Official 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

NCT Number: NCT03625141

Document Date: Statistical Analysis Plan (SAP) Version 2: 02-June-2021

STATISTICAL ANALYSIS PLAN

STUDY 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

STUDY NUMBER: MO39136

STUDY NAME: Tricotel

VERSION NUMBER: 2

ROCHE COMPOUND(S): Cobimetinib (RO5514041)
Atezolizumab (RO5541267)
Vemurafenib (RO5185426)

EUDRACT NUMBER: 2018-000759-41

IND NUMBER: 117296, 135717, and 111271

PLAN PREPARED BY: [redacted] (Cytel)

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
02-Jun-2021 20:21:18	Company Signatory	[redacted] ([redacted])

SPONSOR: F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS: Grenzacherstrasse 124
4070 Basel, Switzerland

DATE FINAL: See electronic date stamp above

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This statistical analysis plan (SAP) was developed based on Roche SAP model document updated on 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2.0	see electronic date stamp on title page |day month year|	Version 4.0, 26 February 2020
1.0	17 April 2019	Version 2.0, 6 November 2018

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationales for each change, are summarized below.

Section	Description of Change	Rationale for Change
4	Patient-reported outcome (PRO)-evaluable population added for the PRO analysis	It is stated in the protocol that "Only patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment will be included in PRO analyses." For clarify purpose, we added PRO population in the Section 4 and clarified that this population will be used for PRO analysis to ensure compliance with the protocol.
5.1	Only a subset of efficacy analysis will be done on Cohort 1	Given that the recruitment of Cohort 1 was stopped prematurely, it is no longer appropriate to produce all the efficacy analysis due to small sample size. Thus, the Statistical Analysis Plan is updated to limit the efficacy analysis.
5.3.1	No analysis on primary endpoint on Cohort 1	After the premature discontinuation of Cohort 1, it was decided to not perform the independent review of scan for patients in Cohort 1. Thus, all analyses on the primary endpoint will be performed on Cohort 2 only.
5.3.3	Adding sensitivity analysis of primary endpoints on all treated patients (safety population)	The analysis on primary endpoint is planned on evaluable population only, which excludes subjects with less than 2 scans. Excluding these subjects could lead to an inflation of the response rate by excluding the early progression or death. Therefore, we add an analysis on all treated patients to assess the bias introduced by excluding these patients.
5.3.4.1	New subgroup	Additional subgroup added to better explore the effect of demographic characteristics and clinical and biological prognostic factors on the efficacy endpoint.
5.4	Adding analysis secondary efficacy endpoints on all treated patients (safety population)	The analysis on efficacy endpoint (objective response rate [ORR], progression-free survival [PFS], and disease control rate [DCR]) are planned on evaluable population, which excludes subjects with less than 2 scans. Excluding these subjects could lead to an inflation of the response rate by excluding the early progression or death. Therefore, we add an analysis on all treated patients to assess the bias introduced by excluding these patients.
5.4.2.8	Update the definition of time to deterioration (TTD) to a decrease of 10 point from baseline for functional scale TTD will be performed on each scale separately	A high score on functional scale and a low score on symptom scale is an improvement as per the scoring manual. Thus, a deterioration for functioning scale and Global Health Status (GHS)/ Quality-of-Life (QoL) for Core 30 (QLQ-C30) is defined by a decrease of 10 point from baseline. A deterioration for symptoms scale for QLQ-C30 and items for Quality-of-Life Questionnaire brain cancer module (QLQ-BN20) is defined by an increase of 10 point from baseline.

		Each scale measure different functions and symptoms. Thus, it is more meaningful to evaluate the TTD on each symptom and function separately.
5.5.1.6	Add analysis on change in corticosteroid use	New analyses are added to explore the change in corticosteroid use based on data collected case report form (CRF).
5.5.1.8	Add PFS, duration of response (DoR) and DCR by independent review committee (IRC)	To assess the bias introduced on efficacy endpoint as determined by investigator using response evaluation criteria in solid tumors (RECIST).
5.6	Safety analysis will be done separately for patients in Cohort 2 who actually received and didn't receive the triplet combination during the treatment period	To evaluate safety on patients who actually received the triplet combination and those who received only cobimetinib and vemurafenib. Patients in Cohort 2 will receive cobimetinib and vemurafenib during the run-in period (Cycle 1) and with the triplet combination (cobimetinib, atezolizumab, and vemurafenib) post run-in (Cycle 2 onwards).
6.2	Replaced analysis of adverse events (AEs) by highest grade by analysis of AE by System Organ Class (SOC) and Preferred Term (PT)	Summary of some AEs (such as AE leading to study drug discontinuation, etc.) by highest grade are removed when not appropriate. They are replaced by a summary of the incidence by SOC and PT only.
5.6.2	Add a list of suspected Coronavirus Disease (COVID) case	To identify potential COVID case in the study, if any.
5.6.2	Add analysis on AE during run-in and post run-in in Cohort 2	To evaluate safety during triple combination period and during the period where only cobimetinib and vemurafenib are administered.
5.7.1	Add summary of pharmacodynamic related to COVID	To assess potential impact of COVID.

Additional minor changes have been made throughout to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
$BRAF^{V600}$	V600 codon of the BRAF oncogene
CI	confidence interval
CNS	central nervous system
COVID	Coronavirus Disease
CR	complete response
CRF	case report form
DCR	disease control rate
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for the Research and Treatment of Cancer
GHS	Global Health Status
HRQoL	health-related qualify of life
IMC	Internal Monitoring Committee
iRANO	immunotherapy Response Assessment for Neuro-Oncology
IV	intravenous (ly)
IRC	independent review committee
LDH	Lactic Acid Dehydrogenase
LPI	last patient in (last patient enrolled)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NA	not applicable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death ligand 1
PFS	progression free survival
PR	partial response
PRO	patient-reported outcome
PT	Preferred Term
QLQ-C30	Quality-of-Life Questionnaire Core 30

QLQ-BN20	Quality-of-Life Questionnaire - Brain Cancer Module
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of longest diameter
SOC	System Organ Class
SRT	stereotactic radiotherapy
TEAE	treatment-emergent adverse event
TTD	time to deterioration
ULN	upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study MO39136 (TRICOTEL): 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. The background for the study can be found in the study protocol.

1.1 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 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 $BRAFV^{600}$ 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	• 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

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives	Corresponding Endpoints
	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/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective(s)	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

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective(s)	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(s)	**Corresponding Endpoints**
• 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; PD-L1 = programmed death ligand 1; PRO=patient-reported outcome; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SD=stable disease; SRT=stereotactic radiotherapy.

1.2 STUDY DESIGN

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:

- Cohort 1: Patients with $BRAF^{V600}$ wild-type disease will be assigned to treatment with cobimetinib plus atezolizumab in Cohort 1.
- Cohort 2: 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.

Study treatment will consist of:

- Cohort 1: orally administered cobimetinib and intravenously (IV) administered atezolizumab in 28-day cycles.

- Cohort 2: 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:

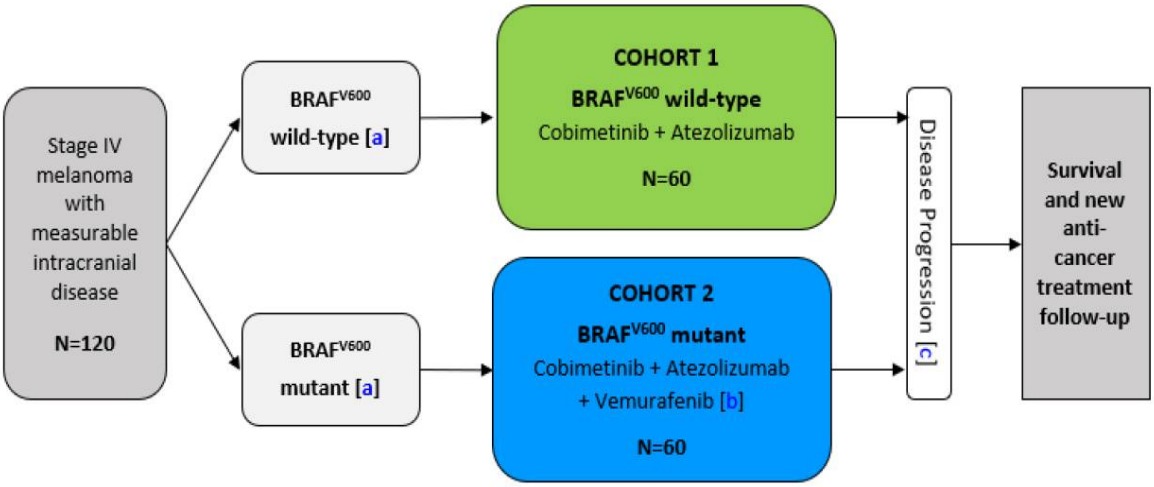
- pseudoprogression due to the effects of immunotherapy is suspected to have occurred or disease progression is limited to ≤3 intracranial lesions that can be controlled with stereotactic radiotherapy (SRT).
- Patient is clinically stable, have a favourable benefit-risk ratio (all the criteria listed in the protocol have to be met).

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 within 28±7 days of their last study treatment dose. All AEs 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.

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.

$BRAF^{V600}$ = V600 codon of the BRAF oncogene; N = number of patients

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). 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).

Approximately 60 patients will be enrolled into each treatment cohort for a total of 120 patients enrolled. With an estimated study drop-out rate of 15%, approximately 50 patients in each cohort are expected to be evaluable for the primary efficacy endpoint. To ensure approximately equal sample sizes in each treatment cohort, study eligibility and screening may be adjusted with respect to $BRAF^{V600}$ status once enrolment reaches 60 patients in either treatment cohort.

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 of the study protocol), 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.

1.2.1 Treatment Assignment

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.

1.2.2 Independent Review Facility

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

1.2.3 Data Monitoring

The Internal Monitoring Committee (IMC) will monitor patient safety throughout the study and will assess the benefit-risk, as described in the IMC charter. 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), serious adverse 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 and assess the benefit-risk.

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, enrolment 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 are described in the IMC charter.

2. STATISTICAL HYPOTHESES

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

3. SAMPLE SIZE DETERMINATION

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 planned total sample size of approximately 120 patients (60 patients/cohort) is based on based on an estimated study drop-out rate of 15%, the primary endpoint and 95% confidence intervals (CIs) for each treatment regimen. If necessary, study eligibility and screening may be adjusted with respect to $BRAF^{V600}$ status once enrolment reaches 60 patients in either treatment cohort. No power calculation has been performed.

Point estimates and 95% CIs for a range of possible outcomes produced using nQuery (Version 7) with 100 evaluable patients (50 per treatment cohort) are provided in Table 2.

Table 2 Objective Response Rate Estimates and Confidence Intervals with 50 Evaluable Patients per Treatment Cohort

Intracranial Response Rate in Each Cohort	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%)

4. ANALYSIS SETS

The following populations are defined:

Population	Definition
Safety-evaluable Population	All participants received at least one dose of study treatment (e.g., atezolizumab, cobimetinib, or vemurafenib)
Evaluable Population	All enrolled patients who received study medication and have at least two post-baseline intracranial tumour assessments for response evaluation
PRO-evaluable Population	All patients who received any amount of any study medication (e.g., atezolizumab, cobimetinib, or vemurafenib) and have a baseline and at least one post baseline PRO assessment in the questionnaire of interest (EORTC QLQ-C30 or EORTC QLQ-BN20)

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; PRO=patient-reported outcome.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATION

A primary study analysis that includes analyses of all efficacy endpoints and safety summaries will be conducted based on data collected up to 6 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 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, survival, corticosteroid use, and time to subsequent intracranial or systemic anti-cancer treatment endpoints will be conducted based upon the Safety evaluable population in each cohort consisting of all patients who received at least one dose of study medication. Analyses of patient-reported outcome (PRO) endpoints will be conducted based upon the PRO-evaluable population.

Any incomplete or missing death date will be handled separately for safety and efficacy analyses. In safety analyses, all deaths will be included, regardless of completeness of death date; patients who died with a partial or missing death date will be included as an event. In efficacy analyses, a death is considered an event only if a complete death date is available; patients who died with only a partial or missing death date will not be considered as a death event.

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 of the study protocol), enrollment in the $BRAF^{V600}$ wild-type cohort was discontinued. The primary endpoint will not be evaluated on Cohort 1. Only a subset of analysis on efficacy secondary endpoints will be performed.

5.2 PARTICIPANT DISPOSITION

The analysis of patient disposition will be based on the safety population.

Study enrollment and reasons for study discontinuation will be summarized by cohort. Study treatment administration and reasons for discontinuation from study treatment will be summarized.

5.3 PRIMARY ENDPOINT ANALYSIS

The primary endpoint will be derived and analyzed on Cohort 2 only.

5.3.1 Definition of Primary Endpoint

Intracranial objective response rate (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.

5.3.2 Main Analytical Approach for Primary Endpoint

The primary efficacy analysis will be the analysis of the intracranial ORR. The intracranial ORR will be presented together with a 95% Pearson-Clopper CI using the evaluable population.

5.3.3 Sensitivity Analyses for Primary Endpoint

Sensitivity analyses of the primary endpoint will be conducted in order to detect a potential bias with regard to the primary analysis.

- The analysis on primary endpoint will be replicated on Safety evaluable population to assess the response rate of all patients enrolled and treated in this study.
- The intracranial ORR will include patients with unconfirmed complete response (CR) or partial response (PR) based on the safety population. Unconfirmed Intracranial ORR will be analyzed using the same methods as described in Section 5.3.2.

In addition, a summary of concordance between investigator and IRC intracranial response assessments, 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, will be provided.

5.3.4 Supplementary Analyses for Primary Endpoint

Not applicable.

5.3.4.1 Subgroup Analyses for Primary Endpoint

The consistency of the primary efficacy results will be examined in subgroups defined by demographic characteristics and clinical and biological prognostic factors. Summaries of intracranial ORR, including 95% Pearson-Clopper CIs, will be produced for each of the defined subgroups, and displayed in a Forest plot (Lewis and Clarke 2001).

The subgroups to be considered include, but may not be limited to, the following:

- Age (≤65 years, >65 years)
- Race (non-White, White)
- Sex (female, male)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1)
- programmed death ligand 1 (PD–L1) status
- Lactic Acid Dehydrogenase (LDH) (≤upper limit of normal [ULN], >ULN)

- BRAF mutation subtype (V600E, V600K)
- Extracranial sum of longest diameter
- Number of target lesion (intracranial, extracranial)
- Receiving prior steroid therapy
- Organ involvement (site of target lesion): patients with brain lesion(s) only, patients with brain lesion(s) and other lesions.

5.4 SECONDARY ENDPOINTS ANALYSES

Unless otherwise noted, all efficacy analyses will be performed on both the evaluable patient population and all treated patients (safety population).

5.4.1 Key/Confirmatory Secondary Endpoint

Not applicable.

5.4.2 Supportive Secondary Endpoints

5.4.2.1 Intracranial Objective Response Rate – RECIST

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 the investigator 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.

The intracranial ORR will be presented together with a 95% Pearson-Clopper CI.

5.4.2.2 Extracranial Objective Response Rate – RECIST

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.

The extracranial ORR will be presented together with a 95% Pearson-Clopper CI.

5.4.2.3 Overall Objective Response Rate – RECIST

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.

The overall ORR will be presented together with a 95% Pearson-Clopper CI.

5.4.2.4 Intracranial, Extracranial and Overall Progression-Free Survival – RECIST

Intracranial, extracranial, and overall progression-free survival (PFS) are defined as the time from study treatment initiation to the first occurrence of disease progression, as

determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death at the time of analysis data cutoff will be censored at the last evaluable tumor assessment date.

Kaplan-Meier methodology will be used to estimate median intracranial, extracranial, and overall PFS. Kaplan-Meier curves will be provided. The 95% CI of the median PFS will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982).

5.4.2.5 Intracranial, Extracranial and Overall Duration of Response – RECIST

For patients who achieve respectively an intracranial, extracranial, and objective response, 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 the one described for PFS analysis in Section 5.4.2.4.

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.

5.4.2.6 Intracranial, Extracranial and Overall Disease Control Rate at 16 Weeks – RECIST

Intracranial, extracranial, and overall disease control rates (DCR) are defined as the proportion of patients with a CR or PR (based on two consecutive assessments ≥4 weeks apart) or stable disease (SD) at 16 weeks from study treatment initiation, as determined by the investigator according to RECIST v1.1. The denominator is all patients in the evaluable population.

Week 16 occurs at Study Day 112. Allowing 7 days after the exact Week 16, assessments that occur between Study Day 112 and Study Day 119 (inclusive) will be considered as a Week 16 assessment.

Patients with a CR or PR or SD at 16 weeks from study treatment initiation are patients:

- With a CR or PR assessed within the window of Study Days 112-119 inclusive and followed by a consecutive CR or PR assessment in the next ≥4 weeks.

OR

- With a CR or PR assessed prior to the Study Day 112 and followed by a consecutive CR or PR assessment in the next ≥4 weeks and on or after Study Day 112.

OR

- With a SD assessed within the window of Study Days 112-119 inclusive.

DCR will be presented together with a 95% Pearson-Clopper CI.

5.4.2.7 Overall Survival

The overall survival (OS) analysis will be based on the safety population (all treated patients) only.

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 cutoff, OS time will be censored at the date the patient was last known to be alive.

Kaplan-Meier methodology will be used to estimate OS. Kaplan-Meier curves will be provided. The 95% CI of the median OS will be constructed using the Brookmeyer and Crowley method.

5.4.2.8 Patient-Reported Outcomes

The analysis of each questionnaire respectively will be performed on PRO-evaluable population only.

The EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and Quality-of-Life Questionnaire brain cancer module (QLQ-BN20) data will be scored according to the EORTC scoring manual (Fayers et al. 2001).

Time from study treatment initiation to cognitive symptom deterioration is defined as the time from study treatment initiation to the first time a patient's score shows a ≥10-point increase above baseline in the following EORTC QLQ-BN20 transformed scale scores: visual disorder (items 6, 7, and 8), motor dysfunction (items 10, 15, and 19), communication deficit (items 11, 12, and 13), headaches (item 4), seizures (item 9) and drowsiness (item 14).

Time from study treatment initiation to symptom deterioration is defined as the time from study treatment initiation to the first time a patient's score shows a ≥10-point increase above baseline in the following EORTC QLQ-C30 transformed symptom subscale scores: fatigue (items 10, 12, and 18).

Time from study treatment initiation to function deterioration is defined as the time from study treatment initiation to the first time a patient's score shows a ≥10-point decrease from baseline in the following EORTC QLQ-C30 transformed functioning subscale scores: physical (items 1 to 5), cognitive (items 20 and 25) and role functioning (items 6 and 7) scales.

Duration of stable/improved HRQoL scores is assessed through use of the two-item Global Health Status (GHS)/ Quality-of-Life (QoL) subscale (items 29 and 30) of the EORTC QLQ-C30. Duration of Stable/Improved HRQoL scores is defined for patients

who achieve a PRO score of “improved” or “stable” as the time from the first occurrence of an “improved” or “stable” score to a “worsened” score.

Data for patients who do not achieve a 10-point change at the time of analysis data cutoff will be censored at the last time PRO data are available.

Patients post-baseline PRO scores will be classified as ”improved”, “stable”, or “worsened”as follow:

- Symptom scales of the EORTC QLQ-C30 and the QLQ-BN20
    - “Improved” if a ≥10-point of decrease is observed.
    - “Worsened” if a ≥10-point of increase is observed.
    - “Stable" if their baseline score changes by any other
- The GHS/QoL and functional scales of the EORTC QLQ-C30:
    - "Improved" if their baseline score increases by ≥10 points,
    - "Worsen" if their baseline score decreases by ≥10 points,
    - "Stable" if their baseline score changes by any other

Time to deterioration (TTD) in BN20 scales (visual disorder, motor dysfunction, communication deficit, headaches, seizures and drowsiness), TTD in symptom (fatigue), TTD in each functioning scales (physical, role, cognitive), and duration of stable/improved HRQoL scores for GHS/QoL subscale will be analyzed using the same method as the analysis of PFS described in Section 5.4.2.4.

The number and proportion of patients who improve, remain stable, or worsen from baseline will be summarized by study visit.

Questionnaire completion and compliance (based on the number of patients who were expected to reach a given visit) will be summarized at each timepoint.

In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

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 follow-up. The mean and median of the absolute scores and the change from baseline will be reported for interval and continuous variables.

5.5 EXPLORATORY ENDPOINTS ANALYSIS

5.5.1.1 Intracranial Objective Response Rate - iRANO

Intracranial ORR is 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.

Intracranial ORR will be analyzed using the same methods as described in Section 5.3.2.

5.5.1.2 Intracranial, Extracranial and Overall Objective Response Rate – Immune-Modified RECIST

ORR in intracranial, extracranial and overall disease are defined as described in Sections 5.4.2.1, 5.4.2.2, and 5.4.2.3 but 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 ORR will be analyzed using the same methods as described in Section 5.3.2.

5.5.1.3 Intracranial, Extracranial, and Overall Progression-Free Survival – Immune-Modified RECIST

Intracranial, extracranial, and overall PFS are defined as described in Section 5.4.2.4 but determined by the investigator according to immune-modified RECIST.

Intracranial, extracranial, and overall PFS will be analyzed using the same methods as described in Section 5.4.2.4.

5.5.1.4 Intracranial, Extracranial, and Overall Duration of Response – Immune-Modified RECIST

Intracranial, extracranial, and overall DOR are defined as described in Section 5.4.2.5 but determined by the investigator according to immune-modified RECIST.

Intracranial, extracranial, and overall DOR will be analyzed using the same methods as described in Section 5.4.2.5.

5.5.1.5 Radiotherapy-Assisted Progression-Free Survival – RECIST

Radiotherapy-assisted intracranial PFS is 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 modified by excluding ≤3 lesions that can be treated by SRT from the sum of largest diameters from baseline onwards. The censoring method is the same as the one described for PFS analysis in Section 5.4.2.4.

For the purpose of the analysis of radiotherapy-assisted PFS, the disease status will be derived by removing the lesions treated by SRT (3 maximum) from sum of longest diameters (SLD), from baseline onwards.

Radiotherapy-assisted PFS will be analyzed using the same methods as described in Section 5.4.2.4.

5.5.1.6 Timing of Increase or Change in Corticosteroid Use

The analysis of timing of increase in corticosteroid use during treatment will be based on the safety population.

A summary table of the status of corticosteroids (None / Stable or decreased / Increased) during treatment, as collected in the 'iRANO Response assessment' electronic Case Report Form (eCRF) page will be provided by visit.

The time to increase in corticosteroid use is defined as the time from study treatment initiation to the first increase in corticosteroid use during treatment. Data for patients who have not experienced any increase in corticosteroid use during treatment, at the time of analysis data cutoff, will be censored at the last iRANO response assessment date during treatment. Timing of increase or change in corticosteroid use will be analyzed using the same methods as described in Section 5.4.2.4.

For patients on corticosteroids for disease control at study entry, the number of patients with a change in the corticosteroid use (increase/decrease/off) will be summarized descriptively based on the medication case report form (CRF) page if applicable.

5.5.1.7 Time to Subsequent Intracranial and Systemic Anti-Cancer Treatment

The analysis of time to subsequent intracranial and systemic anti-cancer treatment will be based on the safety population.

Time from study treatment initiation to subsequent intracranial and systemic anti-cancer treatment is defined as the time from study treatment initiation to the date of first administration of subsequent systemic anti-cancer therapy. Data for patients who have not received any subsequent anti-cancer treatment at the time of analysis data cutoff will be censored at the time of study termination or at the cutoff data, whichever occurs first.

Time to subsequent intracranial and systemic anti-cancer treatment will be analyzed using the same methods as described in Section 5.4.2.4.

5.5.1.8 DoR, DCR and PFS by IRC – RECIST

Intracranial PFS, DoR, and DCR, as determined by the IRC according to RECIST v1.1, will be analyzed using the same methods described for intracranial PFS, DoR, and DCR determined by investigator on all patients who received at least one dose of study medication (safety evaluable population).

5.6 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population.

In addition, patients in Cohort 2 will receive cobimetinib and vemurafenib during the run-in period (Cycle 1) and the triplet combination (cobimetinib, atezolizumab and vemurafenib) from Cycle 2 onwards. For the purpose of safety analyses in Cohort 2, the patients will be grouped according to whether they have received the triplet combination:

- cobimetinib+vemurafenib (Patients who discontinued therapy prior to any atezolizumab administration): patients who received any amount of cobimetinib and/or vemurafenib without any amount of atezolizumab
- atezolizumab+cobimetinib+vemurafenib: patients who received any amount of atezolizumab in addition to cobimetinib+vemurafenib.

5.6.1 Extent of Exposure

Study drug (atezolizumab, cobimetinib, and vemurafenib) exposure will be summarized for each cohort using descriptive statistics.

The overall number of cycles initiated (i.e., for drug combination) and the overall duration of treatment (in months) will be provided.

For each study drug separately, the total number of cycles initiated, the duration of treatment (in months), the duration categories in months, the cumulative dose, the dose intensity (%), the number of dose modification during the study and the reason for dose modification will be summarized.

5.6.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus levels and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. AEs that occur during or after the first dose of study treatment (i.e., treatment-emergent adverse events [TEAEs]) will be included in the summary tables.

Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (System Organ Class [SOC] and Preferred Term [PT]), and when specified by NCI CTCAE grade. For each patient, multiple occurrences of the same event will be counted once at the maximum severity.

The following adverse events will be summarized by SOC or medical concept for AEs of special interest (AESIs), PT, and NCI CTCAE grade, for each cohort:

- Adverse events (AEs)
- AEs and AESIs of Grade 3 or higher
- Adverse events related to i) any study treatment, ii) atezolizumab, iii) cobimetinib, iv) vemurafenib (Cohort 2 only), v) all study treatment.

- SAEs
- AESIs

The following AEs will be summarized by SOC or medical concept for AESIs and PT for each cohort:

- AEs
- SAEs
- AEs and SAEs related to i) any study treatment, ii) atezolizumab, iii) cobimetinib, iv) vemurafenib (Cohort 2 only), v) all study treatment.
- Adverse events leading to discontinuation of i) any study treatment, ii) atezolizumab, iii) cobimetinib, iv) vemurafenib (Cohort 2 only), v) all study treatment.
- Adverse events leading to dose modification or interruption of i) any study treatment, ii) atezolizumab, iii) cobimetinib, iv) vemurafenib (Cohort 2 only), v) all study treatment.
- AESIs specific to i) atezolizumab, ii) cobimetinib+vemurafenib, iii) the combination, based on lists of pre-defined terms.
- AESIs leading to discontinuation of i) atezolizumab, ii) cobimetinib, iii) vemurafenib
- AESIs leading to dose modification or interruption of i) atezolizumab, ii) cobimetinib, iii) vemurafenib
- Fatal AEs
- Serious AESIs

Adverse events will be summarized by PT for each cohort. In addition, deaths, SAEs, AESIs, and AEs during the run-in period and the triple combination period (i.e., post run-in), will be summarized for Cohort 2 only.

All listings of AEs will include all AEs. AEs associated with coronavirus disease (COVID-19) will be listed.

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

5.6.3 Laboratory Data

Laboratory data will be summarized over time including change from baseline. Values outside the normal ranges will be summarized. Additionally, selected laboratory data will be classified in accordance with NCI CTCAE Version 4.0 and will be summarized by grade.

Highest NCI CTCAE grade post-baseline will also be reported, and shift tables from baseline to worst value during the study post-baseline will be presented.

Patient meeting the criteria for Hy's Law will be summarized.

5.6.4 Vital Signs

Actual values and changes from baseline in selected vital signs will be summarized over time.

5.7 OTHER ANALYSES

A shift table presenting the baseline ECOG performance status to worst post-baseline value will be provided by cohort.

A shift table presenting the baseline ECG assessment result to post-baseline value will be displayed by visit for the Cohort 2.

5.7.1 Summaries of Conduct of Study

Major protocol deviations, including violations of inclusion/exclusion criteria and deviations during study conduct, will be summarized by cohort.

All COVID-19 related major protocol deviations will be summarized by cohort.

5.7.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

The following analyses will be based on the safety population.

Demographic characteristics such as age, sex, race/ethnicity, ECOG and other relevant baseline characteristics will be summarized by cohort. The disease baseline characteristics will include:

- Time since initial diagnosis (years)
- Primary diagnosis (Local regional, Metastasis, Unknown)
- Histologically confirmed sites
- Histological subtypes
- Initial diagnosis staging
- Time since initial diagnosis of metastatic melanoma (months)
- Stage at study entry
- $BRAF^{V600}$ mutation status and type

Descriptive statistics (mean, median, standard deviation [SD], and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

The baseline value will be defined as the last available value recorded on or prior to the first administration of any study medication.

Prior cancer therapy, prior cancer radiotherapy, prior cancer surgery, follow-up cancer therapy, on-study radiotherapy, on-study targeted surgeries and procedures, follow-up

cancer radiotherapy, follow-up cancer therapy and follow-up cancer-related surgical procedures will be summarized by cohort. Previous and concurrent medical history, as well as medications, will also be summarized by cohort. In addition, the prior and concomitant anticonvulsants and systemic corticosteroid for disease control will also be summarized.

5.8 INTERIM ANALYSES

5.8.1 Planned Interim Analyses

A first safety interim analysis will be performed after at least 10 patients in each of both cohorts have completed their first tumor 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.

Full details on interim analyses are provided in the IMC charter.

5.8.2 Optional Interim Analyses

Not applicable.

6. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

APPENDIX 1: CHANGES TO PROTOCOL-PLANNED ANALYSES

The TTD for functional scale on QLQ-C30 is defined as 10 point of decrease from baseline instead of 10 point of increase as defined in the protocol. Indeed, a high score on functioning scale represent a high / healthy level of functioning as per the QLQ-C30 manual, thus an improvement.

The TTD analysis will be performed on the selected symptoms and functional scales for QLQ-C30 and BN20 separately since each item measures different level of functioning and symptomatology/problems.

7. REFERENCES

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