after approximately 51 months as follows:

- 246 patients to the tebentafusp arm
- 123 patients to the Investigator's Choice arm

Three analyses of OS are planned: 2 formal interim analyses and the final analysis. The details of the interim analyses are described in Section 9.7.

In order to randomize 369 patients (assuming a 10% screen failure rate), 410 patients will need to be enrolled. In order to enroll 410 patients, approximately 900 patients will need to be pre-screened (allowing for a 5% attrition rate and assuming 48% of patients are HLA-A*0201 positive). The prevalence of HLA-A*0201 varies depending on the region, so additional patients may be needed to be pre-screened to enroll 410 patients.

9.6.2 RAS Analysis

The study is also powered for the RAS analysis of OS. Assuming 50% of the tebentafusp-treated patients develop a rash within the first week of treatment, there will be an approximate 1:1 ratio between patients in the tebentafusp arm and the Investigator's Choice arm. One hundred sixty-four events (deaths) are needed to provide 89% power to detect a difference in the survival distributions that can be characterized by a 0.531 HR for OS with a 2-sided significance level of 0.005. Assuming OS is exponentially distributed, this may translate to a median OS of 22.6 months in the tebentafusp-treated arm and 12 months in the Investigator's Choice arm.

9.7 Interim Analysis

For both primary objectives, two interim analyses will be performed using a 3-stage group sequential design (Figure 9-1). The first interim analysis on the ITT population will be based on approximately 60% of the events (150 events) and the second interim analysis will be based on approximately 80% of the events (200 events). The interim analyses on the RAS population will occur at the same time as the interim analyses on the ITT population and will therefore be based on the number of events available in the snapshot used for the ITT analysis. O'Brien-Fleming boundaries (O'Brien and Fleming, 1979) will be used to maintain the desired Type I error rates across the interim and final analyses of OS. The Lan-DeMets approach (Lan and DeMets, 1983) that approximates the O'Brien-Fleming spending function will be used to adjust for situations where the actual number of events up to the data cut-off date for a given interim analysis does not match the planned number. The significance level for the OS analyses will be calculated by specifying the information fraction for each analysis. The information fraction is calculated as the actual number of OS events up to the data cut-off date divided by the total required number of events for the final analysis. For example, for an ITT interim analysis of OS conducted after 150 death events, the information fraction would be entered as 0.60 (150 of 250 events). The first interim analysis of OS will occur after the end of accrual. The same approach will be used for the RAS OS analyses, using 164 as the total target number of events and the denominator when calculating the information fraction.

Further details of the stopping boundaries will be provided in the SAP.

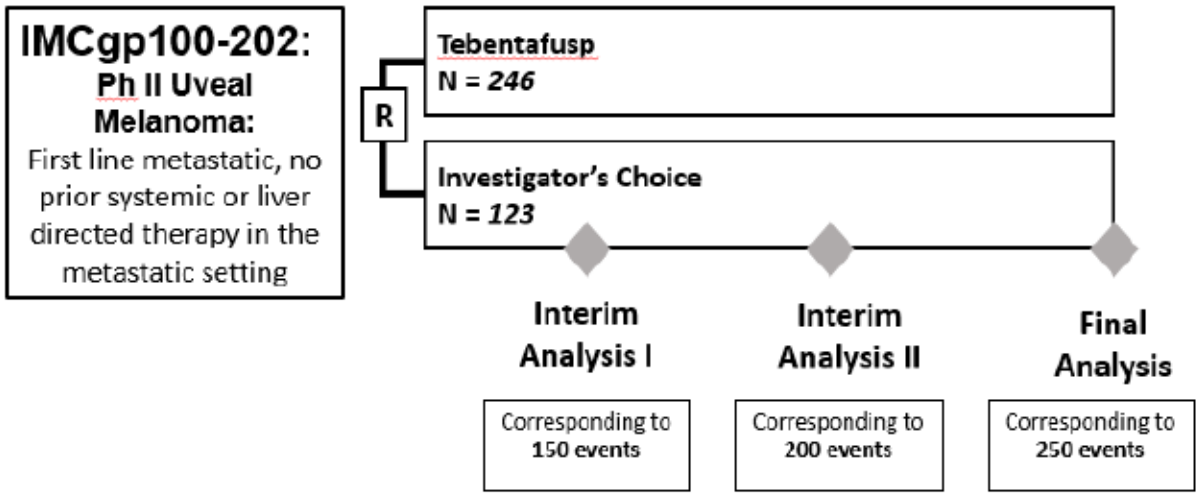

Figure 9-1 Study Design and Interim Analysis for the ITT Population

Ph II = Phase 2; R = randomized.

In order to provide strong control of the type I error rate, the primary endpoint of OS in the ITT population and key secondary endpoints, PFS and BOR, will be tested in this sequential order. If any previous analysis in the sequence is not statistically significant, the alpha cannot be transferred to subsequent analyses. The α to be used for the ITT OS analyses will depend on the results of the analyses of OS in the RAS. Using graphical approaches as described by Mauer and Bretz (Mauer and Bretz, 2013), if the hypothesis associated with OS in the RAS is rejected, then any remaining alpha will be transferred to the remaining OS ITT analyses.

Further details of the stopping boundaries will be provided in the SAP.

The final analysis of PFS will be based on 288 progression and death events. Assuming a Type I error rate of 4.5%, a median PFS of 5 months in the tebentafusp arm and 3.3 months in the Investigator's Choice arm, an HR of 0.66, and the same accrual and drop-out assumptions described earlier for OS, the analysis of PFS would have 90% power to demonstrate a difference in the PFS distributions between the 2 arms. Given that this analysis will only be conducted if the OS ITT analysis, which has 89% power, is rejected, the power to actually demonstrate a significant PFS difference is 89% x 90% = 80%.

Due to the higher hazard of progression events relative to death events, the required number of PFS events is expected to occur prior to the first interim analysis of OS. If the required number of events have not occurred at the time of the first OS interim analysis, then the PFS analysis will occur at a later time when 288 progression events have occurred.

The analysis of BOR in the ITT population will occur after all 369 randomized patients have been followed for approximately 6 months (ie, 2 planned assessments) for response. It will only be

formally tested for statistical significance if the null hypotheses for OS and PFS in the ITT populations are both rejected.

Neither PFS nor BOR are therefore expected to be tested on an interim basis.

9.8 Independent Data Monitoring Committee

An IDMC will be established to provide oversight of safety and efficacy considerations in the current protocol (IMCgp100-202). The IDMC will act in an advisory capacity and make recommendations regarding steps to ensure both patient safety and the ethical integrity of the trial. The voting members of the committee are external to Immunocore and will not otherwise be involved with the trial. The IDMC will include 3 clinicians experienced in oncology/melanoma and 1 statistician. Specific details regarding IDMC responsibilities, governance, and documentation will be described in a separate charter that is reviewed and approved by the IDMC members. Immunocore has primary responsibility for the design and conduct of the study.

The IDMC will recommend if the trial should continue in accordance with the protocol. The IDMC will also monitor trial safety data 3 times annually or at a frequency described in the IDMC charter to ensure the ongoing protection of the patients enrolled in the study. Efficacy and safety data will be reviewed at the interim analyses to evaluate the overall risk-benefit profile.

9.9 Patient Demographics and Other Baseline Characteristics

Demographic data, baseline disease characteristics, and other baseline data will be listed in detail. Qualitative data (eg, performance status) and quantitative data (eg, weight) will be summarized by descriptive statistics.

9.10 Treatment Data

Actual dose and duration in days of treatment for tebentafusp and Investigator's Choice, as well as the dose intensity (actual dose received/actual duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration), will be summarized by descriptive statistics by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by Anatomical Therapeutic Chemical term and treatment group.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last doses, duration of exposure to each study drug, and date of discontinuation for each patient.

10 DATA HANDLING AND MANAGEMENT

10.1 Data Confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the protected health information that will be collected and the use or disclosure of that information. If the patient revokes authorization to collect or use this information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. To protect the health information of study patients, access to the data collection system will be controlled by a sequence of individual user identification codes and passwords that are made available only to authorized trained personnel.

The ICFs will include language required by the recent European Union General Data Protection Regulation, which became effective 25 May 2018.

10.2 Site Monitoring

Before study initiation at trial sites, Sponsor and/or CRO study team members will review the protocol and eCRFs with the investigators and the site study staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, and the progress of enrollment and to ensure that study treatments are being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. The investigator must assure that the site monitor is allowed access to all study files, including all site medical records, case and visit notes, and laboratory reports.

10.3 Data Collection

The investigator is required to maintain source documents for each patient in the study, consisting of case and visit notes (site medical records), containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded in the eCRF must be traceable to source documents in the patient's file. The investigator must also keep the original, signed ICF, with 1 signed copy given to the patient.

This study will use an electronic data capture (EDC) system and the principal investigator and site study staff will enter the data required by the protocol into the eCRF. The eCRF have been built using fully validated secure web-enabled software that conforms to Title 21 of the United States Code of Federal Regulations Part 11 requirements. The principal investigator and all identified site staff will not be given access to the EDC system until they have been trained. The principal investigator is responsible for assuring that the data entered into the eCRF is complete and accurate and that entry and updates are performed in a timely manner. Field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions.

Tissue samples obtained during the study (eg, tumor, blood for PK or other analyses) will be collected from the investigator sites and analyzed by Sponsor laboratories, contracted central laboratories, or local laboratories. Radiological assessments will be reviewed retrospectively in a central repository as described. Field monitors will review the eCRF and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample by the site staff and 1 copy will be retained at the investigational site.

10.4 Database Management

Sponsor clinical study personnel and trial field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system.

Concomitant treatment and prior medication data in the database will be coded using the World Health Organization Drug Reference List, based on the Anatomical Therapeutic Chemical classification. Medical history, current medical conditions and AEs in the database will be coded using the Medical Dictionary for Regulatory Activities terminology. After database lock, the investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory and Ethical Compliance

This clinical study was designed, and will be implemented and reported, in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and United States Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the Investigator and Institutional Review Board/Independent Ethics Committee/Research Ethics Board

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB or IEC or Research Ethics Board (REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to field monitors, auditors, designated agents of the Sponsor, the IRB or IEC or REB, and regulatory authorities as required.

11.3 Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures; the 1 exception to this note are radiologic assessments performed before Screening within the specified window. The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be captured in the eCRF.

11.4 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 3.6.

11.5 Publication of Study Protocol and Results

The Sponsor will publish the key design elements of this protocol in a publicly accessible database (clinicaltrials.gov). At the time of study and clinical study report completion, the results of this study will be either submitted for publication and/or posted in a publicly accessible database.

11.6 Study Documentation, Record Keeping, and Retention of Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6(R2): Good Clinical Practice, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine any clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported in the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested in the eCRF must be recorded.

The investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6(R2) Section 8) and as required by applicable regulations and guidelines. The investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for a period of not less than 15 years from the completion of the clinical trial unless the Sponsor provides written permission to dispose of them or requires their retention for an additional period of time because of applicable laws, regulations, and guidelines.

11.7 Confidentiality of Study Documents and Patient Records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the Sponsor or the CRO. Signed ICFs and patient enrollment logs must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and Inspections

Source data and all trial documents must be available to inspections by the Sponsor, the CRO or designee, or Health Authorities.

11.9 Financial Disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site prior to study start.

12 REFERENCES

Algazi AP, Tsai KK, Shoushtari AN, Munhoz RR, Eroglu Z, Piulats JM, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-1L antibodies. *Cancer*. Epub 2016 Aug 17.

Andreoli MT, Mieler WF, Leiderman YI. Epidemiological trends in uveal melanoma. *Br J Ophthalmol*. 2015;99(11):1550–3.

Augsberger JJ, Correa ZM, Shaika AH. Effectiveness of treatments for metastatic uveal melanoma. *Am J Ophthalmol*. 2009;148(1):119–27.

Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. European Society of Medical Oncology. Poster abstract 4958. Sep 2014. Madrid, Spain.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–39.

Bronkhorst IH, Ly LV, Jordanova ES, Vrolijk J, Versluis M, Luyten GP, et al. Detection of M2-macrophages in uveal melanoma and relation with survival. *Invest Ophthalmol Vis Sci*. 2011;52(2):643–50.

Bronkhorst IH, Vu TH, Jordanova ES, Luyten GP, Burg SH, Jager MJ. Different subsets of tumor-infiltrating lymphocytes correlate with macrophage influx and monosomy 3 in uveal melanoma. *Invest Ophthalmol Vis Sci*. 2012;53(9):5370–8.

Buder K, Gesierich A, Gelbrich G, Goebeler M. Systemic treatment of metastatic uveal melanoma: review of literature and future perspectives. *Cancer Med*. 2013;2(5):674–86.

Campbell RJ, Sobin LH, Zimmerman LE & World Health Organization. Histological typing of tumours of the eye and its adnexa. International histological classification of tumours. Springer: Berlin; London 1998.

Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol*. 2017;101(1):38–44.

Carvajal RD, Sosman JA, Quevedo JF, Milhem MM, Joshua AM, Kudchadkar RR, et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *JAMA*. 2014;311(23):2397–405.

Dunavoelgyi R, Dieckmann K, Gleiss A, Sacu S, Kircher K, Georgopoulos M, et al. Local tumor control, visual acuity, and survival after hypofractionated stereotactic photon radiotherapy of choroidal melanoma in 212 patients treated between 1997 and 2007. *Int J Radiat Oncol Biol Phys*. 2011;81(1):199–205.

Eastern Cooperative Oncology Group Performance Status. http://ecog-acrin.org/resources/ecog-performance-status. Accessed: 25 Jun 2015.

Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. Malignant melanoma of the uvea. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer. 2010:547–59.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–47.

Field MG, Harbour JW. Recent developments in prognostic and predictive testing in uveal melanoma. *Curr Opin Ophthalmol*. 2014;25(3):234–9.

Furney SJ, Turajlic S, Stamp G, Thomas JM, Hayes A, Strauss D, et al. The mutational burden of acral melanoma revealed by whole-genome sequencing and comparative analysis. *Pigment Cell Melanoma Res*. 2014;27(5):835-8.

Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540–50.

Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol*. 2016;34(13):1510–7.

Karydis I, Chan PY, Wheater M, Arriola E, Szlosarek PW, Ottensmeier CH. Clinical activity and safety of pembrolizumab in ipilimumab pre-treated patients with uveal melanoma. *Oncoimmunology*. 2016;18;5(5):e1143997.

Khattak MA, Fisher R, Hughes P, Gore M, Larkin J. Ipilimumab activity in advanced uveal melanoma. *Melanoma Res*. 2013;23(1):79–81.

Khoja L, Atenafu EG, Joshua AM, Suciu S, Leyvraz S, Sato T, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. *Ann Oncol*. 2019;30(8):1370-80.

Lan KK and DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70(3):659-63.

Lee DW, Gardner R, Porter, DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188–95

Luke JJ, Callahan MK, Postow MA, Romano E, Ramaiya N, Bluth M, et al. Clinical activity of ipilimumab for metastatic uveal melanoma: a retrospective review of the Dana-Farber Cancer Institute, Massachusetts General Hospital, Memorial Sloan-Kettering Cancer Center, and University Hospital of Lausanne experience. *Cancer*. 2013;119(20):3687–95.

Maat W, Ly LV, Jordanova ES, de Wolff-Rouendaal D, Schalij-Delfos NE, Jager MJ. Monosomy of chromosome 3 and an inflammatory phenotype occur together in uveal melanoma. *Invest Ophthalmol Vis Sci*. 2008;49(2):505–10.

Maio M, Danielli R, Chiarion-Sileni V, Pigozzo J, Parmiani G, Ridolfi R, et al. Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. *Ann Oncol*. 2013;24(11):2911–5.

Middleton D, Menchaca L, Rood H, Komerofsky R. New allele frequency database: http://www.allelefrequencies.net. *Tissue Antigens*. 2003;61:403–7.

Middleton M, Corrie P, Sznol M, Infante J, Mulatero C, Evans J, et al. A phase I/IIa study of IMCgp100: partial and complete durable responses with a novel first-in-class immunotherapy for advanced melanoma. American Academy for Cancer Research Annual Meeting, Philadelphia, PA. April 2015.

Middleton M, Corrie P, Sznol M, et al. Safety, pharmacokinetics and efficacy of IMCgp100, a first-in-class soluble TCR-antiCD3 bispecific T cell redirector with solid tumour activity: results from the FIH study in melanoma. American Society for Clinical Oncology, 2016 Annual Meeting, Chicago, USA.

Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015;373(19):1803–13.

Nicholas MN, Khoja L, Atenafu EG, et al. Prognosticators of first line treatment for metastatic uveal melanoma (mUM). A review of the Princess Margret Cancer Centre 12 year experience. American Society of Clinical Oncology, Annual meeting 2016 (Poster presentation).

Nishino A, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. *Clin Cancer Res*. 2013;19(14):3936–43.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549–56.

Patel M, Smyth E, Chapman PB, Wolchok JD, Schwartz GK, Abramson DH, et al. Therapeutic implications of the emerging molecular biology of uveal melanoma. *Clin Cancer Res*. 2011;17(8):2087–100.

Ramaiya KJ, Harbour JW. Current management of uveal melanoma. *Exp Rev Ophthal*. 2007;2:939–46.

Shoushtari AN, Carvajal RD. GNAQ and GNA11 mutations in uveal melanoma. *Melanoma Res*. 2014;24(6):525–34.

Shoushtari AN, Evans J, Corrie P, et al. A Phase 1 study of IMCgp100, a soluble HLA-A2 restricted gp100-specific T cell receptor-CD3 therapeutic with solid tumor activity in patients with advanced uveal melanoma. Society for Melanoma Research International Congress, Annual Meeting 2016 (Oral presentation).

Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118(9):1881–5.

Takase H, Yu CR, Mahdi RM, Douek DC, Dirusso GB, Midgley FM, et al. Thymic expression of peripheral tissue antigens in humans: a remarkable variability among individuals. *Int Immunol*. 2005;17(8):1131–40.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for

Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205–16.

Valpione S, Moser JC, Parrozzani R, Bazzi M, Mansfield AS, Mocellin S, et al. Development and external validation of a prognostic nomogram for metastatic uveal melanoma. *PLoS One*. 2015;10(3):e0120181.

van Dinten LC, Pul N, van Nieuwpoort AF, Out CJ, Jager MJ, van den Elsen PJ. Uveal and cutaneous melanoma: shared expression characteristics of melanoma-associated antigens. *Invest Ophthalmol Vis Sci*. 2005;46(1):24–30.

Wagner SN, Wagner C, Schultewolter T, Goos M. Analysis of Pmel17/gp100 expression in primary human tissue specimens: implications for melanoma immuno- and gene-therapy. *Cancer Immunol Immunother*. 1997;44(4):239–47.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412–20.

Woodman SE. Metastatic uveal melanoma: biology and emerging treatments. *Cancer J*. 2012;18(2):148–52.

Yu FX, Luo J, Mo JS, Liu G, Kim YC, Meng Z, et al. Mutant Gq/11 promote uveal melanoma tumorigenesis by activating YAP. *Cancer Cell*. 2014;25(6):822–30.

Zimmer L, Vaubel J, Mohr P, Hauschild A, Utikal J, Simon J, et al. Phase II DeCOG study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. *PLoS One*. 2015;11:10(3):e0118564.

13 LIST OF APPENDICES

13.1 Appendix 1: Immnune-related RECIST Comparision to RECIST v1.1

Removed as of Amendment 4.

13.2 Appendix 2: Guidelines for Implementation of RECIST

13.2.1 Efficacy Assessments

Tumor evaluations for the purposes of the primary endpoint are made based on RECIST v1.1 (Therasse, 2000) and revised RECIST guidelines (version 1.1) (Eisenhauer, 2009). The efficacy assessments and definitions of best response and PD for the purposes of the primary endpoint of ORR described in this study are based on the RECIST v1.1 (Table 13-1).

13.2.2 Definitions of Measurable and Non-measurable Disease

Measurable disease represents the presence of at least 1 measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions (both nodal and non-nodal) — the minimum size of a measurable non-nodal target lesion at Baseline should be no less than double the slice thickness or 10 mm, whichever is greater — eg, the minimum non-nodal lesion size for CT/MRI with 5 mm cuts will be 10 mm.

Lytic bone lesions or mixed lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions, if the soft tissue component meets the definition of measurability. Measurable nodal lesions (ie, lymph nodes) — lymph nodes ≥ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥ 10 mm and < 15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at Baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. Simple cysts with non-enhancing walls and low CT density are not considered malignant lesions unless proven by biopsy.

Non-measurable lesions: All other lesions are considered non-measurable, including small lesions (eg, longest diameter < 10 mm with CT/MRI or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis), as well as truly non-measurable lesions, eg, blastic bone lesions, ascites, pleural/pericardial effusion, inflammatory breast disease.

13.2.3 Methods of Tumor Measurement

All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment (ie, C1D1). Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment. For optimal evaluation of patients, the same methods of assessment and technique should be used to assess each reported lesion at Baseline and during follow-up. Contrast-enhanced CT of the chest, abdomen, and pelvis should preferably be performed using a 5 mm slice thickness. If a patient is known to have a medical

contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI is not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

13.2.3.1 Other Tumor Response Considerations

Fluorodeoxyglucose-positron emission tomography, endoscopy, and laparoscopy: The utilization of positron emission tomography imaging, endoscopy, and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. The utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers; however, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology: Cytology and histology can be used to differentiate between PR and CR in rare cases (ie, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Clinical examination: Clinical lesions will only be considered measurable when they are superficial (ie, skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Clinical PD is acceptable and wherever possible should be confirmed by imaging studies.

13.2.4 Definitions of Target and Non-target Lesions

For the evaluation of lesions at Baseline and throughout the study, the lesions are classified at Baseline as either target or non-target lesions:

Target Lesions: All measurable lesions (nodal and non-nodal) up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at Baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Each target lesion must be uniquely and sequentially numbered in the eCRF (even if it resides in the same organ). A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference by which to characterize the objective tumor response. Each target lesion identified at Baseline must be followed at each subsequent evaluation and documented in the eCRF.

Non-target Lesions: All other lesions are considered non-target lesions, ie, lesions not fulfilling the criteria for target lesions at Baseline. The presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (ie, multiple liver metastases). Each non-target lesion identified at Baseline must be followed at each subsequent evaluation and documented in the eCRF.

13.2.5 Determination of Target Lesion Response

Table 13-1 Response Criteria for Target Lesions

Response Criteria	Evaluation of Target Lesions
Complete Response	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm[a]
Partial Response	At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters
Progressive Disease	At least a 20% increase in the sum of diameters of all measured target lesions, taking as reference the nadir/smallest sum of diameters of all target lesions recorded at or after Baseline. In addition to the relative increase of 20% or greater, the sum must also demonstrate an absolute increase of at least 5 mm
Stable Disease	Neither sufficient shrinkage to qualify for partial response or complete response nor an increase in lesions which would qualify for progressive disease

a. Sum of diameters for complete response may not be 0 when nodal lesions are part of target lesions.

Notes on Target Lesion Response

- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at Baseline and appears to be 1 mass can split to become 2 or more smaller sub-lesions. When this occurs, the diameters (long axis — non-nodal lesion, short axis - nodal lesions) of the 2 split lesions should be added together and the sum recorded in the diameter field in the eCRF under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions and will not automatically trigger a PD designation
- **Lesions coalesced**: Conversely, it is also possible that 2 or more lesions which were distinctly separate at Baseline become confluent at subsequent visits. When this occurs, a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis — non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. In the eCRF, the diameter of the "merged lesion" should be recorded for the size of 1 of the original lesions while a size of "0" mm should be entered for the remaining lesion numbers which have coalesced.

13.2.6 Determination of Non-target Lesion Response

Table 13-2 Response Criteria for Non-target Lesions

Response Criteria	Evaluation of Non-target Lesions
Complete Response	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease	Unequivocal progression of existing non-target lesions[a]
Non-complete response/ Non-progressive disease	Neither complete response nor progressive disease

a. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the central review.

Non-target Lesion Response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at Baseline are now all absent and with all non-target nodal lesions returned to normal size (ie, < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (ie, ≥ 10 mm), the response can only be "**Non-CR/Non-PD**."
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in the presence of CR, PR, or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at Baseline.

New Lesions

The appearance of a new lesion is always associated with PD and has to be recorded as a new lesion in the eCRF.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new disease. If repeat scans confirm that there is definitely a new lesion, then PD should be declared using the date of the first observation/initial appearance of the lesion.
- If new disease is observed in a region which was **not scanned at Baseline** or where the particular baseline scan is not available for some reason, then this should be considered PD.
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of PD if the short axis increases in size to ≥ 10 mm for the first time in the study and has a plus 5 mm absolute increase.

13.2.7 Evaluation of Overall Lesion Response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response, and presence of new lesions as shown in Table 13-3.

Table 13-3 Overall Lesion Response at Each Assessment (RECIST v1.1)

Target Lesions	Non-target Lesions	New Lesions	Overall Lesion Response
CR	CR	No	CR[a]
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR[a]
SD	Non-PD	No	SD[a]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

a. This overall lesion response also applies when there are no non-target lesions identified at Baseline.