PROTOCOL

TITLE:	**A PHASE II TWO COHORT STUDY EVALUATING THE SAFETY AND EFFICACY OF COBIMETINIB PLUS ATEZOLIZUMAB IN BRAF^{V600} WILD-TYPE MELANOMA WITH CENTRAL NERVOUS SYSTEM METASTASES AND COBIMETINIB PLUS ATEZOLIZUMAB AND VEMURAFENIB IN BRAF^{V600} MUTATION-POSITIVE MELANOMA WITH CENTRAL NERVOUS SYSTEM METASTASES**
PROTOCOL NUMBER:	MO39136
VERSION NUMBER:	*5*.0
EUDRACT NUMBER:	2018-000759-41
IND NUMBER:	117296, 135717, and 111271
NCT NUMBER:	NCT03625141
TEST PRODUCTS:	Cobimetinib (RO5514041) Atezolizumab (RO5541267) Vemurafenib (RO5185426)
MEDICAL MONITOR:	Dr [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
04-Mar-2022 17:21:18	Company Signatory	[redacted] ([redacted])

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on title page
4	26 February 2020
3	12 August 2019
2	10 October 2018
1	5 April 2018

PROTOCOL AMENDMENT, VERSION 5.0: RATIONALE

The protocol for study MO39136 has been amended to include the following updates and clarifications:

- The list of approved indications for atezolizumab has been updated to include hepatocellular carcinoma and melanoma (Section 1.2.2).
- Provisions related to performing the study in the setting of the coronavirus disease 2019 (COVID-19) pandemic have been added (Sections 1.3, 4.1, and 5.1; Appendix 14).
- Benefit-risk assessment and guidance on concomitant administration of COVID-19 vaccines with atezolizumab have been added (Sections 1.3 and 4.4).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 18 (Appendices 10, 12, 13, and 14).
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 3.1, 4.1, 4.3, 4.4, 4.5, and 5.1; Appendices 10, 12, 13, and 14).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product (IMP) transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.3).
- Immunosuppressive medications have been removed from the prohibited therapy section (4.4.5) and added to the cautionary therapy section (4.4.2.2) to align with atezolizumab management guidelines in Appendix 14 that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events.
- Updates related to the risks associated with atezolizumab:
  - The list of identified risks for atezolizumab has been revised to include severe cutaneous adverse reactions (SCARs, previously a potential risk; Section 5.1.2). This update aligns with a Dear Investigator Letter (DIL) issued on 12 October 2020.
  - Language has been added to clarify that hemophagocytic lymphohistiocytosis and macrophage activation syndrome are considered potential risks for atezolizumab (Section 5.1.2 and Appendix 14).
  - Guidelines for management of atezolizumab-associated dermatologic adverse events have been revised to provide guidance on severe cutaneous adverse reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis (Appendices 12, 13, and 14).
  - Appendix 10 has been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent.

- To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) have replaced systemic inflammatory response syndrome on the list of atezolizumab-associated adverse events of special interest (Section 5.2.3).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- Language regarding investigator reporting of pregnancies has been clarified (Section 5.4.3.2).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).
- The management guidelines for Grade 4 myositis have been removed because Version 4.0 of the Common Terminology Criteria for Adverse Events does not have a Grade 4 category for myositis. Instructions regarding recurrent Grade 3 events have been modified accordingly (Appendix 14).
- To align with the Atezolizumab Investigator's Brochure, Version 17, the management guidelines for HLH and MAS have been modified to indicate that HLH should be considered when CRS presentation is atypical or prolonged, to add anticytokine therapy as an option for treating HLH or MAS, and to suggest that published guidelines should be followed for HLH or MAS events that do not respond to treatment within 24 hours (Appendix 14).
- Minor updates to the management guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome (Appendix 14).
- The medical term “primary biliary cirrhosis” has been replaced by the term “primary biliary cholangitis” to align with the updated preferred term in MedDRA (Appendix 10).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

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PHASE:	II
INDICATION:	Metastatic Melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of cobimetinib plus atezolizumab in patients with BRAF^{V600} wild-type melanoma with central nervous system (CNS) metastases and of cobimetinib plus atezolizumab and vemurafenib in BRAF^{V600} mutation-positive melanoma patients with CNS metastases. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Efficacy Objectives	Corresponding Endpoints
• To evaluate intracranial ORR with cobimetinib plus atezolizumab in BRAF^{V600} wild-type melanoma as assessed by an IRC • To evaluate intracranial ORR with cobimetinib plus atezolizumab and vemurafenib in BRAF^{V600} mutation-positive melanoma as assessed by an IRC	• Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart. Disease status for this endpoint will be determined by an IRC in accordance with RECIST v1.1 with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma with CNS metastases • To evaluate the efficacy of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma with CNS metastases	• Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart as determined by the investigator according to RECIST v1.1 with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions • Extracranial ORR, defined as the proportion of patients with either a CR or PR in their extracranial disease based on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • Overall ORR, defined as the proportion of patients with either a CR or PR in their overall disease (i.e., including intracranial and extracranial disease) based on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • Intracranial, extracranial and overall PFS defined as the time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1 • Intracranial, extracranial and overall DOR, defined as the time from the first occurrence of a documented objective response based on two consecutive assessments ≥ 4 weeks apart to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Intracranial, extracranial and overall DCR, defined as the proportion of patients with a CR or PR or SD at 16 weeks from study treatment initiation, as determined by the investigator according to RECIST v1.1 • OS defined as the time from study treatment initiation to death from any cause • Time from study treatment initiation to cognitive symptom deterioration, defined as a change (≥ 10 points on a 0-100 scale) on selected scales of the EORTC-BN20 (visual disorder, motor dysfunction, communication deficit, headaches, seizures and drowsiness) • Time from study treatment initiation to symptom and function deterioration defined as a change (≥ 10 points on a 0-100 scale) in fatigue, physical functioning, cognitive functioning, or role functioning as measured by the Fatigue, Physical, Cognitive, Role Functioning scales of the EORTC QLQ-C30 • Duration of Stable/Improved HRQoL scores as assessed through use of the two-item GHS/HRQoL subscale (Questions 29 and 30) of the EORTC QLQ-C30
Exploratory Efficacy Objective	**Corresponding Endpoints**

• To evaluate the efficacy of cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma with CNS metastases • To evaluate the efficacy of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma with CNS metastases	• Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart. Disease status for this endpoint will be determined by the investigator according to iRANO criteria. • ORR in intracranial, extracranial and overall disease as determined by investigator according to immune-modified RECIST with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions • Intracranial, extracranial and overall PFS as determined by the investigator according to immune-modified RECIST • Intracranial, extracranial and overall DOR as determined by the investigator according to immune-modified RECIST • Radiotherapy-assisted PFS defined as time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1 modified by excluding ≤ 3 lesions that can be treated by SRT from the sum of largest diameters from baseline onwards • Timing of increase or change in corticosteroid use during treatment • Time from study treatment initiation to subsequent intracranial and systemic anti-cancer treatment • Change from baseline scores over time in treatment/disease-related symptoms as evaluated by the EORTC QLQ-C30 and QLQ-BN20 questionnaires
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma with CNS metastases • To evaluate the safety of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma with CNS metastases	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To perform molecular characterization of melanoma disease in plasma and tumour tissue	• Relationship between biomarkers (including, but not limited to; PD-L1, BRAF and NRAS) in plasma and tumour tissue and clinical efficacy parameters

CR = complete response; DCR = disease control rate; DOR = duration of response; EORTC QLQ-C30 and QLQ-BN20 = European Organization for Research and Treatment of Cancer Quality of Life questionnaire core questionnaire and brain cancer specific module; GHS = Global Health Status; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; iRANO = immunotherapy Response Assessment for Neuro-Oncology; IRC = Independent Review Committee; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; SRT = stereotactic radiotherapy.

Study Design

Description of Study

Study MO39136 is a Phase II, two cohort, efficacy and safety study of $BRAF^{V600}$ status-specific combination treatment with cobimetinib, atezolizumab and vemurafenib for melanoma with CNS metastases. Study patients will be assigned to a study treatment cohort based on locally determined $BRAF^{V600}$ disease status. Patients with $BRAF^{V600}$ wild-type disease will be assigned to treatment with cobimetinib plus atezolizumab in Cohort 1. Patients with $BRAF^{V600}$ mutation-positive disease will be assigned to treatment with cobimetinib plus atezolizumab and vemurafenib in Cohort 2. The study includes assessment of patient reported quality of life outcomes as well as exploratory biomarker evaluations.

Based on the results of the primary analysis for Study CO39722 (IMspire170) of cobimetinib plus atezolizumab combination in previously untreated advanced $BRAF^{V600}$ wild-type melanoma patients (see Section 1.3.2.4), enrollment in the $BRAF^{V600}$ wild-type cohort has been discontinued. Ongoing patients in this cohort may continue study treatment as per protocol, according to investigator's medical judgement.

Following provision of informed consent, potential patients will be screened for study eligibility over a 28-day period. Eligible patients will be assigned to a treatment cohort at enrollment. Study treatment in Cohort 1 will consist of orally administered cobimetinib and intravenously (IV) administered atezolizumab. Study treatment in Cohort 2 will consist of orally administered cobimetinib and vemurafenib for an initial 28-day treatment run-in period, followed by cobimetinib, vemurafenib and IV atezolizumab for subsequent 28-day cycles. Disease status for the purposes of treatment decisions will be determined by the investigator. Study treatment for all patients in both cohorts will be continued until investigator-determined disease progression according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (with two exceptions as described below), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first.

Study treatment may be continued beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 3 intracranial lesions that can be controlled with stereotactic radiotherapy (SRT). Clinically stable patients who have a favourable benefit-risk ratio may continue study treatment beyond progression per RECIST v1.1 for either reason if all of the following criteria are met:

- Clinically stable patient with evidence of clinical benefit and favourable benefit−risk ratio as determined by the investigator
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Documented investigator/patient discussion of treatment options alternative to continuing study treatment at the time of RECIST v1.1-defined disease progression
- *Consultation with* the Medical Monitor *is advised*

Study treatment will be discontinued in any patient who continues treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at

any time or if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later. Post-progression assessments may be conducted sooner if necessary e.g., due to clinical progression. The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

Patients will attend a Study Treatment Discontinuation Visit after 28 ± 7 days of their last study treatment dose. All adverse events will be reported until 30 days after the last study treatment dose. After the Study Treatment Discontinuation Visit, patients who have not yet progressed will be followed every 8 or 12 weeks for disease status until disease progression has been confirmed, and all patients will be followed every three months for survival and new anti-cancer treatments.

Figure 1 presents an overview of the study design.

Efficacy will be assessed in intracranial disease alone (primary efficacy endpoint) as well as in extracranial and overall (both intracranial and extracranial) disease (secondary and exploratory efficacy endpoints). Disease status will be determined according to RECIST v1.1 with a modified measurability definition for intracranial lesions (≥ 0.5 cm by magnetic resonance imaging [MRI]) and allowing up to five intracranial target lesions (in addition to any extracranial target lesions). Exploratory analyses of disease status will include evaluations by immune-modified RECIST, RECIST v1.1 modified by excluding any SRT-treated lesions from the sum of largest diameters from baseline onwards (if applicable), and immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria. Disease status for the primary endpoint will be determined by an Independent Review Committee (IRC). IRC membership and procedures will be described in the IRC Charter. All other efficacy endpoints will be analysed according to investigator disease status determinations. Disease responses for all endpoints will be confirmed by two consecutive assessments at least four weeks apart. Regardless of whether patients continue treatment beyond disease progression per RECIST v1.1, tumour assessments must be repeated approximately four weeks later (or sooner if necessary e.g., due to clinical progression).

Efficacy will also be evaluated according to patient-reported outcomes (PROs) measured at baseline and during study treatment. Patients will complete the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and brain cancer module (QLQ-BN20) to assess disease and/or treatment-related symptoms (e.g., headache, seizure, diarrhoea, functioning, and health-related quality of life). After study treatment discontinuation, a subset of the EORTC QLQ-C30 only will be administered.

Safety will be assessed by regular evaluation of adverse events and conduct of physical examinations, vital signs, clinical laboratory tests (haematology, blood chemistry) and electrocardiograms. Adverse events will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study and will provide safety-related recommendations. Details of the IMC including its responsibilities, composition, and operating procedures will be provided in the IMC charter.

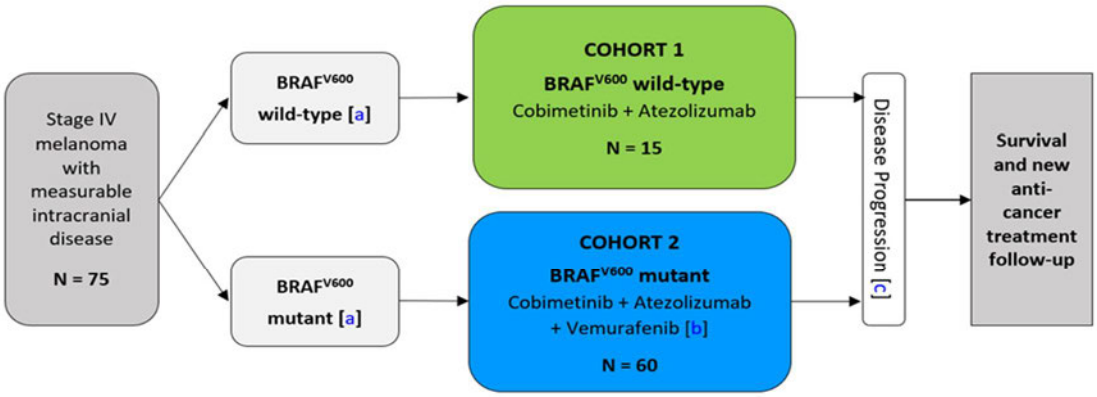
To evaluate molecular biomarkers associated with disease outcomes including response to study treatment, tumour tissue obtained prior to treatment initiation will be collected (if available) and plasma will be collected at baseline and at the time of disease progression.

Schedules of activities are provided Appendix 1 and Appendix 2 . The schedule of biomarker sampling is provided in Appendix 3 .

The study will be conducted at approximately 23 sites worldwide. Approximately 60 patients will be enrolled into the $BRAF^{V600}$ mutation-positive cohort, and 15 patients have been enrolled into the $BRAF^{V600}$ wild-type cohort, for a total of approximately 75 patients enrolled. With an estimated study drop-out rate of 15%, approximately 50 patients in the $BRAF^{V600}$ mutation-positive cohort are expected to be evaluable for the primary efficacy endpoint. Patients in the $BRAF^{V600}$ wild-type cohort will be analysed descriptively. *Patients who do not meet the criteria for participation in this study (screen failure) may qualify for re-screening once at the investigator's discretion.*

A Steering Committee (SC) will provide scientific oversight of the trial. Details of the composition and mandate of the SC will be provided in the SC Charter.

Figure 1 Study Schema



a. Documented BRAF^{V600} status in melanoma tumour tissue
b. Treatment regimen begins with a 28-day run-in period with vemurafenib and cobimetinib only
c. Clinically stable patients who have a favorable benefit-risk ratio as defined in the protocol may continue study treatment following radiographic progression per RECIST v1.1 with Medical Monitor approval

Number of Patients

Approximately 60 patients will be enrolled in the BRAF^{V600} mutation-positive cohort and 15 patients in the BRAF^{V600} wild-type cohort for a total of approximately 75 patients enrolled. Based on an estimated 15% study drop-out rate, 50 patients will be evaluable in the BRAF^{V600} mutation-positive cohort for the primary study endpoint.

Target Population

Patients must meet the following criteria for study entry.

Inclusion Criteria

Disease-specific criteria

- Histologically confirmed melanoma with radiologically confirmed brain metastases
- Documented BRAF^{V600} mutation status of melanoma tumour tissue using a validated genetic test.
- Measurable brain metastases defined as any lesion that can be accurately measured in at least one dimension as ≥ 0.5 cm. Patients who have received prior SRT or surgery for brain metastases must have untreated brain lesions that can be accurately measured in at least one dimension as ≥ 0.5 cm by MRI.
- Prior anti-cancer therapy for metastatic melanoma is allowed, with the following exceptions:
  - Prior BRAF or MEK inhibitors are not allowed in either the metastatic or adjuvant settings
  - Prior immunotherapy is not allowed. As an exception, for patients in Cohort 1 (BRAF^{v600} wild-type) prior immunotherapy is allowed in the adjuvant setting if completed ≥ 90 days prior to study treatment initiation. Examples of immunotherapy include, but are not limited to, nivolumab, pembrolizumab and ipilimumab.
  - Any anti-cancer therapy, including chemotherapy, hormonal therapy and radiotherapy, is prohibited within two weeks prior to initiation of study treatment.
- Prior SRT or surgical therapy of ≤ 10 brain metastases is allowed but prior whole brain radiation therapy (WBRT) is not allowed.
- Adverse effects of all prior systemic or local treatment must have either returned to baseline or become stable and manageable prior to initiation of study treatment.

General criteria

- Willing and able to provide informed consent and have signed the study Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status ≤ 2
- Life expectancy of > 3 months
- Willing and able to complete health and quality of life questionnaires required by the protocol
- Adequate hematologic and end-organ function, defined using the following laboratory results obtained within 14 days prior to first dose of study treatment with the exception of amylase and lipase which may be obtained within 28 days prior to study treatment initiation:
  - Absolute neutrophil count ≥ 1.5 × 10^9/L without granulocyte colony-stimulating factor support
  - White blood cell count ≥ 2.5 x 10^9/L
  - Lymphocyte count ≥ 0.5 × 10^9/L
  - Platelet count ≥ 100 × 10^9/L without transfusion
  - Haemoglobin ≥ 90 g/L without transfusion
  - Serum albumin ≥ 25 g/L
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
  - Aspartate transaminase and alanine aminotransferase ≤ 2.0 × ULN, or for patients with documented liver metastases, ≤ 5.0 ULN
  - *For patients assigned to Cohort 2 only*: Amylase and lipase ≤ 1.5 × ULN
  - Alkaline phosphatase (ALP) ≤ 2.5 × ULN or, for patients with documented liver or bone metastases ALP ≤ 5 × ULN
  - Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault glomerular filtration rate estimation as follows:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \; (\times 0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

  - For patients not receiving therapeutic anticoagulation: international normalised ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN within 28 days prior to initiation of study treatment

    For patients receiving therapeutic anticoagulation: stable anticoagulant regimen that does not include coumarin anticoagulants, stable INR, and stable aPTT during the 28 days immediately preceding initiation of study treatment
- Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two effective forms of contraception including at least one method with a failure rate of < 1% per year during the course of this study and for at least six months after completion of study therapy.
  - Females of childbearing potential are defined as sexually mature women without prior oophorectomy or hysterectomy who have had menses within the last 12 months.
  - Females are not considered to be of childbearing potential if amenorrhoeic for > 12 months and follicle-stimulating hormone (FSH) level ≥ 40 IU/L. For females who have been amenorrhoeic for ≥ 2 years, the requirement for FSH measurement at screening will be waived.

  - Examples of effective contraception methods with a failure rate of < 1% per year include bilateral tubal ligation and male surgical sterilization; hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices; and copper intrauterine devices. A reliable barrier method may be used as the second contraceptive method. Hormonal contraceptive methods must be supplemented by a barrier method. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.
  - Male patients who are surgically sterilized are required to use barrier methods of contraception.
- Female patients of childbearing potential must agree to refrain from donating eggs during the course of the study and for at least 5 months after their final dose of atezolizumab
- Male patients must agree to refrain from donating sperm during the course of the study and for at least six months after the last dose of cobimetinib

Exclusion Criteria

Patients who meet any of the following cancer-related or general criteria will be excluded from study entry:

Cancer-related criteria

- Ocular melanoma
- Leptomeningeal involvement
- Uncontrolled tumour-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at start of study treatment.

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

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days. Note: indwelling drainage catheters (e.g., PleurX®) are allowed.
- Prior WBRT treatment for CNS disease
- Increasing corticosteroid dose during the seven days prior to initiation of study treatment or current dexamethasone or equivalent dose of > 8 mg/day
- Prior treatment with a BRAF or MEK inhibitor
- Major surgical procedure other than for diagnosis within four weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells or to any formulation component of cobimetinib or atezolizumab or, *for patients assigned to Cohort 2 only*, vemurafenib.
- *Patients assigned to Cohort 2 only*: Concomitant treatment with anticonvulsants other than gabapentin, vigabatrin and levetiracetam
- *Patients assigned to Cohort 2 only*: acetaminophen is prohibited within seven days prior to initiation of study treatment unless the patient has an absolute contraindication to the use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (i.e., severe allergy or reactive airway disease sensitive to NSAIDs or aspirin).
- Active malignancy (other than melanoma) or a prior malignancy within the past three years

Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma *in situ*, breast carcinoma *in situ*, prostate cancer *in situ* or limited stage bladder cancer, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.

General criteria

- Known risk factors for ocular toxicity, consisting of any of the following:
  - History of serous retinopathy
  - History of retinal vein occlusion (RVO)
  - Evidence of ongoing serous retinopathy or RVO at baseline
- History of clinically significant cardiac dysfunction, including the following:
  - Unstable angina or new-onset angina within three months prior to initiation of study treatment
  - Current symptomatic congestive heart failure, defined as New York Heart Association Class II or higher
  - Myocardial infarction within three months prior to initiation of study treatment
  - Unstable arrhythmia
  - Left ventricular ejection fraction below the institutional lower limit of normal or below 50%, whichever is lower
  - Poorly controlled hypertension, defined as sustained, uncontrolled, non-episodic baseline hypertension consistently above 159/99 mmHg despite optimal medical management
  - *For patients assigned to Cohort 2 only*: History of congenital long QT syndrome
  - *For patients assigned to Cohort 2 only*: Mean (average of triplicate measurements) QTc interval corrected using Fridericia's method (QTcF) ≥ 480 ms at screening, or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium and phosphorus)
- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Traumatic injury within two weeks prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti−phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see complete list in Appendix 10), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
  - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded from the study) are eligible for the study provided all of following conditions are met:
    - Rash covering < 10% of body surface area
    - Well-controlled disease at baseline requiring only low-potency topical corticosteroids
    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within 12 months of study treatment initiation

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

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Uncontrolled diabetes or symptomatic hyperglycaemia
- Any Grade ≥ 3 haemorrhage or bleeding event within 28 days of study treatment initiation
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within six months prior to study treatment initiation
- Positive human immunodeficiency virus test at screening
- Hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening or a positive quantitative HBV DNA test.

  If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, a quantitative HBV DNA test must be performed. If positive, the patient is not eligible.

  Patients receiving anti-viral therapy for HBV are not eligible for study enrollment.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test and a positive HCV RNA test at screening
- Active tuberculosis
- History of severe allergic, anaphylactic or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Severe infection within four weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*
- Signs or symptoms of infection within two weeks prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in, and completion of, the study
- Any psychological, familial, sociological, or geographical condition that may hamper compliance with the protocol and follow-up after treatment discontinuation
- Pregnancy, breastfeeding, or intention of becoming pregnant during the study. Women of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment.
- Treatment with therapeutic oral or IV antibiotics within two weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Administration of a live, attenuated vaccine within four weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, interleukin-2) within 28 days or 5 half-lives of the drug, whichever is shorter, prior to study treatment initiation
- Treatment with systemic immunosuppressive medications (including, but not limited to cyclophosphamide, azathioprine, methotrexate and thalidomide) within two weeks prior to study treatment initiation.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with investigational drug within 28 days or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment

- *For patients to be assigned to Cohort 2 only:* anticipated use of any concomitant medication during or within seven days prior to initiation of study treatment that is known to cause QT prolongation
- Consumption of foods, supplements, or drugs that are strong or moderate CYP3A4 enzyme inducers or inhibitors at least seven days prior to initiation of study treatment

  These include St. John's wort or hyperforin (strong CYP3A4 enzyme inducer) and grapefruit juice (strong cytochrome P450 CYP3A4 enzyme inhibitor)

End of Study

The study will end when all patients enrolled have either been followed for at least 24 months, died, withdrawn consent, or been lost to follow-up; or the Sponsor decides to end the trial; whichever occurs first.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

Investigational Medicinal Products

Test Product (Investigational Drugs)

Cobimetinib and atezolizumab are investigational drugs in Cohort 1 and cobimetinib, atezolizumab and vemurafenib are investigational drugs in Cohort 2.

Cohort 1 – $BRAF^{V600}$ wild-type melanoma patients

Patients with $BRAF^{V600}$ wild-type disease treated in Cohort 1 will receive the following test drugs in 28-day treatment cycles:

Cobimetinib: 60 mg (three tablets of 20 mg each) orally (PO) once a day (QD) on Days 1−21 of each 28-day cycle.

Atezolizumab: 840 mg IV on Days 1 and 15 of each treatment cycle

Cohort 2 – $BRAF^{V600}$ mutation-positive melanoma patients

Patients with $BRAF^{V600}$ mutation-positive disease treated in Cohort 2 will receive cobimetinib, atezolizumab and vemurafenib in 28-day treatment cycles. Treatment in the cohort will include a 28-day run-in period wherein patients will receive cobimetinib and vemurafenib only. Upon completion of the 28-day run-in period, atezolizumab will be added to their treatment regimen.

Test drug administration in Cohort 2 will be as follows:

Cobimetinib	Run-in Period (Cycle 1)	
	Days 1−21	60 mg (three tablets of 20 mg each) PO QD
	≥ Cycle 2	
	Days 1-21	60 mg (three tablets of 20 mg each) PO QD
Vemurafenib	Run-in Period (Cycle 1)	
	Days 1-21	960 mg (four 240-mg tablets) PO twice daily (BID)
	Days 22−28	720 mg dose (three 240-mg tablets) PO BID
	≥ Cycle 2	
	Days 1-28	720 mg dose (three 240-mg tablets) PO BID

Atezolizumab	Run-in Period (Cycle 1)	
	Not administered during run-in period	
	≥ Cycle 2	
	Days 1 and 15	840 mg intravenously (IV)

Statistical Methods

There is no formal statistical study hypothesis. All statistical analyses will be entirely descriptive.

Primary Analysis

The primary analysis will include analyses of the primary, secondary and exploratory efficacy endpoints and safety summaries. It will be conducted six months after the last patient is enrolled in the study (last patient in [LPI]). The final study analysis including all updated safety and efficacy endpoints will be conducted approximately 24 months after LPI.

The primary efficacy objective is to evaluate the intracranial objective response rate (ORR) in each study cohort. Intracranial ORR is defined as the proportion of patients with a complete or partial response in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart. Disease status will be determined by an IRC according to RECIST v1.1 with a modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions. Data for patients with no post-baseline intracranial tumour assessment will be excluded from efficacy analyses.

Analysis Populations

The primary efficacy analysis population will be the Evaluable Patient population in each cohort consisting of all enrolled patients who received study medication and have at least two post-baseline tumour assessments for response evaluation.

The safety analysis population will be the Safety population in each cohort consisting of all patients who received at least one dose of study medication.

Determination of Sample Size

The purpose of this Phase II study is estimation and hypothesis generation regarding the effect of cobimetinib plus atezolizumab on CNS metastases from $BRAF^{V600}$ wild-type melanoma and the effect of cobimetinib plus atezolizumab and vemurafenib on CNS metastases from $BRAF^{V600}$ mutation-positive melanoma. The 15 patients enrolled into the $BRAF^{V600}$ wild-type cohort at the time of recruitment stop will be analysed descriptively only. There are no reference data available on the use of these combination therapies in these patient populations.

There is no formal statistical hypothesis in this study. The originally planned total sample size of approximately 60 patients per cohort was based on an estimated study drop-out rate of 15%, the primary endpoint and 95% confidence intervals (CIs) for each treatment regimen. No power calculation has been performed.

In a Dear Investigator Letter dated 9 July 2019, the Sponsor communicated the decision to discontinue enrollment in the $BRAF^{v600}$ wild-type cohort (Cohort 1). As of 9 July 2019, 15 patients were enrolled in Cohort 1.

Point estimates and 95% CIs for a range of possible outcomes produced using nQuery (version 7) with 50 evaluable patients in the $BRAF^{V600}$ mutation-positive cohort are provided below.

Intracranial Response Rate in Cohort 2	95% Confidence Interval
35%	(21.8%, 48.2%)
40%	(26.4%, 53.6%)
45%	(31.2%, 58.8%)
50%	(36.1%, 63.9%)
55%	(41.2%, 68.8%)

Interim Analyses

A safety interim analysis will be performed by the Sponsor and reviewed by the IMC after at least 10 patients in both cohorts have completed their first tumour assessment (i.e., approximately eight weeks after the start of study treatment). The analysis will be conducted by the Sponsor according to the Sponsor's standard operating procedures for safety reviews. The conduct of the IMC safety interim review will be as described in the IMC charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase (aspartate aminotransferase)
AUC	under the concentration-time curve
BID	twice daily
$BRAF^{V600}$	V600 codon of the BRAF oncogene
CHMP	Committee for Medicinal Products Human Use
CI	confidence interval
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRS	*cytokine-release syndrome*
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	*coronavirus disease 2019*
CPK	creatine phosphokinase
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
cuSCC	cutaneous squamous cell carcinoma
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
FSH	follicle-stimulating hormone
GHS	Global Health Status
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HEENT	head, eyes, ears, nose, throat
HIV	human immunodeficiency virus
HLH	*hemophagocytic lymphohistiocytosis*
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IFN-α	interferon-α
IL-2	interleukin-2
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
INR	international normalised ratio
iRANO	immunotherapy Response Assessment for Neuro-Oncology
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous(ly)
LPI	last patient in
LVEF	left ventricular ejection fraction
MAPK	RAS/RAF/MEK/ERK mitogen-activated protein kinase (cascade)
MAS	*macrophage activation syndrome*
MRI	magnetic resonance imaging
NCCN	*National Comprehensive Cancer Network*
NCI	National Cancer Institute
NGS	next-generation sequencing
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non−small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PO	orally
PR	partial response
PRO	patient-reported outcome
QD	once-daily (or once a day)
Q2W	every two weeks
Q3W	every three weeks

Abbreviation	Definition
QLQ-C30	Quality-of-Life Questionnaire Core 30
QLQ-BN20	Quality-of-Life Questionnaire brain cancer module
QTcF	QTc interval corrected using Fridericia's method
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RVO	retinal vein occlusion
SAE	serious adverse event
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SC	Steering Committee
SCC	squamous cell carcinoma
SD	stable disease
SITC	*Society for Immunotherapy of Cancer*
SmPC	Summary of Product Characteristics
SRT	stereotactic radiotherapy
ULN	upper limit of normal
WBRT	whole brain radiation
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA AND MELANOMA WITH CENTRAL NERVOUS SYSTEM METASTASES

In 2012, the worldwide incidence of cutaneous melanoma is estimated to have been more than 232 000 cases with approximately 55 500 associated deaths. The highest per capita incidence and mortality rates were observed in Australia/New Zealand (14 738 cases, 2019 deaths), Europe (100 442 cases, 22 211 deaths) and North America (74 515 cases, 11 343 deaths) (Ferlay et al. 2013). The number of melanoma cases worldwide is increasing with some countries reporting at least doubling of melanoma incidence over the last two decades particularly within fair-skinned populations (Australian Institute of Health and Welfare 2016, Centers for Disease Control and Prevention 2015, World Health Organization 2018).

Cutaneous melanoma arises from melanocyte cells of skin. If recognized early, primary lesions can be excised without significant sequelae. Once metastatic however, the disease is characterized by mortality and morbidity. Until recently, treatment options for metastatic melanoma were limited. Dacarbazine was considered to be the standard first-line treatment; however, outcomes were poor, with response rates of 5–12%, median progression-free survival (PFS) of less than two months, and median overall survival (OS) of 6.4 to 9.1 months (Middleton et al. 2000; Bedikian et al. 2006; Chapman et al. 2011; Robert et al. 2011). Combination chemotherapy and chemotherapy combined with interferon-α (IFN-α) or interleukin-2 (IL-2), although showing improved response rates, did not result in improved OS (Chapman et al. 1999; Ives et al. 2007).

Unfortunately, brain metastases are common in melanoma. Central nervous system (CNS) disease detected due to symptoms or surveillance imaging occurs in approximately 37-44% of metastatic patients and autopsy studies show brain metastases in 75% of fatal melanoma cases (Sloan et al. 2009, Goyal et al. 2015). Brain metastases represent a unique therapeutic challenge due to limitations in drug delivery across the blood-brain barrier (Agarwala et al. 2000). Surgery, whole brain radiation (WBRT) and stereotactic radiotherapy (SRT) have been mainstays of melanoma brain metastases treatment, but these approaches do not dramatically ameliorate outcomes as shown by a median OS of 6.7 months determined in a retrospective analysis of this patient population (Sperduto et al. 2012). Difficulties in treating melanoma brain metastases patients are exacerbated by their exclusion from large clinical trials (Larkin et al. 2015, Long et al. 2015, Robert et al. 2015a, Robert et al. 2015b, Ascierto et al. 2016).

The RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK) cascade is a key intracellular signalling network that transduces multiple proliferative and differentiating signals from the extracellular environment to cell nuclei to activate cellular growth and differentiation (Johnson and Lapadat 2002, Roberts and Der 2007). Mutations in the V600 codon of the BRAF oncogene ($BRAF^{V600}$) occur in approximately 50% of all

cutaneous melanomas and, though mostly mutually exclusive to these BRAF mutations, NRAS is mutated in 15–25% of melanomas (Davies et al. 2002, Lee et al. 2011, Goel et al. 2006). These BRAF and NRAS mutations trigger constitutive activation of the MAPK pathway resulting in growth factor-independent cellular proliferation and survival characteristic of oncogenesis. Notably, the presence of BRAF mutations has been associated with an increased risk of CNS metastases in patients with advanced melanoma as indicated by a 24% rate of CNS metastases in BRAF mutation-positive melanoma versus a 12% rate in patients with BRAF wild-type disease (Jakob et al. 2012).

In the last decade, immunotherapies disrupting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) pathways as well as agents targeting the MAPK pathway have been introduced into the treatment of advanced melanoma leading to improved outcomes. In one large randomized study comparing PD-1 pathway blockade with pembrolizumab to CTLA-4 blockade with ipilimumab, 24-month survival rates of 55% were observed (Schachter et al. 2017). In studies of BRAF inhibitors alone or combined with MEK inhibitors in patients with $BRAF^{V600}$ mutations, OS of 22.3 to 25.1 months were observed (McArthur et al. 2014, Long et al. 2015).

The activity of these agents in melanoma brain metastases has been shown in clinical trials limited to patients with CNS disease. In a study of PD-1 pathway blockade with pembrolizumab, intracranial responses were observed in 4/18 (22%) of melanoma patients enrolled. A tolerable safety profile was observed (Goldberg et al. 2016). In an open-label trial comparing nivolumab (an anti-PD-1 monoclonal antibody) with or without ipilimumab in patients unselected for BRAF mutation, at a median follow-up of 16.4 months, complete or partial intracranial responses were observed in 11/26 (42%) patients receiving both agents and 5/25 (20%) patients receiving nivolumab alone. PFS at six months was 46% and 29% respectively (Long et al. 2017). Combined nivolumab/ipilimumab showed similar activity in another single arm trial with an intracranial objective response rate (ORR) of 55% and 6-month PFS greater than 60% at 9 months median follow-up in 75 patients (Tawbi et al. 2017). No new or unexpected adverse events were observed in these studies.

In a clinical trial of 146 patients with $BRAF^{V600}$ mutation-positive disease (n=90 with no prior treatment for brain metastases, n=56 with prior treatment for brain metastases), MAPK pathway disruption via BRAF inhibition with vemurafenib (Zelboraf®) produced an intracranial ORR of 18% in both prior treated and untreated patient cohorts. Median OS was 9.6 months (range 0.6–34.5) in the prior treatment cohort and 8.9 months (range 0.7–34.3) in the cohort of patients who had not received prior treatment for brain metastases. Study treatment was reported as well tolerated (McArthur et al. 2017). In a study of dual MAPK pathway blockade with combined BRAF and MEK inhibition with dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) in patients with $BRAF^{V600}$ mutation-positive disease, intracranial responses were observed in 58% of the patients

with asymptomatic disease and no prior treatment. Preliminary OS analyses in this patient subset found median survival ranging from approximately 10 to 24 months. No unexpected safety issues were observed (Davies et al. 2017).

These results suggest that immunotherapy and BRAF-MEK targeted approaches may provide systemic alternatives to established, but arguably inadequate, local methods for treating melanoma patients with intracranial disease.

1.2 BACKGROUND ON STUDY MEDICATIONS

1.2.1 Background on Cobimetinib

Cobimetinib (Cotellic®) is a potent and highly selective inhibitor of mitogen-activated protein kinases MEK1 and MEK2, central components of the MAPK pathway. Activated MEK triggers downstream signalling to promote growth. Cancer cells transformed by $BRAF^{V600}$ mutation are exceptionally sensitive to MEK inhibition *in vitro*. Allosteric MEK inhibitors can result in G1 phase growth arrest in melanoma cells (Solit et al. 2006; Haass et al. 2008). *In vitro*, MEK inhibitors reduce cell proliferation, soft agar colony formation, and matrigel invasion of $BRAF^{V600}$ mutation−positive melanoma cells, and are also effective against $BRAF^{V600}$ mutation−positive melanoma xenografts, which is suggestive of a potentially important role for MEK inhibitors in melanoma and other tumours that harbour the $BRAF^{V600}$ mutation (Solit et al. 2006).

Cobimetinib shows anti-tumour activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies and in combination with chemotherapy, other targeted therapies and cancer immunotherapy.

Cobimetinib is approved in the United States, European Union and multiple other countries across the world for combined use with vemurafenib for the treatment of advanced $BRAF^{V600}$ mutation-positive melanoma.

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

1.2.2 Background on Atezolizumab

Atezolizumab (Tecentriq®) is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumour-specific T cell responses, resulting in improved anti-tumour activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fcγ receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumour activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy and cancer immunotherapy.

Atezolizumab is approved in the United States and the European Union for the treatment of patients with locally advanced or metastatic urothelial bladder carcinoma and metastatic non−small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy (see current Tecentriq Summary of Product Characteristics [SmPC]). Atezolizumab has also received United States FDA approval and Committee for Medicinal Products Human Use (CHMP) opinion for extensive-stage small-cell lung cancer and for triple-negative breast cancer. *Atezolizumab is approved for the treatment of hepatocellular carcinoma and melanoma in some countries.* Atezolizumab is also currently in clinical development for other indications.

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

1.2.3 Background on Vemurafenib

Vemurafenib is a compound that selectively inhibits oncogenic BRAF kinase. Discovery of oncogenic BRAF mutations highlights the central role of this kinase in signalling pathways that control cellular proliferation. Oncogenic mutations in BRAF result in constitutive activation of BRAF kinase, which causes dysregulated downstream signalling via MEK and ERK, leading to increased cell proliferation and survival.

Vemurafenib is approved as a treatment for adult patients with unresectable or metastatic $BRAF^{V600}$ mutation−positive melanoma in numerous countries worldwide, including the European Union, Switzerland, Canada, Australia, New Zealand and Israel, and as a treatment for $BRAF^{V600}$ mutation−positive melanoma in the United States, Brazil and Korea.

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The rationale for evaluating combination advanced melanoma treatment with PD-1/PD-L1 pathway blockade via atezolizumab and MAPK pathway blockade via cobimetinib and, in $BRAF^{V600}$ mutation-positive disease, vemurafenib, is based upon preclinical evidence for synergistic anti-tumoural effects of these approaches (see Section 1.3.1), clinical evidence of efficacy of each approach in advanced melanoma with and without CNS disease (see Section 1.1), and preliminary clinical data showing activity and tolerability of combined immunotherapy/MAPK pathway inhibition regimens in melanoma (see Section 1.3.2).

1.3.1 Immunomodulation and the MAPK Pathway in Melanoma: Preclinical Data

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD- L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T cell activation. PD-1 expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T cell proliferation and activation, cytokine production and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumour cells has been reported to impede anti-tumour immunity, resulting in immune evasion (Blank and Mackensen 2007). Melanoma tumour cells are highly immunogenic highlighting the applicability of immunomodulation as a potential treatment for melanoma. Removal of suppression of T cell activation through PD-1/PD-L1 blockade may render tumours especially prone to elimination by an active immune response (Zito et al. 2012). Importantly, studies of excised melanoma brain metastases show PD-L1 expression and lymphocytic infiltration within the intracranial tumour microenvironment. These findings were independent of $BRAF^{V600}$ status (Berghoff et al. 2015).

There is preclinical evidence of MAPK pathway involvement in the regulation of the immune microenvironment of tumours. In cell lines, increased antigen expression and enhanced reactivity to antigen-specific T cells is observed with MAPK pathway inhibition (Boni et al. 2010). MEK inhibition has also been shown to increase tumour major histocompatibility complex expression and PD-L1 expression in triple-negative breast cancer cells *in vivo* and *in vitro* (Loi et al. 2016). In $BRAF^{V600}$ mutation-positive melanoma, nonclinical studies show induction of an immunosuppressive tumour microenvironment that can be reversed by BRAF or MEK inhibition (Sumimoto et al. 2006). Furthermore, BRAF and MEK inhibitors, alone or in combination, have been shown to increase melanoma antigen expression, MHC expression, T cell infiltration and PD-L1 expression in tumour biopsies from melanoma patients (Wilmott et al. 2012; Frederick et al. 2013; Kavakand et al. 2015; Liu et al. 2015; Hu Lieskovan et al. 2015). Additional effects of MAPK inhibition that may further modulate the microenvironment to enable enhanced anti-tumour immune reactivity include: increased recruitment and activation status of CD8-positive and CD4-positive T cells and reduced secretion of granulocyte-colony stimulating factor (which reduces mobilization and activity of myeloid-derived suppressor cells), as well as suppression of angiogenesis (Phan et al. 2013; Ebert et al. 2016; Ciuffreda et al. 2009; Chang et al. 2013; Mohan et al. 2015).

Synergistic anti-tumoural activity with combined anti-PD-L1 or anti-PD-1 and MAPK inhibitory agents has been shown in murine cancer model studies. The MEK inhibitor G-38963, which is mechanistically similar to cobimetinib, has been shown to promote the

effector phenotype and longevity of tumour-infiltrating T cells and combine synergistically with anti−PD-L1 in inhibiting tumour growth (Ebert et al. 2016). In addition, concurrent administration of the MEK inhibitor trametinib and an anti-PD-1 immunomodulator has been shown to produce enhanced anti-tumoural activity over these agents alone (Liu et al. 2015).

1.3.2 Clinical Experience with Cobimetinib, Atezolizumab and Vemurafenib in Melanoma

1.3.2.1 Study PCD4989g: Atezolizumab Monotherapy

Study PCD4989g is an ongoing Phase Ia trial evaluating the safety and pharmacokinetics of single agent atezolizumab in patients with locally advanced or metastatic solid tumours or hematologic malignancies. Response within melanoma patients evaluated thus far is comparable to that of two PD-1 inhibitors that are currently approved for the treatment of melanoma (pembrolizumab and nivolumab) (Hodi et al. 2014).

As of a December 15, 2015 data cut-off, patients with metastatic non-ocular melanoma (n=37) enrolled in this study who received doses of at least 10 mg/kg atezolizumab every three weeks (n=37), ORR by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 32% and median PFS was 5.5 months (Roche data on file). In addition, atezolizumab monotherapy was well tolerated by patients with metastatic melanoma.

Further details of safety findings in this study are found in the current Atezolizumab Investigator's Brochure.

1.3.2.2 Study GP28363: Cobimetinib plus Atezolizumab

Study GP28363 is an ongoing Phase Ib, open-label, multicentre, global study of cobimetinib and atezolizumab in patients with metastatic or locally advanced solid tumours, including those who carry a KRAS or $BRAF^{V600}$ mutation, for which no recognized standard therapy exists.

As of a January 17, 2017, clinical data cut-off, there were 20 metastatic melanoma patients (10 with $BRAF^{V600}$ mutation-positive disease) enrolled in the dose escalation or expansion stages who were evaluable for efficacy. These patients had received one or more prior lines of treatment for advanced disease. The median duration of survival follow-up at data cut-off was 25.1 months. The investigator-assessed ORR per RECIST v1.1 was 45.0% (9 of 20; 4 of whom were $BRAF^{V600}$ mutation-positive) for all patients, with all nine responders having a partial response (PR). The comparable ORRs in $BRAF^{V600}$ mutation-positive and wild-type subgroups suggests that all patients may receive benefit regardless of $BRAF^{V600}$ status. This observation is also supported by the median PFS observed in each subgroup (16.2 months in $BRAF^{V600}$ mutation subgroup, 15.7 months in BRAF wild-type subgroup).

Safety data up to January 17, 2017, are available for 150 safety-evaluable patients with various tumour types including colorectal cancer, metastatic melanoma and NSCLC. Of these, 148 (98.7%) experienced an adverse event. The most frequently observed adverse events (≥ 30%) were diarrhoea (70.7%), fatigue (56%), rash (48%), vomiting (42%), nausea (36%), pruritus (35.3%), decreased appetite (34.7%) and constipation (29.3%).

Grade 3/4 adverse events were observed in 96 (64%) of these patients. The most common (≥ 2.7% or 4 patients) included fatigue (10%), anaemia (9.3%), diarrhoea (8%), abdominal pain (5.3%), rash and blood creatine phosphokinase (CPK) increased (4.7% each), dyspnoea and aspartate aminotransferase (AST) increased (4% each), amylase increased and hypertension (3.3% each), and ascites, vomiting, peripheral oedema, asthenia, pleural effusion, pulmonary embolism, blood bilirubin increased, neutrophil count decreased and hypophosphatemia (2.7% each).

Seven patients (4%) were reported to have had Grade 5 adverse events. The following events led to death in 7 patients (4.7%): pneumonia, large intestine perforation, small intestinal perforation, sepsis, road traffic accident and respiratory failure. Sixty-seven safety-evaluable patients (44.7%) had a serious adverse event (SAE), most of which were single reports. The exceptions were pneumonia (6%), pyrexia (4%), abdominal pain and dyspnoea (3.3% each), vomiting (2.7%), sepsis and pulmonary embolism (2% each), and bacteraemia, cellulitis, lung infection, ascites, intestinal obstruction, nausea, fatigue, peripheral oedema, pain, pleural effusion, pneumonitis, dehydration and fall (1.3% each).

These findings are consistent with the known adverse event profiles for cobimetinib and atezolizumab and did not represent additive toxicity.

Further details of this study are found in the current Cobimetinib and Atezolizumab Investigator's Brochures.

1.3.2.3 Study GP28384: Cobimetinib plus Atezolizumab and Vemurafenib in BRAF^{V600} Mutation-Positive Melanoma

Study GP28384 is an ongoing multicentre study expected to enrol a total of approximately 70 patients with previously untreated BRAF^{V600} mutation–positive melanoma. There are two stages in this study: a dose escalation stage and an expansion stage. The study objectives are to assess the safety, tolerability and pharmacology of combined cobimetinib, atezolizumab and vemurafenib (the triplet regimen). Following dose-escalating evaluation of combined atezolizumab and vemurafenib, evaluation of the triplet regimen was initiated and is ongoing. Preliminary safety and efficacy information are currently available for the atezolizumab plus vemurafenib cohorts (median follow-up of approximately 1 year, data cut-off March 1, 2016) and for the triplet cohorts (median follow-up of approximately 10 months, data cut-off January 17, 2017).

The study enrolled four dose-escalation cohorts and is currently enrolling three expansion cohorts. Approximately 24 to 30 patients evaluable for dose-limiting toxicities were enrolled in the dose-escalation cohorts according to a modified 3 + 3 dose-escalation design to evaluate the safety, tolerability and pharmacokinetics of the regimens. There were no dose-limiting toxicities observed in any of the dose-escalation cohorts.

Based on data from the preceding cohorts, treatment in the fourth escalation cohort and expansion cohorts has been established as an initial 28-day run-in with 21 days 960 mg vemurafenib twice daily (BID) then seven days 720 mg vemurafenib BID plus 60 mg cobimetinib once daily (QD) Days 1-21. Following completion of the 28-day run-in, atezolizumab is added to the combination for a final regimen of 60 mg cobimetinib QD (21 days on, 7 days off each cycle) plus 800 mg atezolizumab every two weeks (Q2W) plus 720 mg vemurafenib BID (Days 1-28 of each cycle).

As of the January 17, 2017 clinical cut-off date, 38 patients had received combination treatment with cobimetinib, atezolizumab and vemurafenib and the median survival follow-up was 10.1 months (95% confidence interval [CI]: 8.6, 11.0). Approximately two-thirds (25/38 or 65.8%) of the efficacy-evaluable patients had a confirmed response as assessed by the investigator per RECIST v1.1, with the majority (19/25) as partial responders. The median duration of response (DOR) could not yet be estimated based on only 28.0% of patients reporting a PFS event.

Thirty-nine patients receiving the triplet regimen were evaluable for safety at the clinical cut-off. Thirty-eight of these patients reported an adverse event. The most common adverse events (≥ 20%) following completion of the run-in period included diarrhoea (59%), nausea and arthralgia (56.4% each), pyrexia (53.8%), photosensitivity reaction and fatigue (48.7% each), AST increased (46.2%), pruritus and alanine aminotransferase (ALT) increased (38.5% each), oedema peripheral (35.9%), constipation and hypertension (33.3% each), vomiting, influenza-like illness and cough (30.8% each), chills, rash maculopapular and anaemia (28.2% each), decreased appetite (25.6%), myalgia and back pain (23.1% each), and dry skin, blood creatinine increased, hypophosphatemia and headache (20.5% each).

Grade 3/4 events were reported in 22 patients (56.4%). These events were generally reported in one patient each, with the exception of ALT increased (5 patients [12.8%]), AST increased and hypophosphatemia (4 patients [10.3%] each), and sepsis, rash macular, rash, blood bilirubin increased, blood CPK increased, hyponatremia, urinary tract infection, hypertension and diarrhoea (2 patients [5.1%] each). Eleven patients experienced SAEs, which were each reported in a single patient (2.6%), with the exception of sepsis, which was reported in two patients (5.1%). One patient died as a result of Grade 5 duodenitis.

Overall, there were no unexpected adverse events or apparent additive effects and the majority of adverse events were mild or moderate in severity, manageable with dose modification, and generally reversible. In summary, treatment with cobimetinib, atezolizumab and vemurafenib was associated with a safety profile that appears tolerable and manageable.

Further details of this study are found in the current Cobimetinib, Atezolizumab and Vemurafenib Investigator's Brochures.

1.3.2.4 Ongoing Phase III Studies CO39722 and CO39262

Combined treatment with cobimetinib and atezolizumab with/without vemurafenib, are currently being evaluated in two ongoing, randomized, placebo-controlled, Phase III studies. Study CO39722 is comparing cobimetinib plus atezolizumab versus pembrolizumab in approximately 450 patients with advanced $BRAF^{V600}$ wild-type melanoma. On 18 June 2019, F. Hoffmann-La Roche Ltd. reviewed the results of the primary analysis for Study CO39722 (IMspire170) that showed cobimetinib plus atezolizumab combination did not meet the study primary endpoint of improved progression-free survival by independent review committee compared to pembrolizumab. Safety for the combination of cobimetinib plus atezolizumab was consistent with the known safety profile of the individual medicines, and no new safety signals were identified with the combination. As expected, the overall incidence of adverse events was higher in the combination therapy arm than in the single-agent pembrolizumab arm.

Study CO39262 is comparing combined cobimetinib, atezolizumab and vemurafenib versus cobimetinib, vemurafenib and placebo in approximately 500 patients with previously untreated $BRAF^{V600}$ mutation-positive metastatic melanoma. A significant and clinically meaningful improvement in the primary endpoint of PFS was demonstrated in the study, showing that adding atezolizumab to cobimetinib and vemurafenib helped reduce the risk of disease worsening or death, compared to placebo plus cobimetinib and vemurafenib. The safety profile observed was consistent with the known safety profiles of the individual medicines.

These studies do not allow patients with untreated, actively progressing CNS disease; patients with metastases to the brain stem (study CO39722 only), midbrain, pons or medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm); patients who have received prior WBRT; or patients who require corticosteroids. Patients with melanoma CNS metastases are therefore largely excluded from these studies.

Further details of these studies are found in the current Cobimetinib, Atezolizumab and Vemurafenib Investigator's Brochures.

1.3.3 Benefit-Risk Assessment

As described in Section 1.1, melanoma patients with CNS metastases suffer poor outcomes and are largely excluded from trials that investigate potentially efficacious treatments for advanced melanoma. MAPK inhibition and immune checkpoint blockade are treatment approaches known to be efficacious and tolerable in advanced melanoma. Smaller studies in CNS melanoma metastases populations specifically have shown these approaches exert anti-tumoural activity within the CNS when used as treatment strategies on their own.

Preclinical and preliminary clinical data outlined in Sections 1.3.1 and 1.3.2 indicate the potential for synergistic anti-tumoural activity when these approaches are combined. Based on these data, Phase III studies evaluating combined cobimetinib and atezolizumab treatment in $BRAF^{V600}$ wild-type melanoma and combined cobimetinib, atezolizumab and vemurafenib treatment in $BRAF^{V600}$ mutation-positive disease have been initiated. Study MO39136 will address the exclusion of most CNS melanoma metastases patients from these studies (see Section 1.3.2.4).

Preliminary safety data from studies of combined cobimetinib and atezolizumab with or without vemurafenib outlined in Section 1.3.2 indicate safety profiles of these agents are as expected and without additive toxicity. Importantly, $BRAF^{V600}$ mutation status is required for enrollment and will be the basis by which patients are assigned to treatment cohort thereby ensuring only patients with the potential to benefit from added vemurafenib are exposed to the drug.

Patients enrolled in Study MO39136 will be closely monitored for safety during the study. Guidelines for adverse event management (including dose modifications, interruptions or discontinuations) that are currently used in ongoing trials (see Section 1.3.2.4) will be followed. In addition to Medical Monitor oversight, an Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will review cumulative safety data at regular intervals throughout the study as well as the results of an interim safety review conducted for each treatment cohort after approximately 10 patients enrolled in the cohort have completed their first tumour assessment.

As described in the Dear Investigator Letter dated 9 July 2019, the Sponsor concluded based on results from Study CO39722 that the benefit-risk of atezolizumab in combination with cobimetinib in first-line treatment for patients with $BRAF^{V600}$ wild-type melanoma was uncompelling (see Section 1.3.2.4) when compared to pembrolizumab monotherapy.

Nevertheless, the benefit-risk assessment for cobimetinib in combination with atezolizumab and vemurafenib or in combination with other agents, or in other disease indications remains unchanged, with no new safety signals derived from ongoing studies. Also, the overall benefit-risk profile of cobimetinib or atezolizumab for the currently approved indications is not impacted.

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

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

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

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

Overlapping toxicities of the combination use of atezolizumab, cobimetinib, and vemurafenib may include gastrointestinal toxicity, liver laboratory abnormalities and hepatotoxicity, dermatologic toxicity, pancreatitis, nephritis or increased creatinine, hyperglycemia, ocular events, and pneumonitis. While vemurafenib is thought to have some immune modulating effect, it is not expected that there will be any interaction between vemurafenib and SARS-CoV-2 infection in the approved indications and ongoing clinical studies. In addition, it is also not expected that there will be any interaction between vemurafenib +cobimetinib and SARS-CoV-2 infection. Clinical trials with the treatments in this study are ongoing during this pandemic and, although the study numbers are small, have not shown any increased risk of developing COVID-19 or of having a worse outcome in patients on the treatments used in this study.

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

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of cobimetinib plus atezolizumab in patients with $BRAF^{V600}$ wild-type melanoma with CNS metastases and of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma patients with CNS metastases. Specific objectives and corresponding endpoints for the study are outlined Table 1 below.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objectives	Corresponding Endpoints
• To evaluate intracranial ORR with cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma as assessed by an IRC • To evaluate intracranial ORR with cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma as assessed by an IRC	• Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart. Disease status for this endpoint will be determined by an IRC in accordance with RECIST v1.1 with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions.
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma with CNS metastases • To evaluate the efficacy of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma with CNS metastases	• Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart as determined by the investigator according to RECIST v1.1 with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions • Extracranial ORR, defined as the proportion of patients with either a CR or PR in their extracranial disease based on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • Overall ORR, defined as the proportion of patients with either a CR or PR in their overall disease (i.e., including intracranial and extracranial disease) based on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • Intracranial, extracranial and overall PFS defined as the time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1 • Intracranial, extracranial and overall DOR, defined as the time from the first occurrence of a documented objective response based on two consecutive assessments ≥ 4 weeks apart to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Intracranial, extracranial and overall DCR, defined as the proportion of patients with a CR or PR or SD at 16 weeks from study treatment initiation, as determined by the investigator according to RECIST v1.1

	• OS defined as the time from study treatment initiation to death from any cause • Time from study treatment initiation to cognitive symptom deterioration, defined as a change (≥ 10 points on a 0-100 scale) on selected scales of the EORTC-BN20 (visual disorder, motor dysfunction, communication deficit, headaches, seizures and drowsiness) • Time from study treatment initiation to symptom and function deterioration defined as a change (≥ 10 points on a 0-100 scale) in fatigue, physical functioning, cognitive functioning, or role functioning as measured by the Fatigue, Physical, Cognitive, Role Functioning scales of the EORTC QLQ-C30 • Duration of Stable/Improved HRQoL scores as assessed through use of the two-item GHS/HRQoL subscale (Questions 29 and 30) of the EORTC QLQ-C30
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma with CNS metastases • To evaluate the efficacy of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma with CNS metastases	• Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart. Disease status for this endpoint will be determined by the investigator according to iRANO criteria. • ORR in intracranial, extracranial and overall disease as determined by investigator according to immune-modified RECIST with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions • Intracranial, extracranial and overall PFS as determined by the investigator according to immune-modified RECIST • Intracranial, extracranial and overall DOR as determined by the investigator according to immune-modified RECIST • Radiotherapy-assisted PFS defined as time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1 modified by excluding ≤ 3 lesions that can be treated by SRT from the sum of largest diameters from baseline onwards • Timing of increase or change in corticosteroid use during treatment • Time from study treatment initiation to subsequent intracranial and systemic anti-cancer treatment

	• Change from baseline scores over time in treatment/disease-related symptoms as evaluated by the EORTC QLQ-C30 and QLQ-BN20 questionnaires
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma with CNS metastases • To evaluate the safety of cobimetinib plus atezolizumab and vemurafenib in $BRAF^{V600}$ mutation-positive melanoma with CNS metastases	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To perform molecular characterization of melanoma disease in plasma and tumour tissue	• Relationship between biomarkers (including, but not limited to; PD-L1, BRAF and NRAS) in plasma and tumour tissue and clinical efficacy parameters

CR = complete response; DCR = disease control rate; DOR = duration of response; EORTC QLQ-C30 and QLQ-BN20 = European Organization for Research and Treatment of Cancer Quality of Life questionnaire core questionnaire and brain cancer specific module; GHS = Global Health Status; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; iRANO = immunotherapy Response Assessment for Neuro-Oncology; IRC = Independent Review Committee; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; SRT = stereotactic radiotherapy.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study MO39136 is a Phase II, two cohort, efficacy and safety study of $BRAF^{V600}$ status-specific combination treatment with cobimetinib, atezolizumab and vemurafenib for melanoma with CNS metastases. Study patients will be assigned to study treatment cohort based on locally determined $BRAF^{V600}$ disease status. Patients with $BRAF^{V600}$ wild-type disease will be assigned to treatment with cobimetinib plus atezolizumab in Cohort 1. Patients with $BRAF^{V600}$ mutation-positive disease will be assigned to treatment with cobimetinib plus atezolizumab and vemurafenib in Cohort 2. The study includes assessment of patient reported quality of life outcomes as well as exploratory biomarker evaluations.

Based on the results of the primary analysis for Study CO39722 (IMspire170) of cobimetinib plus atezolizumab combination in previously untreated advanced $BRAF^{V600}$ wild-type melanoma patients (see Section 1.3.2.4), enrollment in the $BRAF^{V600}$ wild-type cohort has been discontinued. Ongoing patients in this cohort may continue study treatment as per protocol, according to investigator's medical judgement.

Following provision of informed consent, potential patients will be screened for study eligibility over a 28-day period. Eligible patients will be assigned to a treatment cohort at enrollment. Study treatment in Cohort 1 will consist of orally administered cobimetinib and intravenously (IV) administered atezolizumab (see Section 4.3.2.1). Study treatment in Cohort 2 will consist of orally administered cobimetinib and vemurafenib for an initial 28-day treatment run-in period, followed by cobimetinib, vemurafenib and IV atezolizumab for subsequent 28-day cycles (Section 4.3.2.2). Disease status for the purposes of treatment decisions will be determined by the investigator. Study treatment for all patients in both cohorts will be continued until investigator-determined disease progression according to RECIST v1.1 (with two exceptions as described below), death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first.

Study treatment may be continued beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 3 intracranial lesions that can be controlled with SRT. Clinically stable patients who have a favourable benefit-risk ratio may continue study treatment beyond progression per RECIST v1.1 if all of the following criteria are met:

- Clinically stable patient with evidence of clinical benefit and favourable benefit−risk ratio as determined by the investigator
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Documented investigator/patient discussion of treatment options alternative to continuing study treatment at the time of RECIST v1.1-defined disease progression
- *Consultation with* the Medical Monitor *is advised*

Study treatment will be discontinued in patients who continue treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at any time subsequently or if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later. Post-progression assessments may be conducted sooner if necessary e.g., due to clinical progression. The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

Patients will attend a Study Treatment Discontinuation Visit after 28 ± 7 days of their last study treatment dose. All adverse events will be reported until 30 days after the last study treatment dose. After the Study Treatment Discontinuation Visit, patients who have

not yet progressed will be followed every 8 or 12 weeks for disease status until disease progression is confirmed, and all patients will be followed every three months for survival and new anti-cancer treatments.

Figure 2 presents an overview of the study design.

Efficacy will be assessed in intracranial disease alone (primary efficacy endpoint) as well as in extracranial and overall (both intracranial and extracranial) disease (secondary and exploratory efficacy endpoints). Disease status will be determined according to RECIST v1.1 with a modified measurability definition for intracranial lesions (≥ 0.5 cm by magnetic resonance imaging [MRI]) and allowing up to five intracranial target lesions (in addition to any extracranial target lesions). Exploratory analyses of disease status will include evaluations by immune-modified RECIST, RECIST v1.1 modified by excluding any SRT-treated lesions from the sum of largest diameters from baseline onwards (if applicable), and immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria. Disease status for the primary endpoint will be determined by an Independent Review Committee (IRC). IRC membership and procedures will be described in the IRC Charter. All other efficacy endpoints will be analysed according to investigator disease status determinations. Disease responses for all endpoints will be confirmed by two consecutive assessments at least four weeks apart. Regardless of whether patients continue treatment beyond disease progression per RECIST v1.1, tumour assessments must be repeated approximately four weeks later (or sooner if necessary e.g., due to clinical progression).

Efficacy will also be evaluated according to patient-reported outcomes (PROs) measured at baseline and during study treatment. Patients will complete the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and brain cancer module (QLQ-BN20) to assess disease and/or treatment-related symptoms (e.g., headache, seizure, diarrhoea, functioning, and health-related quality of life [HRQoL]). After study treatment discontinuation, a subset of the EORTC QLQ-C30 only will be administered.

Safety will be assessed by regular evaluation of adverse events and conduct of physical examinations, vital signs, clinical laboratory tests (haematology, blood chemistry) and electrocardiograms (ECGs). Adverse events will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. An IMC will monitor patient safety throughout the study (see Section 3.1.2).

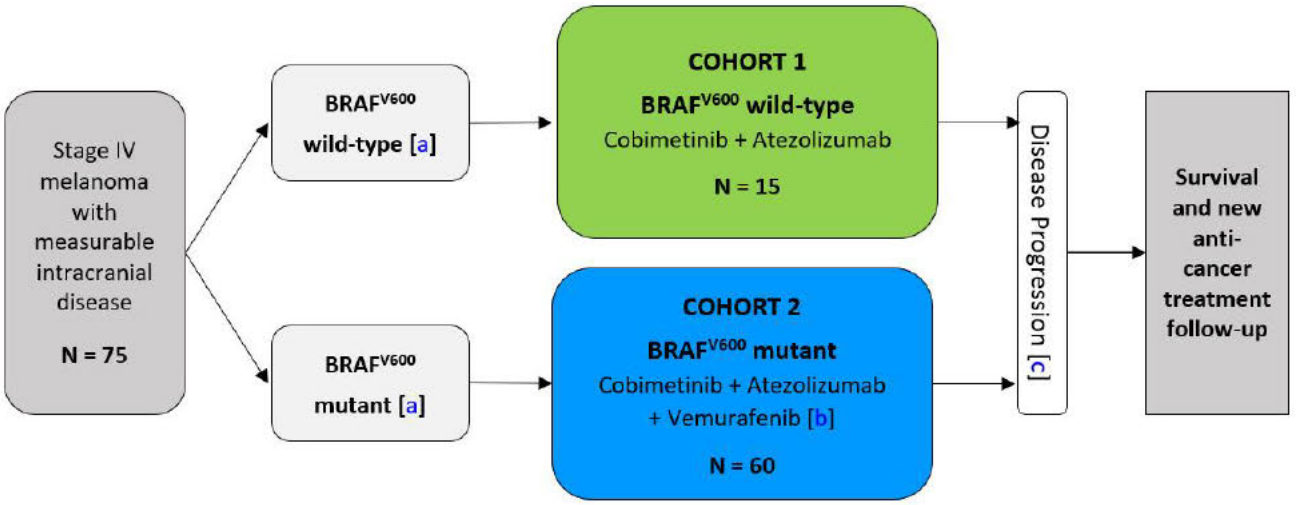
To evaluate molecular biomarkers associated with disease outcomes including response to study treatment, tumour tissue obtained prior to treatment initiation will be collected (if available) and plasma will be collected at baseline and at the time of disease progression.

Schedules of activities are provided in Appendix 1 and Appendix 2. The schedule of biomarker sampling is provided in Appendix 3.

The study will be conducted at approximately 23 sites worldwide. Approximately 60 patients will be enrolled into the $BRAF^{V600}$ mutation-positive cohort and, 15 patients have been enrolled into the $BRAF^{V600}$ wild-type cohort, for a total of approximately 75 patients enrolled. With an estimated study drop-out rate of 15%, approximately 50 patients in the $BRAF^{V600}$ mutation-positive cohort are expected to be evaluable for the primary efficacy endpoint. Patients in the $BRAF^{V600}$ wild-type cohort will be analysed descriptively. *Patients who do not meet the criteria for participation in this study (screen failure) may qualify for re-screening once at the investigator's discretion.*

A Steering Committee (SC) will provide scientific oversight of the trial. Details of the composition and mandate of the SC will be provided in the SC Charter.

Figure 2 Study Schema



a. Documented $BRAF^{V600}$ status in melanoma tumour tissue
b. Treatment regimen begins with a 28-day run-in period with vemurafenib and cobimetinib only
c. Clinically stable patients who have a favorable benefit-risk ratio as defined in the protocol may continue study treatment following radiographic progression per RECIST v1.1 with Medical Monitor approval

3.1.1 Independent Review Committee

Disease status for the primary endpoint will be determined by an IRC. IRC membership and procedures will be described in the IRC charter.

3.1.2 Internal Monitoring Committee

The IMC will monitor patient safety throughout the study. The IMC will include Sponsor representatives from Clinical Science, Drug Safety, and Biostatistics. In addition to the ongoing assessment of the incidence and nature of AEs (particularly Grade 3 events),

SAEs, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review cumulative data at regular intervals throughout the conduct of the study.

At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, additional analyses should be performed, enrollment should be held pending further safety evaluations).

Decisions will be made in consideration of the totality of the available data. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any potential new safety signals. Specific operational details such as the committee's composition, frequency and timing of meetings, members' roles and responsibilities, and data to be reviewed will be described in the IMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The study will end when all patients enrolled have either completed the study (been followed for at least 24 months), died, withdrawn consent, or been lost to follow-up; or the Sponsor decides to end the trial; whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Cobimetinib and Atezolizumab Dosing in Cohort 1

In Cohort 1, cobimetinib will be administered at a dose of 60 mg QD for Days 1-21 of each 28-day cycle. Atezolizumab will be administered at a dose 840 mg Q2W on Days 1 and 15 of every 28-day cycle. These doses and schedule are also being assessed in the ongoing CO39722 study in advanced melanoma (see Section 1.3.2.4).

Cobimetinib is approved for administration at a dose 60 mg QD for Days 1-21 of each 28-day cycle in combination with vemurafenib for the treatment of $BRAF^{V600}$ mutation-positive metastatic melanoma (see the current Cotellic Summary of Product Characteristics).

Atezolizumab will be administered at a fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle), which is an approved dosage for atezolizumab, as outlined in the prescribing information. The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg Q3W. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on

the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy and safety data (refer to the Atezolizumab Investigator's Brochure for details).

Concomitant administration of cobimetinib 60 mg QD for Days 1-21 of each 28-day cycle and atezolizumab 800 mg IV Q2W has been shown to be safe and tolerable in Study GP28363 (see Section 1.3.2.2). Atezolizumab is formulated at a concentration of 60 mg/mL; thus, 800 mg corresponds to a volume of 13.33 mL. To ensure consistent, precise and clinically feasible administration in this study and Study CO39722 (see Section 1.3.2.4), the volume has been rounded up to 14 mL, corresponding to a dose of 840 mg. This nominal increase is further supported by nonclinical dosing data and is not expected to be different from the 800 mg dose.

3.3.2 Rationale for Cobimetinib, Atezolizumab and Vemurafenib Dosing in Cohort 2

In Cohort 2, treatment will begin with a 28-day run-in period wherein only vemurafenib and cobimetinib will be administered. During the run-in, cobimetinib will be administered at a dose of 60 mg QD Days 1-21. Vemurafenib will be administered at a dose of 960 mg BID Days 1-21 and at a dose of 720 mg BID Days 22-28. Following completion of the 28-day run-in, atezolizumab will be added to the combination for a final regimen of 60 mg cobimetinib QD (Days 1-21) plus 840 mg atezolizumab Q2W plus 720 mg vemurafenib BID (Days 1-28). These doses and schedule are also being assessed in the ongoing CO39262 study in advanced melanoma (see Section 1.3.2.4).

Cobimetinib is approved for administration at a dose 60 mg QD for Days 1-21 of each 28-day cycle in combination with vemurafenib for the treatment of $BRAF^{V600}$ mutation-positive metastatic melanoma (see the current Cotellic Summary of Product Characteristics).

Atezolizumab will be administered at a fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle), which is an approved dosage for atezolizumab, as outlined in the prescribing information (also see Section 3.3.1).

Vemurafenib is approved for administration as monotherapy at a dose of 960 mg BID for the treatment of $BRAF^{V600}$ mutation-positive advanced melanoma (see the current Zelboraf Summary of Product Characteristics).

Concomitant administration of cobimetinib 60 mg QD (Days 1-21), atezolizumab 800 mg IV (Days 1 and 15) and vemurafenib 720 mg QD (Days 1-28) following the 28-day run-in dosing and schedule as described above is being studied in Study GP28384 (see Section 1.3.2.3). Cobimetinib, atezolizumab and vemurafenib have been found to be safe and tolerable at these doses. Atezolizumab is formulated at a concentration of 60 mg/mL; thus, 800 mg corresponds to a volume of 13.33 mL. To ensure consistent, precise and clinically feasible administration in this study and Study CO39262 (see

Section 1.3.2.4), the volume has been rounded up to 14 mL, corresponding to a dose of 840 mg. This nominal increase is further supported by nonclinical dosing data and is not expected to be different from the 800 mg dose.

3.3.3 Rationale for Patient Populations

Brain metastases represent a significant therapeutic challenge and are particularly common in advanced melanoma (see Section 1.1). Immunotherapy and MAPK targeted treatments have shown promise in the treatment of advanced melanoma including in patients with CNS disease (see Sections 1.1 and 1.3.2) and are being studied in combination in large, randomized Phase III studies that unfortunately exclude most patients with CNS disease (see Section 1.3.2.4). Study MO39136 will enrol patients with CNS disease that may otherwise be excluded from research into this dual-pronged treatment approach that has the potential to be of benefit in this hard-to-treat population.

$BRAF^{V600}$ status must be known prior to study enrollment in order to determine appropriate treatment cohort assignment. Patients with $BRAF^{V600}$ mutation-positive disease will be assigned to Cohort 2 wherein treatment includes the BRAF inhibitor vemurafenib that abrogates constitutive MAPK activation due to $BRAF^{V600}$ mutation. Patients whose disease does not harbour a $BRAF^{V600}$ mutation will be assigned to treatment in Cohort 1.

All patients must have measurable CNS disease to enable assessment of the primary study endpoint, intracranial ORR. Though consistent with RECIST v1.1, the criteria for CNS disease measurability have been adapted as in other trials of CNS melanoma metastases to ensure CNS lesions can be accurately assessed (Tawbi et al. 2017).

To enable inclusion of patients who have few other treatment options, prior systemic treatment for advanced disease and local treatments for brain metastases, with the exception of treatments that may directly affect the experimental regimens in this study or assessment of efficacy, are allowed. Additional study eligibility criteria have been established to ensure adequate health to undergo experimental therapy and ensure the absence of potential contraindications to the study regimens.

3.3.4 Rationale for Intracranial Objective Response Rate as Primary Endpoint

The primary endpoint of IRC-assessed intracranial ORR was selected in this hypothesis generating, Phase II study in order to identify the activity of the experimental regimens within the CNS in particular. If found promising, additional studies required to evaluate the effect of these treatments on PFS and OS may be conducted.

3.3.5 Rationale for Treatment beyond Disease Progression per RECIST v1.1

Patients in either study cohort may continue treatment beyond disease progression per RECIST v1.1 for two reasons: possible pseudoprogression due to immunotherapy, or disease progression is limited to ≤ 3 intracranial lesions that may be controlled by SRT.

In studies of immunotherapeutic agents, complete response (CR), PR and stable disease (SD) have each been shown to occur after radiographic evidence of an apparent increase in tumour burden. This initial increase in tumour burden caused by immune-cell infiltration in the setting of a T cell response has been termed pseudoprogression (Hales et al. 2010). In single agent atezolizumab studies (Study PCD4989g – see Atezolizumab Investigator's Brochure), evidence of tumour growth followed by a response was observed in several tumour types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed infiltrating immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow treatment in either cohort to continue after apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favourable (see criteria in Section 3.1).

The blood brain barrier limits drug delivery to intracranial disease sites (Agarwala et al. 2000). A probable result of this sequestration is that, while disease outcomes have improved with the introduction of new systemic agents (see Section 1.1), intracranial disease progression despite stable or responding extracranial disease has become more common (Soliman et al. 2015). Though randomized studies evaluating systemic treatment with SRT are limited, the practice of managing brain lesions with SRT in patients whose extracranial disease is controlled by systemic treatment has become a common clinical practice. The value of this approach has been supported by multiple retrospective analyses in melanoma patients receiving SRT with immunotherapy and/or targeted agents (Anderson et al. 2017; Choong et al. 2017, Ahmed et al. 2016; Mathew et al. 2013; Knisely et al. 2012).

Study treatment will be discontinued in any study patient who continues treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at any time or if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later (or sooner if indicated due to clinical progression). Notably, the disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

3.3.6 Rationale for Patient-Reported Outcome Assessments

The goal of cancer treatment is to increase survival and delay of tumour progression not at the expense of the patients' quality of life (Peppercorn et al. 2011). Melanoma has

one the highest percentage of brain metastases relative to other primary tumours. The role of immunotherapy in treatment of brain metastases is unknown because most trials exclude patients with active brain lesions (Preusser et al. 2012, Section 1.1). Therefore, assessing the impact of treatment and disease burden on patients' HRQoL and activities of daily living provides a holistic view of how the full treatment profile impacts patients' lives.

The EORTC QLQ-C30, a generic cancer questionnaire that assesses commonly reported symptoms, functioning, and Global Health Status (GHS)/HRQoL; and the brain cancer module (QLQ-BN20) are validated instruments selected for this study to obtain patient-relevant information. Secondary efficacy PRO endpoints evaluated in this study will be based on changes detected in the QLQ-C30 or QLQ-BN20 symptoms subscale scores that are perceived by patients as clinically significant (Osoba et al. 1998). These data will therefore provide meaningful measures of patients' experience with melanoma treatment.

Assessment of the effects of combination treatment with cobimetinib and atezolizumab or with cobimetinib, atezolizumab and vemurafenib in relation to disease and treatment burden will allow oncologists to appropriately educate patients on the benefits and risks of treatment with these regimens.

3.3.7 Rationale for Biomarker Assessments

Melanoma is a heterogeneous disease driven by aberrations in cancer-related genes including BRAF and NRAS gene mutations. Differences in the genetic makeup of melanoma is likely to influence clinical response and changes in the genetic makeup give insights into potential mechanisms of acquired resistance. The aim is to characterize melanoma disease among patients, to better understand clinical responses, and to assess potential mechanisms of acquired resistance.

Tumour tissue obtained from study participants prior to study treatment initiation will be collected only if such samples are already available. It will be examined for the expression of PD-L1 protein. In addition, if sufficient tumour material is available, an analysis of cancer related genes (such as, but not limited to, BRAF and NRAS) may be performed using next-generation sequencing (NGS). The results will be analysed in relation to clinical response to identify those patients with a greater likelihood of benefiting from study treatment.

Factors in plasma hold important clues regarding the disease pathobiology of cancer patients and may serve as a surrogate for tumour tissue in cases where tissue is not easily accessible. An exploratory objective of this study is to assess biomarkers in plasma at baseline and at the time of relapse. Analysis of plasma may include the analysis of cancer related genes by performing NGS of circulating tumour DNA.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 60 patients with $BRAF^{V600}$ mutation-positive melanoma patients with CNS metastases (Cohort 2) will be enrolled in this study. Enrollment has been discontinued into Cohort 1 ($BRAF^{V600}$ wild-type cohort).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry.

Disease-specific criteria

- Histologically confirmed melanoma with radiologically confirmed brain metastases
- Documented $BRAF^{V600}$ mutation status of melanoma tumour tissue using a validated genetic test.
- Measurable brain metastases defined as any lesion that can be accurately measured in at least one dimension as ≥ 0.5 cm by MRI. Patients who have received prior SRT or surgery for brain metastases must have untreated brain lesions that can be accurately measured in at least one dimension as ≥ 0.5 cm by MRI.
- Prior anti-cancer therapy for metastatic melanoma is allowed, with the following exceptions:
  - Prior BRAF or MEK inhibitors are not allowed in either the metastatic or adjuvant settings
  - Prior immunotherapy is not allowed. As an exception, for patients in Cohort 1 ($BRAF^{v600}$ wild-type) prior immunotherapy is allowed in the adjuvant setting if completed ≥ 90 days prior to study treatment initiation. Examples of immunotherapy include, but are not limited to, nivolumab, pembrolizumab and ipilimumab.
  - Any anti-cancer therapy, including chemotherapy, hormonal therapy and radiotherapy, is prohibited within two weeks prior to initiation of study treatment
- Prior SRT or surgical therapy of ≤ 10 brain metastases is allowed but prior WBRT is not allowed.
- Adverse effects of all prior systemic or local treatment must have either returned to baseline or become stable and manageable prior to initiation of study treatment.

General criteria

- Willing and able to provide informed consent and have signed the study Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status ≤ 2
- Life expectancy of > 3 months

- Willing and able to complete health and quality of life questionnaires required by the protocol
- Adequate hematologic and end-organ function, defined using the following laboratory results obtained within 14 days prior to first dose of study treatment with the exception of amylase and lipase which may be obtained within 28 days prior to study treatment initiation:
  - Absolute neutrophil count ≥ 1.5 × 10^9/L without granulocyte colony-stimulating factor support
  - White blood cell count ≥ 2.5 × 10^9/L
  - Lymphocyte count ≥ 0.5 × 10^9/L
  - Platelet count ≥ 100 × 10^9/L without transfusion
  - Haemoglobin ≥ 90 g/L without transfusion
  - Serum albumin ≥ 25 g/L
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN)
  - Aspartate transaminase and ALT ≤ 2.0 × ULN, or for patients with documented liver metastases, ≤ 5.0 ULN
  - *For patients assigned to Cohort 2 only*: Amylase and lipase ≤ 1.5 × ULN
  - Alkaline phosphatase (ALP) ≤ 2.5 × ULN or, for patients with documented liver or bone metastases ALP ≤ 5 × ULN
  - Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockcroft-Gault glomerular filtration rate estimation as follows:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \ (\times 0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

  - For patients not receiving therapeutic anticoagulation: international normalised ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN within 28 days prior to initiation of study treatment

    For patients receiving therapeutic anticoagulation: stable anticoagulant regimen that does not include coumarin anticoagulants, stable INR and stable aPTT during the 28 days immediately preceding initiation of study treatment.
- Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two effective forms of contraception including at least one method with a failure rate of < 1% per year during the course of this study and for at least six months after completion of study therapy.
  - Females of childbearing potential are defined as sexually mature women without prior oophorectomy or hysterectomy who have had menses within the last 12 months.
  - Females are not considered to be of childbearing potential if amenorrhoeic for > 12 months and follicle-stimulating hormone (FSH) level ≥ 40 IU/L. For

females who have been amenorrhoeic for ≥ 2 years, the requirement for FSH measurement at screening will be waived.

  - Examples of effective contraception methods with a failure rate of < 1% per year include bilateral tubal ligation and male surgical sterilization; hormonal contraceptives that inhibit ovulation; hormone-releasing intrauterine devices; and copper intrauterine devices. A reliable barrier method may be used as the second contraceptive method. Hormonal contraceptive methods must be supplemented by a barrier method. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.
  - Male patients who are surgically sterilized are required to use barrier methods of contraception.

- Female patients of childbearing potential must agree to refrain from donating eggs during the course of the study and for at least 5 months after their final dose of atezolizumab
- Male patients must agree to refrain from donating sperm during the course of the study and for at least six months after the last dose of cobimetinib

4.1.2 Exclusion Criteria

Patients who meet any of the following cancer-related or general criteria will be excluded from study entry:

Cancer-related criteria

- Ocular melanoma
- Leptomeningeal involvement
- Uncontrolled tumour-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at start of study treatment.

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

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to enrollment.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage more than once every 28 days. Note: indwelling drainage catheters (e.g., PleurX®) are allowed.
- Prior WBRT treatment for CNS disease
- Increasing corticosteroid dose during the seven days prior to initiation of study treatment or current dexamethasone or equivalent dose of > 8 mg/day

- Prior treatment with a BRAF or MEK inhibitor
- Major surgical procedure other than for diagnosis within four weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the course of the study
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells or to any formulation component of cobimetinib or atezolizumab or, *for patients assigned to Cohort 2 only*, vemurafenib.
- *Patients assigned to Cohort 2 only*: Concomitant treatment with anticonvulsants other than gabapentin, vigabatrin and levetiracetam
- *Patients assigned to Cohort 2 only*: acetaminophen is prohibited within seven days prior to initiation of study treatment unless the patient has an absolute contraindication to the use of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (i.e., severe allergy or reactive airway disease sensitive to NSAIDs or aspirin).
- Active malignancy (other than melanoma) or a prior malignancy within the past three years

  Patients with completely resected basal cell carcinoma, cutaneous squamous cell carcinoma (cuSCC), cervical carcinoma *in situ*, breast carcinoma *in situ*, prostate cancer *in situ* or limited stage bladder cancer, and patients with isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer are eligible for the study.

General criteria

- Known risk factors for ocular toxicity, consisting of any of the following:
  - History of serous retinopathy
  - History of retinal vein occlusion (RVO)
  - Evidence of ongoing serous retinopathy or RVO at baseline
- History of clinically significant cardiac dysfunction, including the following:
  - Unstable angina or new-onset angina within three months prior to initiation of study treatment
  - Current symptomatic congestive heart failure, defined as New York Heart Association Class II or higher
  - Myocardial infarction within three months prior to initiation of study treatment
  - Unstable arrhythmia
  - Left ventricular ejection fraction below the institutional lower limit of normal or below 50%, whichever is lower
  - Poorly controlled hypertension, defined as sustained, uncontrolled, non-episodic baseline hypertension consistently above 159/99 mmHg despite optimal medical management
  - *For patients assigned to Cohort 2 only*: History of congenital long QT syndrome

  - *For patients assigned to Cohort 2 only*: Mean (average of triplicate measurements) QTc interval corrected using Fridericia's method (QTcF) ≥ 480 ms at screening, or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium and phosphorus)
- Inability to swallow medications
- Malabsorption condition that would alter the absorption of orally administered medications
- Traumatic injury within two weeks prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, anti−phospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see complete list in Appendix 10), with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
  - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded from the study) are eligible for the study provided all of following conditions are met:
    - Rash covering < 10% of body surface area
    - Well-controlled disease at baseline requiring only low-potency topical corticosteroids
    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within 12 months of study treatment initiation
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Uncontrolled diabetes or symptomatic hyperglycaemia
- Any Grade ≥ 3 haemorrhage or bleeding event within 28 days of study treatment initiation
- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within six months prior to study treatment initiation
- Positive human immunodeficiency virus (HIV) test at screening

- Hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening or a positive quantitative HBV DNA test.

  If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, a quantitative HBV DNA test must be performed. If positive, the patient is not eligible.
- Patients receiving anti-viral therapy for HBV are not eligible for study enrollment.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test and a positive HCV RNA test at screening
- Active tuberculosis
- History of severe allergic, anaphylactic or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Severe infection within four weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia*, or any active infection that, in the opinion of the investigator, could impact patient safety*
- Signs or symptoms of infection within two weeks prior to initiation of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in, and completion of, the study
- Any psychological, familial, sociological, or geographical condition that may hamper compliance with the protocol and follow-up after treatment discontinuation
- Pregnancy, breastfeeding, or intention of becoming pregnant during the study. Women of childbearing potential must have a negative serum pregnancy test result within seven days prior to initiation of study treatment.
- Treatment with therapeutic oral or IV antibiotics within two weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Administration of a live, attenuated vaccine within four weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons, IL-2) within 28 days or 5 half-lives of the drug, whichever is shorter, prior to study treatment initiation
- Treatment with systemic immunosuppressive medications (including, but not limited to cyclophosphamide, azathioprine, methotrexate and thalidomide) within two weeks prior to study treatment initiation.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose

corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Treatment with investigational drug within 28 days or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment
- *For patients to be assigned to Cohort 2 only:* anticipated use of any concomitant medication during or within seven days prior to initiation of study treatment that is known to cause QT prolongation
- Consumption of foods, supplements, or drugs that are strong or moderate CYP3A4 enzyme inducers or inhibitors at least seven days prior to initiation of study treatment.

  These include St. John's wort or hyperforin (strong CYP3A4 enzyme inducer) and grapefruit juice (strong cytochrome P450 CYP3A4 enzyme inhibitor).

4.2 METHOD OF TREATMENT ASSIGNMENT

Study patients will be assigned to study treatment cohort based on locally determined $BRAF^{V600}$ disease status. Patients with $BRAF^{V600}$ mutation-positive disease will be assigned to treatment with cobimetinib plus atezolizumab and vemurafenib in Cohort 2. As per the Dear Investigator Letter dated 9 July 2019, no new patients will be enrolled into Cohort 1. Ongoing patients in Cohort 1 may continue study treatment as per protocol, according to investigator's medical judgement.

4.3 STUDY TREATMENT

Cobimetinib and atezolizumab are the investigational medicinal products (IMPs) in Cohort 1 and cobimetinib, atezolizumab and vemurafenib are the IMPs in Cohort 2.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e. atezolizumab and cobimetinib in Cohort 1, and cobimetinib, atezolizumab and vemurafenib in Cohort 2).

4.3.1 Study Treatment Formulation, Packaging and Handling

4.3.1.1 Cobimetinib

Cobimetinib will be supplied by the Sponsor as 20-mg, film-coated, immediate-release tablets.

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

4.3.1.2 Atezolizumab

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

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

4.3.1.3 Vemurafenib

Vemurafenib will be supplied by the Sponsor as 240-mg, film-coated tablets.

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

4.3.2 Study Treatment Dosage, Administration and Compliance

4.3.2.1 Study Treatment Dosage – Cohort 1

Patients in Cohort 1 will receive cobimetinib and atezolizumab in 28-day treatment cycles as outlined in Table 2:

Table 2 Cohort 1 Treatment Regimen

Cobimetinib:	60 mg (three tablets of 20 mg each) orally (PO) once a day (QD) on Days 1−21 of each 28-day cycle.
Atezolizumab:	840 mg intravenously (IV) on Days 1 and 15 of each treatment cycle

Study treatment will be continued until investigator-determined disease progression according to RECIST v1.1, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first. Clinically stable patients who have a favourable benefit-risk ratio may continue study treatment beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 3 intracranial lesions that can be controlled with SRT and if all of the criteria listed in Section 4.3.2.3 are met. No change to the administration of Cohort 1 study treatment is required during intracranial SRT (if applicable).

Study treatment will be discontinued in patients who continue treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at any time subsequently or if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later (or sooner if necessary e.g., due to clinical progression). The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for Cohort 1 patients who experience adverse events are provided in Section 5.1.6.1 and in the respective Investigator's Brochures.

4.3.2.2 Study Treatment Dosage – Cohort 2

Patients in Cohort 2 will receive vemurafenib, cobimetinib and atezolizumab in 28-day treatment cycles. Treatment will include a 28-day run-in period wherein patients will receive vemurafenib and cobimetinib only. Upon completion of the 28-day run-in period, atezolizumab will be added to their treatment regimen.

Study treatment administration in Cohort 2 is outlined in Table 3:

Table 3 Cohort 2 Treatment Regimen

Cobimetinib	Run-in Period (Cycle 1)	
	Days 1−21	60 mg (three tablets of 20 mg each) PO QD
	≥ Cycle 2	
	Days 1-21	60 mg (three tablets of 20 mg each) PO QD
Vemurafenib	Run-in Period (Cycle 1)	
	Days 1-21	960 mg (four 240-mg tablets) PO twice daily (BID)
	Days 22−28	720 mg dose (three 240-mg tablets) PO BID
	≥ Cycle 2	
	Days 1-28	720 mg dose (three 240-mg tablets) PO BID
Atezolizumab	Run-in Period (Cycle 1)	
	Not administered during run-in period	
	≥ Cycle 2	
	Days 1 and 15	840 mg IV

Study treatment will be continued until investigator-determined disease progression according to RECIST v1.1, death, unacceptable toxicity, withdrawal of consent, or pregnancy, whichever occurs first. Clinically stable patients who have a favourable benefit-risk ratio may continue study treatment beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 3 intracranial lesions that can be controlled with SRT and if all of the criteria listed in Section 4.3.2.3 are met. No change to the administration of cobimetinib and atezolizumab are required during intracranial SRT (if applicable). Caution should be used when administering vemurafenib during SRT and standard local treatment practices should be followed. It is recommended that vemurafenib be interrupted at last one day prior to SRT, and to resume at least 1 day

after the procedure. Please refer to Section 5.1.3.10 and to the Vemurafenib Investigator's Brochure for information regarding the risks associated with concomitant vemurafenib and radiation treatment.

Study treatment will be discontinued in patients who continue treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at any time subsequently or if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later (or sooner if necessary e.g., due to clinical progression). The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

Any overdose or incorrect administration of any of the study treatments and any adverse events associated with an overdose or incorrect study drug administration should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for Cohort 2 patients who experience adverse events are provided in Section 5.1.6.2 and in the respective Investigator's Brochures.

4.3.2.3 Dosing of Study Treatment Beyond Disease Progression

Study treatment may be continued beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 3 intracranial lesions that can be controlled with SRT. Clinically stable patients in either cohort who have a favourable benefit-risk ratio may continue study treatment beyond progression per RECIST v1.1 for either reason if all of the following criteria are met:

- Clinically stable patient with evidence of clinical benefit and favourable benefit−risk ratio as determined by the investigator
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal disease progression
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Documented investigator/patient discussion of treatment options alternative to continuing study treatment at the time of RECIST v1.1-defined disease progression
- *Consultation with* the Medical Monitor *is advised*

Study treatment will be discontinued in any patient who continues treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at any time or if persistent disease growth is confirmed on follow-up

disease assessments performed approximately four weeks later. Post-progression assessments may be conducted sooner if necessary e.g., due to clinical progression. The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

Note that it is recommended that vemurafenib be interrupted at last one day prior to SRT, and to resume at least 1 day after the procedure.

4.3.2.4 Cobimetinib Administration

Cobimetinib should be taken at the same time every day. It can be taken with or without food. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a daily dose of cobimetinib is missed (i.e. is not taken within 12 hours after the scheduled dosing time), or if vomiting occurs when the dose is taken, resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

4.3.2.5 Atezolizumab Administration

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 11. Atezolizumab infusions will be administered per the instructions outlined in Table 4.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion.	• If the patient experienced an IRR with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics (acetaminophen is prohibited for patients in Cohort 2 only - see Section 4.4.5) may be administered for subsequent doses at the discretion of the investigator.
• Vital signs (pulse rate, respiratory rate, blood pressure and temperature) should be measured within 60 minutes prior to the infusion.	• Vital signs should be measured within 60 minutes prior to the infusion.
• Atezolizumab should be infused over 60 (±15) minutes.	• Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an IRR, or 60 (±15) minutes if the patient experienced an IRR with the previous infusion.
• If clinically indicated, vital signs should be measured at 15, 30, 45 and 60 minutes (±5 minutes for all timepoints) during the infusion and at 30 (±10) minutes after the infusion.	• If the patient experienced an IRR with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.
• Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	

IRR = infusion-related reaction

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed.

4.3.2.6 Vemurafenib Administration

Vemurafenib should be taken in the morning and in the evening, approximately 12 hours later. Vemurafenib may be taken with or without food. Vemurafenib tablets should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of vemurafenib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

4.3.2.7 Assessment of Compliance

To assess patient compliance with self-administration of cobimetinib in Cohort 1 and cobimetinib and vemurafenib in Cohort 2, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits (see Appendix 1 [Cohort 1] and Appendix 2 [Cohort 2]) for assessments of compliance.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (cobimetinib and atezolizumab in Cohort 1 and cobimetinib, atezolizumab and vemurafenib in Cohort 2) will be provided by the Sponsor where required by local health authority regulations. *The study site should follow all instructions included with each shipment of IMP.* The study site will acknowledge receipt of IMPs supplied by the Sponsor, by returning the appropriate documentation to confirm the shipment condition and content. Any damaged shipments will be replaced. *The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

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

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

4.3.4 Continued Access to Cobimetinib, Atezolizumab and Vemurafenib

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

A patient will be eligible to receive Roche IMPs atezolizumab and cobimetinib (Cohort 1 and Cohort 2 patients) and vemurafenib (Cohort 2 patients only) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being

- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs cobimetinib and atezolizumab (Cohort 1 and Cohort 2 patients) and vemurafenib (Cohort 2 patients only) after completing the study if any of the following conditions are met:

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

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

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from seven days prior to initiation of study treatment until 28 days after the last dose of study treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic anticoagulation therapy (such as low-molecular-weight heparin at a stable dose level), or other allowed maintenance therapy should continue their use. Male and female patients of reproductive potential should use highly effective means of contraception (see Section 4.1.1).

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy such as low-molecular-weight heparin. Note that coumarin anticoagulants are not permitted during the study.

- *V*accinations *(such as influenza, COVID-19); however, live, attenuated vaccines are not permitted (see Section 4.4.5)*
- Megestrol acetate administered as an appetite stimulant
- Inhaled corticosteroids administered for COPD or asthma
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Pain medications as indicated, as per standard practice

In general, investigators should manage a patient's care (including pre-existing conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 4.4.2 and 4.4.5) as clinically indicated, per local standard practice.

Anti-emetic medications, antidiarrheal medications and hematopoietic growth factors are not to be administered prophylactically prior to initiation of study treatment. However, at the discretion of the investigator, anti-emetic medications, antidiarrheal medications and hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of study treatment. In addition, premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

Patients who experience infusion-associated symptoms may be treated symptomatically with ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice (acetaminophen is prohibited for patients in Cohort 2 only - see Section 4.4.5). Serious infusion-associated events manifested by dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 11).

4.4.2 Cautionary Therapy

4.4.2.1 Antiplatelet Agents

Antiplatelet agents should be used with caution during study treatment.

4.4.2.2 Systemic Corticosteroids*, Immunosuppressive Medications,* and TNF-α Inhibitors

Systemic corticosteroids*, immunosuppressive medications,* and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. If feasible, alternatives to these agents should be considered.

Corticosteroids administered to control symptoms of cerebral oedema and mass effect must be reported in the eCRF. Dosage, frequency, dates of administration and route of administration must be recorded in the dedicated eCRF pages.

For treatment of vemurafenib-related adverse events in Cohort 2 (other than hepatotoxicity as outlined in Section 5.1.5.2), systemic corticosteroids may be administered at the lowest effective dose and for the shortest possible duration deemed necessary by the investigator.

Topical corticosteroids are allowed for suspected cutaneous autoimmune reactions. Megestrol may be administered as an appetite stimulant during the study. In situations in which systemic corticosteroids*, immunosuppressive medications,* or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids*, immunosuppressive medications,* and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids *or immunosuppressive medications* are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

4.4.2.3 Bisphosphonates

Patients who are receiving bisphosphonates to enrollment should be maintained on bisphosphonate during study treatment. Initiation of bisphosphonates is discouraged during study treatment because of their potential immunomodulatory properties. However, initiation of such treatment should not result in study treatment discontinuation.

4.4.2.4 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Cautionary therapies applicable to patients receiving cobimetinib (Cohorts 1 and 2):

- Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided during cobimetinib treatment because cobimetinib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).
- Strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) should be avoided during cobimetinib treatment because they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

Cautionary therapies applicable to patients receiving vemurafenib (Cohort 2 only):

- Vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer. Concomitant use of vemurafenib with agents with a narrow therapeutic window that are metabolized by CYP1A2 and CYP3A4 is not recommended. If co-administration cannot be avoided, exercise caution, as vemurafenib may increase plasma exposure of CYP1A2 substrate drugs and decrease plasma exposure of CYP3A4 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated. Acetaminophen is a CYP1A2 substrate and is prohibited for patients in Cohort 2 (see Section 4.4.5).
- In two drug-drug interaction studies, vemurafenib increased the exposure of a single, oral dose of digoxin. An approximate 1.8- and 1.5-fold increase in digoxin area under the concentration-time curve (AUC) from Time 0 to the last measurable concentration and maximum concentration, respectively, was observed in a prior study (Study GO28394). Digoxin and other p-glycoprotein substrates with a narrow therapeutic window are prohibited within seven days prior to initiation of vemurafenib, during vemurafenib treatment, and for 28 days after the last dose of vemurafenib.
- *In vitro* data have demonstrated that vemurafenib is a moderate inhibitor of CYP2C8. CYP2C8 substrates with a narrow therapeutic window should be used with caution, as their concentration may be increased when co-administered with vemurafenib.
- *In vitro* data have demonstrated that vemurafenib is a substrate of CYP3A4. Thus, strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfainavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) should be used with caution when co-administered with vemurafenib

The above lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor *is available to advise* if questions arise regarding medications not listed above.

4.4.2.5 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.2.6 Medications Affecting the QT Interval – Cohort 2 Only

Caution should be exercised when Cohort 2 study treatment is co-administered with drugs that cause QT prolongation or cardiac arrhythmia, especially in patients with a pre-existing cardiac disease or ECG abnormality that may predispose them to cardiac dysrhythmia. Investigators should closely monitor patients who are on medications or

supplements that may affect the QT interval. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their enrollment in this study. Additional information is available at the following Internet site:

https://crediblemeds.org/healthcare-providers/

The effect of vemurafenib 960 mg BID on QT interval was evaluated in a multicentre, open-label, single-arm study in 132 previously-treated patients with $BRAF^{V600}$ mutation−positive metastatic melanoma (Study NP22657). No large changes from baseline in mean QTc interval (i.e., > 20 ms) were detected in the study. However, vemurafenib is associated with concentration-dependent QT prolongation.

Although nonclinical studies showed a low potential for QT-interval prolongation with cobimetinib, no additive effect on QT-interval prolongation was observed when patients were treated with cobimetinib in combination with vemurafenib in Study GO28141. A combined cobimetinib and vemurafenib concentration-QTcF model (for which 433 patients contributed 1031 cobimetinib and vemurafenib observations) provided no evidence that cobimetinib prolonged QTcF interval when co-administered with vemurafenib.

4.4.3 Stereotactic Radiation in Cohort 2

Stereotactic radiation is permissible as described in Section 4.3.2.3. Due to vemurafenib radiation recall and radiation sensitization (see Section 5.1.3.10), caution should be used when giving vemurafenib concomitantly or sequentially with radiation treatment.

4.4.4 Cautionary Food

Due to a possible increased risk of liver toxicity, the consumption of alcohol during study treatment is not recommended.

4.4.5 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Other than SRT as described in Section 4.3.2.3, concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy for palliative or other purposes, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment.
- Investigational therapy is prohibited within 28 days (or 5 half-lives of the drug, whichever is longer), prior to initiation of study treatment and during study treatment.
- Anti-emetic medications, antidiarrheal medications and hematopoietic growth factors are not to be administered prophylactically prior to initiation of study treatment.

- Anti-arrhythmic agents and medications with a risk of torsades de pointes are prohibited within seven days prior to initiation of study treatment, during study treatment, and for 28 days after the last dose of study treatment.
- Denosumab (a RANKL inhibitor) is prohibited during atezolizumab treatment because it could potentially alter the efficacy and safety of atezolizumab. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while in the study.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within four weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 28 days or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- St. John's wort is prohibited during study treatment and for two weeks after the last dose of cobimetinib or vemurafenib (whichever is later)
- Coumarin anticoagulants are prohibited during study treatment
- *For patients in Cohort 2 only*, acetaminophen is prohibited within seven days prior to initiation of study treatment, during study treatment, and for 28 days after the last dose of study treatment, unless the patient has an absolute contraindication to the use of NSAIDs or aspirin (i.e., severe allergy or reactive airway disease sensitive to NSAIDs or aspirin). See Section 4.4.2.4.

4.4.6 Prohibited Food

Use of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of study treatment.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 (Cohort 1) and Appendix 2 (Cohort 2). All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Safety assessments specified in this section are for the purposes of monitoring and management of toxicities known to be associated with the study treatment included in this study (see Section 5.1 for further information).

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before any study-specific screening procedure is performed. All signed Informed Consent Forms (i.e., including for those patients not subsequently enrolled) will be maintained at the study site.

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

Screening Window and Screening Window Extension

All screening assessments must be performed within 28 days prior to study treatment initiation. Exceptionally, results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days prior to study treatment initiation may be used for screening assessments; such tests do not need to be repeated for screening.

The screening window may be extended for an agreed upon and acceptable period to allow re-evaluation of assessments *at the investigator's discretion*.

Re-screening

*R*e-screening may be allowed in certain cases (e.g., patients not initially enrolled due to an aberrant laboratory value, washout of a prior medication, unavailability of study drug, or inability to complete screening within the screening window). Such patients cannot have been previously enrolled in the study nor have received study treatment. Patients may be re-screened only once for the study.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

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

Demographic data will include age, sex and self-reported race/ethnicity (where permissible).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, throat (HEENT), neck, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurological systems. HEENT examination should include visual inspection and/or palpation of the oral cavity and oropharynx, and palpation of the draining lymph nodes of the neck. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations, consisting of an evaluation of the oral cavity, oropharynx, head and neck (including lymph nodes), lungs, heart, abdomen and skin, should be performed at specified post-baseline visits and as clinically indicated. Patients should be asked specifically about skin and vision changes as part of each physical examination. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

As part of tumour assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly and splenomegaly.

4.5.4 Vital Signs

Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure and temperature. Blood pressure and heart rate measurements will be recorded after a 5-minute rest while the patient is in a seated position. Resting oxygen saturation will be measured during screening.

Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1 and Appendix 2).

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Weight and height will be measured at the timepoints specified in the schedule of activities (see Appendix 1 and Appendix 2).

4.5.5 ECOG Performance Status

See Appendix 4

4.5.6 Tumour and Response Evaluations

All measurable and non-measurable lesions must be documented at screening (within 28 days prior to initiation of study treatment). Previously irradiated lesions should not be

selected as measurable (target) lesions. Tumour assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. All measurable and evaluable lesions should be re-assessed at each subsequent tumour evaluation. Intracranial and extracranial tumour assessments after end of Cycle 2 should be conducted every 8 weeks ± 1 week regardless of study treatment delays through 24 months and then every 12 weeks ± 1 week thereafter until confirmed disease progression per RECIST v1.1, initiation of a new anti-cancer treatment, withdrawal of consent, study termination by the Sponsor or death, whichever occurs first.

Tumour assessments must be performed independently of changes to the study treatment administration schedule (i.e. when treatment is withheld). If a tumour assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study treatment administration.

Tumour assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression (unless subsequent anti-cancer therapy is initiated).

Intracranial disease must be followed by MRI. Extracranial tumour assessments will include contrast-enhanced CT or MRI scans of the chest, abdomen and pelvis. Imaging of the neck should be included if clinically indicated. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed along with MRI scans of the abdomen, pelvis and head. In the event a positron emission tomography (PET)/CT scanner is used for tumour assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. Clinical disease assessments by physical examination should be performed for patients with palpable/superficial lesions. Tumour measurements for each patient should be made by the same investigator or radiologist, if feasible, ideally using the same assessment technique or procedure throughout the study. Results must be reviewed by the investigator before dosing at the next cycle.

Disease status will be determined according to RECIST v1.1 (see Appendix 5) with a modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions (in addition to any extracranial target lesions). Exploratory analyses of disease status will include evaluations by immune-modified RECIST (see Appendix 6), RECIST v1.1 modified by excluding any SRT lesions from the sum of largest diameters from baseline onwards (if applicable), and iRANO criteria (see Appendix 7).

Disease responses for all endpoints will be confirmed by two consecutive assessments at least four weeks apart. Tumour assessments showing disease progression must be repeated approximately four weeks later regardless of whether treatment is continued

beyond progression. If disease progression is not confirmed, the subsequent tumour assessment should occur at least four weeks later. However, post-progression assessments may be conducted sooner for patients continuing study treatment beyond progression if necessary e.g., due to clinical progression. Objective response (CR or PR) must be confirmed by repeat assessments ≥ 4 weeks after initial documentation. In the case of SD, tumour measurements must meet criteria for SD ≥ 6 weeks after initiation of study treatment.

Disease status for the primary endpoint will be determined by an IRC. Disease status for the purposes of treatment decisions will be determined by the investigator. All other efficacy endpoints will be analysed according to investigator disease status determinations.

4.5.7 Study-Specific Safety Monitoring Assessments (Cohorts 1 and 2)

4.5.7.1 Ophthalmologic Examinations

Patients will undergo ophthalmologic examinations at specified timepoints during the study. Patients will be evaluated at screening for risk factors for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Risk factors for RVO include history of serous retinopathy or history of RVO, or evidence of ongoing serous retinopathy or RVO at baseline. Patients with such conditions will be excluded from the study as detailed in Section 4.1.2.

Ophthalmologic examinations will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (OCT). If spectral domain OCT is not available, time-domain OCT may be performed instead. Ophthalmologic examination must be performed by a qualified ophthalmologist.

4.5.7.2 Cardiac Monitoring

Evaluation of Left Ventricular Function

Patients will undergo evaluation of left ventricular ejection fraction (LVEF), either by ECHO or MUGA, at specified timepoints during the study, and as clinically indicated for new or worsening symptoms. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of left ventricular function must be performed using the same method for each patient.

Guidelines for management of symptomatic or asymptomatic decreased LVEF are provided in Sections 5.1.6.4 (Cohort 1) and 5.1.6.5 (Cohort 2). All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF, should have LVEF measurements taken more frequently as per Appendix 1 (Cohort 1) or Appendix 2 (Cohort 2) before resuming regular LVEF monitoring every 12 weeks (three cycles).

Electrocardiograms

Triplicate 12-lead ECG recordings will be obtained at screening for both cohorts. For Cohort 2, single 12-lead ECG recordings will be obtained at specified subsequent timepoints, as outlined in the schedule of activities (see Appendix 1 or Appendix 2). For both cohorts, ECG recordings may be obtained at unscheduled timepoints as indicated. ECG results will be evaluated by the investigator for determination of eligibility at screening and for the purposes of real-time cardiac safety monitoring and suitability for continued study treatment.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. ECGs will be obtained in a standardized fashion as described in the ECG manual. ECGs should be performed with the same machine if possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws unless pre-authorized by the Medical Monitor) and should not be obtained within three hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Electronic or paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Guidelines for management of QT prolongation for patients in Cohort 2 (i.e. receiving vemurafenib) are provided in Section 5.1.3.6.

4.5.8 Study-Specific Safety Monitoring Assessments in Cohort 2 Only

4.5.8.1 Monitoring for New Primary Neoplasms

All new primary neoplasms (benign or malignant), including new primary melanoma, will be reported until six months after the last dose of vemurafenib. Any new primary neoplasm other than cuSCC should be reported as an SAE.

Dermatologic Evaluation

Evaluations of the skin by a dermatologist, or qualified equivalent medical specialist, will be performed at specified timepoints during the study. An unscheduled dermatology examination may be performed during treatment for investigation of any new skin lesions that are suspected of being cuSCC or another new primary cutaneous neoplasm.

The dermatologic evaluation should include the following:

- Complete history of prior dermatologic medications and cuSCC risk factors (i.e. radiation therapy, sun exposure, immunosuppression, prior cuSCC, use of tanning beds, precursor lesions and phototherapy for psoriasis)

- Skin examination for cuSCC, BCC, actinic keratosis, keratoacanthoma (KA), and/or second primary melanoma
- Appropriate mapping of any suspicious lesions that may represent cuSCC, BCC, actinic keratosis, KA, or second primary melanoma
- Biopsy and/or excision of any suspicious lesions and submission of specimen blocks or sections for pathologic examination by the local laboratory including the local pathology report if available
- Treatment of identified skin neoplasms or conditions per local standard of care

Head and Neck Examination

To monitor for the occurrence of squamous cell carcinoma (SCC) in the upper aerodigestive tract, a head and neck examination will be performed by the investigator or his or her designee at screening, specified timepoints during the study, and as clinically indicated (e.g., if any new head and neck lesions are suspected of being non-cuSCC). Assessments will include (at a minimum) examination of the HEENT and neck, visual inspection of the oral mucosa and lymph node palpation.

Any suspicious lesions that are identified will be evaluated according to local standard of care and biopsied or excised if indicated. Specimens must be sent for pathological examination, and appropriate follow-up must be instituted.

Lung Examination

Patients will undergo CT or MRI scans of the chest to monitor for the occurrence of lung SCC. The chest CT or MRI scans performed as part of regularly scheduled tumour assessments may be used for lung SCC surveillance.

Anal Examination

To monitor for anal SCC, visual inspection and digital examination of the anus and anal canal will be performed by the investigator or his or her designee at specified timepoints during the study and as clinically indicated. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated. Any suspicious lesions that are identified will need to be evaluated according to local standard of care and biopsied if indicated.

Gynaecological Examination

To monitor for cervical carcinoma, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou (Pap) smear, at specified timepoints during the study and as clinically indicated. Pelvic examinations performed within 12 months prior to screening need not be repeated if found to be normal.

4.5.9 Laboratory, Biomarker and Other Biological Samples

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

- $BRAF^{V600}$ mutation status determined in tumour tissue by a validated genetic test
- Haematology: white blood cell count, red blood cell count, haemoglobin, haematocrit, reticulocyte count, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (bicarbonate and total carbon dioxide are not mandatory if unavailable at site), glucose (non-fasting), BUN or urea, creatinine, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, lactate dehydrogenase and CPK, amylase and lipase.
- Both blood glucose and lipid panel must be obtained after at least an 8-hour fast, at screening only. Lipid panel should include total cholesterol, low-density lipoprotein and triglycerides.
- Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), free thyroxine.
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- HIV serology
- Pregnancy test: All women of childbearing potential will have a negative serum pregnancy test within seven days prior to initiation of study treatment. Urine pregnancy tests (serum pregnancy test if urine test is not available) will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  Females of childbearing potential are defined as sexually mature women without prior oophorectomy or hysterectomy who have had menses within the last 12 months. Females are not considered to be of childbearing potential if amenorrhoeic for > 12 months and FSH level ≥ 40 IU/L. For females who have been amenorrhoeic for ≥ 2 years, the requirement for FSH measurement at screening will be waived.

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

- Formalin-fixed paraffin embedded tumour tissue block or 10 consecutively cut sections from the primary tumour or a metastatic lesion (decalcified tissue is not allowed) obtained any time prior to entry in this study (e.g., archival material).
- Two 10 mL whole blood for plasma obtained at baseline and again at the time of disease progression.

Analyses at central laboratories will include assessment of PD-L1 protein expression and targeted NGS of cancer-related genes (including but not limited to BRAF and NRAS) to evaluate the relationship between molecular biomarkers and clinical efficacy parameters.

Next-generation sequencing will be performed in collaboration with University Hospital Zurich. The investigator can obtain results from these analyses in the form of an NGS report. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed no later than five years after the final Clinical Study Report has been completed, with the following exception:

- Formalin-fixed paraffin embedded tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analysed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data. Data arising from these analyses will be subject to the confidentiality standards described in Section 8.4.

4.5.10 Patient-Reported Outcomes

To more fully characterize disease burden and clinical benefit of study treatment in patients with $BRAF^{V600}$ mutation-positive or negative melanoma with CNS metastases, PRO data will be obtained through the EORTC QLQ-C30 and QLQ-BN20 questionnaires. Paper versions of the questionnaires will be used, and the questionnaires will be translated as appropriate in the local language.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient before the patient receives any information on disease status and prior to the performance of non-patient reported outcome assessments and prior to atezolizumab administration (if applicable). Interviewer assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to complete the measures on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

After the treatment discontinuation visit has occurred, patients will complete Questions 29 and 30 of the EORTC QLQ-C30 only. Post-treatment discontinuation questionnaires may be administered over the telephone.

4.5.10.1 EORTC QLQ-C30

The EORTC QLQ-C30 (version 3.0) is a validated, reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) (see Appendix 8) that is commonly used in clinical trials involving patients with metastatic melanoma (Revicki et al. 2012; Schadendorf et al. 2015). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 10 minutes to complete. A clinically meaningful difference in symptom and function deterioration is defined as a change (≥ 10 points on a 0-100 scale) in fatigue, physical functioning, cognitive functioning, or role functioning as measured by the Fatigue, Physical, Cognitive, Role Functioning scales.

4.5.10.2 QLQ-BN20

The QLQ-BN20 is a validated self-report measure of 20 questions that is used for patients with primary brain neoplasms (Taphoorn et al. 2010) (Appendix 9). A clinically meaningful difference in cognitive symptom deterioration will be defined as ≥ 10 points on a 0-100 scale on selected scales of the EORTC-BN20 (visual disorder, motor dysfunction, communication deficit, headaches, seizures, and drowsiness).

4.5.11 Post-treatment Survival

Post-treatment survival, in addition to PROs and anti-cancer treatments, will be collected via telephone calls and/or clinic visits every three months until death, loss to follow-up, or study termination by the Sponsor.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

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

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

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.12.3 Sample Collection

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

- remaining plasma or derivatives thereof (such as DNA)
- left over cut sections of tumour tissue or derivatives thereof (such as DNA)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), NGS, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the

opportunity for developing new therapeutic approaches. Data will be analysed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important biomarkers and pathways, guiding the development of new targeted agents.

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

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

4.5.12.4 Confidentiality

Specimens and associated data will be labelled with a unique patient identification number.

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

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

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

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

4.5.12.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MO39136 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MO39136.

4.5.12.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (cobimetinib, atezolizumab ± vemurafenib) if they experience any of the following:

- Confirmed disease progression per investigator assessment according to RECIST v1.1

  Note: Study treatment may be continued beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 3 intracranial lesions that can be controlled with SRT. Patients considered for continuation beyond progression per RECIST v1.1 must meet criteria described in Section 4.3.2.3. However, study treatment will be discontinued in patients who continue treatment beyond disease

progression per RECIST v1.1 if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later (or sooner if necessary e.g., due to clinical progression). The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

- Clinical deterioration due to disease progression

  Note: patients who continued study treatment beyond documented disease progression must also discontinue study treatment if clinical deterioration because of disease progression occurs at any time
- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any adverse event that requires study treatment discontinuation including as per the guidelines in Section 5.1
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient (e.g., unwillingness to comply with study assessments that compromise their safety)
- Withdrawal of consent
- Use of an anti-cancer therapy (outside of study treatment per protocol)
- Pregnancy

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

Patients will attend a Study Treatment Discontinuation Visit after 28 ± 7 days of their last study treatment dose. All adverse events will be reported until 30 days after the last study treatment dose. After the Study Treatment Discontinuation Visit, patients who have not yet progressed will be followed every 8 or 12 weeks for disease status until disease progression has been confirmed. Survival, PROs and anti-cancer treatments will be collected via telephone calls and/or clinic visits every three months until death, loss to follow-up, or study termination by the Sponsor.

4.6.2 Patient Discontinuation from Study

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

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

- Study termination or site closure

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

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with cobimetinib, atezolizumab and vemurafenib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1 for cobimetinib, Section 5.1.2 for atezolizumab, Section 5.1.3 for vemurafenib, and Sections 5.1.4 and 5.1.5 for combination use). Cohort-specific guidelines for dose modifications and treatment interruption, as well as management of patients who experience specific adverse events, are provided in Section 5.1.6.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Cobimetinib and vemurafenib will be dispensed with instructions for appropriate self-administration including handling of missed doses. Adverse events will be reported as described in Sections 5.2-5.7.

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

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

During the study, a Medical Monitor and the IMC will be responsible for ongoing safety oversight. In addition, a safety interim analysis will be performed by the Sponsor and reviewed by the IMC once at least 10 patients per cohort have completed their first tumour assessment. The analysis will be conducted by the Sponsor according to the Sponsor's standard operating procedures for safety reviews. The conduct of all IMC reviews and meetings will be as described in the IMC charter.

5.1.1 Risks Associated with Cobimetinib

The following adverse events are classified as identified risks associated with cobimetinib: serous retinopathy, left ventricular dysfunction, photosensitivity (when administered with vemurafenib), severe haemorrhage, rhabdomyolysis and pneumonitis. The following adverse events are classified as potential risks for cobimetinib: severe hepatotoxicity (Grade ≥ 3), impaired female fertility, and teratogenicity and developmental toxicity. In addition, there is the possibility of drug-drug interactions in patients treated with cobimetinib (see Section 4.4 for details). Refer to Section 6 of the Cobimetinib Investigator's Brochure for a detailed description of all anticipated risks for cobimetinib.

Guidelines for management of patients who develop specific adverse events associated with cobimetinib are provided in Sections 5.1.6.4 (Cohort 1) and 5.1.6.5 (Cohort 2).

5.1.1.1 Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK inhibitors, including cobimetinib. Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment and retinopathy. Serous retinopathy events may also be asymptomatic.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to evaluate for risk factors for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Patients will also undergo complete ophthalmologic examinations at specified timepoints throughout the study and as clinically indicated if a patient notes any visual disturbances. Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.5.7.1.

5.1.1.2 Left Ventricular Dysfunction

Decrease from baseline in left ventricular ejection fraction has been reported in patients receiving cobimetinib. Decreased left ventricular ejection fraction may be symptomatic or asymptomatic.

All patients will undergo evaluation of left ventricular ejection fraction, either by echocardiography or multigated acquisition scan at baseline, at specified timepoints during treatment, at the end of treatment, and as clinically indicated.

5.1.1.3 Photosensitivity (When Administered with Vemurafenib)

No evidence of photosensitivity has been observed with cobimetinib as a single agent. However, photosensitivity has been observed when cobimetinib was given in combination with vemurafenib.

5.1.1.4 Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were reported as non-serious and a lower severity (grade).

5.1.1.5 Rhabdomyolysis

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III Study GO28141, and rhabdomyolysis has been reported in post-marketing experience. CPK will be monitored at baseline and monthly during treatment or as clinically indicated.

5.1.1.6 Haemorrhage

Haemorrhage, including major haemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral haemorrhage, gastrointestinal tract haemorrhage, reproductive tract haemorrhage and haematuria, have been reported.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy). Coumarin anticoagulants are not permitted during the study.

5.1.1.7 Severe Hepatotoxicity (Grade ≥ 3)

Liver laboratory test abnormalities, including increases in ALT, AST and ALP, have been reported as adverse events and SAEs in patients treated with cobimetinib plus vemurafenib.

In the Phase III Study GO28141, liver laboratory test abnormalities reported as Grade ≥ 3 adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (20.5% vs. 15.1%, respectively).

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines.

5.1.1.8 Impaired Female Fertility

Results from nonclinical studies indicate that there is a potential for effects on female fertility. While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes were observed in reproductive tissues of dogs. These changes were reversible upon discontinuation of cobimetinib.

5.1.1.9 Teratogenicity and Developmental Toxicity

There are no data regarding the use of cobimetinib in pregnant women. When cobimetinib was administered to pregnant rats, cobimetinib caused embryolethality and foetal malformations of the great vessels and skull at similar systemic exposures to those observed in patients administered the 60-mg dose. Therefore, teratogenicity and developmental toxicity is a potential risk for cobimetinib, and cobimetinib use is not recommended during pregnancy.

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis*, and severe cutaneous adverse reactions*. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)*, which are considered to be potential risks for atezolizumab*. Refer to Appendix 14 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for management of patients who develop specific adverse events associated with atezolizumab are provided in Sections 5.1.6.4 (Cohort 1) and 5.1.6.5 (Cohort 2).

5.1.3 Risks Associated with Vemurafenib

The following adverse events are classified as identified risks associated with vemurafenib: cuSCC, new primary melanoma, progression of RAS-mutant malignancy, photosensitivity and sunburn, liver injury, QT prolongation, hypersensitivity and severe cutaneous reactions, uveitis, VIIth nerve paralysis, radiation recall and radiation sensitization and acute kidney injury. The following adverse events are classified as potential risks for vemurafenib: non-cuSCC, bone marrow toxicity, drug-drug interaction, second primary malignancy, gastrointestinal polyps and RVO. In addition, neutropenia, pancreatitis, Dupuytren's contracture and plantar fascial fibromatosis have been identified as adverse drug reactions in the post-marketing setting. Descriptions of identified risks and selected other risks are provided below. Refer to Section 6 of the Vemurafenib Investigator's Brochure for a detailed description of all identified and potential risks for vemurafenib, including adverse drug reactions in the post-marketing setting.

Guidelines for management of patients who develop specific adverse events associated with vemurafenib are provided in Section 5.1.6.5.

5.1.3.1 Cutaneous Squamous Cell Carcinoma and New Primary Melanoma

Cases of cuSCC, which include those classified as keratoacanthomas or mixed keratoacanthoma subtype, have been reported in patients treated with vemurafenib, usually early in the course of treatment. Potential risk factors associated with cuSCC in three vemurafenib clinical trials included age (≥ 65 years), prior skin cancer and chronic sun exposure. Cases of new primary malignant melanoma have also been reported in patients treated with vemurafenib. Cutaneous SCC and new primary malignant melanoma were managed with excision, and patients were able to continue treatment without dose adjustment.

For patients in Cohort 2, evaluations of the skin by a dermatologist, or qualified equivalent medical specialist, will be performed at specified timepoints during the study (see Section 4.5.8.1 for details). All new primary neoplasms, including new primary melanoma, will be reported until six months after the last dose of vemurafenib.

5.1.3.2 Non-Cutaneous Squamous Cell Carcinoma

Cases of SCC of the head and neck have been reported in patients treated with vemurafenib.

To monitor for the occurrence of SCC, Cohort 2 patients will undergo a head and neck examination, CT or MRI scans of the chest, and visual inspection and digital examination of the anus and anal canal at specified timepoints during the study. To monitor for

cervical carcinoma, all female patients in Cohort 2 will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou smear, at specified timepoints during the study. See Section 4.5.8.1 for details of monitoring assessments. All new primary neoplasms will be reported until six months after the last dose of vemurafenib.

5.1.3.3 *RAS*-Mutant Malignancies

On the basis of its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. In addition, progression of pre-existing RAS-mutant malignancies (chronic myelomonocytic leukaemia, pancreatic cancer) have been reported in patients treated with vemurafenib. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation.

5.1.3.4 Photosensitivity and Sunburn

Mild to severe skin photosensitivity has been reported in patients treated with vemurafenib. All patients should be advised to minimize sun exposure, wear protective clothing, and use a broad-spectrum ultraviolet A/ultraviolet B sunscreen and lip balm (SPF ≥ 30), reapplied every 2 to 3 hours, when outdoors during vemurafenib treatment and for at least 5−10 days after discontinuing vemurafenib.

5.1.3.5 Liver Injury

Liver injury, including cases of severe liver injury, have been reported in patients treated with vemurafenib. ALP, ALT, AST and bilirubin will be monitored at specified timepoints throughout the study.

5.1.3.6 QT Prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase II QT sub-study in patients with metastatic melanoma. QT prolongation may lead to an increased risk of ventricular arrhythmias, including torsades de pointes.

Patients with a history of congenital long QT syndrome, QTcF ≥ 480 ms, or uncorrectable abnormalities in serum electrolytes will be excluded from study inclusion. ECG and electrolytes, including potassium, magnesium and calcium, will be monitored throughout the study. In addition, investigators should closely monitor patients who are on medications or supplements that may affect the QT interval. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to their enrollment in this study.

5.1.3.7 Hypersensitivity and Severe Cutaneous Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with vemurafenib and upon re-initiation of treatment. Severe hypersensitivity reactions included generalized rash and erythema or hypotension. Drug reaction with eosinophilia and systemic symptoms has been reported in association with vemurafenib in the post-marketing setting. Severe dermatologic reactions have been reported in

patients receiving vemurafenib, including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.

5.1.3.8 Uveitis and Retinal Vein Occlusion

Serious ophthalmologic reactions, including uveitis, have been reported in patients treated with vemurafenib. Retinal vein occlusion has been observed and is a potential risk.

Patients will under ophthalmologic examinations at specified timepoints during the study (see Section 4.5.7.1). Patients will be evaluated at screening for risk factors for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Risk factors for RVO include history of serous retinopathy or history of RVO, or evidence of ongoing serous retinopathy or RVO at baseline. Patients with such conditions are excluded from the study.

5.1.3.9 VIIth Nerve Paralysis

Cases of VIIth nerve paralysis have been observed in patients treated with vemurafenib. In clinical trials, these events resolved without sequelae.

5.1.3.10 Radiation Recall and Radiation Sensitization

An adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation prior to, during, or subsequent to vemurafenib treatment. The nature and severity were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation. The reaction was seen in the skin, oesophagus, lung, liver, rectum and urinary bladder. Most cases were cutaneous in nature, but some cases involving visceral organs had fatal outcomes. Further details of radiation recall and sensitization events are provided in the current Vemurafenib Investigator's Brochure. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Radiation therapy should not be administered unless the possible benefits outweigh the possible risks.

It is recommended that vemurafenib be interrupted at least one day prior to SRT, and to resume at least 1 day after the procedure.

Other than SRT applicable as described in Section 4.3.2.3, radiotherapy is not permitted during the study.

5.1.3.11 Acute Kidney Injury and Renal Function Alterations

Acute kidney injury, including interstitial nephritis, has been observed in patients treated with vemurafenib. The majority of these cases have been characterized by mild to moderate increases in serum creatinine (some observed in the setting of dehydration events), with recovery after dose modification.

Serum creatinine will be monitored throughout the study. Vemurafenib acute kidney injury dose modification guidelines should be utilized when applicable and it is

recommended to routinely monitor serum creatinine levels in all patients undergoing vemurafenib therapy.

5.1.3.12 Drug-Drug Interaction

Drug-drug interactions are a potential risk for vemurafenib. Prohibited therapies and food and cautionary therapies are described in Section 4.4.

5.1.3.13 Gastrointestinal Polyps

Rare cases of colonic polyps have been reported in patients treated with vemurafenib for two or more years while enrolled in a clinical study (Chapman et al. 2012).

5.1.3.14 Neutropenia

Neutropenia has been identified as an uncommon adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6−12 weeks of treatment. It appears to be reversible usually within two weeks, with temporary interruption, dose reduction, or discontinuation of vemurafenib, and in some cases has been managed with granulocyte colony-stimulating factor.

5.1.3.15 Pancreatitis

Pancreatitis has been identified as an uncommon adverse drug reaction in patients being treated with vemurafenib. The clinical presentation in terms of severity, mild to moderate, was consistent with the clinical picture of drug-induced pancreatitis (Lankisch et al.1995).

The Sponsor recommends that serum amylase and lipase testing be conducted as part of the workup of any suspected case of pancreatitis in addition to other appropriate testing (e.g., abdomen CT scan).

5.1.3.16 Dupuytren's Contracture and Plantar Fascial Fibromatosis

Dupuytren's contracture and plantar fascial fibromatosis have been reported with vemurafenib. The majority of cases were Grade 1 or 2, but severe, disabling cases of Dupuytren's contracture have also been reported.

5.1.4 Risks Associated with Combination Use of Cobimetinib and Atezolizumab

Special consideration is given to areas of potential overlapping toxicity based on data from previous clinical experience with each compound individually or with other molecules. Potential overlapping toxicities of cobimetinib and atezolizumab include dermatologic reactions, ocular toxicity, hepatic toxicity, liver laboratory abnormalities, pneumonitis and gastrointestinal toxicity as described below. Please also refer to the Cobimetinib Investigator's Brochure and Atezolizumab Investigator's Brochure for details regarding these adverse events.

Patients treated with cobimetinib and atezolizumab should be closely monitored for evidence of overlapping and/or potentiation of these and any other acute toxicities. If any

evidence of overlapping and/or potentiation of the above toxicities is observed, patients should receive maximal supportive care as clinically indicated.

Guidelines for management of patients who develop these toxicities are provided in Section 5.1.6.4.

5.1.4.1 Dermatologic Toxicity

Treatment-emergent rash has been reported with single-agent atezolizumab. The majority of these cases were mild in severity and self-limited, with or without pruritus. Because rash has been observed with cobimetinib, this is a potentially overlapping toxicity and should be closely monitored. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

5.1.4.2 Ocular Toxicity

Uveitis or episcleritis and other immune-mediated ocular disease may be associated with atezolizumab. Ophthalmologic reactions have been observed with cobimetinib (serous retinopathy). Thus, this is a potential overlapping toxicity with this treatment combination.

5.1.4.3 Hepatic Toxicity

Liver laboratory abnormalities and hepatotoxicity have been observed with cobimetinib (with vemurafenib) and atezolizumab monotherapy. Generally, liver laboratory abnormalities following treatment with cobimetinib + vemurafenib are manageable with dose modifications. Rare cases of immune-mediated hepatitis have been associated with the administration of atezolizumab.

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Patients with known liver disease that could increase susceptibility to or exacerbate the effect of any potential hepatotoxicity of study treatment, including those with active hepatitis B or active hepatitis C viral infection, are excluded from the study.

Liver function will be monitored throughout the study. Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests performed immediately and reviewed before administration of the next dose of study treatment. For patients with elevated liver function tests, concurrent medication, viral hepatitis, and toxic or neoplastic aetiologies should be considered and addressed, as appropriate.

5.1.4.4 Pulmonary Toxicity

Dyspnoea, cough, fatigue, hypoxia, pneumonitis and pulmonary infiltrates have been associated with the administration of atezolizumab. Pneumonitis is an identified risk for cobimetinib and is therefore a potential overlapping toxicity with this treatment combination. Patients will be assessed for pulmonary signs and symptoms throughout

the study and will also have CT scans of the chest performed at every tumour assessment. All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.

5.1.4.5 Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of atezolizumab. In addition, because diarrhoea has been commonly observed with cobimetinib, gastrointestinal reactions are a potential overlapping toxicity with this treatment combination. Diarrhoea can frequently be managed with anti-diarrheal agents but can also progress to clinically significant dehydration and/or electrolyte imbalances with effects on other organs, possibly resulting in renal, hepatic and/or cardiac failure. Patients should be instructed to promptly contact the investigators if they develop diarrhoea. Investigators should treat diarrhoea and intervene promptly for patients who appear to be at increased risk of developing significant dehydration, electrolyte imbalances, or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

5.1.5 Risks Associated with Combination Use of Cobimetinib, Atezolizumab and Vemurafenib

Special consideration is given to areas of potential overlapping toxicity based on data from previous clinical experience with each compound individually or with other molecules. Gastrointestinal toxicity, liver laboratory abnormalities and hepatotoxicity, dermatologic toxicity, pancreatitis, nephritis or increased creatinine, hyperglycaemia, ocular events, and pneumonitis represent potential overlapping toxicities with combined cobimetinib, atezolizumab and vemurafenib. These are described below. Please also refer to Investigator's Brochures for cobimetinib, atezolizumab and vemurafenib for more details regarding these adverse events.

Patients treated with cobimetinib, atezolizumab and vemurafenib should be closely monitored for evidence of overlapping and/or potentiation of these and any other acute toxicities. If any evidence of overlapping and/or potentiation of the above toxicities is observed, patients should receive maximal supportive care as clinically indicated.

Guidelines for management of patients who develop these toxicities are provided in Section 5.1.6.5.

5.1.5.1 Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of atezolizumab. In addition, because diarrhoea has been commonly observed with vemurafenib, cobimetinib, and cobimetinib + vemurafenib, gastrointestinal reactions are a potential overlapping toxicity with this treatment combination. Diarrhoea can frequently be managed with anti-diarrheal agents but can also progress to clinically significant

dehydration and/or electrolyte imbalances with effects on other organs, possibly resulting in renal, hepatic and/or cardiac failure. Patients should be instructed to promptly contact the investigators if they develop diarrhoea. Investigators should treat diarrhoea and intervene promptly for patients who appear to be at increased risk of developing significant dehydration, electrolyte imbalances, or multi-organ failure. Patients should receive maximum supportive care per institutional guidelines.

5.1.5.2 Hepatic Toxicity

Liver laboratory abnormalities and hepatotoxicity have been observed with cobimetinib with vemurafenib, vemurafenib monotherapy, and atezolizumab monotherapy. Generally, liver laboratory abnormalities following treatment with cobimetinib + vemurafenib, as well as vemurafenib monotherapy, are manageable with dose modifications. Rare cases of immune-mediated hepatitis have been associated with the administration of atezolizumab. It appears that Grade ≥ 3 ALT or AST elevations may occur at a higher frequency with atezolizumab + cobimetinib + vemurafenib.

Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases. Patients with known liver disease that could increase susceptibility to or exacerbate the effect of any potential hepatotoxicity of study treatment, including those with active hepatitis B or active hepatitis C viral infection, are excluded from the study.

Liver function will be monitored throughout the study. Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests performed immediately and reviewed before administration of the next dose of study treatment. For patients with elevated liver function tests, concurrent medication, viral hepatitis, and toxic or neoplastic aetiologies should be considered and addressed, as appropriate.

5.1.5.3 Dermatologic Toxicity

Treatment-emergent rash has been reported with single-agent atezolizumab. The majority of these cases were mild in severity and self-limited, with or without pruritus. Because rash has been observed with vemurafenib and cobimetinib + vemurafenib, this is a potentially overlapping toxicity and should be closely monitored. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

5.1.5.4 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. Pancreatitis is an adverse drug reaction for vemurafenib and could therefore represent an overlapping toxicity. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

5.1.5.5 Renal Events

Renal failure, ranging from creatinine elevation to acute interstitial nephritis and acute tubular necrosis, has been observed with vemurafenib treatment. Nephritis is a rare risk for atezolizumab. Creatinine will be monitored according to the schedule of activities during study treatment.

5.1.5.6 Hyperglycaemia

Increased blood sugar has been rarely observed with cobimetinib treatment. Rare cases of immune-related diabetes have been observed with atezolizumab treatment. Blood glucose will be assessed throughout the study. Patients with uncontrolled diabetes or symptomatic hyperglycaemia will be excluded.

5.1.5.7 Ocular Toxicity

Uveitis or episcleritis and other immune-mediated ocular disease may be associated with atezolizumab. Ophthalmologic reactions have been observed with vemurafenib (uveitis and RVO) and cobimetinib (serous retinopathy). Thus, this is a potential overlapping toxicity with this treatment combination.

Patients will under ophthalmologic examinations at specified timepoints during the study. An ophthalmologist should evaluate visual complaints.

5.1.5.8 Pulmonary Toxicity

Dyspnoea, cough, fatigue, hypoxia, pneumonitis and pulmonary infiltrates have been associated with the administration of atezolizumab. Pneumonitis is an identified risk for cobimetinib and is therefore a potential overlapping toxicity with this treatment combination. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumour assessment. All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.

5.1.6 Management of Patients Who Experience Specific Adverse Events

5.1.6.1 Dose Modifications – Cohort 1

General dose modification guidelines for cobimetinib are provided in Table 5. Dose modification guidelines for specific adverse events with combination treatment in this cohort are provided in Appendix 12. Additional guidelines for the management of adverse events associated with atezolizumab are provided in Appendix 14 . After dose reduction, consideration may be given to allow for dose escalation of cobimetinib by a maximum of one dose level (20 mg) increments following resolution of the adverse event that resulted in dose modification to ≤ Grade 1 and provided there are no safety concerns.

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

Table 5 Recommended Cobimetinib Dose Modifications

Grade (NCI CTCAE)	Recommended Cobimetinib Dose
Grade 1 or Grade 2 (tolerable)	No dose reduction. Maintain cobimetinib at the same dose of 60 mg QD (3 tablets).
Grade 2 (intolerable) or Grade 3 or 4 (any)	
First appearance:	Interrupt treatment until Grade ≤ 1: restart treatment at 40 mg QD (2 tablets).
Second appearance:	Interrupt treatment until Grade ≤ 1: restart treatment at 20 mg QD (1 tablet).
Third appearance:	Consider permanent discontinuation.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once a day.

5.1.6.2 Dose Modifications – Cohort 2

Run-in period (Cycle 1)

During the run-in period (Cycle 1, Days 1-28), one dose level reduction of cobimetinib and vemurafenib is permitted for management of drug-related toxicities. No further dose reductions are permitted in the run-in period. If toxicities do not improve within 28 days following the one level dose reduction and/or treatment interruption for either cobimetinib and/or vemurafenib, study treatment should be discontinued, unless *the patient is likely to derive clinical benefit. The decision to re-challenge patients with study treatment should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).* The Medical Monitor *is available to advise as needed*. The run-in period may be extended to a total of 56 days to allow patients to recover from drug-related toxicities prior to proceeding to Cycle 2. Following a dose reduction in the run-in period (Cycle 1), no escalation is permitted.

- During the run-in period (Cycle 1), the dose of cobimetinib can be reduced by 20 mg QD (one dose level) from 60 mg daily to 40 mg daily during Days 1-21.
- If a vemurafenib dose reduction is required during Days 1-21, the dose of vemurafenib can be reduced from 960 mg BID to 720 mg BID. No further dose reductions of vemurafenib are allowed during Cycle 1.
- Drug-related toxicities presenting during the run-in period (Cycle 1) that require a vemurafenib dose reduction should be improving or have resolved (see Appendix 13) prior to Cycle 2, Day 1.

Patients must be receiving both study treatments in order to enter the triplet treatment period (Cycle 2, Day 1).

Triplet treatment period (Cycles ≥ 2)

The dose of cobimetinib can be reduced by 20 mg QD (one dose level) decrements up to two times for management of drug-related toxicities (i.e. from 60 to 40 mg and then from 40 to 20 mg), except during the run-in period when only one dose reduction is allowed. If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab and/or vemurafenib at the investigator's discretion. The dose of cobimetinib may be escalated by a maximum of one dose level (20 mg) from 20 mg QD to 40 mg QD at the investigator's discretion in patients who have previously undergone dose reduction, provided there are no safety concerns and the adverse event that resulted in the dose reduction has resolved to ≤ Grade 1. Dose escalation from 40 mg QD to 60 mg QD is not permitted.

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

The dose of vemurafenib dose can be reduced during the triplet combination treatment period from 720 mg BID to 480 mg BID. If further dose reduction is indicated, the patient must discontinue vemurafenib but may continue treatment with atezolizumab and/or cobimetinib at the investigator's discretion.

Dose modification guidelines for specific adverse events with combination treatment in this cohort are provided in Appendix 13 . Additional guidelines for the management of adverse events associated with atezolizumab are provided in Appendix 14.

5.1.6.3 Treatment Interruption or Discontinuation

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks, the patient will be discontinued from atezolizumab. Study treatment may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).* The Medical Monitor *is available to advise as needed.* Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the* investigator *and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

Cobimetinib (Cohort 1) or cobimetinib and vemurafenib (Cohort 2) treatment may be temporarily suspended in patients who experience toxicity considered to be related to

study treatment. If cobimetinib or vemurafenib (if applicable) has been withheld for > 28 days because of toxicity, the patient should be discontinued from that drug, unless *the patient is likely to derive clinical benefit. The decision to re-challenge patients with study treatment should be based on investigator's assessment of benefit–risk and documented by the* investigator *(or an appropriate delegate).* The Medical Monitor *is available to advise as needed.* The Medical Monitor should be consulted for any major surgery (e.g., involving a body cavity), and cobimetinib and vemurafenib (if applicable) should generally be withheld for two days prior to the procedure and for two weeks afterwards.

For dose interruptions required in the run-in period (Cycle 1) in Cohort 2, refer to Section 5.1.6.2.

5.1.6.4 Management Guidelines – Cohort 1

In general, toxicities should be managed with supportive care, dose modifications (as permitted), and treatment interruptions applied to the component of the study treatment judged to be the primary cause. Additional tests or procedures, such as autoimmune serology or biopsies to obtain tissue samples, may be performed to determine a possible immunogenic aetiology. This also applies to cases where the severity exceeds previously observed toxicities, or nature of the toxicity encountered differs from the known safety profile. Special attention to cases of severe cutaneous hypersensitivity reactions, such as Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is warranted from study investigators.

For management of cobimetinib- and atezolizumab-specific toxicities, including IRRs, gastrointestinal toxicity, dermatologic toxicity, hepatotoxicity, pulmonary toxicity, potential eye toxicity, reductions in LVEF from baseline, rhabdomyolysis, elevated CPK and haemorrhage, see Appendix 12. Additional guidelines for the management of adverse events associated with atezolizumab are provided in Appendix 14 .

5.1.6.5 Management Guidelines – Cohort 2

In general, toxicities should be managed with supportive care, dose modifications (as permitted), and treatment interruptions applied to the component of the study treatment judged to be the primary cause. Additional tests or procedures, such as autoimmune serology or biopsies to obtain tissue samples, may be performed to determine a possible immunogenic aetiology.

Cohort 2 patients should be monitored closely upon initiation of atezolizumab as a third treatment component on Days 1 and 15 of Cycles 2 and 3, as well as the days immediately following these visits. Regular telephone contact and, if needed, unscheduled laboratory tests are strongly recommended.

Guidelines for management of patients who experience specific adverse events in this cohort are provided in Appendix 13. The table also includes general guidelines for dose

modifications and treatment delays and discontinuation. Additional guidelines for the management of adverse events associated with atezolizumab are provided in Appendix 14 . The guidelines in Appendix 13 and Appendix 14 are not intended to replace clinical judgment or dictate care of individual patients.

Guidelines for management of cobimetinib and vemurafenib toxicities in Appendix 13 will not apply to reversible laboratory abnormalities with no clinical sequelae or no clinical significance as determined by the investigator in consultation with the Medical Monitor.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

These events may or may not be SAEs and they may or may not be considered related to study medication. Regardless of relationship or severity, these events will be recorded if they start from the time of the first dose of study treatment and will be followed until resolution.

After the end of the adverse event reporting period, the Sponsor should be notified if the Investigator becomes aware of any adverse events of special interest that are believed to be related to prior study treatment.

Adverse events of special interest for this study are as follows:

Events specific to cobimetinib and vemurafenib

- Any RVO
- Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
- Grade ≥ 3 photosensitivity
- Rhabdomyolysis or Grade ≥ 3 CPK elevation
- Grade ≥ 3 haemorrhage or any grade cerebral haemorrhage
- Grade ≥ 3 rash
- Grade ≥ 3 diarrhoea
- Grade ≥ 3 QT interval prolongation
- Symptomatic heart failure and/or Grade ≥ 2 left ventricular ejection fraction reduction
- Pneumonitis
- Hepatitis, including AST or ALT $>$ 10 × ULN

Events specific to atezolizumab

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, or hypophysitis
- Hepatitis, including AST or ALT $>$ 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, IRRs, CRS, influenza-like illness$, HLH, and$ MAS
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune haemolytic anaemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Other adverse events of special interest

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, all adverse events as follows:

- All adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first
- SAEs and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

- Subsequently, the Sponsor should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study treatment.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 5.4.2 for reporting instructions), per the definition of SAEs in Section 5.2.2.
d. Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAEs in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

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

Table 7 Causal Attribution Guidance

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal haemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalaemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalaemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of metastatic melanoma should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within one hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Melanoma

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

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as “special situations”) are defined as follows:

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

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not quality as drug abuse

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

For atezolizumab, cobimetinib, and vemurafenib, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the “Intentional overdose” box. If drug abuse is suspected, check the “Drug abuse” box. If drug abuse is not suspected, check the “Drug misuse” box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the “Drug abuse” box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the “Intentional overdose” and “Drug abuse” boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the “Drug misuse” box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the “Intentional overdose” and “Drug misuse” boxes.

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and “intentional overdose” as the event term. Check the “Intentional overdose” box. If drug abuse is suspected, check the “Drug abuse” box. If drug abuse is not suspected, check the “Drug misuse” box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and “drug abuse” as the event term. Check the “Drug abuse” box.
- Drug abuse that qualifies as an overdose: Enter the drug name and “intentional overdose” as the event term. Check the “Intentional overdose” and “Drug abuse” boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and “drug misuse” as the event term. Check the “Drug misuse” box.
- Drug misuse that qualifies as an overdose: Enter the drug name and “intentional overdose” as the event term. Check the “Intentional overdose” and “Drug misuse” boxes.
- Drug administered to someone other than the patient: Enter the drug name and “patient supplied drug to third party” as the event term. Check the “Drug misuse” box.

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

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Although sites are not expected to review the PRO data, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- SAEs (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.3.5.12 for details on reporting requirements)

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

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, SAEs and adverse events of special interest will be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. New primary neoplasms other than cuSCC (which qualify as SAEs) will continue to be reported until six months after the last

dose of vemurafenib. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting SAEs that occur > 90 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within six months after the last dose of study treatment. *The investigator should report the pregnancy on the* paper Clinical Trial Pregnancy Reporting Form *and submit the form* to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health

Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form *with additional* information on the *pregnant partner and the* course and outcome of the pregnancy *as it* becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for SAEs and adverse events of special interest (defined as 90 days after the last dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

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

- Cobimetinib Investigator's Brochure
- Atezolizumab Investigator's Brochure
- Vemurafenib Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

A primary study analysis that includes analyses of all efficacy endpoints and safety summaries will be conducted based on data collected up to six months after the last patient is enrolled in the study (last patient in [LPI]). The final study analysis including updated analyses of safety and efficacy endpoints will be conducted based on data collected up to 24 months after LPI.

Unless otherwise indicated, efficacy analyses will be based upon the Evaluable Patient population in each cohort consisting of all enrolled patients who received study medication and have at least two post-baseline tumour assessments for response evaluation. Analyses of safety, PRO, survival, timing of change in corticosteroid use, and time to subsequent intracranial or systemic anti-cancer treatment endpoints will be conducted based upon the Safety population in each cohort consisting of all patients who received at least one dose of study medication.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this Phase II study is estimation and hypothesis generation regarding the effect of cobimetinib plus atezolizumab on CNS metastases from $BRAF^{V600}$ wild-type melanoma and the effect of cobimetinib plus atezolizumab and vemurafenib on CNS metastases from $BRAF^{V600}$ mutation-positive melanoma. There are no reference data available on the use of these combination therapies in these patient populations.

There is no formal statistical hypothesis in this study. The originally planned total sample size of approximately 60 patients per cohort was based on an estimated study drop-out rate of 15%, the primary endpoint and 95% CIs for each treatment regimen. No power calculation has been performed.

In a Dear Investigator Letter dated 9 July 2019, the Sponsor communicated the decision to discontinue enrollment in the $BRAF^{v600}$ wild-type cohort (Cohort 1). As of 9 July 2019, 15 patients were enrolled in Cohort 1. The 15 patients enrolled into the $BRAF^{V600}$ wild-type cohort at the time of recruitment stop will be analysed descriptively only.

Point estimates and 95% CIs for a range of possible outcomes produced using nQuery (version 7) with 50 evaluable patients in the $BRAF^{V600}$ mutation-positive cohort are provided in Table 8 below.

Table 8 Objective Response Rate Estimates and Confidence Intervals with 50 Evaluable Patients per Treatment Cohort

Intracranial Response Rate in Cohort 2	95% Confidence Interval
35%	(21.8%, 48.2%)
40%	(26.4%, 53.6%)
45%	(31.2%, 58.8%)
50%	(36.1%, 63.9%)
55%	(41.2%, 68.8%)

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations and patient disposition will be summarized for patients by cohort. Study treatment administration will be summarized by cohort for all treated patients.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic variables and other baseline and disease characteristics will be summarized by cohort using descriptive statistics.

6.4 EFFICACY ANALYSES

There is no formal statistical study hypothesis. All efficacy analyses will be entirely descriptive with 95% CIs will be provided where applicable.

The primary efficacy analysis population will be the Evaluable Patient population in $BRAF^{V600}$ mutation-positive cohort consisting of all enrolled patients who received study medication and have at least two post-baseline tumour assessments for response evaluation. Patients in the $BRAF^{V600}$ wild-type cohort may not be evaluable as per this definition and will be analysed descriptively.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective is to evaluate the intracranial ORR in the $BRAF^{V600}$ mutation-positive study cohort. Intracranial ORR is defined as the proportion of patients with a complete or partial response in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart. Disease status will be determined by an IRC according to RECIST v1.1 with a modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions. Data for patients with no post-baseline intracranial tumour assessment will be excluded from efficacy analyses. For intracranial response rate, a 95% Pearson-Clopper CI will be calculated and presented.

A sensitivity analysis of the primary endpoint that includes patients with unconfirmed CR or PR will also be conducted in each cohort based upon the Safety population in order to detect a potential bias with regard to the primary analysis.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed in Table 1.

Intracranial ORR is defined as the proportion of patients with either a CR or PR in their intracranial disease based on two consecutive assessments ≥ 4 weeks apart as determined by investigator according to RECIST v1.1.

Extracranial ORR is defined as the proportion of patients with either a CR or PR in their extracranial disease based on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. For extracranial response rate a 95% Pearson-Clopper CI will be calculated and presented.

Overall ORR is defined as the proportion of patients with either a CR or PR in their overall disease (i.e. including intracranial and extracranial disease) based on two consecutive assessments ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. For overall ORR a 95% Pearson-Clopper CI will be calculated and presented.

Intracranial, extracranial and overall PFS are defined as the time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1. Kaplan-Meier methodology will be used to estimate median intracranial, extracranial and overall PFS; Kaplan-Meier curves will be provided. Data for patients who have not experienced disease progression or have died will be censored at the last tumour assessment date.

Intracranial, extracranial and overall DOR are defined as the time from the first occurrence of a documented objective response based on two consecutive assessments ≥ 4 weeks apart to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. The censoring method for DOR is the same as for PFS. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be estimated using the Brookmeyer and Crowley method.

Intracranial, extracranial and overall disease control rates (DCR) are defined as the proportion of patients with a CR or PR or SD at 16 weeks from study treatment initiation, as determined by the investigator according to RECIST v1.1. For DCR, a 95% Pearson-Clopper CI will be calculated and presented.

OS is defined as the time from study treatment initiation to death from any cause. For patients who are alive at the time of analysis data cut-off, OS time will be censored at the date the patient was last known to be alive. Survival time for patients with no post-baseline survival information will be censored at one day after the study treatment initiation date. Kaplan-Meier methodology will be used to estimate median OS and Kaplan-Meier curves will be provided.

6.4.2.1 Patient-reported Secondary Efficacy Endpoints

Time from study treatment initiation to cognitive symptom deterioration is defined as the time from baseline to the first time a patient's score shows a ≥ 10-point increase above baseline in any of the following EORTC QLQ-BN20 transformed symptom subscale scores (whichever comes first): visual disorder, motor dysfunction, communication deficit, headaches, seizures and drowsiness.

Time from study treatment initiation to symptom and function deterioration is defined as the time from baseline to the first time a patient's score shows a ≥ 10-point increase above baseline in any of the following EORTC QLQ-C30 transformed symptom subscale scores (whichever comes first): fatigue or physical, cognitive and role functioning scales.

Duration of Stable/Improved HRQoL scores is assessed through use of the two-item GHS/HRQoL subscale (Questions 29 and 30) of the EORTC QLQ-C30. Patients post-baseline PRO scores will be classified as "improved", "stable", or "worsened" according to a ≥ 10-point change in the GHS/QoL, functional, and symptom scores of the EORTC QLQ-C30 and the QLQ-BN20. The number and proportion of patients who improve, remain stable, or worsen from baseline will be summarized by treatment group and study visit, at each time point, including progression, treatment discontinuation and post-study treatment.

Only patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included in PRO analyses. Questionnaire completion and compliance will be summarized at each time point by treatment arm.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are listed in Table 1 and are as follows:

- Intracranial ORR defined as the proportion of patients with either a CR or PR in their intracranial disease as assessed by the investigator according to iRANO criteria based on two consecutive assessments ≥ 4 weeks apart.
- Objective response rate in intracranial, extracranial and overall disease as determined by investigator according to immune-modified RECIST with modified measurability definition for intracranial lesions (≥ 0.5 cm by MRI) and allowing up to five intracranial target lesions.
- Intracranial, extracranial and overall PFS is determined by the investigator according to immune-modified RECIST.

- Intracranial, extracranial and overall DOR is determined by the investigator according to immune-modified RECIST

  Objective response, PFS and DOR, as determined by the investigator according to immune modified RECIST, will be analysed using the same methods as described in Section 6.4.2.
- Radiotherapy-assisted PFS defined as time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1 modified by excluding ≤ 3 lesions that can be treated by SRT from the sum of largest diameters from baseline onwards
- Timing of increase or change in corticosteroid use during treatment will be based on corticosteroid used for symptomatic control as indicated in the eCRF
- Time from study treatment initiation to subsequent intracranial and systemic anti-cancer treatment
- Change from baseline scores over time in treatment/disease-related symptoms as evaluated by the EORTC QLQ-C30 and QLQ-BN20 questionnaires will be summarized descriptively including the mean change from baseline of linear-transformed scores for all subscales of the EORTC QLQ-C30 and QLQ-BN20 according to the EORTC scoring manual guideline at each assessment time point for each cohort, including progression, treatment discontinuation and post-study discontinuation. The mean (and 95% CI) and median of the absolute scores and the change from baseline will be reported for interval and continuous variables. Only patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included in PRO analyses.

6.5 SAFETY ANALYSES

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

Verbatim description of adverse events will be summarized by mapped terms and appropriate thesaurus levels and graded according to NCI CTCAE v4.0. All adverse events that occur during or after the first dose of study treatment will be summarized by cohort and NCI CTCAE grade. In addition, SAEs, severe adverse events (Grades 3, 4, and 5), adverse events of special interest, and adverse events leading to discontinuation or interruption of study treatment will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one adverse event will be reported by toxicity term and cohort.

Exposure to study treatment, including treatment duration, number of cycles and dose intensity, will be summarized for each cohort using descriptive statistics. Number of dose reductions, treatment interruptions and cycle delays will also be summarized by treatment cohort.

All deaths and causes of death will be summarized by cohort.

Laboratory data with values outside the normal ranges will be identified. In addition, relevant laboratory data and vital signs will be summarized by cohort.

6.6 BIOMARKER ANALYSES

The relationship between clinical efficacy parameters and biomarkers in tumour tissue and plasma (including, but not limited to; PD-L1, BRAF and NRAS) will be explored at the conclusion of this study.

6.7 INTERIM ANALYSIS

A safety interim analysis will be performed after at least 10 patients in both cohorts have completed their first tumour assessment (i.e. approximately eight weeks after start of study treatment). The analysis will be conducted by the Sponsor according to the Sponsor's standard operating procedures for safety reviews. The results of the interim analysis will be reviewed by the IMC as described in the IMC charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data.

Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's

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

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/EC. Investigators are also

responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately 23 sites worldwide will participate to enrol approximately 120 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for biomarker analyses as specified in Section 4.5.9. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An SC will provide scientific oversight of the trial. Disease status for the primary endpoint will be determined by an IRC.

9.6 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within six months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre trials only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities for Cohort 1

	Screening [a]		Treatment						End of Treatment [b]	Long-Term Follow-Up [c]
			Cycle 1		Cycle 2		Cycle 3+			
Day	–28 to –1	–14 to –1	1	15	1	15	1	15	28 days after last study treatment	Every 3 months
Visit window (days)	-28 to -1	-14 to -1		±3	±3	±3	±3	±3	±7	±7
Informed consent	x [d]									
Demographic data	x									
Medical history and baseline conditions	x									
HBV, HCV and HIV serology [e]	x									
$BRAF^{V600}$ mutation status	x									
Vital signs [f]	x		x	x	x	x	x	x	x	
Weight	x		x		x		x		x	
Height	x									
Complete physical examination [g]	x								x	
ECOG performance status	x		x		x		x		x	
Tumour tissue for biomarkers [h]	x									
ECHO or MUGA [i]	x				x		x [i]		x [i]	
Patient-reported outcomes [j]			x		x		x		x	x [j]
Limited physical examination [k]			x		x		x			
12-lead ECG	x		as clinically indicated							
Haematology [l]		x	x [l]		x		x		x	

Appendix 1 Schedule of Activities for Cohort 1

	Screening [a]		Treatment						End of Treatment [b]	Long-Term Follow-Up [c]
			Cycle 1		Cycle 2		Cycle 3+			
Day	–28 to –1	–14 to –1	1	15	1	15	1	15	28 days after last study treatment	Every 3 months
Chemistry [m]		x	x [m]	x	x	x	x	x	x	
Pregnancy test [n]		x	x		x		x		x	x [n]
Thyroid function tests [o]	x				x		x [o]		x	
Fasting blood glucose and lipids [p]	x									
INR and aPTT	x									
Urinalysis [q]		x								
Ophthalmologic examination [r]	x				x		x [r]		x	
Intracranial disease assessment [s]	x					Last week of Cycle 2 then every 8 or 12 [s] weeks thereafter until PD				
Extracranial disease assessment [s]	x					Last week of Cycle 2 then every 8 or 12 [s] weeks thereafter until PD				
Plasma for biomarkers [t]			x						At PD	
Concomitant medications [u]		x	x	x	x	x	x	x	x	
Adverse events [v]	x		x	x	x	x	x	x	x	Until 30 days after last study treatment
Dispense cobimetinib			x		x		x			
Atezolizumab administration			x	x	x	x	x	x		
Study drug accountability [w]				x	x	x	x	x	x	
Survival follow-up										x

aPTT = activated partial thromboplastin time; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; INR = International Normalized Ratio; NA = not applicable; PD = progressive disease; RBR = Research Biosample Repository.

Appendix 1 Schedule of Activities for Cohort 1

Notes: All safety assessments (laboratory tests, ECGs, etc) should be performed within three days prior to Day 1. Unless otherwise specified, other assessments should be performed within seven days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date.

a. Exceptionally, results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to initiation of study treatment may be used; such tests do not need to be repeated for screening.

b. Patients who discontinue study treatment will return to the clinic for a Study Treatment Discontinuation Visit after 28 days (± 7 days) after their last dose of any study drug.

c. Survival, patient-reported outcomes and anti-cancer treatments will be collected via telephone calls and/or clinic visits every three months until death, loss to follow-up, or study termination by the Sponsor.

d. Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

e. HIV, HBV and HCV tests will be conducted locally.

f. Includes respiratory rate, pulse rate, systolic and diastolic blood pressure and temperature. Blood pressure and heart rate measurements will be recorded after a 5-minute rest while the patient is in a seated position. Resting oxygen saturation will be measured during screening. Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

g. Includes evaluation of the head, eyes, ears, nose and throat (HEENT), neck, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

h. Submission of formalin-fixed paraffin embedded tumour tissue (one block or 10 consecutively cut sections) from the primary tumour or a metastatic lesion (decalcified tissue is not allowed) obtained any time prior to study entry (e.g., archival material).

i. Left ventricular dysfunction will be evaluated by ECHO or MUGA at screening, on Day 1 of Cycle 2 (± 1 week) and on Day 1 of every three treatment cycles thereafter starting at Cycle 5 (± 2 weeks for each), at the treatment discontinuation visit (unless evaluation performed within the previous 12 weeks showed no clinically significant findings or changes from baseline) and as clinically indicated. All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2, 4, 10 and 16 weeks (or as clinically indicated) and then resume monitoring LVEF every 12 weeks (three cycles).

j. During the study treatment period, paper versions of the EORTC QLQ-C30 and QLQ-BN20 questionnaires will be self-administered before the patient receives any information on disease status and prior to the performance of any non-patient reported outcome assessments and prior to atezolizumab administration (if applicable). After the treatment discontinuation visit, patients will complete Questions 29 and 30 of the EORTC QLQ-C30 only. Post-treatment discontinuation visit questionnaires may be administered over the telephone.

k. Perform a limited, symptom-directed examination including an evaluation of the oral cavity, oropharynx, head and neck (including lymph nodes), lungs, heart, abdomen and skin at specified time points or as clinically indicated. Patients should be asked specifically about skin and vision changes as part of each physical examination. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

l. Haematology includes white blood cell count, red blood cell count, haemoglobin, haematocrit, reticulocyte count, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If screening haematology is performed within 7 days of initiation of study treatment, it does not need to be repeated for Day 1 of Cycle 1.

m. Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (bicarbonate and total carbon dioxide are not mandatory if unavailable at site), glucose (non-fasting), BUN or urea, creatinine, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, lactate dehydrogenase and CPK, amylase and lipase. If screening blood chemistry is performed within 7 days of initiation of study treatment, it does not need to be repeated for Day 1 of Cycle 1.

n. All women of childbearing potential will have a negative serum pregnancy test within seven days prior to initiation of study treatment. Women without prior oophorectomy or hysterectomy who have been amenorrhoeic for >12 months but < 2 years must have a FSH level test to determine childbearing potential. Urine pregnancy tests will be performed on Day 1 of each treatment cycle, at the treatment discontinuation visit and at study follow up until six months post-study treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

o. Includes thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), free thyroxine. Thyroid-function tests are to be performed at screening, on Day 1 of Cycles 1-5 and every second cycle thereafter (e.g., Day 1 of Cycles 7, 9, 11, etc.), and at the treatment discontinuation visit.

p. Both blood glucose and lipid panel must be obtained after at least an 8-hour fast, at screening only. Lipid panel should include total cholesterol, low-density lipoprotein and triglycerides

q. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

r. Ophthalmologic examinations should be performed at screening; on Day 1 of Cycle 2 (± 1 week), Cycles 5, 8, 11, 15, 19, 23, and every six cycles thereafter (i.e., Cycles 29, 35, 41, etc.) (± 2 weeks for each); at the treatment discontinuation visit; and as clinically indicated (including in the event of any visual changes).

s. Intracranial disease must be followed by magnetic resonance imaging (MRI). Extracranial tumour assessments will include contrast-enhanced CT or MRI scans of the chest, abdomen, and pelvis. Imaging of the neck should be included if clinically indicated. Intracranial and extracranial tumour assessments after end of Cycle 2 should be conducted every 8 weeks ± 1 week regardless of study treatment delays through 24 months and then every 12 weeks ± 1 week thereafter until confirmed disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor or death, whichever occurs first. Tumour assessments showing disease progression must be repeated approximately four weeks later regardless of whether treatment is continued beyond progression. Post-progression assessments may be conducted sooner if necessary e.g., due to clinical progression. Objective response (complete or partial response) must be confirmed by repeat assessments ≥ 4 weeks after

initial documentation. In the case of stable disease, tumour measurements must meet criteria for stable disease ≥ 6 weeks after initiation of study treatment.

t. Two 10 mL whole blood samples will be collected for preparation of EDTA plasma.

u. Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from seven days prior to initiation of study treatment until 28 days after the last dose of study treatment.

v. After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last study treatment dose. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study treatment.

w. Medication diaries should be collected and reviewed and unused medications should be collected for assessment of compliance.

Appendix 2
Schedule of Activities for Cohort 2

	Screening [a]		Treatment Run-in (vemurafenib + cobimetinib)			Treatment (vemurafenib + cobimetinib + atezolizumab)										End of Treatment [b]	Long-Term Follow-Up [c]
			Cycle 1			Cycle 2				Cycle 3				Cycle 4+			
Day	–28 to –1	–14 to –1	1	15	21	1	8	15	22	1	8	15	22	1	15	28 days after last study treatment	Every 3 months
Visit window (days)	-28 to -1	-14 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7
Informed consent	x [d]																
Demographic data	x																
Medical history and baseline conditions	x																
HBV, HCV and HIV serology [e]	x																
$BRAF^{V600}$ mutation status	x																
Vital signs [f]		x [f]		x		x	x	x	x	x	x	x	x	x	x	x	
Weight	x		x			x				x				x		x	
Height	x																
Complete physical examination [g]	x															x	

Appendix 2 Schedule of Activities for Cohort 2

	Screening [a]		Treatment Run-in (vemurafenib + cobimetinib)			Treatment (vemurafenib + cobimetinib + atezolizumab)										End of Treatment [b]	Long-Term Follow-Up [c]
			Cycle 1			Cycle 2				Cycle 3				Cycle 4+			
Day	–28 to –1	–14 to –1	1	15	21	1	8	15	22	1	8	15	22	1	15	28 days after last study treatment	Every 3 months
ECOG performance status	x		x			x				x				x		x	
Tumour tissue for biomarkers [h]	x																
ECHO or MUGA [i]	x					x								x [i]		x [i]	
Patient-reported outcomes [j]			x			x		x		x				x		x	x [j]
Limited physical examination [k]			x			x				x				x			
12-lead ECG [l]		x		x				x				x			x [l]		
Haematology [m]		x	x [m]			x				x				x		x	
Chemistry [n]		x	x [n]	x		x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test [o]		x [o]	x			x				x				x		x	x [o]
Thyroid function tests [p]	x					x				x				x [p]		x	

Appendix 2 Schedule of Activities for Cohort 2

	Screening [a]		Treatment Run-in (vemurafenib + cobimetinib)			Treatment (vemurafenib + cobimetinib + atezolizumab)										End of Treatment [b]	Long-Term Follow-Up [c]
			Cycle 1			Cycle 2				Cycle 3				Cycle 4+			
Day	–28 to –1	–14 to –1	1	15	21	1	8	15	22	1	8	15	22	1	15	28 days after last study treatment	Every 3 months
Fasting blood glucose and lipids [q]	x																
INR and aPTT	x																
Urinalysis [r]		x															
Head and neck examination [s]	x													x [s]		x [s]	x [s]
Anal and gynaecological examinations [t]	x															x	x [t]
Dermatologic examination [u]	x					x								x [u]		x [u]	x [u]
Ophthalmologic examination [v]	x					x								x [v]		x	
Intracranial disease assessment [w]	x								Last week of Cycle 2 then every 8 or 12 [w] weeks thereafter until PD								
Extracranial disease assessment [w]	x								Last week of Cycle 2 then every 8 or 12 [w] weeks thereafter until PD								

Appendix 2 Schedule of Activities for Cohort 2

	Screening [a]		Treatment Run-in (vemurafenib + cobimetinib)			Treatment (vemurafenib + cobimetinib + atezolizumab)										End of Treatment [b]	Long-Term Follow-Up [c]
			Cycle 1			Cycle 2				Cycle 3				Cycle 4+			
Day	–28 to –1	–14 to –1	1	15	21	1	8	15	22	1	8	15	22	1	15	28 days after last study treatment	Every 3 months
Plasma for biomarkers [x]			x													At PD	
Concomitant medications [y]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [z]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	Until 30 days after last study treatment
Dispense vemurafenib [aa]			x		x	x				x				x			
Dispense cobimetinib			x			x				x				x			
Atezolizumab administration [bb]						x		x		x		x		x	x		
Study drug accountability [cc]				x	x	x	x	x	x	x	x	x	x	x	x	x	
Survival follow-up																	x

aPTT = activated partial thromboplastin time; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; INR= International Normalized Ratio; NA = not applicable; PD = progressive disease; RBR = Research Biosample Repository.

Appendix 2 Schedule of Activities for Cohort 2

Notes: All safety assessments (laboratory tests, ECGs, etc) should be performed within three days prior to Day 1. Unless otherwise specified, other assessments should be performed within seven days of the scheduled visit. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If a protocol mandated study visit coincides with a holiday and/or weekend that preclude the visit, the visit should be scheduled on the nearest following feasible date.

a. Results of standard-of-are tests or examinations performed prior to obtaining informed consent and within 28 days prior to initiation of study treatment may be used; such tests do not need to be repeated for screening.

b. Patients who discontinue study treatment will return to the clinic for a Study Treatment Discontinuation Visit after 28 days (± 7 days) after their last dose of any study drug.

c. Survival, patient-reported outcomes and anti-cancer treatments will be collected via telephone calls and/or clinic visits every three months until death, loss to follow-up, or study termination by the Sponsor.

d. Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

e. HIV, HBV and HCV tests will be conducted locally.

f. Includes respiratory rate, pulse rate, systolic and diastolic blood pressure and temperature. Blood pressure and heart rate measurements will be recorded after a 5-minute rest while the patient is in a seated position. Resting oxygen saturation will be measured during screening. Vital signs at screening must be performed within seven days prior to initiation of study treatment. Vital signs should be measured within 60 minutes prior to each atezolizumab infusion and, if clinically indicated, during or after the infusion. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

g. Includes evaluation of the head, eyes, ears, nose and throat (HEENT), neck, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

h. Submission of formalin-fixed paraffin embedded tumour tissue (one block or 10 consecutively cut sections) from the primary tumour or a metastatic lesion (decalcified tissue is not allowed) obtained any time prior to study entry (e.g., archival material).

i. Left ventricular dysfunction will be evaluated by ECHO or MUGA at screening, on Day 1 of Cycle 2 (± 1 week) and on Day 1 of every three treatment cycles thereafter starting at Cycle 5 (± 2 weeks for each), at the treatment discontinuation visit (unless evaluation performed within the previous 12 weeks showed no clinically significant findings or changes from baseline), and as clinically indicated. All patients who restart treatment with a reduced dose of cobimetinib because of a decrease in LVEF should have LVEF measurements taken after approximately 2, 4, 10 and 16 weeks (or as clinically indicated) and then resume monitoring LVEF every 12 weeks (three cycles).

j. During the study treatment period, paper versions of the EORTC QLQ-C30 and QLQ-BN20 questionnaires will be self-administered before the patient receives any information on disease status and prior to the performance of any non-patient reported outcome assessments and prior to

atezolizumab administration (if applicable). After the treatment discontinuation visit, patients will complete Questions 29 and 30 of the EORTC QLQ-C30 only. Post-treatment discontinuation visit questionnaires may be administered over the telephone.

k. Perform a limited, symptom-directed examination including an evaluation of the oral cavity, oropharynx, head and neck (including lymph nodes), lungs, heart, abdomen and skin, at specified time points or as clinically indicated. Patients should be asked specifically about skin and vision changes as part of each physical examination. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

l. During the treatment period, ECG recordings must be obtained prior to the morning doses of cobimetinib and vemurafenib on Day 15 (± 3 days) of Cycles 1, 2, 3 and 4. Thereafter ECG recordings will be obtained on Day 15 of every three cycles (i.e. Day 15 of Cycles 7, 10, 13, etc.) (± 3 days); at the treatment discontinuation visit (± 3 days); and as clinically indicated. EGCs should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws unless pre-authorized by the Medical Monitor) and after the patient has been resting in a supine position for at least 10 minutes.

m. Haematology includes white blood cell count, red blood cell count, haemoglobin, haematocrit, reticulocyte count, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). If screening haematology is performed within seven days of initiation of study treatment, it does not need to be repeated for Day 1 of Cycle 1.

n. Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (bicarbonate and total carbon dioxide are not mandatory if unavailable at site), glucose (non-fasting), BUN or urea, creatinine, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, lactate dehydrogenase and CPK, amylase and lipase. If screening blood chemistry is performed within seven days of initiation of study treatment, it does not need to be repeated for Day 1 of Cycle 1.

o. All women of childbearing potential will have a negative serum pregnancy test within seven days prior to initiation of study treatment. Women without prior oophorectomy or hysterectomy who have been amenorrhoeic for >12 months but < 2 years must have a FSH level test to determine childbearing potential. Urine pregnancy tests will be performed on Day 1 of each treatment cycle, at the treatment discontinuation visit and at study follow up until six months post-study treatment discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

p. Includes thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), free thyroxine. Thyroid-function tests are to be performed at screening, on Day 1 of Cycles 2−6 and every second cycle thereafter (e.g., Day 1 of Cycles 8, 10, 12, etc.), and at the treatment discontinuation visit.

q. Both blood glucose and lipid panel must be obtained after at least an 8-hour fast, at screening only. Lipid panel should include total cholesterol, low-density lipoprotein and triglycerides

r. Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

s. To monitor for the occurrence of squamous cell carcinoma (SCC) in the upper aerodigestive tract, a head and neck examination will be performed at screening, Day 1 of Cycle 4 and every three cycles thereafter during treatment (i.e., Day 1 of Cycles 7, 10, 13, etc.), at the treatment discontinuation visit (unless performed within the previous 12 weeks), at 3 and 6 months (± 2 weeks) after the last dose of study treatment, and

as clinically indicated (e.g., if any new head and neck lesions are suspected of being non-cuSCC). Assessments will include (at a minimum) examination of the HEENT and neck, visual inspection of the oral mucosa, and lymph node palpation.

t. To monitor for anal SCC, visual inspection and digital examination of the anus and anal canal will be performed at screening, at the treatment discontinuation visit, 6 months (± 2 weeks) after the last dose of vemurafenib, and as clinically indicated. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated. To monitor for cervical carcinoma, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou (Pap) smear, at screening, at the treatment discontinuation visit, 6 months (± 2 weeks) after the last dose of vemurafenib, and as clinically indicated. Pelvic examinations performed within 12 months prior to screening need not be repeated if found to be normal.

u. A complete dermatologic evaluation should be performed at screening, on Day 1 of Cycle 2 and every three cycles thereafter during treatment (i.e., Day 1 of Cycles 5, 8, 11, etc.) (± 1 week), at the treatment discontinuation visit (unless performed within the previous 12 weeks), 6 months (± 2 weeks) after the last dose of study treatment, and as clinically indicated.

v. Ophthalmologic examinations should be performed at screening; on Day 1 of Cycle 2 (± 1 week), Cycles 5, 8, 11, 15, 19, 23, and every six cycles thereafter (i.e., Cycles 29, 35, 41, etc.) (± 2 weeks for each); at the treatment discontinuation visit; and as clinically indicated (including in the event of any visual changes).

w. Intracranial disease must be followed by magnetic resonance imaging (MRI). Extracranial tumour assessments will include contrast-enhanced CT or MRI scans of the chest, abdomen, and pelvis. Imaging of the neck should be included if clinically indicated. Intracranial and extracranial tumour assessments after end of Cycle 2 should be conducted every 8 weeks ± 1 week regardless of study treatment delays through 24 months and then every 12 weeks ± 1 week thereafter until confirmed disease progression per RECIST v1.1, initiation of a new anti-cancer treatment, withdrawal of consent, study termination by the Sponsor or death, whichever occurs first. Tumour assessments showing disease progression must be repeated approximately four weeks later regardless of whether treatment is continued beyond progression. If disease progression is not confirmed, the subsequent scheduled tumour assessment should occur not earlier than 4 weeks since the confirmatory scan. Post-progression assessments may be conducted sooner if necessary e.g., due to clinical progression. Objective response (complete or partial response) must be confirmed by repeat assessments ≥ 4 weeks after initial documentation. In the case of stable disease, tumour measurements must meet criteria for stable disease ≥ 6 weeks after initiation of study treatment.

   Chest CT or MRI scans will be used to monitor for lung SCC. An additional chest CT or MRI scan must be performed 6 months (± 2 weeks) after study treatment discontinuation for SCC monitoring.

x. Two 10 mL whole blood samples will be collected for preparation of EDTA plasma.

y. Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from seven days prior to initiation of study treatment until 28 days after the last dose of study treatment.

z. After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last study treatment dose. The investigator

should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study treatment.

aa. All patients will receive vemurafenib at a dose of 960 mg (four 240-mg tablets) PO BID on Days 1-21 of Cycle 1. Patients will receive vemurafenib at a dose of 720 mg (three 240-mg tablets) on Days 1-28 of all subsequent treatment cycles. Vemurafenib will be dispensed on Day 1 of each treatment cycle and on Day 21 or 22 of the run-in period.

bb. For patients in Cohort 2, atezolizumab will be administered beginning in Cycle 2 only.

cc. Medication diaries should be collected and reviewed and unused medications should be collected for assessment of compliance.

Appendix 3
Schedule of Biomarker Samples

Cohort 1 and Cohort 2		
Visit	**Timepoint**	**Sample Type**
Screening (Day –28 to Day –1)	N/A	**Tumour tissue for biomarkers** Submission of formalin-fixed paraffin embedded tumour tissue block or 10 consecutively cut sections from the primary tumour or a metastatic lesion (decalcified tissue is not allowed) obtained any time prior to entry in this study (e.g., archival material).
Day 1, Cycle 1	N/A	**Plasma for biomarkers** Two 10 mL whole blood samples will be collected for preparation of EDTA plasma.
At progressive disease	N/A	

Appendix 4
ECOG Performance Status Scale

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

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

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

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

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

Appendix 5Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than four weeks before the beginning of the treatment.

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

Appendix 5Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

Appendix 5Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

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

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

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Appendix 5Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent

evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

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

- Complete response (CR): Disappearance of all target lesions
- Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)
- In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
- All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target

lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

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

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

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

Appendix 5Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

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

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

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

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled

assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

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

Appendix 6
Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (imRECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al. 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between imRECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and imRECIST

	RECIST v1.1	imRECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden [a] and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥30% decrease in tumor burden, [a] in the absence of CR
PD	≥20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥20% increase in tumor burden [a]
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

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

[a] Tumor burden is the sum of diameters of target lesions and measurable new lesions.

Appendix 6:Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST)

TUMOR MEASURABILITY

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

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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

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

Malignant Lymph Nodes

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

DEFINITION OF NON-MEASURABLE LESIONS

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

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone

lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

CLINICAL LESIONS

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

CHEST X-RAY

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

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans

have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

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

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

ASSESSMENT OF TUMOR BURDEN

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

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

Appendix 6:Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST)

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

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

NEW LESIONS

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

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and

should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is < 10 mm, the lymph node should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm and all other lesions are no longer detectable or have also decreased to a short axis of < 10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included in the sum of diameters, the sum may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

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

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be

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

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

Measuring Lesions That Split or Coalesce on Treatment

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

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

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

- Complete response (CR): Disappearance of all lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per

organ), taking as reference the smallest sum of diameters on study (including baseline)

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

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall imRECIST tumor response.

- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

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

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

Target Lesions and Measurable New Lesions [a]	Non-Target Lesions and Non-Measurable New Lesions [b]	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

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

[a] Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

[b] Also includes measurable new lesions in excess of five total or two per organ.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

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

Appendix 6:Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST)

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 1.

REFERENCES

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

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

Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Cancer 2014;2:17.

Appendix 7
Immunotherapy Response Assessment for Neuro-Oncology (iRANO) Criteria

The iRANO criteria are summarized in Table 1 below. For a complete description, please refer to: Okada H, Weller M, Huang R et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 2015 Nov;16(15):e534-42; located at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4638131

Table 1: iRANO criteria

	Brain metastases
Complete response	Disappearance of all enhancing target and non-target lesions for ≥ 4 week; no new lesions; no steroids; clinically stable or improved
Partial response	≥ 30% decrease in sum of longest diameters of target lesions for ≥ 4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved
Minor response	Not applicable
Stable disease	Does not qualify for complete response, partial response, or progressive disease
Progressive disease	≥ 20% decrease in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline

The iRANO criteria integrate into the existing RANO criteria for malignant glioma, low-grade glioma, and brain metastases by providing recommendations for the interpretation of progressive imaging changes. Specifically, iRANO recommends confirmation of disease progression on follow-up imaging three months after initial radiographic progression if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is six months or less from starting immunotherapy. If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression. The appearance of new lesions six months or less from the initiation of immunotherapy alone does not define progressive disease.

Appendix 7:Immunotherapy Response Assessment for Neuro-Oncology (iRANO) Criteria

Table 2: Key considerations for RANO criteria, immune-related response criteria and iRANO criteria

	RANO [1]	Immune-related response criteria [2]	iRANO (if ≤ 6 M after start of immunotherapy)	iRANO (if > 6 M after start of immunotherapy)
Is a repeat scan needed to confirm radiographic progressive disease for patients without significant clinical decline?	No	Yes	Yes	No
Minimum time interval for confirmation of disease progression for patients without significant clinical decline	N/A	≥ 4 weeks	≥ 3 months	N/A
Is further immunotherapy treatment allowed after initial radiographic progressive disease (if clinically stable) pending disease progression confirmation?	N/A	Yes	Yes	N/A
Does a new lesion define progressive disease?	Yes	No	No	Yes

iRANO = immunotherapy Response Assessment in Neuro-Oncology; M = months; N/A = not applicable.

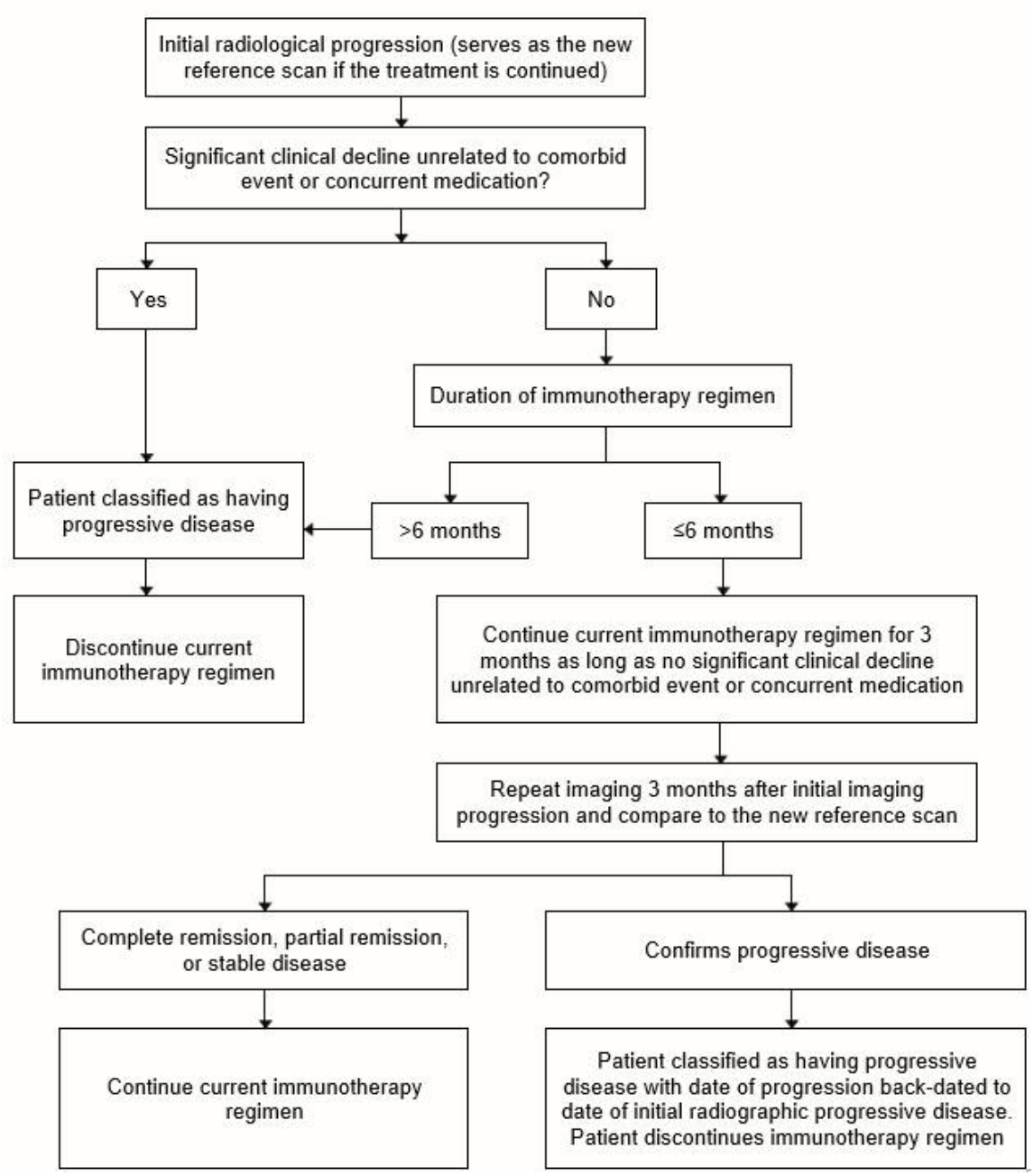
REFERENCES

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010; 28: 1963–72.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009; 153: 7412–20.

Appendix 7:Immunotherapy Response Assessment for Neuro-Oncology (iRANO) Criteria

Figure 1: iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy.



iRANO = immunotherapy Response Assessment in Neuro-Oncology.

Appendix 8
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30

Do not reproduce or distribute. *The Sponsor will provide sites with all instruments to be completed in this study.*

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 8:European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: EORTC QLQ-C30

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9
EORTC QLQ-BN20 Questionnaire

Do not reproduce or distribute. *The Sponsor will provide sites with all instruments to be completed in this study.*

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

Appendix 10
Pre-existing Autoimmune Diseases and Immune Deficiencies

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

Autoimmune Diseases and Immune Deficiencies

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

Appendix 11
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

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

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.

Appendix 12
Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 1: General Guidance and Infusion-Related Reactions

General guidance and infusion-related reactions	
Event	**Action to be taken**
General guidance for dose modifications and treatment delays and discontinuation	• There will be no dose modifications for atezolizumab. • If atezolizumab is withheld and corticosteroids are initiated for an atezolizumab-related toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed [a, b, c] • The dose of cobimetinib can be reduced by 20 mg (one dose level) up to two times (i.e., from 60 mg to 40 mg and then from 40 mg to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab at the investigator's discretion. • If cobimetinib is withheld for > 28 days because of toxicity, the patient should be discontinued from cobimetinib, unless *the patient is likely to derive clinical benefit. The decision to re-challenge patients with study treatment should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).* The Medical Monitor *is available to advise as needed.* • After dose reduction, consideration may be given to allow for dose escalation of cobimetinib by a maximum of one dose level following resolution of the adverse event that resulted in dose modification, provided there are no safety concerns. • If atezolizumab is withheld for > 12 weeks because of toxicity, the patient should be discontinued from atezolizumab. *Study treatment may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for 12 weeks if the patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*
Grade 1 or Grade 2 (tolerable) treatment related events not described below	• No dose reduction. Maintain cobimetinib at the same dose of 60 mg QD (3 tablets).

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

General guidance and infusion-related reactions	
Event	**Action to be taken**
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described below	• Withhold all study treatment. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. Cobimetinib dose reductions should be as follows: ○ First appearance: interrupt treatment until Grade ≤ 1: restart treatment at 40 mg ○ Second appearance: interrupt treatment until Grade ≤ 1: restart treatment at 20 mg ○ Third appearance: consider permanent discontinuation.
IRRs, anaphylaxis and hypersensitivity reaction	• Guidelines for management of IRRs are provided in the Atezolizumab Investigator's Brochure. • For anaphylaxis precautions, see Appendix 11. • For severe hypersensitivity reactions, permanently discontinue all study treatment.

IRR = infusion-related reaction; QD = once a day.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 2: Gastrointestinal Toxicity

Gastrointestinal toxicity	
Event	**Action to be taken**
Gastrointestinal events: general guidance	• All events of diarrhoea or colitis should be thoroughly evaluated for more common aetiologies other than drug-induced effects. • For events of significant duration or severity or associated with signs of systemic inflammation or acute-phase reactants, check for immune-mediated colitis. • Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines, such as at the first report of watery diarrhoea or loose stool, initiate maximal anti-diarrheal supportive care (Lomotil® and loperamide). • Suggested regimen: o Loperamide: Initiate dose with 4 mg, then 4 mg/6 hr around the clock, alternating with Lomotil.® o Lomotil® (diphenoxylate and atropine): Dispense 2 tablets (diphenoxylate 5 mg, atropine 0.05 mg) every 6 hours around the clock. o Continue Lomotil® and loperamide until no loose stools for 24 hours. o If Grade ≤ 2 diarrhoea persists after 48 hours of total treatment with Lomotil® and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). • Oral supplementation: o Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. o Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥ 1 diarrhoea or vomiting. • Dietary modifications: o Stop all lactose-containing products and instruct patient to eat small meals. o Suggest the BRAT diet (banana, rice, apples, toast) diet, without fibre (other vegetables and fruits). o Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade®.
Diarrhoea, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab and cobimetinib. • Investigate aetiology, referring patient to GI specialist for evaluation of possible colitis if appropriate. • Initiate supportive care and monitor patient closely

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Gastrointestinal toxicity	
Event	**Action to be taken**
Diarrhoea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating aetiology. • Investigate aetiology and refer patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with the dose reduced by one level. If not, permanently discontinue cobimetinib.
Diarrhoea, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating aetiology. • Rule out bowel perforation. • Investigate aetiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.
Colitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with the dose reduced by one level. If not, permanently discontinue cobimetinib.

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Gastrointestinal toxicity	
Event	**Action to be taken**
Colitis, Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; IV = intravenous; LLN = lower limit of normal; NSAID = non-steroidal anti-inflammatory drug.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 3: Dermatologic Toxicity

Dermatologic toxicity	
Event	**Action to be taken**
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • *For Grade 2, if unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.* • For Grade 2 rash, consider referral to dermatologist. Acneiform rash: • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1−2 mg/kg/day if event does not improve within 48−72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. Acneiform rash: • Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	***Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:*** • *Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.*

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Dermatologic toxicity	
Event	**Action to be taken**
	• *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Steven-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.*

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 4: Elevated Liver Enzymes

Elevated liver enzymes	
Event	**Action to be taken**
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN	• Continue atezolizumab and cobimetinib. • Continue with the standard monitoring plan (i.e., LFTs Q4W before dosing).
AST/ALT > 3 × ULN to < 5 × ULN with total bilirubin < 2 × ULN	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune-mediated events of > 5 days duration ○ Consider withholding atezolizumab [c] ○ Consider administering 1−2 mg/kg/day oral prednisone or equivalent followed by ≥ 1-month taper ○ Restart atezolizumab if event resolves to Grade 1 or better within 12 weeks [a, b] ○ Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin < 2 × ULN	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune-mediated events: ○ Withhold atezolizumab ○ Consider administering 1−2 mg/kg/day oral prednisone or equivalent followed by ≥ 1-month taper ○ If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. ○ Permanently discontinue atezolizumab and cobimetinib if event does not resolve to Grade 1 or better within 12 weeks [a, b, c]
AST/ALT > 3 × ULN with bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Consult hepatologist and consider liver biopsy. • Consider administering 1−2 mg/kg/day oral prednisone or equivalent followed by ≥ 1-month taper (for possible autoimmune hepatitis). • If LFTs do not decrease within 48 hours after initiation of systemic steroids, consider adding an immunosuppressive agent (e.g., mycophenolate mofetil or TNF-α antagonist). • Monitor LFTs every 48−72 hours until decreasing and then follow weekly. • Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction after *consultation* with *the* Medical Monitor if AST/ALT < 3 × ULN with bilirubin < 2 × ULN and steroid dose < 10 mg oral prednisone equivalent per day. [a, b, c] • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events, and contact the Medical Monitor.

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Elevated liver enzymes	
Event	**Action to be taken**
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib [c] • Consult hepatologist and consider liver biopsy. • Consider administering 1−2 mg/kg/day oral prednisone or equivalent (for possible autoimmune hepatitis). If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If LFTs do not decrease within 48 hr after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate mofetil or TNF-α antagonist) or dose escalation of corticosteroids may be considered. • Monitor LFTs every 48−72 hours until decreasing and then follow weekly.

LFT = liver function test; Q4W = every 4 weeks; ULN = upper limit of normal.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed*.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 5: Pulmonary Events

Pulmonary events	
Event	**Action to be taken**
General guidance	• Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. • For events concerning for pneumonitis, consider comprehensive infectious evaluation including viral aetiologies.
Pneumonitis, Grade 1 (asymptomatic)	• Continue cobimetinib. • *Consider withholding atezolizumab.* • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as Grade 3 or 4 event.
Pneumonitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated aetiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and cobimetinib if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pneumonitis, Grade 3 or 4	• Permanently discontinue atezolizumab and cobimetinib [c] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated aetiology, initiate treatment with 1−2 mg/kg/day *IV methylprednisolone* or equivalent. • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent (e.g., infliximab, cyclophosphamide, IVIg, or mycophenolate). • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage; IVIg = intravenous immunoglobulin.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Pulmonary events

in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Table 6: Ocular Toxicity

Ocular toxicity	
Event	**Action to be taken**
General guidance and NCI CTCAE v4.0 scale for Eye Disorders–Other	• An ophthalmologist should evaluate visual complaints. • Uveitis or episcleritis and other immune−mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular event that is unresponsive to local immunosuppressive therapy. • Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic) per NCI CTCAE v4.0 (see below). Most events in clinical trials resolved or improved to asymptomatic Grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to Grade 1 or better. Serous retinopathy can be managed with treatment interruption, dose reduction, or with treatment discontinuation. • RVO has been reported in patients treated with MEK inhibitors other than cobimetinib. • NCI CTCAE v4.0 "Eye Disorders–Other" scale: o Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. o Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL. o Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL. o Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.
Serous retinopathy, Grade 1 or 2 (tolerable) per NCI CTCAE v4.0 scale for "Eye Disorders–Other"	• Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated.

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Ocular toxicity	
Event	**Action to be taken**
Serous retinopathy, Grade 2 (intolerable) or Grade 3 or 4 per NCI CTCAE v4.0 scale for Eye Disorders–Other"	• Interrupt cobimetinib until Grade 1 or better. • Continue atezolizumab as clinically indicated. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • The dose of cobimetinib should be reduced by one dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite two dose level reductions.
Potential immune-mediated ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Continue cobimetinib as clinically indicated.
RVO (any grade)	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab.

ADL = activities of daily living; OCT = optical coherence tomography; Q4W = every 4 weeks; RVO = retinal vein occlusion.

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Table 7: Left Ventricular Ejection Fraction Decrease from Baseline

Left ventricular ejection fraction decrease from baseline				
Patient	**LVEF Value**	**Recommended Action with Cobimetinib and Atezolizumab**	**LVEF Value following Treatment Break**	**Recommended Cobimetinib Daily Dose**
Asymptomatic	≥ 50% (or 40%−49% and < 10% absolute decrease from baseline)	• Continue atezolizumab and cobimetinib at current dose	Not Applicable	Not Applicable
	< 40% (or 40%−49% and ≥ 10% absolute decrease from baseline)	• Interrupt cobimetinib treatment for 2 weeks • Continue atezolizumab as clinically indicated	< 10% absolute decrease from baseline	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	Not Applicable	• Interrupt cobimetinib treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	First occurrence: 40 mg
				Second occurrence: 20 mg
				Third occurrence: permanent discontinuation
		• Consider withholding atezolizumab. *The* Medical Monitor *is available to advise as needed* regarding resumption of atezolizumab.	Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
		• Cardiology consultation is strongly recommended.	Symptomatic regardless of LVEF	Permanent discontinuation

LVEF = left ventricular ejection fraction.

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 8: Rhabdomyolysis or CPK Elevation

Rhabdomyolysis or CPK elevation	
Event	**Action to be taken**
General guidance	• Rule out cardiac cause (check ECG, serum cardiac troponin and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections.
For Grade ≤ 3 CPK elevations that are asymptomatic and deemed not clinically significant	• Cobimetinib and atezolizumab dosing does not need to be modified or interrupted to manage asymptomatic Grade ≤ 3 CPK elevations. • Recheck CPK at least once a week.
For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant	• Interrupt cobimetinib and atezolizumab treatment. • If improved to Grade ≤ 3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If CPK elevations do not improve to Grade ≤ 3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment. • Resumption of atezolizumab may be considered in patients who are deriving benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.*
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib and atezolizumab treatment. • If severity is improved by at least one grade and symptoms resolve within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. • If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, permanently discontinue cobimetinib treatment • Resumption of atezolizumab may be considered in patients who are deriving benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).* The Medical Monitor *is available to advise as needed.*

CPK = creatine phosphokinase.

Appendix 12: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 1

Table 9: Haemorrhage

Haemorrhage	
Event	**Action to be taken**
Grade 3 haemorrhage	• Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for haemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. • Continue atezolizumab treatment.
Grade 4 haemorrhage or any grade cerebral haemorrhage	• Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for haemorrhage events attributed to cobimetinib. • Continue atezolizumab treatment.

Appendix 13
Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 1: General Guidance and Infusion-Related Reactions

General guidance and infusion-related reactions	
Event	**Action to be taken**
General guidance for dose modifications and treatment delays and discontinuation	• There will be no dose modifications for atezolizumab. • The dose of cobimetinib and vemurafenib can be reduced by one dose level in the run-in period (Cycle 1) (see Section 5.1.6.2). • During the triplet combination period (Cycles ≥ 2), the dose of cobimetinib can be reduced by 20 mg (one dose level) up to two times (i.e., from 60 mg to 40 mg and then from 40 mg to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab and/or vemurafenib at the investigator's discretion. • During the triplet combination period (Cycles ≥ 2), vemurafenib dose can be reduced from 720 mg BID to 480 mg BID. If further dose reduction is indicated, the patient must discontinue vemurafenib but may continue treatment with atezolizumab and/or cobimetinib at the investigator's discretion. • If atezolizumab is withheld and corticosteroids are initiated for treatment of a toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks, the patient should be discontinued from atezolizumab. Study treatment may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.* • If either cobimetinib or vemurafenib is withheld for > 28 days because of toxicity, the patient should be discontinued from that drug, unless *the patient is likely to derive clinical benefit. The decision to re-challenge patients with study treatment should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).* The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

General guidance and infusion-related reactions	
Event	**Action to be taken**
	• After dose reduction, consideration may be given to allow for dose escalation of cobimetinib or vemurafenib by a maximum of one dose level following resolution of the adverse event that resulted in dose modification, provided there are no safety concerns. Dose escalation is not permitted during the run-in period (Cycle 1). See Section 5.1.6.2.
IRRs, anaphylaxis and hypersensitivity reaction	• Guidelines for management of IRRs are provided in the Atezolizumab Investigator's Brochure for atezolizumab. • For anaphylaxis precautions, see Appendix 11 . • For severe hypersensitivity reactions, permanently discontinue all study treatment.

IRR = infusion-related reaction.

Table 2: Gastrointestinal Toxicity

Gastrointestinal toxicity	
Event	**Action to be taken**
Gastrointestinal events: general guidance	• All events of diarrhoea or colitis should be thoroughly evaluated for other more common aetiologies. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP, platelet count, or bandemia): ○ Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
Abdominal pain in combination with blood or mucus in stool and/or Grade ≥ 3 diarrhoea with possible colitis (e.g., peritoneal signs, ileus, or fever)	• Withhold all study treatment. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Initiate maximum supportive care and monitor patient closely. • Investigate aetiology, ruling out bowel perforation. Refer patient to GI specialist. • If immune-mediated colitis is suspected, consider treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. Consider TNF antagonists for refractory diarrhoea. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab [a, b, c]. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib. • When study treatment is resumed, administer supportive care and/or prophylactic treatment.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Gastrointestinal toxicity	
Event	**Action to be taken**
Diarrhoea, Grade 1 or 2	• Continue all study treatment • Initiate maximum supportive care and monitor patient closely. • Investigate aetiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhoea, Grade 3	• Withhold all study treatment. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating aetiology. • Initiate maximum supportive care and monitor patient closely. • Investigate aetiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab [a, b, c]. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Diarrhoea, Grade 4	• Permanently discontinue all study treatment and contact Medical Monitor [c] • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating aetiology. • Initiate maximum supportive care and monitor patient closely. • Investigate aetiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

CRP = C-reactive protein; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug; TNF = tumour necrosis factor.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 3: New Skin Lesion

New skin lesion	
Event	**Action to be taken**
Cutaneous primary malignancy or skin lesion suggestive of cutaneous primary malignancy	• Continue all study treatment • Treat per institutional guidelines

Table 4: Dermatologic Toxicity

Dermatologic toxicity	
Event	**Action to be taken**
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Photosensitivity, Grade 1	• Continue all study treatment. • Initiate supportive care.
Photosensitivity, Grade 2	• Continue atezolizumab. • Initiate supportive care per institutional guidelines. First episode: • If event does not resolve to Grade 1 or better within 7 days, withhold cobimetinib and vemurafenib. • If treatment is withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. • If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib. Subsequent episodes: • Withhold cobimetinib and vemurafenib. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. • If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib.
Photosensitivity, Grade 3	• Withhold cobimetinib and vemurafenib. Continue atezolizumab • Initiate supportive care per institutional guidelines. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Photosensitivity, Grade 4	• Initiate supportive care per institutional guidelines. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib. • Continue atezolizumab if clinically indicated.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Dermatologic toxicity	
Event	**Action to be taken**
Dermatologic event, Grade 1	• Continue all study treatment. • Initiate maximum supportive care (e.g., antihistamines, topical corticosteroids).
Dermatologic event, Grade 2	• Continue all study treatment. • Consider patient referral to dermatologist. • Initiate maximum supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*
Dermatologic event, Grade 3	• Refer patient to dermatologist. A biopsy should be performed if appropriate and, if possible, photographs of the rash should be obtained and submitted to the Sponsor. Acneiform rash: • Withhold atezolizumab and cobimetinib. Continue vemurafenib. • Refer patient to dermatologist • If event does not improve within 48−72 hours, consider treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1−2 mg/kg/day if event still does not improve. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab [a, b, c]. • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • When study treatment is resumed, consider treatment with topical corticosteroids and oral antibiotics. Non-acneiform (e.g., maculo-papular) rash: • Withhold vemurafenib. Continue atezolizumab and cobimetinib. • If event resolves to Grade 2 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib.
Dermatologic event, Grade 4	• Permanently discontinue all study treatment and contact Medical Monitor [c].

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Dermatologic toxicity	
Event	**Action to be taken**
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	***Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:*** • *Withhold atezolizumab and vemurafenib for suspected Stevens-*Johnson syndrome or toxic epidermal necrolysis. • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab and vemurafenib.*

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed*.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

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Table 5: Elevated Liver Enzymes

Elevated liver enzymes	
Event	**Action to be taken**
Elevations in ALT, AST and/or bilirubin during run-in period (Cycle 1)	
Elevation in ALT, AST and/or bilirubin, Grade 1 or 2 (run-in period/Cycle 1)	• Continue cobimetinib and vemurafenib.
Elevation in ALT, AST and/or bilirubin, Grade 3 (run-in period/Cycle 1)	• Withhold vemurafenib. Continue cobimetinib. • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, discontinue patient from study
Elevation in ALT, AST and/or bilirubin, Grade 4 (run-in period/Cycle 1)	First episode: • Withhold cobimetinib and vemurafenib. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, discontinue patient from study. Subsequent episodes: • Discontinue patient from study
Elevations in ALT, AST and/or bilirubin during triple combination period (Cycles ≥ 2)	
ALT, AST and bilirubin ≤ 3 × ULN (triple combination period/Cycles ≥ 2)	• Continue all study treatment. • Monitor ALT, AST and bilirubin at least weekly.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Elevated liver enzymes	
Event	**Action to be taken**
ALT or AST > 3 × ULN to 5 × ULN in combination with bilirubin ≤ 3 × ULN (triple combination period/Cycles ≥ 2)	• Consider withholding all study treatment. • Monitor ALT, AST and bilirubin at least weekly. If values worsen, monitor at least every other day. • If values have not worsened and have not resolved to ≤ 3 × ULN upon re-evaluation 1−20 days after event onset, consider treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If values have not worsened and have not resolved to ≤ 3 × ULN upon re-evaluation ≥ 21 days after event onset, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If values have worsened upon re-evaluation, initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If treatment is withheld and values resolve to ≤ 3 × ULN before or within 12 weeks after initiation of corticosteroids, resume atezolizumab at fixed dose [a, b]. • If values do not resolve to ≤ 3 × ULN within 12 weeks after initiation of corticosteroids, permanently discontinue atezolizumab [a, b, c]. • If treatment is withheld and values resolve to ≤ 3 × ULN before or within 28 days after initiation of corticosteroids, resume cobimetinib and vemurafenib as follows: ○ If values did not worsen prior to resolution, resume cobimetinib and vemurafenib at current doses. ○ If values worsened prior to resolution: First Episode: Resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. Second Episode: Resume cobimetinib and vemurafenib with doses reduced by one level. Third Episode: Resume cobimetinib with dose reduced by one level and permanently discontinue vemurafenib. Fourth Episode: Permanently discontinue cobimetinib. • If values do not resolve to ≤ 3 × ULN within 28 days after initiation of corticosteroids, permanently discontinue cobimetinib and vemurafenib.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Elevated liver enzymes	
Event	**Action to be taken**
ALT or AST > 5 × ULN to 10 × ULN in combination with bilirubin ≤ 1.5 × ULN (triple combination period/Cycles ≥ 2)	• Withhold all study treatment. • Monitor ALT, AST and bilirubin at least every other day. • If values do not improve within 48 hours, initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If values improve within 48 hours but subsequently worsen or do not resolve to ≤ 3 × ULN within 14 days after event onset, initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If values resolve to ≤ 3 × ULN before or within 12 weeks after initiation of corticosteroids, resume atezolizumab at fixed dose [a, b]. • If values do not resolve to ≤ 3 × ULN within 12 weeks after initiation of corticosteroids, permanently discontinue atezolizumab [a, b, c]. • If values resolve to ≤ 3 × ULN before or within 28 days after initiation of corticosteroids, resume cobimetinib and vemurafenib as follows: First Episode: Resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. Second Episode: Resume cobimetinib and vemurafenib with doses reduced by one level. Third Episode: Resume cobimetinib with dose reduced by one level and permanently discontinue vemurafenib. Fourth Episode: Permanently discontinue cobimetinib. • If values do not resolve to ≤ 3 × ULN within 28 days after initiation of corticosteroids, permanently discontinue cobimetinib and vemurafenib.
ALT or AST > 5 × ULN to 10 × ULN in combination with bilirubin > 1.5 × ULN to 3 × ULN or ALT or AST ≤ 10 × ULN in combination with bilirubin > 3 × ULN (triple combination period)	• Withhold all study treatment. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • Monitor ALT, AST and bilirubin at least every other day. • If values resolve to ≤ 3 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab [a, b, c]. • If values resolve to ≤ 3 × ULN within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Elevated liver enzymes	
Event	**Action to be taken**
ALT > 10 × ULN with or without elevation of AST or bilirubin or Confirmed cases of Hy's law with no identifiable cause other than study treatment (triple combination period)	• Permanently discontinue all study treatment and contact Medical Monitor [c]. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. If values do not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.

ULN = upper limit of normal.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

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Table 6: Pulmonary Events

Pulmonary events	
Event	**Action to be taken**
Pulmonary event, Grade 1	• Continue all study treatment and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent events, treat as a Grade 3 or 4 event. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab. Consider withholding cobimetinib and vemurafenib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor [a, b, c]. • If cobimetinib and vemurafenib are withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib at current doses. • If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib. • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Withhold cobimetinib and vemurafenib. • Bronchoscopy or BAL is recommended. • Initiate treatment with 1−2 mg/kg/day *IV methylprednisolone* or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If event resolves to Grade 1 or better within 28 days, cobimetinib and vemurafenib may be resumed with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

BAL = bronchoscopic alveolar lavage.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 7: Endocrine Disorders

Endocrine disorders	
Event	**Action to be taken**
Asymptomatic hypothyroidism	• Continue all study treatment. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • When symptoms are controlled and thyroid function is improving, resume atezolizumab.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue all study treatment. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist.*
Symptomatic hyperthyroidism	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • When symptoms are controlled and thyroid function is improving, resume atezolizumab. • For life-threatening immune-mediated hyperthyroidism, permanently discontinue atezolizumab, withhold cobimetinib and vemurafenib, and contact Medical Monitor [c]. If event becomes clinically manageable within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Adrenal insufficiency, Grade 2, 3, or 4	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy within 12 weeks, resume atezolizumab at current dose. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy within 12 weeks, permanently discontinue atezolizumab and contact Medical Monitor [a, b, c].

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Endocrine disorders	
Event	**Action to be taken**
Hyperglycaemia, Grade 1 or 2	• Continue all study treatment. • Initiate treatment with insulin if needed. Consider cobimetinib dose modification per general guidelines as clinically indicated. • Monitor for glucose control.
Hyperglycaemia, Grade 3 or 4	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Initiate treatment with insulin. • *Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.* • Monitor for glucose control. • When symptoms resolve and glucose levels are stable, resume atezolizumab.

TSH = thyroid-stimulating hormone.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 8: Pancreatic Events

Pancreatic events	
Event	**Action to be taken**
Amylase and/or lipase elevation, Grade 1	• Continue all study treatment. • Monitor amylase and lipase prior to dosing.
Amylase and/or lipase elevation, Grade 2	***Amylase and/or lipase >1.5–2.0 ×ULN:*** • Continue all study treatment. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. ***Asymptomatic with amylase and/or lipase >2.0–5.0 ×ULN:*** • *Treat as a Grade 3 event.*
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab and vemurafenib. Continue cobimetinib. • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor [a, b, c]. • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib. • For recurrent events, permanently discontinue all study treatment and contact Medical Monitor [c].
Pancreatitis, Grade 3	• Withhold all study treatment. • Refer patient to GI specialist. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor [a, b, c]. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib. • For recurrent events, permanently discontinue all study treatment and contact Medical Monitor [c].

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Pancreatic events	
Event	**Action to be taken**
Pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. Consider permanently discontinuing cobimetinib and vemurafenib. • Refer patient to GI specialist. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If cobimetinib and vemurafenib are withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib and vemurafenib.

GI = gastrointestinal.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 9: Neuropathy Disorders

Neuropathy disorders	
Event	**Action to be taken**
Neuropathy, Grade 1	• Continue all study treatment. • Investigate aetiology.
Neuropathy, Grade 2	• Withhold atezolizumab. Continue cobimetinib and vemurafenib. • Investigate aetiology *and refer patient to neurologist.* • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor [a,b,c].
Neuropathy, Grade 3	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Continue cobimetinib and vemurafenib. • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Neuropathy, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Withhold cobimetinib and vemurafenib. • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines. • If patient stabilizes within 28 days, consider resuming cobimetinib at current dose and vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.
Myasthenia gravis or Guillain-Barre syndrome, Grades 1, 2, or 3	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Continue cobimetinib and vemurafenib. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with 1−2 mg/kg/day oral or IV prednisone or equivalent.
Myasthenia gravis or Guillain-Barré syndrome, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Withhold cobimetinib and vemurafenib. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with 1−2 mg/kg/day oral or IV prednisone or equivalent. • If patient stabilizes within 28 days, resume cobimetinib and vemurafenib at current doses. If not, permanently discontinue cobimetinib and vemurafenib.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Neuropathy disorders	
Event	**Action to be taken**
Immune-mediated meningoencephalitis, any grade	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Withhold cobimetinib and vemurafenib. • Refer patient to neurologist. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If patient stabilizes within 28 days, resume cobimetinib and vemurafenib at current doses. If not, permanently discontinue cobimetinib and vemurafenib.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 10: Ocular Toxicity

Ocular toxicity	
Event	**Action to be taken**
Potential immune-mediated ocular toxicity (e.g., uveitis, retinal events), Grade 1	• Continue all study treatment. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Potential immune-mediated ocular toxicity (e.g., uveitis, retinal events), Grade 2	• Withhold atezolizumab and vemurafenib. Continue cobimetinib. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor [a, b, c]. • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib.
Potential immune-mediated ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. Withhold cobimetinib and vemurafenib. • Refer patient to ophthalmologist. • Initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose and resume vemurafenib with dose reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Ocular toxicity	
Event	**Action to be taken**
Other ocular toxicity (i.e., not immune related)	• Withhold cobimetinib and vemurafenib. Continue atezolizumab. • Refer patient to ophthalmologist. Retinal vein occlusion: • Permanently discontinue cobimetinib and vemurafenib. Serous retinopathy, Grade 1: • Resume cobimetinib and vemurafenib at current doses. • Continue ophthalmology follow-up. Serous retinopathy, Grade 2 or 3: • Resume vemurafenib at current dose. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. Serous retinopathy, Grade 4: • Permanently discontinue cobimetinib. Withhold vemurafenib. • If event resolves to Grade 1 or better within 28 days, resume vemurafenib with dose reduced by one level. If not, permanently discontinue vemurafenib. All other ocular events, Grade 1: • Resume cobimetinib and vemurafenib at current doses. All other ocular events, Grade 2, 3, or 4: • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib at current doses. If not, permanently discontinue cobimetinib and vemurafenib.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 11: QT Interval Prolongation

QT interval prolongation	
Event	**Action to be taken**
QTcF ≤ 500 ms with change from baseline in QTcF of < 60 ms	• Continue all study treatment.
QTcF > 500 ms with change from baseline in QTcF of < 60 ms or QTcF ≤ 500 ms with change from baseline in QTcF of ≥ 60 ms	• Withhold vemurafenib. Continue atezolizumab and cobimetinib. • Rule out other risk factors for arrhythmia (e.g., myocardial ischemia). Check for electrolyte disturbances (e.g., potassium, magnesium and calcium). • Evaluate concomitant medications to determine if there is co-administration of drugs that prolong QT interval. • Refer patient to cardiologist. • Monitor ECG weekly. • If QTcF improves to ≤ 500 ms or baseline within 28 days, resume vemurafenib with dose reduced by one level. Repeat ECG at 2 and 4 weeks after resuming vemurafenib, on Day 15 of each subsequent cycle for three cycles, and then every 3 months thereafter. • If QTcF does not improve to ≤ 500 ms or baseline within 28 days, permanently discontinue vemurafenib.
QTcF > 500 ms with change from baseline in QTcF of ≥ 60 ms	• Permanently discontinue vemurafenib. Continue atezolizumab and cobimetinib. • Rule out other risk factors for arrhythmia (e.g., myocardial ischemia). Check for electrolyte disturbances (e.g., potassium, magnesium and calcium). • Evaluate concomitant medications to determine if there is co-administration of drugs that prolong QT interval. • Refer patient to cardiologist. • Monitor ECG weekly until QTcF improves to ≤ 500 ms or baseline.

ECG = electrocardiogram; QTcF = QT interval corrected using Fridericia's method.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 12: Left Ventricular Ejection Fraction Decrease from Baseline

<table>
<tr><th colspan="5">Left ventricular ejection fraction decrease from baseline</th></tr>
<tr><th>Patient</th><th>LVEF Value</th><th>Recommended Action with Cobimetinib, Atezolizumab and Vemurafenib</th><th>LVEF Value following Treatment Break</th><th>Recommended Cobimetinib Daily Dose</th></tr>
<tr><td rowspan="6">Asymptomatic</td><td>≥ 50%
or
40%−49% and < 10% absolute decrease from baseline</td><td>• Continue all study treatment.</td><td>Not Applicable</td><td>Not Applicable</td></tr>
<tr><td rowspan="4">< 40%
or
40%−49% and ≥ 10% absolute decrease from baseline</td><td rowspan="4">• Withhold cobimetinib for at least 2 weeks
• Continue atezolizumab and vemurafenib
• Re-evaluate LVEF at 14 days</td><td rowspan="3">< 10% absolute decrease from baseline</td><td>First occurrence: 40 mg [a]</td></tr>
<tr><td>Second occurrence: 20 mg [a]</td></tr>
<tr><td>Third occurrence: permanent discontinuation</td></tr>
<tr><td>< 40% or ≥ 10% absolute decrease from baseline</td><td>Permanent discontinuation</td></tr>
<tr><td colspan="3">For all patients restarting treatment:
• re-evaluate LVEF at 2, 4, 10 and 16 weeks and then every 12 weeks (3 cycles as per protocol) or as clinically indicated until treatment discontinuation
For patients who permanently discontinue cobimetinib:
• LVEF assessments should continue post treatment every 6 weeks or as clinically indicated until the LVEF recovers to LLN or 50%</td></tr>
</table>

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

<table>
<tr><th colspan="5">Left ventricular ejection fraction decrease from baseline</th></tr>
<tr><th>Patient</th><th>LVEF Value</th><th>Recommended Action with Cobimetinib, Atezolizumab and Vemurafenib</th><th>LVEF Value following Treatment Break</th><th>Recommended Cobimetinib Daily Dose</th></tr>
<tr><td rowspan="5">Symptomatic</td><td rowspan="5">Not Applicable</td><td rowspan="4">• Withhold cobimetinib for at least 4 weeks
• Continue atezolizumab and vemurafenib.
• Patient referral to cardiologist is strongly recommended
• Re-evaluate LVEF at 28 days</td><td rowspan="3">Asymptomatic and < 10% absolute decrease from baseline</td><td>First occurrence: 40 mg [a]</td></tr>
<tr><td>Second occurrence: 20 mg [a]</td></tr>
<tr><td>Third occurrence: permanent discontinuation</td></tr>
<tr><td>Asymptomatic and < 40% or ≥ 10% absolute decrease from baseline</td><td>Permanent discontinuation</td></tr>
<tr><td>Symptomatic regardless of LVEF</td><td>Permanent discontinuation</td></tr>
<tr><td colspan="3">For all patients restarting treatment:
• re-evaluate LVEF at 2, 4, 10 and 16 weeks and then every 12 weeks (3 cycles as per protocol) or as clinically indicated until treatment discontinuation
For patients (asymptomatic and symptomatic) who permanently discontinue cobimetinib:
• LVEF assessments should continue post treatment every 6 weeks or as clinically indicated until the LVEF recovers to LLN or 50% and or symptoms resolve</td></tr>
</table>

LLN = lower limit of normal; LVEF = left ventricular ejection fraction.

a. Patients on a cobimetinib dose less than 60 mg will reduce by one dose level reduction (a 20-mg daily reduction), from a 40 mg daily dose to a 20 mg daily dose, and patients on a 20 mg daily dose at the time of the interruption (for LVEF decline) should discontinue cobimetinib.

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 13: Rhabdomyolysis or CPK Elevation

Rhabdomyolysis or CPK elevation	
Event	**Action to be taken**
General guidance	• Consider withholding cobimetinib while investigating aetiology. Continue atezolizumab and vemurafenib. • Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections. • Evaluate for cardiac injury and rhabdomyolysis. If evidence of clinically significant cardiac injury or rhabdomyolysis, consider permanent discontinuation of cobimetinib.
Asymptomatic CPK elevation, Grade 1, 2, or 3	• Continue all study treatment.
Rhabdomyolysis or symptomatic CPK elevation, Grade 1, 2, or 3	• Withhold cobimetinib. Continue atezolizumab and vemurafenib. • If event improves by at least one grade within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Rhabdomyolysis or CPK elevation (symptomatic or asymptomatic), Grade 4	• Withhold cobimetinib. Continue atezolizumab and vemurafenib. • If event improves to Grade ≤ 3 within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above	• Withhold all study treatment. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab [a, b, c]. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib and vemurafenib with doses reduced by one level. If not, permanently discontinue cobimetinib and vemurafenib.

CPK = creatine phosphokinase.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 13: Guidelines for Management of Patients Who Experience Specific Adverse Events in Cohort 2

Table 14: Haemorrhage

Haemorrhage	
Event	**Action to be taken**
Grade 3 events	• Interrupt cobimetinib treatment. There is no data on the effectiveness of cobimetinib dose modifications for haemorrhage events. • Clinical judgment should be applied when considering restarting cobimetinib treatment. • Vemurafenib dosing can be continued when cobimetinib treatment is interrupted, if clinically indicated. • Continue atezolizumab treatment
Grade 4 events or cerebral haemorrhage (all grades)	• Interrupt cobimetinib treatment. • Permanently discontinue cobimetinib for haemorrhage events attributed to cobimetinib. • Interrupt vemurafenib and restart if event improves within 28 days. • Continue atezolizumab unless clinically indicated.

Appendix 14
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

DOSE MODIFICATIONS

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

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.* Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of*

treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnoea, cough, fatigue, hypoxia, pneumonitis and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumour assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported aetiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1: Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab [b]. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c]. • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day *IV methylprednisolone* or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

a. Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an*

assessment of benefit–risk by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

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

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

Table 2: Management Guidelines for Hepatic Events

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

	• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhoea or colitis are provided in Table 3.

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

Table 3: Management Guidelines for Gastrointestinal Events (Diarrhoea or Colitis)

Event	Management
Diarrhoea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhoea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab [b]. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c].

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

GI = gastrointestinal.

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests

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(e.g., TSH, growth hormone, luteinizing hormone, FSH, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4: Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist.*
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism [c].
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab [b]. • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c].
Hyperglycaemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed.

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

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

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

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OCULAR EVENTS

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

Table 5: Management Guidelines for Ocular Events

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

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnoea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

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Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

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

Table 6: Management Guidelines for Immune-Mediated Myocarditis

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

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

a. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an IRR or CRS with atezolizumab may receive premedication with antihistamines, antipyretics and/or analgesics (acetaminophen is prohibited for patients in Cohort 2 only; see Section 4.4.5) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

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

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

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

Table 7: Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment [c], including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.

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Event	Management
	• For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment [c]. • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy [e]. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather	• Permanently discontinue atezolizumab and contact Medical Monitor [f]. • Administer symptomatic treatment [c]. • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).

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Event	Management
mask, or Venturi mask	• Consider anti-cytokine therapy [e]. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor [f]. • Administer symptomatic treatment [c]. • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy [e]. For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

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Event	Management

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

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

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

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

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

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

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

f. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after after consulting the Medical Monitor and considering the benefit–risk ratio.

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

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

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Table 8: Management Guidelines for Pancreatic Events, Including Pancreatitis

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

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Event	Management
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. *Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.* A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9: Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist *for evaluation and, if indicated, biopsy.* • Initiate treatment with topical corticosteroids.

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

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative aetiologies. Management guidelines for neurologic disorders are provided in Table 10.

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Table 10: Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate aetiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Investigate aetiology *and refer patient to neurologist.* • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab [b]. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor [c].
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor [c]. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from

potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 11.

Table 11: Management Guidelines for Immune-Mediated Meningoencephalitis

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

a. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

RENAL EVENTS

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

Patients with signs and symptoms of nephritis, in the absence of an identified alternate aetiology, should be treated according to the guidelines in Table 12 below.

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Table 12: Management Guidelines for Renal Events

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

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

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Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

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

Table 13 Management Guidelines for Immune-Mediated Myositis

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

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

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

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

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

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challeng *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

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

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

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

- Fever $\geq$38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$90 g/L (9 g/dL) ($<$100 g/L [10 g/dL] for infants $<$4 weeks old)
  - Platelet count $<100\times10^9$/L (100,000/μL)
  - ANC $<1.0\times10^9$/L (1000/μL)
- Fasting triglycerides $>$2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node or liver
- Low or absent natural killer cell activity
- Ferritin $>$500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated $\geq$2 standard deviations above age-adjusted laboratory-specific norms

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

- Ferritin $>$684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq181\times10^9$/L (181,000/μL)
  - AST $\geq$48 U/L
  - Triglycerides $>$1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

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Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

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

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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