Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS201943-0029
Title:	A Phase Ib Safety Run-in and Randomized Phase II, Open-label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of M6620 in Combination with Avelumab and Carboplatin in Comparison to Standard of Care Therapy in Participants with PARPi-resistant Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Trial Phase	Ib/II
Investigational Medicinal Product(s)	M6620 in combination avelumab and carboplatin
Clinical Trial Protocol Version	30 November 2018 / Version 2.0
Statistical Analysis Plan Author	PPD
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Statistical Analysis Plan Reviewers	PPD, PPD, PPD, Merck KGaA PPD, PPD, Merck KGaA PPD, PPD, EMD Serono PPD, PPD, Merck KGaA PPD, PPD, EMD Serono PPD, PPD, Merck KGaA PPD, PPD, Merck KGaA PPD, PPD, PPD

Approval Page

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Approval of the IAP by all Merck Data Analysis Responsible is documented within ELDORADO via eSignature. With the approval within Eldorado, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
BOR	Best overall response
CA-125	Cancer antigen 125
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicities
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
GCIG	Gynecologic Cancer Intergroup
iAP	Integrated analysis plan
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic(s)
PP	Patient profile
PR	Partial response
PT	Preferred Term
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase II dose
SAE	Serious adverse event
SOC	System Organ Class
StDev	Standard deviation
TEAE	Treatment emergent adverse event
TFST	Time to first subsequent therapy
TTP	Time to progression

3 Modification History

Unique Identifier for iAP Version	Date of iAP Version	Author	Changes from the Previous Version
1.0	27 November 2019	PPD	N/A – first version

4 Purpose of the Integrated Analysis Plan

The purpose of this integrated analysis plan (iAP) is to document technical and detailed specifications for the main analysis of Protocol MS201943-0029.

The Part A of the study was completed after enrollment of three patients and confirmation of the safety combination dose by the SMC. It was however decided not to continue with Part B. Details will provided in the study report.

This core iAP is based upon Section 9 (Statistical Considerations) of the trial protocol and protocol amendment and is prepared in compliance with ICH E9.

5 Objectives and Endpoints

Part A (Safety Run-in Period)

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To evaluate a safe, tolerable recommended Phase II dose (RP2D) of carboplatin + M6620 in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	Occurrence of dose-limiting toxicities (DLTs) during the DLT observation period	15
Secondary		
To evaluate the safety and tolerability of carboplatin+ M6620 at the RP2D when used in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	Occurrence of Treatment Emergent Adverse Events (TEAEs) and treatment-related adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)	15
To evaluate the antitumor activity of carboplatin+ M6620 at the RP2D in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	• Confirmed best overall response (BOR) • Progression-free survival (PFS) from date of first dose of study intervention until progressive disease (PD) or death • Duration of response (DOR) as assessed from complete response (CR) or partial response (PR) until PD, death, or last tumor assessment • Time to progression (TTP) from first dose of study intervention until PD All the above by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and/or cancer antigen 125 (CA-125) response (Gynecologic Cancer Intergroup [GCIG] criteria),as assessed by the Investigator. • Time to first subsequent therapy (TFST)	14
To characterize the pharmacokinetic (PK) profiles of avelumab and M6620 when given in combination with carboplatin	• PK parameter estimates for M6620 • PK summary statistics for avelumab	NA

6 Overview of Planned Analyses

6.1 Main Analysis

The reduced-scope main analysis is being completed following study cancellation and database lock.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The analyses stated in the protocol will not be completed in their entirety due to study cancellation. Time to first subsequent therapy (TFST) cannot be calculated since the date of first subsequent treatment was not recorded in the eCRF, and the decision was taken not to correct the error due to study stop.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants that are dosed on the study despite not satisfying the inclusion criteria or meeting one or more exclusion criteria;
- Participants that meet withdrawal criteria whilst on the study but are not withdrawn;
- Participants that receive the wrong treatment or an incorrect dose;
- Participants that receive an excluded concomitant medication;
- Deviation from Good Clinical Practice.

Important protocol deviations will be based upon the study database and determined for all participants by either medical review processes, site monitoring or programming based on the inclusion/exclusion criteria or other criteria presented in the protocol.

All important protocol deviations are documented in SDTM datasets whether identified through site monitoring, medical review, or programming.

8.2 Definition of Analysis Sets

The analysis sets that are applicable to the analyses are defined in Table 1.

Table 1 Analysis Sets

Population	Description
Enrolled	All participants who provided informed consent.
Safety (SAF)	All participants who receive at least 1 dose of any study intervention. Analyses performed on the Safety Analysis Set will consider participants as treated.

There are no subgroup analyses planned.

9 General Specifications for Statistical Analyses

Tables will show data summarized overall; listings will be provided by participant; complete patient profiles will be generated based on collected data.

Definition of on-treatment period:

On-treatment period is defined as the time from the first dose of study intervention through 30 days + last dose of study intervention, unless otherwise stated.

Study intervention groups:

The study intervention group is defined and labelled as 'Avelumab + M6620'.

Data handling after cut-off date:

Not applicable, as this will be the final analysis and no further data collection is planned.

Significance level:

There will be no statistical tests performed.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

- number of participants, number of participants with non-missing values
- median
- minimum, maximum

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of participants in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Definition of baseline:

In general, the last non-missing measurement prior to the first dose of study intervention will serve as the baseline measurement.

Definition of duration:

If not otherwise specified, duration will be calculated by the difference of start and stop date + 1 (e.g. survival time (days) = date of death – date of first study intervention + 1).

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

Conversion factors:

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data:

Missing data will not be replaced.

In all listings, imputed values will be presented and flagged as such.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd".

Treatment day is defined relative to the date of first study intervention administration. Treatment Day 1 is the day of start of study intervention; the day before is defined as Treatment Day -1 (no Treatment Day 0 is defined).

All analyses will be performed using SAS® Software version 9.4 or higher.

10 Trial Subjects

The subsections in this section include specifications for reporting participant disposition and treatment/trial discontinuations.

10.1 Disposition of Subjects and Discontinuations

Analysis sets: SAF

Subject disposition and treatment discontinuations will be summarized in a table which will include the following:

- Total number of participants screened overall
- Number of participants who discontinued from the trial prior to receiving any study intervention, overall and grouped by the main reason (i.e. screen failures)
- Number of treated participants
- Number and percentage of participants who discontinued treatment, and reasons for treatment discontinuation
- Number and percentage of treated participants who discontinued the trial, and reasons for trial discontinuation

A summary of participant enrollment by geographic region and country. Site codes will be used for the determination of the participant's geographic region and country.

A by-participant listing will also be provided.

10.2 Protocol Deviations

Analysis sets: SAF

A listing of important protocol deviations will be provided.

11 Demographics and Other Baseline Characteristics

Analysis sets: SAF

11.1 Demographics

Demographic characteristics will be summarized using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown
  - Ethnic origin: Hispanic/Latino (Yes/No)
  - Age (years): summary statistics
  - Age categories: < 65 years, ≥ 65 years
    - 65-< 75
    - 75-< 85
    - ≥ 85
  - Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, ≥2
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)
  - Body Surface Area (BSA) (m^2)

Specifications for computation:

- Age (years)
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day for at least one date, but month and year available for both dates:

    For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In case of missing month for at least one date, but year available for both dates:

    For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used
- BSA (m^2) = ([height (cm) x weight (kg)] / 3600)$^{1/2}$
- BMI (kg/m^2) = weight (kg) / [height (cm) x height (cm)] x 10000

A listing of participant demographics will be provided.

12 Previous or Concomitant Medications/Procedures

Data presented in patient profiles.

13 Treatment Compliance and Exposure

Data presented in patient profiles.

14 Endpoint Evaluation

14.1 Primary Endpoint Analyses

Analysis sets: SAF

The primary objective is to assess the safety of the investigational treatment to safeguard the interests of trial participants and monitor the overall conduct of the clinical trial. The details regarding safety outputs are contained in Section 15.

14.2 Secondary Endpoint Analyses

Analysis sets: SAF

All efficacy endpoints described below will be listed by participant.

14.2.1 Best Overall Response

Analysis sets: SAF

Best overall response (BOR) will be assessed based on reported overall timepoint responses at different evaluation timepoints from the start date until documented disease progression in accordance to RECIST v1.1 according to the Investigator assessment, taking requirements for confirmation into account as detailed below. Dates of subsequent anti-cancer therapies were not collected, so that information will not be taken into account. Clinical deterioration will not be considered as documented disease progression.

1) BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks apart (with no PD in-between)
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR) (with no PD in-between)
- SD (applicable only to participant with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after start date (and not qualifying for CR or PR).

- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after start date (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after start date (and not qualifying for CR, PR or SD).
- Not Evaluable (NE) = all other cases.

SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

2) BOR Based on Unconfirmed Responses:

- Unconfirmed CR = one objective status of CR documented before progression.
- Unconfirmed PR = one objective status of PR documented before progression (and not qualifying for CR).
- SD (applicable only to participant with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after start date and before progression (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to participants with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after start date and before progression (and not qualifying for unconfirmed CR or unconfirmed PR).
- PD = progression ≤ 12 weeks after start date (and not qualifying for unconfirmed CR, unconfirmed PR, SD or non-CR/non-PD).
- NE = all other cases.

Confirmed and Unconfirmed BOR will be presented in the efficacy listing.

14.2.2 Progression Free Survival

The progression free survival (PFS) time is defined as the time (in months) from the date of first dose of study intervention to the date of the first documentation of objective PD as per RECIST v1.1 as assessed by the Investigator, or death due to any cause, whichever occurs first.

The PFS data will be censored on the date of the last adequate tumor assessment in the following cases:

- For participants who do not have an event (PD or death)
- For participants with an event after 2 or more missing tumor assessments.

Participants who do not have a baseline tumor assessment or who do not have any postbaseline tumor assessments will be censored on the date of the first study intervention, unless death

occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

PFS time = (date of PD or death/censoring - date of first dose + 1)/30.4375 (months)

The PFS event or censoring, PFS time or censoring time, and the reasons for censoring will be presented in the efficacy listing.

15 Safety Analyses

Analysis sets: SAF

The reduced scope limits safety analyses to Adverse Events; all other data will be presented in the patient profiles.

15.1 Adverse Events

The severity of adverse events (AEs) will be graded using the latest NCI-CTCAE version, except where CTCAE grades are missing. No imputation of missing grades will be performed. Adverse events will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version at the time of database lock.

- **TEAEs**: Any AEs that are reported (serious and non-serious) will be considered treatment emergent adverse events (TEAEs) with onset dates occurring on-treatment, or events which worsen on-treatment.

- **Related Adverse Events**: AEs with relationship to study treatment of 'Related' reported by the Investigator, as well as those of unknown relationship (i.e., no answer to the question, 'Relationship with study treatment'). Relationship is judged separately for each study treatment.

- **SAEs**: Serious adverse events (as recorded on the Adverse Events Details eCRF page, Serious Adverse Event = 'Yes').

- **AEs Leading to Treatment Discontinuation**: AEs leading to permanent discontinuation of study treatment (as recorded on the Adverse Events Details eCRF page, Action taken with study treatment = 'Drug withdrawn'). Treatment discontinuation is recorded separately for each study treatment.

- **AEs Leading to Death**: AEs leading to death (as recorded on the Adverse Events Details eCRF page, Change in grade and outcome = 'Fatal' or Grade = 'Grade 5 or death related to AE').

AEs will be summarized by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. In general, each participant will be counted only once within each PT or SOC.

AEs with missing classifications regarding relationship to study treatment, and those with start date on or after the start of study treatment, will be considered as related to the study treatment.

Incomplete AE-related dates will be handled as follows:

- If the onset date is missing completely or missing partially – but the onset month and year, or year, are equal to that of the study treatment start – then the onset date will be replaced by the minimum of the start of study treatment and the AE resolution date.
- In all other cases, the missing onset day or month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if only day is missing), if not resulting in a date later than the date of participant's death or database lock. In the latter case, the date of death or database lock will be used to complete the stop date.
- In all other cases the incomplete stop date will not be imputed. If the stop date of an AE is after the date of database lock, the outcome of the AE is ongoing at study close.

All AE tables will be restricted to TEAEs only. The AE tables will include the number and percentage of participants with at least one TEAE, by MedDRA SOC and PT (both sorted alphabetically), unless otherwise stated.

15.1.1 All Adverse Events

All AEs will be tabulated in an overall summary table to include:

- Any TEAE
- TEAEs leading to death
- Serious TEAEs
- TEAEs, grade ≥ 3
- TEAEs leading to permanent treatment discontinuation
- TEAEs leading to dose reduction
- AESIs
- DLTs
- Related TEAEs
- Related TEAEs, grade ≥ 3
- Related serious TEAEs
- Related TEAEs leading to death
- Related TEAEs leading to permanent treatment discontinuation
- Related TEAEs leading to dose reduction
- Related AESIs

A listing of all AEs with TEAEs flagged will be provided. This listing will be sorted by participant. This listing will additionally contain SOC, PT, grade, SAE (yes/no), DLT (yes/no), AESI (yes/no), relatedness to study treatment (Avelumab [yes/no] / M6620 [yes/no] / Carboplatin [yes/no]), start date (+treatment day), stop date (+treatment day), grade, and outcome.

Additional TEAE summary tables include:

- TEAEs by SOC, PT, and worst grade
- Related TEAEs by SOC, PT, and worst grade
- Non-serious TEAEs with frequency ≥ 5% by SOC and PT (as per CT.gov requirement)

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Analysis sets: SAF

15.2.1 Deaths

A table for death events will be provided.

15.2.2 Serious Adverse Events

A table for SAEs will be provided.

15.2.3 Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be determined using the following information from the 'Adverse Events Details' eCRF page.

Categories that qualify the event:

- Infusion-related reactions / hypersensitivity
- irAEs / autoimmune disorders

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

A listing of the pharmacokinetic (PK) results will be provided.

17 References

There are no references.

ELECTRONIC SIGNATURES

Document: ctp-ms201943-0029-iap-v1-0

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	12-Dec-2019 23:38
PPD	Task Completed (Approval eSign): Approved	Business Approval	13-Dec-2019 15:57