A PHASE 1B/2 STUDY TO EVALUATE SAFETY AND CLINICAL ACTIVITY OF COMBINATIONS OF AVELUMAB, BINIMETINIB AND TALAZOPARIB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC RAS-MUTANT SOLID TUMORS

STATISTICAL ANALYSIS PLAN – B9991033

Compounds:	MSB0010718C MDV3800, BMN 673 MEK162
Compound Name:	Avelumab Talazoparib Binimetinib
Version:	3.0
Date:	13-Nov-2019

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991033 is based on the Protocol Amendment 3 dated 24-Sep-2019.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
3.0	13-Nov-2019	Updates were made to the title of the SAP and the following Sections of the SAP, as per Protocol Amendment 3. Section 2.1 "Study Objectives", Section 2.2 "Study Design", Section 3.2.3 "Pharmacokinetic endpoints", Section 3.3 "Exploratory Endpoints", Section 3.4 "Baseline variables" – treatment group definitions, Section 4.3 "Other Analysis Set", Section 5.1 "Hypotheses and Decision Rules", Section 5.2 "General Methods" – description of summary and tabulations, Section 6.2.3 "Pharmacokinetic endpoints", Section 6.2.4 "Population pharmacokinetic endpoints CCI [redacted] Section 6.4 "Subset Analyses", Section 6.5.3 "Study treatment compliance and exposure" – derivations for binimetinib, Appendix 4 "Detailed Dose Escalation/De-escalation Scheme for BLRM Design -per implementation of Protocol Amendment 3". In addition, the following changes were implemented. Section 2 "Introduction" – changed the primary analysis cut-off date from 18 months to 12 months after the last patient is randomized (for randomized cohorts) or receives the first dose of study treatment (for non-randomized cohorts). A 12-month minimum follow-up is deemed adequate for the primary assessment of the safety and efficacy of the experimental treatments for the target population in this study. Section 3.1 "Primary endpoint(s)" – added the definition of dose limiting toxicity before and after implementation of Protocol Amendment 3. Section 6.5.3 "Study treatment compliance and exposure"- removed summaries by cycle for avelumab. Section 6.6.1 "Adverse events" – removed summary of 'TEAEs Excluding SAEs, with frequency ≥ 5% in any treatment group by SOC and PT'. Section 6.6.7 "Electrocardiogram" – removed the derivation of QTcP as the number of patients in each of the doublet and triplet combinations is too small to enable the derivation. Appendix 1 "Immune-Related Adverse Events" – provided additional specifications for the programmatic selection of irAEs prior to adjudication. Minor editorial and consistency changes throughout the document.
2.0	09-May-2019	Section 2.1 "Study Objectives", CCI [redacted] Section 3.5.1 "Adverse events" – updated the definition of treatment-emergent adverse events. Section 5.1.2 "Decision rules" - clarified that all available data including in-trial doublet data and DLT-dose data from study B9991025, will be incorporated in the determination of the starting dose for the triplet; Section 5.2 "General Methods" - Table 6 updated and removed some pooled and by treatment group summaries. Section 6.2.2.2 "Duration of response" – added details regarding censoring for duration of response since "no adequate baseline assessment" which is used in

		censoring for PFS analyses is not applicable to analyses of duration of response for patients with objective response. Section 6.2.6 "Endpoints for immunogenicity data of avelumab" the analysis of efficacy by immunogenicity status was removed. Section 6.5.1.1 "Demographic characteristics": added 'multiracial' to the summary of race. Section 6.5.3.5 "Dose interruptions" - the counting of the number of dose interruption for oral drugs was updated since reasons for dose adjustment are not collected in the eCRF. Section 6.6 "Safety Summaries and Analyses" - subsection "Physical examination" was removed. Section 6.6.5.1 "Hematology and chemistry parameters" - added summary for patients with newly occurring or worsening laboratory abnormalities. Section 6.6.5.2 "Other laboratory parameters" - coagulation parameter prothrombin time (PT) was removed. Section 8 "References" – updated. Appendix 3 "Detailed Dose Escalation/De-escalation Scheme for BLRM Design" preliminary safety data for the Phase 1b portion of the B9991025 study was added. It was also clarified that the information from B9991025 study will be incorporated into the BLRM to guide the starting dose and dose finding for the triplet combination using direct down-weighting approach. Minor editorial and consistency changes throughout the document.
1.0	15-Jun-2018	Not applicable (N/A)

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991033. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, pharmacokinetics [PK], immunogenicity, and biomarker data). The primary analysis will include all data up to a cut-off date corresponding to 12 months after the last patient is randomized (for randomized cohorts) or receives the first dose of study treatment (for non-randomized cohorts). The final analysis of the data will be performed after last patient last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

Throughout this document 'start date' refers to date of randomization for randomized cohorts and first dose of study treatment for non-randomized cohorts.

2.1. Study Objectives

Primary Objective(s)

- Phase 1b: To assess the dose-limiting toxicity (DLT) rate of the doublet and triplet combinations in patients with mPDAC in order to determine the recommended Phase 2 dose (RP2D) for the combinations;

- Phase 2: To assess the objective response rate (ORR) of the doublet and triplet combinations based on the Investigator assessment per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) in patients with mPDAC, and other KRAS- or NRAS-mutant advanced solid tumors.

Secondary Objectives

- To assess the overall safety and tolerability of the doublet and triplet combinations;
- To characterize the PK of avelumab, binimetinib and talazoparib when given in combination;
- To evaluate the immunogenicity of avelumab when given in combination with the other study drugs;
- To assess the anti-tumor activity of the doublet and triplet combinations;
- To assess the correlation of anti-tumor activity of the doublet and triplet combinations with PD-L1 expression, DNA Damage Repair (DDR) gene alterations, and tumor mutational burden (TMB) in baseline tumor tissue.

Exploratory Objectives

[redacted]

2.2. Study Design

This is a Phase 1b/2, open label, multi-center study of combinations of avelumab, binimetinib and talazoparib in eligible adult patients with mPDAC (regardless of KRAS status), and other locally advanced or metastatic KRAS- or NRAS-mutant solid tumors.

Initially, this study examined avelumab given IV Q2W and binimetinib given twice daily (BID) on a continuous dosing schedule with the objective of identifying an RP2D for this doublet combination before proceeding to assess the triplet combination of avelumab, binimetinib on a continuous dosing schedule and talazoparib. Due to observed DLTs with continuous binimetinib dosing, the dosing schedule for binimetinib has been modified (Protocol Amendment 3) to an intermittent dosing schedule(s) which is expected to mitigate these potential toxicities.

Per Protocol Amendment 3, the study will include a sequential dose-finding phase (Phase 1b) for binimetinib in combination with talazoparib (doublet) and avelumab in combination with binimetinib and talazoparib (triplet) followed by Phase 2.

Approximately 122 patients will be enrolled into the study, including 52 patients in Phase 1b (inclusive of the 22 patients enrolled prior to implementation of Protocol Amendment 3) and 70 patients in Phase 2. The actual number of patients will depend on the number of DLT events, dose levels/cohorts and dosing schedules that are tested during Phase 1b.

Once Phase 1b is completed and the RP2Ds for the doublet and triplet combinations have been determined, Phase 2 will be initiated to evaluate the safety and anti-tumor activity of the RP2D for each combination. Up to 40 patients within mPDAC will be randomized in a 1:1 ratio to the doublet and the triplet combinations (ie, 20 patients per combination) to reduce potential treatment selection bias. In the case that an RP2D is determined for the doublet combination using more than 1 binimetinib dosing schedule (ie, Schedules 7d/7d and 5d/2d), only one will be chosen to be evaluated in Phase 2 on the basis of all available safety, PK and anti-tumor activity data.

In addition to the above mPDAC tumor cohorts, 30 patients with other locally advanced or metastatic KRAS- or NRAS-mutant solid tumors (such as NSCLC, CRC, melanoma and endometrial cancer) will be enrolled in a 'tumor agnostic' cohort to receive the triplet combination as this may provide clinical benefit to a broader population of patients than primarily planned for this study (ie, mPDAC).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- Phase 1b: DLT during the primary DLT evaluation period (Cycle 1).

  Prior to implementation of protocol amendment 3, in Phase 1b, any of the following AEs occurring in the first cycle of treatment (28 days) which are attributable to any or all study drugs administered in the combination will be classified as DLTs:

  - Hematologic:
    - Grade 4 neutropenia (absolute neutrophil count [ANC] $<500/mm^3$ or $<0.5 \times 10^9/L$) lasting >5 days.
    - Febrile neutropenia, defined as ANC $<1000/mm^3$ with a single temperature of >38.3°C (>101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
    - Neutropenic infection (ANC $<1,000/mm^3$ or $<1.0 \times 10^9/L$, and Grade >3 infection).
    - Grade ≥3 thrombocytopenia (platelet count $<50,000$ mm^3 or $<50.0 \times 10^9/L$) with bleeding.
    - Grade 4 thrombocytopenia (platelet count $<25,000/mm^3$ or $<25.0 \times 10^9/L$).

  - Grade 4 anemia (life-threatening consequences; urgent intervention indicated).

- Non-Hematologic:
  - Grade ≥3 toxicities of any duration except:
    - Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours;
    - Grade 3 fatigue lasting <5 days;
    - Grade 3 hypertension that can be controlled with medical therapy;
    - Grade 3 serum lipase and/or serum amylase ≤7 consecutive days without clinical signs or symptoms of pancreatitis;
    - Grade ≥3 laboratory abnormalities without a clinical correlate and that do not require medical intervention;
    - Grade ≥3 laboratory abnormalities that do not represent a clinically relevant shift from baseline;
    - Grade 3 endocrinopathies controlled with hormonal therapy.
  - CK elevation Grade ≥3 associated with an increase in creatinine ≥1.5 × the patient's baseline creatinine.
  - Grade 3 troponin increase associated with any sign of cardiac toxicity (as determined by a cardiac evaluation).
  - Potential Hy's Law cases defined as: ALT or AST >3 x upper limit of normal (ULN) if normal at baseline OR >3 x ULN and doubling the baseline (if >ULN at baseline) associated with total bilirubin >2 x ULN and an alkaline phosphatase <2 x ULN.
- Eye Disorders:
  - Retinopathy or retinal detachment Grade ≥3, confirmed by ophthalmic examination.
  - Retinal vascular disorder including RVO, confirmed by ophthalmic examination.
  - Any Grade 2 immune-related uveitis or eye pain or blurred vision or decreased visual acuity that does not improve to Grade 1 despite topical therapy OR requires systemic treatment.
  - Any other eye disorder Grade ≥3 for >21 consecutive days.
  - Any other eye disorder Grade 4 confirmed by ophthalmic examination.
- Cardiac Disorders
  - Absolute decrease of left ventricular ejection fraction (LVEF) >10% compared to baseline and the LVEF is below the institution's lower limit of normal (LLN).
  - Symptomatic left ventricular systolic dysfunction Grade ≥3.
  - Other cardiac disorders Grade ≥3.

- Respiratory Disorders:
  - Interstitial lung disease/pneumonitis Grade ≥2.
  - Bronchospasm Grade 3.
- Skin and Subcutaneous Tissue Disorders:
  - Rash, hand foot skin reaction (HFSR), or photosensitivity CTCAE Grade 3 for >14 consecutive days despite maximal skin toxicity treatment (as per local practice).
  - Grade 3 rash that does not improve to Grade 1 within 14 days, limits self-care, or which is associated with infection.
  - Rash, HFSR, or photosensitivity CTCAE Grade 4.
- Non-Adherence to Treatment Schedule:
  - Failure to deliver at least 75% of the planned doses of any study drug during the first cycle of treatment due to treatment-related toxicities.
- Dose Reductions:
  - Any AE that results in a dose reduction of talazoparib or binimetinib during the first cycle of treatment.

Per protocol amendment 3, in Phase 1b, any of the following AEs occurring in the first cycle of treatment (28 days) which are attributable to any or all study drugs administered in the combination will be classified as DLTs:

- Hematologic
  - Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 or <0.5 x 10^9/L) lasting >5 days.
  - Febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3°C (>101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
  - Neutropenic infection (ANC <1,000/mm3 or <1.0 x 10^9/L, and Grade >3 infection).
  - Grade ≥3 thrombocytopenia (platelet count <50,000 mm^3 or <50.0 × 10^9/L) with bleeding.
  - Grade 4 thrombocytopenia (platelet count <25,000/mm^3 or <25.0 x 10^9/L).
  - Grade 4 anemia (life-threatening consequences; urgent intervention indicated).
- Non-Hematologic
  - Grade ≥3 toxicities of any duration except:
    - Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours;

- Grade 3 fatigue lasting <5 days;
- Grade 3 hypertension that can be controlled to Grade ≤2 within ≤14 days with or without ongoing medical therapy;
- Grade 3 serum lipase and/or serum amylase without clinical signs or symptoms of pancreatitis;
- Grade ≥3 laboratory abnormalities without a clinical correlate and that do not require medical intervention;
- Grade ≥3 laboratory abnormalities that do not represent a clinically relevant shift from baseline;
- Grade 3 endocrinopathies controlled with hormonal therapy.

  - CK elevation Grade ≥3 associated with an increase in creatinine ≥1.5 × the patient's baseline creatinine.
  - Grade 3 troponin increase associated with any sign of cardiac toxicity (as determined by a cardiac evaluation).
  - Potential Hy's Law cases defined as: ALT or AST >3 x upper limit of normal (ULN) if normal at baseline OR >3 x ULN and doubling the baseline (if >ULN at baseline) associated with total bilirubin >2 x ULN and an alkaline phosphatase <2 x ULN.

- Eye Disorders
  - Retinopathy or retinal detachment Grade ≥3, confirmed by ophthalmic examination.
  - Retinal vascular disorder including RVO, confirmed by ophthalmic examination.
  - Any Grade ≥3 uveitis, blurred vision, flashing lights, or floaters.
  - Any other eye disorder Grade ≥3 for >21 consecutive days.
  - Any other eye disorder Grade 4 confirmed by ophthalmic examination.
- Cardiac Disorders
  - Absolute decrease of left ventricular ejection fraction (LVEF) >10% compared to baseline and the LVEF is below the institution's lower limit of normal (LLN).
  - Symptomatic left ventricular systolic dysfunction Grade ≥3.
  - Other cardiac disorders Grade ≥3.
- Respiratory Disorders
  - Interstitial lung disease/pneumonitis Grade ≥2.
  - Bronchospasm Grade 3.
- Skin and Subcutaneous Tissue Disorders

- Rash, hand foot skin reaction (HFSR), or photosensitivity CTCAE Grade 3 for >14 consecutive days despite maximal skin toxicity treatment (as per local practice).
- Rash, HFSR, or photosensitivity CTCAE Grade 4.

- Non-Adherence to Treatment Schedule
  - Failure to deliver at least 75% of the planned doses of any study drug during the first cycle of treatment due to treatment-related toxicities.
- Dose Reductions
  - Any AE that results in a dose reduction of talazoparib or binimetinib during the first cycle of treatment.

While the rules for adjudicating DLTs in the context of Phase 1b are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT following assessment, based on the emerging safety profile for the combinations.

- Phase 2: Confirmed objective response (OR) based on Investigator assessment per RECIST v1.1.

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the 'start date' until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- Adverse Events (AEs) as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03), timing, seriousness, and relationship to study treatment;

  AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v4.03) and timing.

3.2.2. Efficacy endpoints

- Phase 1b: Confirmed OR based on Investigator assessment per RECIST v1.1;
- Time to tumor response (TTR), duration of response (DR), and PFS based on Investigator assessment per RECIST v1.1, and overall survival (OS);

  DR is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause.

TTR is defined, for patients with an OR, as the time from the 'start date' to the first documentation of objective response (CR or PR) which is subsequently confirmed.

PFS is defined as the time from the 'start date' to the date of the first documentation of PD or death due to any cause, whichever occurs first.

OS is defined as the time from the 'start date' to the date of death due to any cause.

3.2.3. Pharmacokinetic endpoints

- PK parameters, ie, concentration at the end of the dosing interval (C_{trough}) for avelumab, binimetinib and talazoparib, and maximum plasma concentration (C_{max}) for avelumab and binimetinib, at various cycles.

  Pharmacokinetic parameters C_{max} and C_{trough} for avelumab and binimetinib, and C_{trough} for talazoparib will be reported at steady state. Other parameters will be evaluated include T_{max} for avelumab and binimetinib may include dose normalized parameters (C_{max} and/or C_{trough}) for binimetinib and talazoparib.

  For avelumab, the difference of actual time of end of infusion (EOI) captured in the eCRF relative to start of the infusion (T_{EOI}), the difference of actual PK sampling time relative to the start of infusion (T_{max}) will be reported.

  For avelumab, talazoparib and binimetinib, the post-dose concentration value and its actual time relative to the last dose prior to the sampling (T_{trough}) will also be reported.

Table 2. PK Parameters to be Determined for Avelumab, talazoparib, and/or binimetinib (as applicable)

Parameter	Definition	Method of Determination
C_{max} for avelumab and binimetinib	Maximum observed plasma concentration	Observed directly from data
T_{max} for avelumab and binimetinib	Time for C_{max}	Observed directly from data as time of first occurrence
T_{EOI} for avelumab	Time difference between actual end of infusion and the start of infusion	Observed directly from data
C_{trough} for avelumab, binimetinib, and talazoparib	Pre-dose concentration during multiple dosing	Observed directly from data
T_{trough} for avelumab, binimetinib and talazoparib	Time difference between PK sampling time and dosing time of last dose prior to the sampling	Observed directly from data
C_{max} (dn) for binimetinib	Dose normalized C_{max}	C_{max} / Dose
C_{trough} (dn) for binimetinib and/or talazoparib	Dose normalized C_{trough}	C_{trough} / Dose

3.2.4. Immunogenicity endpoints

- Avelumab anti-drug antibody (ADA) levels and neutralizing antibodies (nAb) against avelumab.

3.2.5. Biomarker endpoints

- PD-L1 expression level, DNA Damage Repair (DDR) gene alterations, and tumor mutational burden (TMB) in baseline tumor tissue.

Table 3. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression level in baseline tumor tissue	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and inflammatory cells in regions of interest	Pathologist, assisted by image analysis.
Genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue	Quantitation of genomic scarring in the form of loss of heterozygosity; The number of somatic and germline mutations present in a panel of genes associated with DDR in baseline tumor derived nucleic acid, in germline nucleic acid and in circulating tumor DNA.	Next generation sequencing followed by computational analysis.
Tumor mutational burden	Determination/estimation of the frequency of mutations (total and non-synonymous) present in baseline tumor derived nucleic acid samples and in baseline circulating tumor DNA	Whole exome or genome sequencing and/or RNAseq

3.3. Exploratory Endpoints

[redacted]

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to avelumab or talazoparib or binimetinib and '**study treatment**' (or '**treatment group**') refers to one of the treatments in Table 4.

Table 4. Treatment Groups

Phase	Treatment groups (Dose Level)	Avelumab (mg Q2W IV)	Binimetinib (mg BID PO)	Talazoparib (mg QD PO)
1b	D0	800	45 (continuous)	N/A
1b	D-1	800	30 (continuous)	N/A
1b	BT1	N/A	45 (7d/7d)	1.0
1b	BT0	N/A	45 (7d/7d)	0.75
1b	BT-1	N/A	45 (7d/7d)	0.5
1b	BT-2	N/A	30 (7d/7d)	1.0
1b	BT-3	N/A	30 (7d/7d)	0.75
1b	BT-4	N/A	30 (7d/7d)	0.5
1b	BT2-1	N/A	30 (5d/2d)	0.5
1b	BT2-2	N/A	30 (5d/2d)	0.75
1b	BT2-3	N/A	30 (5d/2d)	1.0
1b	BT2-4	N/A	45 (5d/2d)	0.5
1b	BT2-5	N/A	45 (5d/2d)	0.75
1b	BT2-6	N/A	45 (5d/2d)	1.0
1b	ABT1	800	30 (7d/7d)	0.5
1b	ABT2	800	30 (7d/7d)	0.75
1b	ABT3	800	30 (7d/7d)	1.0
1b	ABT4	800	45 (7d/7d)	0.5
1b	ABT5	800	45 (7d/7d)	0.75
1b	ABT6	800	45 (7d/7d)	1.0
2	BT:mPADC	N/A	RP2D (for doublet)	RP2D (for doublet)
2	ABT:mPADC	800	RP2D (for triplet)	RP2D (for triplet)
2	ABT:tumor agnostic	800	RP2D (for triplet)	RP2D (for triplet)

7d/7d=7 days on/7 days off; 5d/2d=5 days on/2 days off.
N/A = not applicable.

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

Definition of baseline for efficacy analyses in randomized cohorts

The last measurement prior to randomization will serve as the baseline measurement for efficacy analyses. If such a value is missing, the last measurement prior to the first dose of study treatment will be used as the baseline measurement except for analyses of tumor assessments data where the baseline assessment would be considered as missing.

Definition of baseline for immunogenicity analyses

The last available assessment prior to the start of treatment with avelumab is defined as 'baseline' result or 'baseline' assessment. If an assessment is planned to be performed prior to the first dose of avelumab in the protocol and the assessment is performed on the same day as the first dose of avelumab, it will be assumed that it was performed prior to avelumab administration, if assessment time point is not collected or is missing.

Definition of baseline for efficacy analyses in non-randomized cohorts and for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy (for non-randomized cohorts) analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs (at screening and pre-dose Cycle 1 Day 1) and Single ECGs (following start of study drug) are collected in the study. The baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. In the case of triplicate ECGs, the average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

3.4.2. Baseline characteristics

Baseline characteristics (including demographics, physical measurements, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are described in Appendix 1 and Appendix 2, respectively.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

For the Phase 1b cohorts and the non-randomized cohort in Phase 2: The FAS will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one treatment the patient will be classified according to the first study treatment received.

For the randomized cohorts in Phase 2: The full analysis set (FAS) will include all randomized patients. Patients will be classified according to the study treatment assigned at randomization.

4.2. Safety Analysis Set

For the Phase 1b cohorts and the non-randomized cohort in Phase 2: The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be

classified according to the study treatment actually received. If a patient receives more than one study treatment, the patient will be classified according to the first study treatment received. For these non-randomized cohorts of the study, the FAS and the safety analysis set are identical.

For the randomized cohorts in Phase 2: The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case patients will be classified according to the first study treatment received.

4.3. Other Analysis Set

4.3.1. DLT-evaluable set

The DLT-evaluable analysis set is a subset of the safety analysis set and includes all enrolled patients in Phase 1b who are eligible for the study, receive at least one dose of the combination treatment, and either experience DLT during the first cycle (28 days) of treatment, or complete the DLT observation period for the first cycle of treatment without DLT.

Patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of avelumab, binimetinib or talazoparib (if applicable) in Cycle 1 for reasons other than toxicity which are attributable to the investigational products are not evaluable for DLT.

4.3.2. Per-protocol analysis set for OR

Applicable to Phase 2 only. Per-protocol (PP) analysis set is a subset of the FAS and will include patients who do not meet any of the following criteria that could impact the primary objective of the Phase 2 of the study. Patients who meet any of the following criteria will be excluded from the PP analysis set:

- Patient did not receive at least one dose of the assigned study treatment.
- Patient without a tumor assessment >7 weeks after 'start date' (unless PD or death is observed before that time in which case the patient will not be excluded from the PP analysis set).
- Patient without measurable disease at baseline by Investigator.
- Baseline ECOG status ≥ 2.
- Patients did not meet inclusion criteria 1, 2, or 3.

4.3.3. PK analysis sets

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one concentration measurement for avelumab, talazoparib or binimetinib.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least one of the PK parameters of interest for avelumab, talazoparib or binimetinib.

4.3.4. Biomarker analysis set

The biomarker analysis set is a subset of the safety analysis set and will include patients who have at least one baseline biomarker assessment.

Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

4.3.5. Immunogenicity analysis set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least one ADA/nAb assessment for avelumab.

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[redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

There is no formal hypothesis testing in this study.

During the Phase 1b dose finding, prior to implementation of Protocol Amendment 3, it was estimated that approximately up to 12 and 15 patients would be enrolled and assigned to treatment with the doublet and the triplet combinations, respectively. Per Protocol Amendment 3, it is estimated that approximately up to 18 and 12 patients will be enrolled and assigned to treatment with the doublet and the triplet combinations, respectively (in addition to the 22 patients previously enrolled during Phase 1b prior to implementation of Protocol Amendment 3). Each combination will include at least 6 patients treated at the MTD as described in Section 2.2 and at least 9 patients at the RP2D. The actual number of patients will depend on the number of DLT events and dose levels/cohorts and dosing schedules that are tested.

In Phase 2, the primary objective is to assess the ORR of the doublet and the triplet combinations.

For patients with mPDAC, with 20 treated patients per treatment group (doublet and triplet combinations), ORR can be estimated with a maximum standard error of 0.112. For patients in the 'tumor agnostic' cohort of the triplet combination, ORR can be estimated with a maximum standard error of 0.091 with 30 treated patients.

Further, assuming a beta-binomial distribution for the ORR and a beta (0.5, 0.5) prior,

- mPDAC cohort treated with the doublet combination at the RP2D: if 5 responders (out of 20 patients, ORR of 25%) are observed, the posterior probability of a true ORR ≥15% (considered a clinically relevant effect) will be ≥80% (89.0%).
- mPDAC cohort treated with the triplet combination at the RP2D: if 7 responders (out of 20 patients, ORR of 35%) are observed, the posterior probability of a true response rate ≥25% (considered a clinically relevant effect) will be ≥80% (84.9%).
- 'Tumor agnostic' KRAS- or NRAS -mutant solid tumor cohort treated with the triplet combination at the RP2D: if 12 responders (out of 30 patients, ORR of 40%) are observed, the posterior probability of a true ORR ≥30% (considered a clinically relevant effect) will be ≥80% (88.2%).

The determination of what constitutes a clinically meaningful response rate was based upon a review of historical ORR data for clinical studies in mPDAC, second line NSCLC, and CRC[5,11].

5.1.2. Decision rules

Identification of a recommended Phase 2 dose

The dosing decision and estimation of the MTDs of the doublet and the triplet combinations will be guided by the estimation of the probability of DLT in Cycle 1. However, other evidence such as safety data beyond DLT, clinical activity, PK, and PD data will play an important role in the final decision. A RP2D below the MTD may be determined based on these considerations.

Prior to implementation of Protocol Amendment 3, the doublet of avelumab in combination with binimetinib on continuous dose schedule was evaluated to determine the RP2D.

Per Protocol Amendment 3, the doublet combination of binimetinib on intermittent 7d/7d dosing schedule and talazoparib will be evaluated to determine the RP2D. Upon the completion of the dose finding for the doublet combination, the triplet combination will then be evaluated to determine the triplet RP2D.

Bayesian adaptive approach

The dose finding in the Phase 1b of the study will be guided by a Bayesian analysis of Cycle 1 DLTs in DLT-evaluable patients (Neuenschwander et al. 2014)[13].

A. Doublet combination model:

Prior to implementation of Protocol Amendment 3, the Bayesian model for the doublet combination of avelumab and binimetinib consists of three parts, representing:

- Single-agent avelumab toxicity
- Single-agent binimetinib toxicity
- Interaction between avelumab and binimetinib

Per Protocol Amendment 3, the Bayesian model for the doublet combination of talazoparib and binimetinib consists of three parts, representing:

- Single-agent talazoparib toxicity;
- Single-agent binimetinib toxicity;
- Interaction between talazoparib and binimetinib.

B. Triplet combination model:

For the triplet combination of avelumab, binimetinib, and talazoparib, the Bayesian model consists of seven parts, representing:

- Single-agent talazoparib toxicity
- Single-agent binimetinib toxicity
- Single-agent avelumab toxicity
- Interaction between binimetinib and talazoparib
- Interaction between talazoparib and avelumab
- Interaction between binimetinib and avelumab
- Triple interaction among binimetinib, talazoparib, and avelumab

Single-agent toxicities are modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two/three single-agent toxicities, and interaction is accounted for by adjusting these odds with an additional model parameter (odds multiplier). Details of the model are given in Appendix 3 (prior to implementation of Protocol Amendment 3) and Appendix 4 (per Protocol Amendment 3).

Assessment of patient risk

After each cohort of patients completes the DLT evaluation period, the posterior distribution for the risk of DLT for different dose combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

- Underdosing: [0, 0.16)
- Target toxicity: [0.16, 0.33)
- Excessive toxicity: [0.33, 1]

The EWOC principle

Dosing decisions are guided by the EWOC principle (Babb et al. 1998)[1]. A combination dose may only be used for the next cohort of patients if the risk of excessive toxicity ([0.33, 1]) at that combination dose is less than 0.25.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (Neuenschwander et al. 2010[12]; Neuenschwander et al. 2014[13]; Spiegelhalter et al. 2004[14]). MAP priors are derived using Bayesian hierarchical models, which take into account possible differences between the studies.

A full description of the application of the MAP approach to derive the prior distributions of the single-agent model parameters is given in Appendix 3 (prior to implementation of Protocol Amendment 3) and Appendix 4 (per Protocol Amendment 3).

The prior distribution for the interaction parameters (doublet and triplet combinations) were based on the prior understanding of possible drug safety interactions. This prior allows for the possibility of either synergistic or antagonistic interaction and is fully described in Appendix 3 (prior to implementation of Protocol Amendment 3) and Appendix 4 (per Protocol Amendment 3).

Starting dose levels

Prior to implementation of Protocol Amendment 3, the starting dose for the doublet combination was D0 (800 mg avelumab IV Q2W and 45 mg binimetinib orally twice daily continuous dosing). For this dose the prior risk of excessive toxicity was 0.1, which satisfied the EWOC criterion.

Per Protocol Amendment 3, the starting dose for the doublet combination is 0.75 mg talazoparib orally once daily, and 45 mg binimetinib orally twice daily, 7 days on, 7 days off (Schedule 7d/7d). For this dose the prior risk of excessive toxicity is 0.189, which satisfies the EWOC criterion.

The starting dose for the triplet combination will be determined after completion of the dose finding for the doublet combination.

A full assessment of the prior risk to patients is given in Appendix 3 (prior to implementation of Protocol Amendment 3) and Appendix 4 (per Protocol Amendment 3).

5.2. General Methods

The definition of 'treatment group' in this study is provided in Table 4.

Table 5 provides an overview of the summaries and the tabulations for this study.

Table 5. Study Summaries and Tabulations

Summaries	Analysis Sets	Phase 1b	Phase 2	Phase 1b and Phase 2 combined
Baseline characteristics	FAS	- by treatment group - pooled: D0+D-1 - pooled: BT doublet (7d/7d) - pooled: BT doublet (5d/2d) - pooled: ABT triplet - pooled: all patients in avelumab containing treatment groups	- by treatment group - pooled ABT:mPADC and ABT:tumor agnostic	- pooled: all doublet at the RP2D - pooled: all triplet at the RP2D -pooled: all patients in avelumab containing treatment groups
Disposition	FAS	- by treatment group - pooled: D0+D-1 - pooled: BT doublet (7d/7d) - pooled: BT doublet (5d/2d) - pooled: ABT triplet	- by treatment group - ABT:mPADC and ABT:tumor agnostic	Not Done
DLTs	DLT-evaluable set	- by treatment group - pooled: D0+D-1 - pooled: BT doublet (7d/7d) - pooled: BT doublet (5d/2d) - pooled: ABT triplet	Not Done	Not Done
Efficacy data	FAS, Per-protocol analysis set[a]	- by treatment group - pooled: D0+D-1 - pooled: BT doublet (7d/7d) - pooled: BT doublet (5d/2d) - pooled: ABT triple	- by treatment group	Not Done
Other safety data, exposure data, concomitant medications, non-drug treatment	Safety analysis set	- by treatment group - pooled: D0+D-1 - pooled: BT doublet (7d/7d) - pooled: BT doublet (5d/2d) - pooled: ABT triplet	- by treatment group - ABT:mPADC and ABT:tumor agnostic	- pooled: all doublet at the RP2D - pooled: all triplet at the RP2D

PK data for avelumab	PK analysis set	- by treatment group (for avelumab containing treatment groups only) - pooled: D0+D-1 - pooled: ABT triplet - pooled: all patients in avelumab containing treatment groups [b]	- by treatment group - ABT:mPADC and ABT:tumor agnostic	-pooled: all patients in avelumab containing treatment groups [b]
PK data for talazoparib	PK analysis set	- by treatment group (for talazoparib containing treatment groups only)	- by treatment group (for talazoparib containing treatment groups) - ABT:mPADC and ABT:tumor agnostic	- pooled: all doublet at the RP2D - pooled: all triplet at the RP2D
PK data for binimetinib	PK analysis set	- by treatment group	- by treatment group - ABT:mPADC and ABT:tumor agnostic	- pooled: all doublet at the RP2D - pooled: all triplet at the RP2D
Biomarker data	Biomarker analysis set	Not Done	- by treatment group	Not Done
Immunogenicity data	Immunogenicity analysis set	- by treatment group (for avelumab containing treatment groups only) - pooled: D0+D-1 - pooled: ABT triplet - pooled: all patients in avelumab containing treatment groups	- by treatment group (for avelumab containing treatment groups only) - ABT:mPADC and ABT:tumor agnostic	-pooled: all patients in avelumab containing treatment groups

[a] Per-protocol analysis set is used only for the analysis of OR in Phase 2;

[b] Pool all patients only if no evidence of impact of binimetinib or talazoparib on avelumab exposure; RP2D=recommended phase 2 dose

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing,

the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Cancer Therapy' eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment for non-randomized cohorts or after the date of randomization for randomized cohorts amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'On-Study Anti-Cancer Surgery', and 'Follow-up Anti-Cancer Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'On-Study Anti-Cancer Surgery', and 'Follow-up Anti-Cancer Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)

- In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including enrollment date. In this study, the date of treatment assignment will be considered the "date of enrollment", Investigational product administration should begin within 3 days after enrollment.

- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics may not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter is missing, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.

- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. Date of last contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Last date of contact collected on the 'Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Randomization date

- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

5.3.3.3. Tumor assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment. If the imputation results in an end date prior to the imputed start date then the imputed start date should be set to the end date.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

    IF

    YYYY = Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM < Month of min [max (PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY;

    ELSE IF

    YYYY = Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max (PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = min [max (PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max (PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b

6.1.1.1. Primary analysis

The following analyses will be based on the DLT-evaluable set for patients in the Phase 1b. DLTs will be listed and summarized as shown in Table 5.

The posterior distribution of DLT rate (posterior probabilities that DLT rate is in the intervals of underdosing (<0.16), target toxicity (≥0.16 and <0.33) and overdosing (≥0.33) at the end of Phase 1b will be provided as shown in Table 5.

6.1.2. Objective response as assessed by the Investigator per RECIST v1.1

6.1.2.1. Primary analysis

The following analyses will be based on the FAS as shown in Table 5. Assessment of response will be made using RECIST v1.1 based on investigator assessment.

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the 'start date' until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the 'start date' and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the 'start date' and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the 'start date' (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. 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.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR will also be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of patients with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), PD, and NE will be tabulated. Patients with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the 'start date' without further evaluable tumor assessments)
- PD too late (>12 weeks after the 'start date')

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (ie, SD of insufficient duration).

6.1.2.2. Sensitivity analysis for ORR

Sensitivity analysis for ORR (Phase 2 only) will be performed using the methodology described in Section 6.1.2.1 based on the per-protocol analysis set.

6.2. Secondary Endpoints

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The OR for Phase 1b will be summarized using the methodology described in Section 6.1.2.1, as shown in Table 5.

The following analyses will be based on the FAS as shown in Table 5.

Assessment of response will be made using RECIST v1.1. Tumor-related endpoints will be analyzed based on investigator assessment.

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. Duration of response

Duration of Response (DR) is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 6.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Table 6. Outcome and Event Dates for DR Analyses

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the 'start date'	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the 'start date'; if the criteria were met the censoring will be on the 'start date'.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rates at 2, 4, 6, 8, 10, and 12 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[3] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[9] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 7 following the hierarchy shown.

Table 7. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments/'start date'	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments

The DR time or censoring time and the reasons for censoring will also be presented in a patient listing.

6.2.2.3. Time to response

Time to response (TTR) is defined, for patients with OR, as the time from the 'start date' to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR (in months) = [first date of OR – 'start date' +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.4. Progression-free survival

Progression-Free Survival (PFS) is defined as the time from the 'start date' to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the 'start date' unless death occurred on or before the time of the second planned tumor assessment (ie ≤ 16 weeks after the 'start date') in which case the death will be considered an event.

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks (± 7 days) for 52 weeks from the 'start date', and then every 16 weeks (± 7 days) thereafter until PD regardless of initiation of subsequent anti-cancer therapy.

The censoring and event date options to be considered for the PFS analysis are presented in Table 8.

PFS (months) = [date of event or censoring– 'start date' +1]/30.4375

Table 8. Outcome and Event Dates for PFS Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	'Start date' [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the 'start date'	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤16 weeks after the 'start date' and did not initiate new anti-cancer therapy, the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the 'start date'; if the criteria were met the censoring will be on the 'start date'

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rates at 2, 4, 6, 8, 10, 12, 16, and 20 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[3] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[9] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented. Reasons for censoring will be summarized according to the categories in Table 9 following the hierarchy shown.

Table 9. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/'start date'	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for PFS

A plot will be generated to compare planned and actual relative day of tumor assessments. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median time of follow-up for PFS with 2-sided 95% CIs. In particular, the rates at 2, 4, 6, 8, 10, 12, 16, and 20 months will be estimated with corresponding 2-sided 95% CIs.

6.2.2.5. Overall Survival

Overall survival (OS) is defined as the time from the 'start date' to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– 'start date' +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rates at 2, 4, 6, 8, 10, 12, 16, 20, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[3] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[9] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 14 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median time of follow-up for OS with 2-sided 95% CIs. In particular, the rates at 2, 4, 6, 8, 10, 12, 16, 20, and 24 months will be estimated with corresponding 2-sided 95% CIs.

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK analyses set as shown in Table 5.

C_{trough}, C_{max}, T_{max}, defined in Section 3.2.3 for avelumab and binimetinib, T_{EOI} for avelumab, C_{trough} and the time relative to the previous dosing time (T_{trough}) for avelumab, binimetinib and talazoparib will be reported. Dose normalized parameter C_{trough}(dn) for binimetinib and talazoparib will be reported as appropriate.

Pharmacokinetic parameters for avelumab, binimetinib and talazoparib will be taken from observed values.

Presentation of pharmacokinetic data will include:

- Pharmacokinetic parameters will be listed and summarized by cycle and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI). For T_{max}, the range (min, max) will also be provided. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. For talazoparib and binimetinib, if an intra-patient dose escalation or reduction occurs, dose-dependent PK parameter C_{trough} for that

patient may be dose-normalized or may only be included in descriptive statistics and summary plots up to the time of the dose change.

- Box plots for C_{trough} and C_{max} for avelumab and binimetinib (C_{max} is not available for D0 and D-1), C_{trough} for talazoparib will be generated by dose, cycle, and study day and may be separated by treatment group or combination. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment group has limited evaluable PK data (n<4), matchstick plots showing changes in C_{max} for avelumab and C_{trough} for each drug in individual patients will then be generated.
- For C_{trough} of binimetinib and talazoparib in Phase 2, an arithmetic mean of the C_{trough} across all PK samples collected at different cycles and days within each patient may be calculated (only 1 value per patient) and the descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and associated CV% and 95% CI) of the individual arithmetic mean would be summarized as shown in Table 5 and/or presented in box plot accordingly.
- PK parameters of avelumab, binimetinib, and talazoparib from this study may be compared with the historical PK parameters when avelumab, binimetinib or talazoparib were administered as single agents.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies investigating avelumab, binimetinib or talazoparib to : 1) further assess the effect of binimetinib with or without avelumab on the PK of talazoparib, 2) assess the effect of talazoparib with or without avelumab on the PK of binimetinib, and 3) assess the effect of talazoparib and/or binimetinib on the PK of avelumab, and 4) explore any association between avelumab, binimetinib and/or talazoparib exposure and biomarkers or significant safety/efficacy endpoints. If performed, the details of these analyses will be outlined in a separate pharmacometrics analysis plan (PMAP). The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker endpoints

Secondary biomarker endpoints include PD-L1 expression level, DDR gene alterations, and TMB in baseline tumor tissue.

Biomarker data will be analyzed based on the biomarker analysis sets as defined in Section 4.3.4. Data will be summarized as shown in Table 5.

Biomarkers values at screening will be listed and summarized.

For PD-L1 expression, patients will be classified as positive or negative according to scoring algorithms and cut-offs established from internal or external sources. For continuous measurement biomarker results, summary statistics (eg, the mean, standard deviation, median, percent of coefficient of variation, and minimum/maximum levels) will be determined at baseline and on-treatment/end of treatment time points, as appropriate.

Change from baseline measurements will be provided, as appropriate.

For discrete measurement biomarker results (eg, tumor marker status), frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/end of treatment time points. Shift tables may also be provided.

For genomic scarring, as measured by loss of heterozygosity score, for the total number of DDR gene mutations and for the number of mutations in DDR genes, patients may be classified as positive, negative, or some other category according to scoring algorithms and cut-offs established from external sources. If no external standards exist, patients may be stratified using the median, quartiles and tertiles. For example, patients will be classified as positive if they have a mutation in any one of the assessed DDR genes and will otherwise be classified as negative. The number and percentage of patients in each category will be tabulated.

BOR will be summarized and for each category following the methodology outlined in Section 6.1.2.1. The number of responders (patients with BOR of CR or PR) will be tabulated relative to biomarker classifications using a contingency table.

6.2.6. Endpoints for immunogenicity data of avelumab

All analyses described below are performed as shown in Table 5.

Blood samples for avelumab immunogenicity testing will be collected pre-dose on Day 1 and Day 15 of Cycle 1 and Cycle 2; on Day 1 of Cycles 3, 5, 9, and 12.

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb. The analyses of nAb data described in the following sections will only be conducted contingent upon data availability at the time of reporting.

Patients will be characterized into different ADA categories based on the criteria defined in Table 11.

Table 11. Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
ADA never-positive	No positive ADA results at any time point; ADA-negative patients (titer < cutpoint)	Number of patients with at least one valid ADA result at any time point
ADA ever-positive	At least one positive ADA result at any time point; ADA-positive patients (titer ≥ cutpoint)	Number of patients with at least one valid ADA result at any time point
Baseline ADA positive	A positive ADA result at baseline	Number of patients with valid baseline ADA result
Treatment-boosted ADA	A positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab	Number of patients with valid baseline ADA results and at least one valid post-baseline ADA result
Treatment-induced ADA	Patient is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if patient does not have a baseline sample, the patient has at least one positive post-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Transient ADA response	If patients with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive.	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent ADA response	If patients with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)

ADA: anti-drug antibody, NR = not reportable.

Patients will be characterized into different nAb categories based on the criteria in Table 12. For nAb, treatment-boosted is not applicable since no titer result is available.

Table 12. Patients Characterized Based on Neutralizing Antibody Results (nAb Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
nAb never-positive	No positive nAb results at any time point	Number of patients with at least one valid ADA result at any time point
nAb ever-positive	At least one positive nAb result at any time point	Number of patients with at least one valid ADA result at any time point
Baseline nAb positive	A positive nAb result at baseline	Number of patients with valid baseline ADA result
Treatment-induced nAb	Patient is not nAb positive at baseline and has at least one positive post-baseline nAb result; or if patient does not have a baseline sample, the patient has at least one positive post-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)
Transient nAb response	If patients with treatment-induced nAb have (a single positive nAb result or duration between first and last positive result <16 weeks) and nAb result at the last assessment is not positive.	Number of patients with at least one ADA valid post-baseline result and without positive baseline nAb result (including missing, NR)
Persistent nAb response	If patients with treatment-induced nAb have duration between first and last positive nAb result ≥16 weeks or a positive nAb result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)

ADA = antidrug antibody, nAb = neutralizing antibody, NR = no result.

The number and percentage of patients in each ADA and nAb category will be summarized.

6.2.6.1. Time to and Duration of ADA and nAb response

The ADA and nAb analyses described below will include patients with treatment-induced ADA or nAb, respectively.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of avelumab + 1)/7.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- the last ADA assessment is positive AND patient is ongoing treatment with avelumab, or

- the last ADA assessment is positive AND patient discontinued treatment with avelumab AND the last planned ADA assessment (day 30 follow-up visit) is after the cut-off date.

Time to nAb response and duration of nAb response are defined similarly based on first and last positive nAb result.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median ADA response time with 2-sided 95% CIs. ADA response rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[3] and the CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[9] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Duration of ADA response will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with ADA response is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided

As data permit, the analyses described above will be repeated for patients with treatment-induced nAb.

6.2.6.2. ADA titer

For patients who are ADA ever positive, the maximum observed ADA titer for a patient will be summarized, overall and by ADA subcategories (baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, persistent ADA response) of patients having each discrete maximum titer value will be tabulated. The denominator to calculate the percentages will be the total number of patients in the associated ADA subcategory.

For patients with treatment-induced ADA, a cross tabulation of duration of ADA response and maximum ADA titer will be provided. The following categories for duration of ADA response will be used: ≤1, >1 to ≤3, >3 to ≤5, >5 to ≤7, >7 to ≤13, >13 to ≤16, >16 to ≤25, >25 weeks. In this categorization, the censoring in duration of ADA response is ignored.

6.2.6.3. Analysis of PK and safety by immunogenicity status

The following ADA and nAb status will be used for the analyses described below.

ADA

- ADA ever-positive versus ADA never-positive
- ADA: treatment-induced ADA versus ADA never-positive or baseline ADA positive

nAb

- nAb ever-positive versus nAb never-positive
- nAb: treatment-induced nAb versus nAb never-positive or baseline nAb positive

Data listings will include immunogenicity data together with relevant PK, and safety data.

PK parameters and immunogenicity status

The following analyses will include patients in both the immunogenicity analysis set and in the PK parameter analysis set. The PK endpoints pertinent to the immunogenicity analyses are C_{trough} and C_{max} for avelumab.

Blood samples for avelumab PK will be collected at pre-dose (within 1 hour prior to taking binimetinib/talazoparib dose) and at the end of infusion (within 10 minutes after the avelumab infusion ends) on Day 1, Day 7 and Day 15 of Cycle 1; Day 1 and Day 15 of Cycle 2; and Day 1 of Cycles 3, 5, 9 and 12.

C_{trough} and C_{max} for avelumab will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) and ADA status and presented via box plot.

Among patients with treatment-induced ADA, analyses will be conducted to assess whether C_{trough} and C_{max} have any changes before and after the first positive ADA assessment. To be included in this analysis, patients must have the same PK parameter available both before and after the first positive ADA assessment. Relative PK day will be calculated as:

(PK assessment nominal day) – (first positive ADA assessment nominal day).

Nominal day is the protocol scheduled timing for an assessment. For example, if C_{trough} is collected on Day 1 of Cycle 2 and the first positive ADA result is observed on Day 1 of Cycle 3, then the relative PK day for this C_{trough} is -28. Plots of mean and median for C_{trough} and C_{max} over relative PK day will be presented.

As data permit, the analyses described above will be repeated for nAb.

Safety and immunogenicity status

The following analyses will include patients in the immunogenicity analysis set.

The frequency (number and percentage) of patients with each of the following will be presented by ADA status.

- TEAEs, by SOC and PT
- TEAEs leading to dose reduction of avelumab, by SOC and PT

- TEAEs leading to discontinuation of avelumab, by SOC and PT
- TEAEs leading to discontinuation of study treatment by SOC and PT
- Grade ≥ 3 TEAEs, by SOC and PT
- SAEs, by SOC and PT
- IRRs, by PT

For patients who had at least one IRR and have treatment-induced ADA, time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be summarized taking into account whether the IRR occurred on or after the first ADA positive assessment or whether the IRR occurred before the first ADA positive assessment.

As data permit, the analyses described above will be repeated for nAb.

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[redacted]

[redacted]

6.4. Subset Analyses

Applicable to Phase 2 only. OR and DR (if meaningful) will be summarized in the following subsets:

- Separately for cohorts BT:mPADC, ABT:mPADC, and ABT:tumor agnostic
  - ECOG performance status at baseline: 0 vs ≥1
  - Number of prior anti-cancer drug therapy regimens for advanced disease: ≤1 vs ≥2
- Separately for Cohorts BT:mPADC and ABT:mPADC
  - Prior anti-cancer platinum-based regimen: Yes vs No
- For cohort ABT:tumor agnostic
  - By tumor type

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS as shown in Table 5.

6.5.1.1. Demographic characteristics

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

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiracial, Not Reported

- Ethnic origin:
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
- Age (years): summary statistics
- Age categories:
  - < 65 years, ≥ 65 years
  - < 65, 65-<75, 75-<85, ≥ 85 years
- Pooled Geographical Region (as applicable):
  - North America
  - Europe
  - Asia
  - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall randomized/treated population)
- Geographic Region (as applicable):
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australasia
  - Asia
  - Africa
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)

Center codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment group, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis', 'Substance Use' and RECIST eCRF pages will be summarized for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Time since initial diagnosis to 'start date' (months), defined as ('start date' – date of initial diagnosis)/30.4375

From the RECIST eCRF page:

- Measurable disease (lesions) at baseline (Yes, No, No disease)
- Involved tumor sites at baseline

From the 'Substance Use' eCRF page:

- Smoking history: Never smoker vs current vs former smoker

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' and 'Substance Use' eCRF pages) and derived variables as above.

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Anti-Cancer Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer therapy
- Patients with at least one prior anti-cancer drug therapy
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥4
- Prior anti-cancer immune therapy (including PD-1, PD-L1, anti-CTLA4, others)
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced – Metastatic, Local regional Disease-Recurrence
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drugs will also be summarized based on the number and percentage of patients by the drug class and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer therapies will be included in the listings that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies
- Listing of anti-cancer radiotherapy
- Listing of anti-cancer surgeries

6.5.2. Study conduct and patient disposition

The following analyses will be based on the FAS as shown in Table 5.

6.5.2.1. Patient disposition

The percentages below will be calculated based on the number of patients in the FAS as applicable.

For randomized cohorts

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to 'start date' overall and by the main reason for discontinuation
- Number and percentage of randomized patients in each of the analysis sets defined in Section 4
- Number and percentage of randomized patients with study drug ongoing (separately for each study drug administered in combination)

- Number and percentage of randomized patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in combination)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation

The results of the randomization algorithm (according to IRT) will be summarized as follows:

- Number and percentage of randomized patients overall, by region (Europe, North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of randomized patients by center
- Cross tabulation: patients randomized (doublet/triplet/none) vs. patients treated (doublet/triplet/none)

For non-randomized cohorts

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation
- Number and percentage of treated patients in each of the analysis sets defined in Section 4
- Number and percentage of patients with study drug ongoing (separately for each study drug administered in combination)
- Number and percentage of patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in combination)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation

In addition, the following will be summarized:

- Number and percentage of treated patients overall, by region (Europe, North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of treated patients by center

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of the study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria or meeting exclusion criteria.

- Patients who develop withdrawal criteria whilst on the study but are not withdrawn
- Patients who receive the wrong treatment or an incorrect dose
- Patients who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set as shown in Table 5.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is

- the earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the patient received study treatment on that visit (ie, any study drug with dose>0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- for the last cycle, actual cycle end date = actual cycle start date + 28 (in days) – 1 day

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (eg, infusion cyclical, oral daily).

The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

The derivations below are provided for the following study drugs (administered alone or in combination):

- Avelumab administered as a 1-hour IV infusion at a dose of 800 mg Q2W.
- Binimetinib: administered orally BID at a dose of 30 mg or 45 mg
  - Patients enrolled prior to implementation of Protocol Amendment 3 (treatment groups D0 and D-1): on continuous dosing schedule;
  - Per Protocol Amendment 3 (treatment groups other than D0 and D-1): administered on intermittent dosing schedule in accordance with the assigned intermittent dosing schedule (ie, Schedule 7d/7d or 5d/2d).
- Talazoparib administered orally QD at a dose of 0.5 mg, 0.75 mg, or 1 mg.

6.5.3.1. Exposure to avelumab

The dose level for avelumab is calculated as actual dose administered (mg).

Intended duration of treatment with avelumab (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 28 – 1

Duration of exposure to avelumab (weeks) =

(last dose date of avelumab – first dose date of avelumab + 14)/7

Cumulative dose is the sum of the actual doses of avelumab received.

Actual Dose Intensity (DI)

- Overall actual DI (mg /4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with avelumab (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg /4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [1600 (mg)] / [1 (4-week cycle)] = 1600 (mg /4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [1600 (mg /4-week cycle)]

6.5.3.2. Exposure to binimetinib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with binimetinib (weeks)= (end date – date of first dose of binimetinib +1)/7,

where end date = date of last dose of binimetinib.

Duration of exposure to binimetinib (weeks) =

(last dose date of binimetinib – first dose date of binimetinib + 1)/7

Cumulative dose is the sum of the actual doses of binimetinib received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of binimetinib to last dose of binimetinib]

  = 100 × [overall cumulative dose] / [7 ×2 × d × f × duration of exposure to binimetinib in weeks]

  where d=30 or 45 mg and

  - f=1 if treatment group is D0 or D-1 (patients enrolled prior to implementation of Protocol Amendment 3)
  - f=1/2 if binimetinib is administered on the 7d/7d dosing schedule
  - f=5/7 if binimetinib is administered on the 5d/2d dosing schedule

6.5.3.3. Exposure to talazoparib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with talazoparib (weeks)= (end date – date of first dose of talazoparib +1)/7,

where end date = date of last dose of talazoparib.

Duration of exposure to talazoparib (weeks) =

(last dose date of talazoparib – first dose date of talazoparib + 1)/7

Cumulative dose is the sum of the actual doses of talazoparib received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of study drug to last dose of study drug]

= 100 × [overall cumulative dose] / [7 × d × duration of exposure to talazoparib in weeks]

where d=0.5 mg, 0.75mg, or 1.0 mg.

6.5.3.4. Dose reductions

Applicable to avelumab. Dose reduction is defined as actual non-zero dose < 90% of the planned dose.

Applicable to binimetinib and talazoparib. Dose reduction is defined as a change to a non-zero dose level lower than that planned in the protocol.

The number and percentage of patients with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.3.5. Dose interruptions

Applicable to binimetinib and talazoparib.

An interruption is defined a 0 mg total daily dose of binimetinib within the dosing periods or talazoparib administered on one or more days. What follows defines how dose interruptions will be counted, for each of binimetinib and talazoparib separately, in the case of multiple dose interruptions. In what follows, d is a value > 0.

- If an interruption occurs consecutively for at least two days, then it will be counted only once (example: If the actual total daily dose on days 1-3 is d mg and actual dose on days 4-5 is 0 mg , then the total number of dose interruptions is 1).
- If an interruption occurs for more than one day, but the days are not consecutive, ie there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (example: If the actual dose on days 1, 3 and 5, is d mg and actual dose on days 2 and 4 is 0 mg, the total number of dose interruptions is 2).

A dose interruption is not considered a dose reduction.

The number and percentage of patients with dose interruptions will be summarized.

6.5.3.6. Dose delays

Applicable to avelumab only.

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

For Cycle 1 Dose 1:

Dose Delay (days) = day of the first day of study drug -1

After Cycle 1 Dose 1:

Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – Planned days between two consecutive doses = Date of Dose x – Date of Dose (x-1) – 14.

Dose delays will be grouped into the following categories:

- No delay
- 1-2 days delay
- 3-6 days delay
- 7 or more days delay

For example, for avelumab, administered on a 2-week schedule, if one patient receives avelumab on Day 1, then the next avelumab administration date will be on Day 15; however, if the patient receives avelumab at Day 16 or 17, this is considered as 1-2 days delay.

No delay and 1-2 days delay will also be summarized together.

The number and percentage of patients with delayed study drug administration and maximum length of delay, ie, the worst case of delay if patients have multiple dose delays will be summarized.

6.5.3.7. Infusion rate reductions

Applicable to avelumab only.

The number and percentage of patients with at least one infusion rate reduction of ≥50% compared to the first infusion rate reported in the eCRF as well as the frequency of patients with 1, 2, 3 or ≥4 infusion rate reductions of ≥50% will be summarized.

6.5.3.8. Infusion interruptions

Applicable to avelumab only.

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (ie, for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of patients with at least one infusion interruption as well as the frequency of patients with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set as shown in Table 5.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study drugs and pre-medications for study drug, which are started before the first dose of study treatment.

Prior and concomitant medications will be summarized from the 'Concomitant Medications' eCRF page. Pre-medications for study drug will also be summarized separately from the 'Pre-Medication Treatment' eCRF page.

Summary of prior medications, summary of concomitant medications and summary of pre-medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of prior medications and a listing of concomitant medications will be created with the relevant information collected on the 'General Concomitant Medications' eCRF page. A listing of pre-medications will be created with the relevant information collected on the 'Pre-Medication Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

6.5.5. Subsequent anti-cancer therapies

The following analyses will be based on the FAS as shown in Table 5.

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'On-study Anti-Cancer Surgery', and 'Follow-up Surgery' eCRF pages.

Number and percentage of patients with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Anti-Cancer Surgery' eCRF pages.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations.

Summaries of AEs and other safety parameters will be based on the safety analysis set as shown in Table 5.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan [SRP] and finalized for analysis of the current study data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs documented in the SRP and finalized for analysis of the current study data prior to DB lock.

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by primary SOC and PT in decreasing frequency.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to dose reduction of avelumab
  - TEAEs leading to dose reduction of binimetinib
  - TEAEs leading to dose reduction of talazoparib
  - TEAEs leading to interruption of avelumab
  - TEAES leading to interruption of binimetinib
  - TEAES leading to interruption of talazoparib
  - TEAEs leading to discontinuation of avelumab
  - TEAEs leading to discontinuation of binimetinib
  - TEAEs leading to discontinuation of talazoparib
  - TEAEs leading to discontinuation of any study drug
  - TEAEs leading to discontinuation of all study drugs
  - Related TEAEs leading to discontinuation of avelumab
  - Related TEAEs leading to discontinuation of binimetinib
  - Related TEAEs leading to discontinuation of talazoparib
  - Related TEAEs leading to discontinuation of any study drug

  - Related TEAEs leading to discontinuation of all study drugs
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
  - irAEs
  - IRRs
- TEAEs by SOC and PT and worst grade
- TEAEs related to avelumab by SOC and PT and worst grade
- TEAEs related to binimetinib by SOC and PT and worst grade
- TEAEs related to talazoparib by SOC and PT and worst grade
- TEAEs related to any study drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to dose reduction

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to dose reduction of each study drug:

- TEAEs leading to dose reduction of avelumab by SOC and PT
- TEAEs leading to dose reduction of binimetinib by SOC and PT
- TEAEs leading to dose reduction of talazoparib by SOC and PT

The listing of all AEs leading to dose reduction will also be provided with the relevant information.

6.6.1.3. Adverse events leading to interruption of study treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion (ie, did not lead to a dose reduction or a dose delay).

As such, AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted' excluding

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (ie IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay (as defined in Section 6.5.3.6). These IRRs will be considered as IRRs leading to interruption of infusion.

- IRRs occurring on the day after infusion and subsequent dose administration had no delay (as defined in Section 6.5.3.6).

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to interruption of each study drug:

- TEAEs leading to interruption of avelumab by SOC and PT
- TEAEs leading to interruption of binimetinib by SOC and PT
- TEAEs leading to interruption of talazoparib by SOC and PT

The listing of all AEs leading to interruption of study treatment will also be provided with the relevant information.

In addition, the frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to both interruption and dose reduction of each study drug:

- TEAEs leading to both interruption and dose reduction of avelumab by SOC and PT
- TEAEs leading to both interruption and dose reduction of binimetinib by SOC and PT
- TEAEs leading to both interruption and dose reduction of talazoparib by SOC and PT

This summary will take into account PTs with both actions as defined in Section 6.6.1, even though the actions may be captured for different PT records (ie, different onset for the PT with action "drug interrupted" and the PT with action "dose reduced".

6.6.1.4. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment:

- TEAEs leading to discontinuation of avelumab by SOC and PT
- Related TEAEs leading to discontinuation of avelumab by SOC and PT
- TEAEs leading to discontinuation of binimetinib by SOC and PT
- Related TEAEs leading to discontinuation of binimetinib by SOC and PT
- TEAEs leading to discontinuation of talazoparib by SOC and PT
- Related TEAEs leading to discontinuation of talazoparib by SOC and PT
- TEAEs leading to discontinuation of any study drug by SOC and PT
- Related TEAEs leading to discontinuation of any study drug by SOC and PT
- TEAEs leading to discontinuation of all study drugs by SOC and PT
- Related TEAEs leading to discontinuation of all study drugs by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression
  - Study treatment toxicity
  - AE not related to study treatment
  - Unknown
  - Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.

6.6.3. Serious adverse events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of patients with each of the following will be presented for irAEs:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT

- irAEs leading to discontinuation of avelumab, by Cluster and PT
- irAEs leading to discontinuation of binimetinib, by Cluster and PT
- irAEs leading to discontinuation of talazoparib, by Cluster and PT
- irAEs leading to discontinuation of any study drug, by Cluster and PT
- irAEs leading to discontinuation of all study drugs, by Cluster and PT
- Serious irAEs, by Cluster and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

The frequency (number and percentage) of patients with each of the following will be presented for IRRs:

- IRRs leading to death, by PT
- IRRs, by PT
- IRRs, Grade ≥ 3, by PT
- IRRs leading to discontinuation of avelumab, by PT
- IRRs leading to discontinuation of any study drug, by PT
- IRRs leading to discontinuation of all study drugs, by PT
- Serious IRRs, by PT
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later).

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Quantitative data will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time (unscheduled measurements would therefore not be included in these summaries as described in Section 5.2.9). End of Treatment visit laboratory results will be summarized separately. The changes computed will be the differences from baseline. Qualitative data based on reference ranges will be described according to the categories (ie, Low, Normal, High).

Abnormalities classified according to NCI-CTCAE toxicity grading v.4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN

- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN .

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by CTCAE grade table will include number and percentage of patients with Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4), laboratory abnormalities during the on-treatment period.
- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of patients with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of patients with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

In this study, these apply to the following parameters:

Serum Chemistry: Chloride, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH), CK isoenzymes (CK-MB, CK-MM and CK-BB), Cardiac Troponin I and/or T.

6.6.5.2. Other laboratory parameters

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

In addition, listings of abnormal values will be provided for hematology, chemistry, urinalysis, coagulation parameters. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included into the listing.

For all tests not mentioned above but present in the clinical data, a listing of patients with at least one result for the relevant test will be provided.

6.6.6. Vital signs

Weight will be recorded at screening and within 2 days pre-dose Day 1 of each cycle and at End of Treatment. Height will be measured at screening only.

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

6.6.7. Electrocardiogram

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. QTcB and QTcF will be derived based on RR and QT (see below). In the case of triplicate ECG (at screening and pre-dose Cycle 1 Day 1), the average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc), during the on-

treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF) and HR using individual (non-averaged) baseline assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

6.6.8. MUGA/ECHO

LVEF% will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time. In addition, LVEF% will be summarized as frequency (number and percentage) of patients with:

- a shift from baseline normal to at least one result below the institutional lower limit of normal during the on-treatment period
- ≥10-point decrease from baseline in LVEF% during the on-treatment period
- ≥10-point decrease from baseline in LVEF% to a post-baseline value < LLN during the on-treatment period
- ≥15-point decrease from baseline in LVEF% during the on-treatment period
- ≥15-point decrease from baseline in LVEF% to a post-baseline value < LLN during the on-treatment period

Clinically significant findings will be listed.

6.6.9. Ophthalmic Examination

Abnormal findings in ophthalmic examination are recorded in the Medical history (at screening) or the Adverse Event eCRF pages. No separate analysis will be performed for ophthalmic examination findings. A listing of ophthalmic examination findings will be provided.

6.6.10. ECOG performance status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized. ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

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9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the Safety Review Plan (SRP) for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 13. This case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step except for Steps 3 and 4 which will be checked in parallel. Step 5 will be checked for patients who meet the criteria in Step 4 (irrespective of whether Step 3 criteria are met).

Table 13. Case Definition for irAEs

Step	Selection Criteria	Additional Notes
1	Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list then it is in for the next step	
2	AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications
3	Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'	
4	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement	Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) OR C) below are met then the AE is in for the next step A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

5	A) No clear etiology (other than immune mediated etiology)	A) From the AE eCRF page. Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No If answer is Yes, check all that apply: • Underlying malignancy / progressive disease. • Other medical conditions. • Prior or concomitant medications / procedures. • Other. Specify.
	B) Histopathology / biopsy consistent with immune-mediated event	B) From the AE eCRF page. B1) Was there a pathology / histology evaluation performed to investigate the AE? Y/N B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text)
	Event is in if [Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)] OR [Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO] OR [Answer to 5B1 is NO AND answer to 5A is NO]	

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. Infusion Related Reactions

For defining an AE as IRR the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.
- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 14 will be identified for IV drugs only.

Table 14. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs

Condition	Selection criterion
If AE meets [1 AND 2] OR [3 AND (4A OR 4B)] then AE is classified as an IRR	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2	• AE onset date = date of infusion of study drug AND • AE timing related to study drug ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date <=2
3	PT is included in the 'IRRs CORE' list
4A	• AE onset date = date of infusion of study drug AND • AE timing related to study drug in ('DURING', 'AFTER')
4B	AE onset on the day after infusion

Appendix 3. Detailed Dose Escalation/De-escalation Scheme for BLRM Design prior to implementation of Protocol Amendment 3.

This appendix provides the details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model.

In this appendix, no data from study B9991025 for the combination of avelumab and talazoparib is considered. However, prior to the initiation of the dose finding for the triplet combination (avelumab, binimetinib and talazoparib), all applicable DLT data from study B9991025 and the doublet combination of study B9991033 will be incorporated into the BLRM to guide the starting dose and dose finding of the triplet combination.

As of protocol amendment 2 (05-Nov-2018), preliminary safety data became available for the Phase 1b portion of study B9991025. A total of 12 patients were enrolled at the starting dose level of 800 mg avelumab Q2W in combination with talazoparib at 1.0 mg once daily. All 12 patients were DLT-evaluable with a DLT rate of 3/12. This information from study B9991025 will be incorporated using direct down-weighting approach. The weight will be calculated using the formula below;

$$w = \frac{1}{1+\frac{2\tau^2}{\sigma^2}N}$$

where N= Total number of patients enrolled in the Phase 1b of study B9991025 (12)

σ = population standard deviation (σ = 2)

τ = heterogeneity between populations in the Phase 1b of study B9991025 and the triplet in terms of DLT (τ =0.25).

In this appendix, the reported avelumab dose is 10 mg/kg. Note that the fixed dose of 800 mg to be investigated in this study is expected to be equivalent to the 10 mg/kg dose.

A.3.1. Statistical Model

The statistical model for triplet combination dose-DLT data comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and interaction parts.

A.3.1.1. Single Agent Parts

Let $\pi_1(d_1)$ be the risk of DLT for avelumab given as a single agent at dose d_1; $\pi_2(d_2)$ be the risk of DLT for binimetinib given as a single agent at dose d_2; and $\pi_3(d_3)$ be the risk of DLT for talazoparib given as a single agent at dose d_3. These single agent dose-DLT models are logistic:

avelumab: $\text{logit}\left(\pi_1(d_1)\right) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

binimetinib: $\text{logit}\left(\pi_2(d_2)\right) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

talazoparib: $\text{logit}\big(\pi_3(d_3)\big) = \log(\alpha_3) + \beta_3 \log(d_3/d_3^*)$

where d_1^*=10 mg/kg, d_2^* =45 mg, and d_3^* =1.0 mg are used to scale the doses of avelumab, binimetinib, and talazoparib, respectively. Hence, α_1, α_2 , and α_3 (all >0) are the single-agent odds of a DLT at d_1^* mg/kg, d_2^* mg, and d_3^* mg, respectively; and β_1, β_2, and β_3(all >0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

A.3.1.2. Interaction Parts

Under an assumption that there is no interaction, the risk of a DLT at dose d_1 of avelumab, dose d_2 of binimetinib, and dose d_3 of talazoparib is:

$$\pi_{123}^0(d_1, d_2, d_3) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)\big(1 - \pi_3(d_3)\big)$$

To model the interaction between avelumab, binimetinib, and talazoparib, the following four odds multipliers are introduced.

- η_{12}: Two-way interaction between avelumab and binimetinib
- η_{13}: Two-way interaction between avelumab and talazoparib
- η_{23}: Two-way interaction between binimetinib and talazoparib
- η_{123}: Three-way interaction between avelumab, binimetinib and talazoparib

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$$\text{odds}\big(\pi_{123}(d_1, d_2, d_3)\big) = g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) \times \text{odds}\big(\pi_{123}^0(d_1, d_2, d_3)\big)$$

$$\begin{aligned} g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) = \; & \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*) \\ & \times \exp(\eta_{13} \times d_1/d_1^* \times d_3/d_3^*) \\ & \times \exp(\eta_{23} \times d_2/d_2^* \times d_3/d_3^*) \\ & \times \exp(\eta_{123} \times d_1/d_1^* \times d_2/d_2^* \times d_3/d_3^*) \end{aligned}$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; η_{ij} is the log-odds ratio between the interaction and no interaction model at the reference doses of drug *i* and *j* and a zero dose of the third drug. For example, η_{12} is the log-odds ratio between the interaction and no interaction model at avelumab = 10 mg/kg, binimetinib= 45 mg, and talazoparib=0 mg. Therefore, $\eta_{12} + \eta_{13} + \eta_{23} + \eta_{123}$ is the log-odds ratio between the interaction and no interaction model at the reference doses for all three drugs. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity respectively.

The dose-DLT data of the doublet combination of avelumab and binimetinib will be modeled using the same model by setting the talazoparib dose $d_3 = 0$ mg. The model will contain parameters related to single agent effects of avelumab ($\log(\alpha_1)$, $\log(\beta_1)$), binimetinib ($\log(\alpha_2)$, $\log(\beta_2)$), and two-way interaction between avelumab and binimetinib (η_{12}).

A.3.2. Prior Specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for avelumab, $\log(\alpha_2)$, $\log(\beta_2)$ for binimetinib, $\log(\alpha_3)$, $\log(\beta_3)$ for talazoparib, and the interaction parameters $\eta = (\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123})$. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters.

A.3.2.1. Prior Distribution for the Logistic Parameters for Single Agent

This section illustrates the derivation of prior distributions for single agent model parameters $(\log(\alpha_s), \log(\beta_s))$'s using the available single agent dose-DLT information via a MAP approach.

A.3.2.1.1. Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*), \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s $(s = 1, \ldots, \langle S \rangle)$. The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi_{g(s)} \sim \text{BVN}\left(\mu, \psi_{g(s)}\right), \qquad s = 1, \ldots, \langle S \rangle$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi_{g(*)} \sim \text{BVN}\left(\mu, \psi_{g(*)}\right)$$

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations (τ_{g1}, τ_{g2}), and correlation ρ (a common value for ρ is used across all groups). The parameters τ_{g1} and τ_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets $\left(\tau_{g1}, \tau_{g2}\right)$ it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_{g1} and τ_{g2}, and
- a uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $\left(log(\alpha^*), log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using JAGS version 4.0.

A.3.2.1.2. Single Agent Avelumab

Dose-DLT data in the avelumab IB[8] from study EMR100070-001 as presented in Table 15 are used to derive the prior of the single agent logistic parameters for avelumab. Based on clinical review, the population of the current study is moderately similar to study EMR100070-001.

Table 15. Historical Dose Limiting Toxicity Data from Study EMR100070-001

Avelumab dose (mg/kg Q2W)	Number of patients	Number of patients with DLTs
1	4	0
3	3	0
10	6	0
20	6	1

Abbreviations: mg=milligram; DLT=dose limiting toxicity; Q2W=every 2 weeks.

Weakly informative normal priors are assumed for μ_{1a} and μ_{2a}, with means corresponding to a 50% chance of DLT at avelumab=10 mg/kg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1a} and τ_{2a} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014[13]).

The prior distributions for the model used for deriving the MAP priors are specified in Table 16 below.

Table 16. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Avelumab Model Parameters

Parameter	Prior distribution
μ_{1a}	N(mean = 0, sd = 2)
μ_{2a}	N(mean = 0, sd=1)
τ_{1a}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2a}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_a	uniform(-1,1)

A.3.2.1.3. Single Agent Binimetinib

Dose-DLT data in the binimetinib IB[2] from studies ARRAY-162-111 and CMEK162X11 as presented in Table 17 are used to derive the prior of the single agent logistic parameters for binimetinib.

Table 17. Historical Dose Limiting Toxicity Data from Studies ARRAY-162-111 and CMEK162X1101

	Study ARRAY-162-111*		Study CMEK162X1101*	
Binimetinib dose (mg BID)	Number of patients	Number of patients with DLTs	Number of patients	Number of patients with DLTs
30	4	0	6	0
45	44	2	15	2
60	41	2		
80	4	2		

Abbreviations: BID=twice a day; DLT=dose limiting toxicity.

Weakly informative normal priors are assumed for μ_{1b} and μ_{2b}, with means corresponding to a 50% chance of DLT at avelumab=45 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. The priors for between-trial heterogeneity parameters are set in the following way:

- Priors for τ_{11b} and τ_{12b} (ARRAY-162-111) are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

- Priors for τ_{21b} and τ_{22b} (CMEK162X1101) are assigned such that (1) their medians correspond to large between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

Study ARRAY-162-111 is a phase 1 study conducted in advanced or metastatic cancer patients the United States. Study CMEK162X1101 is a study in Japanese patients with advanced solid tumors whose disease has progressed despite standard therapy or for whom no standard therapy exists. The patient population in study CMEK162X1101 is less similar to study B9991033 and hence large between trial heterogeneity is assumed.

The prior distributions for the model used for deriving the MAP priors are specified in Table 18 below.

Table 18. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Binimetinib Model Parameters

Parameter	Prior distribution
μ_{1b}	N(mean = 0, sd =2)
μ_{2b}	N(mean = 0, sd=1)
τ_{11b}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{12b}	log-normal(mean = log(0.125), sd = log(2)/1.96)
τ_{21b}	log-normal(mean = log(1), sd = log(2)/1.96)
τ_{22b}	log-normal(mean = log(0.5), sd = log(2)/1.96)
ρ_b	uniform(-1,1)

(τ_{11b}, τ_{12b}) = the degree of between trial heterogeneity for Study ARRAY-162-111; (τ_{21b}, τ_{22b}) = the degree of between-trial heterogeneity for Study CMEK162X1101.

A.3.2.1.4. Single Agent Talazoparib

Dose-DLT data from study PRP-001 (C3441007) (de Bono et al. 2017)[6] presented in Table 19 are used to derive the prior of the single agent logistic parameters for talazoparib.

Table 19. Historical Dose Limiting Toxicity data from study NCT01286987

Talazoparib dose (mg QD)	Number of patients	Number of patients with DLTs
0.025	3	0
0.05	3	0
0.1	3	0
0.2	3	0
0.4	3	0
0.6	6	0
0.9	6	1
1.0	6	0
1.1	6	2

Abbreviations: DLT=dose limiting toxicity; QD=once daily.

Weakly informative normal priors are assumed for μ_{1t} and μ_{2t}, with means corresponding to a 50% chance of DLT at talazoparib=1.0 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1t} and τ_{2t} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

Table 20. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Talazoparib Model Parameters

Parameter	Prior distribution
μ_{1t}	N(mean = 0, sd = 2)
μ_{2t}	N(mean = 0, sd=1)
τ_{1t}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2t}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_t	uniform(-1,1)

A.3.2.2. Prior Distribution for the Interaction Parameters

Based on pharmacometrics assessment, no two-way or three-way drug-drug interaction is expected, although uncertainty remains. Based upon this, normal priors for the log-odds multipliers $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are used. All priors are centered on an assumption of no drug-drug interaction, but with appropriate uncertainty that allows for both synergistic and antagonistic toxicity. The prior for $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses;

η_{12} is normally distributed, with mean 0 and sd 0.639 (corresponds to no increase in DLT odds at median and 3.5-fold increase in DLTs at 97.5th percentile)

η_{23} is normally distributed, with mean 0 and sd 0.207 (corresponds to no increase in DLT odds at median and 1.5-fold increase in DLTs at 97.5th percentile)

η_{13} is normally distributed, with mean 0 and sd 0.207 (corresponds to no increase in DLT odds at median and 1.5-fold increase in DLTs at 97.5th percentile)

η_{123} is normally distributed, with mean 0 and sd 0.025 (corresponds to no increase in DLT odds at median and 1.05-fold increase in DLTs at 97.5th percentile).

A.3.2.3. Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 21. Table 22 and Table 23 illustrate the resulting prior distribution of DLT rate derived from the prior given in Table 21 for the doublet combination and the triplet combination, respectively. Based on the available information the starting dose avelumab= 10 mg/kg and binimetinib= 45 mg for the doublet satisfies the EWOC criteria.

Table 21. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Avelumab single agent parameters: BVN MAP Prior			
$(\log(\alpha_1), \log(\beta_1))$	-2.665,-0.056	0.961, 0.825	-0.234
Binimetinib single agent parameters: BVN MAP Prior			
$(\log(\alpha_2), \log(\beta_2))$	-2.795, 0.313	0.578, 0.854	-0.313
Talazoparib single agent parameters: BVN MAP Prior			
$(\log(\alpha_3), \log(\beta_3))$	-1.757, 0.657	0.727, 0.888	0.191
Interaction parameters: Normal prior			
η_{12}	0	0.639	
η_{13}	0	0.207	
η_{23}	0	0.207	
η_{123}	0	0.0249	

η_{12}: Two-way interaction between avelumab and binimetinib;
η_{13}: Two-way interaction between avelumab and talazoparib;
η_{23}: Two-way interaction between binimetinib and talazoparib;
η_{123}: Three-way interaction between avelumab, binimetinib and talazoparib.

Table 22. Summary of Prior Distribution of Dose Limiting Toxicity Rates for the Doublet Combination of Avelumab in Combination with Binimetinib

Binimetinib dose (mg BID)	**Prior probabilities that DLT rate is in the interval:**			**Mean**	**SD**	**Quantiles**		
	[0, 0.16)	**[0.16, 0.33)**	**[0.33,1]**			**2.5%**	**50%**	**97.5%**
	In combination with Avelumab = 10 mg/kg, Talazoparib = 0 mg							
30	**0.716**	**0.234**	**0.050**	**0.132**	**0.098**	**0.022**	**0.106**	**0.397**
45	0.598	0.302	0.100	0.165	0.120	0.028	0.133	0.486

Abbreviations: BID=twice a day; DLT=dose limiting toxicity; SD=Standard Deviation

From Table 23: in absence of doublet data, avelumab= 10mg/kg, binimetinib= 30 mg and talazoparib= 0.75 mg is an acceptable starting dose. However, the final starting dose for the triplet will be determined after the dose-DLT data for the doublet combination is available. Some hypothetical examples are shown in Table 25.

Table 23. Summary of Prior Distribution of DLT Rates for the Triplet Combination of Avelumab in Combination with Binimetinib and Talazoparib

Bini dose (mg BID)	Tala dose (mg QD)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
30	0.5	0.522	0.374	0.104	0.180	0.113	0.036	0.154	0.465
30	0.75	0.383	0.447	0.170	0.217	0.123	0.050	0.193	0.521
30	1.0	0.212	0.464	0.324	0.282	0.142	0.074	0.258	0.614
45	0.5	0.438	0.385	0.177	0.211	0.137	0.038	0.180	0.557
45	0.75	0.334	0.412	0.254	0.248	0.149	0.048	0.217	0.610
45	1.0	0.208	0.395	0.397	0.309	0.169	0.066	0.281	0.694

Avelumab dose fixed at 10 mg/kg every 2 weeks.
Abbreviations: BID=twice a day; Bini=Binimetinib; QD=once daily; SD=Standard Deviation; Tala=Talazoparib

A.3.3. Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of patients is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future patients, EWOC criteria and maximum amount of escalation allows (100% of current dose). In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 24 shows some hypothetical dose escalation data scenarios for the doublet combination and the corresponding recommendations for the next dose. For example, in Scenario 1, if no DLT is observed among 3 DLT-evaluable patients at the starting dose, the recommendation is to remain at the same dose level with probability of overdosing of 0.03. Note that the starting dose is already the maximum possible dose for the doublet combination. In Scenario 3, if 2 patients experience a DLT out of 3 DLT-evaluable patients at the starting dose, the recommendation is to de-escalate the dose of binimetinib to 30 mg with avelumab remaining at 10 mg/kg; this lower dose combination has a probability of overdosing of 0.21. Scenarios 2, 4, 5 and 6 show clinically plausible next dose recommendations.

Table 24. Doublet Combination: Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

	Dose Evaluated			D/N*	Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
Scenarios	Ave (mg/kg Q2W)	Bini (mg BID)	Tala mg (QD)		Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		
1	(10)	45	-	0/3	(10)	45	-	0.231	0.031
2	(10)	45	-	1/3	(10)	45	-	0.422	0.133
3	(10)	45	-	2/3	(10)	30	-	0.465	0.212
4	(10)	45	-	2/6	(10)	45	-	0.507	0.170
5	(10)	45	-	3/6	(10)	30	-	0.528	0.198
6	(10) (10)	45 30	- -	3/6 1/3	(10)	30	-	0.580	0.225

Abbreviations: Ave=avelumab; BID=twice a day; Bini=Binimetinib; *D=number of patients with DLT, N=number of DLT-evaluable patients; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Tala=Talazoparib; QD=once daily; Q2W=every 2 weeks.

Table 25 shows the plausible starting dose level(s) for the triplet combinations given hypothetical data from the doublet combination. If the dose-DLT profile of the doublet is safe at avelumab= 10mg/kg, binimetinib= 45mg (Scenarios 1 and 2), triplet dose escalation can begin at avelumab= 10mg/kg, binimetinib= 45mg and talazoparib= 0.75mg. If 2-3 patients with DLT observed out of 12 DLT-evaluable patients at avelumab= 10mg/kg, binimetinib= 45mg, the starting dose will be avelumab= 10mg/kg, binimetinib= 30mg and talazoparib= 0.75mg (Scenarios 3 and 4).

Table 25. Triplet Combination: Clinically Meaningful Starting Dose Given Hypothetical Data from the Doublet Combination, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose.

	Doublet Dose			D/N*	Triplet starting dose (SD)			Pr(TT) at SD	Pr(OD) at SD
Scenarios	Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		
1	(10)	45	-	0/9	(10)	45	0.75	0.354	0.070
2	(10)	45	-	1/12	(10)	45	0.75	0.449	0.113
3	(10)	45	-	2/12	(10)	30	0.75	0.544	0.125
4	(10)	45	-	3/12	(10)	30	0.75	0.586	0.217

Abbreviations: Ave=avelumab; BID=twice a day; Bini=Binimetinib; *D=number of patients with DLT, N=number of DLT-evaluable patients; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Tala=Talazoparib;

Table 26 shows data scenarios for the triplet combination and the corresponding recommendations for the next dose.

Table 26. Triplet Combination: Data Scenarios (Given Hypothetical Doublet Data), Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

	Dose evaluated			D/N*	Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
Scenarios	Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		
1	(10) (10)	45 45	- 0.75	0/9 0/3	(10)	45	1.0	0.408	0.103
2	(10) (10)	45 45	- 0.75	0/9 1/3	(10)	45	0.75	0.463	0.099
3	(10) (10)	45 45	- 0.75	0/9 2/3	(10)	30	0.75	0.572	0.172
4	(10) (10)	45 45	- 0.75	0/9 3/3	(10)	30	0.5	0.566	0.170
5	(10) (10)	45 30	- 0.75	3/12 0/3	(10)	45	0.75	0.571	0.225
6	(10) (10)	45 30	- 0.75	3/12 1/3	(10)	30	0.75	0.617	0.239
7	(10) (10)	45 30	- 0.75	3/12 2/3	(10)	30	0.5	0.624	0.249

Abbreviations: Ave=avelumab; BID=twice a day; Bini=Binimetinib; *D=number of patients with DLT; N=number of DLT-evaluable patients; ND=next dose Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; QD=once daily; Q2W=every 2 weeks; Tala=Talazoparib.

Based on Table 24 and Table 26, the recommended next dose is adequate for all considered scenarios.

A.3.4. Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated (Appendix 3.4.1) and in each scenario 1000 trials were simulated, with results summarized in Appendix 3.4.3.

A.3.4.1. Simulation Scenarios

Several scenarios are considered for doublet and triplet combinations. Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenarios 2-3 of the doublet combination and scenarios 2-3 of the triplet combination represent an increased DLT rate compared to Scenario 1. The true DLT rates under different scenarios for doublet and triplet combinations are shown in Table 27 and Table 28, respectively. Scenario 4 in Table 28 represents a true toxicity profile with dose combinations in both under-dose and over-dose regions.

Table 27. Doublet Combination: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10mg/kg Every 2 Weeks)

Scenarios	Binimetinib (mg BID)	
	30	45
1. Prior means	0.132	0.165
2. 50% more toxic	0.199	0.248
3. Higher dose is overly toxic	0.200	0.400

Abbreviations: BID=twice a day; mg=milligramme

Table 28. Triplet Combination: Dose Limiting Toxicity Rate Scenarios (Fixed Avelumab Dose 10mg/kg Every 2 Weeks)

Binimetinib (mg BID)	Talazoparib (mg QD)					
	0.5	0.75	1.0	0.5	0.75	1.0
	Scenario 1. prior means			Scenario 2. 25% more toxic		
30	0.180	0.217	0.282	0.225	0.272	0.352
45	0.211	0.248	0.309	0.264	0.310	0.387
	Scenario 3. 50% more toxic			Scenario 4. With underdose and overdose		
30	0.270	0.326	0.423	0.05	0.15	0.35
45	0.317	0.372	0.464	0.10	0.25	0.50

Abbreviations: BID=twice a day; QD=once daily; Q2W=every 2 weeks.

A.3.4.2. Simulation Details

Simulations were performed using R version 3.3.2 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.0 to perform the MCMC analyses.

For each scenario, data for 1000 trials were generated, with a cohort size of 3. At any time during the course of dose finding, escalation to doses where the risk of overdose exceeds 25% is not permitted. The 'next dose recommendation' is the dose with maximum probability of overdose among all dose levels that meet the EWOC criteria.

For the doublet combination, the starting dose was avelumab 10 mg/kg (fixed) and binimetinib 45 mg. The maximum number of patients per trial was set to 30. The trial was stopped when the following criteria were met:

1. At least 6 patients have been treated at the recommended MTD $\tilde{d}$.
2. The dose $\tilde{d}$ satisfies one of the following conditions:
    - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
    - A minimum of 9 patients have been treated in the trial;

A simulation of the triplet combination is performed using the starting dose of avelumab 10 mg/kg , binimetinib 30mg, and talazoparib 0.5mg. No doublet combination data is considered in this exercise. The maximum number of patients per trial was set to 60. Each trial was stopped when the following criteria were met:

1. At least 6 patients have been treated at the recommended MTD $\tilde{d}$.
2. The dose $\tilde{d}$ satisfies one of the following conditions:
    - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
    - A minimum of 15 patients have been treated in the trial.

The following metrics were assessed in the simulations:

1. Percentage of patients receiving dose combination(s) in the target toxicity interval;
2. Percentage of patients receiving an overdose;
3. Percentage of patients receiving an underdose;
4. Probability that recommended MTD at the end of the trial is in the target toxicity interval;
5. Probability that recommended MTD is an overdose;
6. Probability that recommended MTD is an underdose;
7. Percentage of trials stopped without MTD declaration;
8. Average sample size.

A.3.4.3. Simulation Results

Operating characteristics for the doublet and the triplet combinations are presented in Table 29 and Table 30, respectively. The percentage of trials with a correctly identified MTD ranges from 67.4% to 99%. Furthermore, the percentage of patients treated at overly toxic doses is well controlled. The average sample size for the doublet combination is between 9 and 11 patients, and the average sample size for the triplet combination is between 9 to 17 patients.

Table 29. Doublet Combination: Operating Characteristics

Scenarios	Patient allocation (%)			Pr (declare MTD)			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	95.7	0	4.3	0.927	0	0	7.3	9
2. 50% more toxic	100	0	0	0.857	0	0	14.3	9
3. Higher dose level is overly toxic	48.6	51.4	0	0.674	0	0	32.6	11

Abbreviations: MTD=maximum tolerated dose: OD=overdose; TT=target toxicity; UD=underdose;

Table 30. Triplet Combination: Operating Characteristics

Scenarios	Patient allocation (%)			Pr (declare MTD)			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	100	0	0	0.922	0	0	7.8	14
2. 25% more toxic	83.6	16.4	0	0.877	0	0	12.3	13
3. 50% more toxic	89.6	10.4	0	0.831	0	0	16.9	9
4. With underdose and overdose	35.0	28.9	36.0	0.990	0	0	1.0	17

Abbreviations: MTD=maximum tolerated dose; OD=overdose; TT=target toxicity; UD=underdose;

Appendix 4. Detailed Dose Escalation/De-escalation Scheme for BLRM Design -per implementation of Protocol Amendment 3.

This appendix provides the details of the statistical model, the derivation of prior distributions using historical data, analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study to evaluate the long-run operating characteristics for the model based dose-escalation of the binimetinib (7 days on/7 days off, 7d/7d) + talazoparib doublet and the avelumab + binimetinib (7d/7d) + talazoparib triplet combinations. If the binimetinib 5 days on/2 days off (5d/2d) dosing schedule is explored upon the completion of the binimetinib (7d/7d) + talazoparib doublet, the prior distributions of the model parameters for the binimetinib 5d/2d dosing schedule will be adjusted appropriately to account for new information prior to the initiation.

Note that the fixed dose of 800 mg to be investigated in this study is expected to be equivalent to the 10 mg/kg dose.

A.4.1 Statistical Model

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and interaction parts.

A.4.1.1 Single Agent Parts

Let $\pi_1(d_1)$ be the risk of DLT for talazoparib given as a single agent at dose d_1; $\pi_2(d_2)$ be the risk of DLT for binimetinib given as a single agent at dose d_2; and $\pi_3(d_3)$ be the risk of DLT for avelumab given as a single agent at dose d_3. These single agent dose-DLT models are logistic:

talazoparib: $\text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

binimetinib: $\text{logit}\big(\pi_2(d_2)\big) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

avelumab: $\text{logit}\big(\pi_3(d_3)\big) = \log(\alpha_3) + \beta_3 \log(d_3/d_3^*)$

where d_1^*=1.0 mg, d_2^* =45 mg, and $d_3^* = 10$ mg/kg are used to scale the doses of talazoparib, binimetinib, and avelumab, respectively. Hence, α_1, α_2 , and α_3 (all >0) are the single-agent odds of a DLT at d_1^* mg, d_2^* mg, and d_3^*mg/kg, respectively; and β_1, β_2, and β_3(>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

A.4.1.2 Interaction Parts

Under an assumption that there is no interaction, the risk of a DLT at dose d_1 of talazoparib, dose d_2 of binimetinib, and dose d_3 of avelumab is:

$$\pi_{123}^0(d_1, d_2, d_3) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)\big(1 - \pi_3(d_3)\big)$$

To model the interaction between talazoparib, binimetinib, and avelumab, the following four odds multipliers are introduced.

- η_{12}: two-way interaction between talazoparib and binimetinib.
- η_{13}: two-way interaction between talazoparib and avelumab.
- η_{23}: two-way interaction between binimetinib and avelumab.
- η_{123}: three-way interaction among talazoparib, binimetinib and avelumab.

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$$\text{odds}\left(\pi_{123}(d_1, d_2, d_3)\right) = g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) \times \text{odds}\left(\pi^0_{123}(d_1, d_2, d_3)\right)$$

$$\begin{aligned} g(\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}) = \; & \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*) \\ & \times \exp(\eta_{13} \times d_1/d_1^* \times d_3/d_3^*) \\ & \times \exp(\eta_{23} \times d_2/d_2^* \times d_3/d_3^*) \\ & \times \exp(\eta_{123} \times d_1/d_1^* \times d_2/d_2^* \times d_3/d_3^*) \end{aligned}$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; η_{ij} is the log-odds ratio between the interaction and no interaction model at the reference doses of drug *i* and *j* and a zero dose of the third drug. For example, η_{12} is the log-odds ratio between the interaction and no interaction model at talazoparib=1.0mg, binimetinib= 45 mg, and avelumab=0 mg. Therefore, $\eta_{12} + \eta_{13} + \eta_{23} + \eta_{123}$ is the log-odds ratio between the interaction and no interaction model at the reference doses for all three drugs. Here $\eta = 0$ corresponds to no interaction, with $\eta > 0$ and $\eta < 0$ representing synergistic and antagonistic toxicity respectively.

The dose-DLT data of the doublet combination of talazoparib and binimetinib (7d/7d) will be modeled using the same model by setting the avelumab dose $d_3 = 0$ mg/kg. The model will contain parameters related to single agent effects of talazoparib $(\log(\alpha_1), \log(\beta_1))$, binimetinib $(\log(\alpha_2), \log(\beta_2))$, and the interaction between talazoparib and binimetinib (η_{12}).

A.4.2 Prior Specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for talazoparib, $\log(\alpha_2)$, $\log(\beta_2)$ for binimetinib, $\log(\alpha_3)$, $\log(\beta_3)$ for avelumab, and the interaction parameters $\eta = (\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123})$. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters.

A.4.2.1 Prior Distribution for the Logistic Parameters for Single Agent

This section illustrates the derivation of prior distributions for single agent model parameters $(\log(\alpha_s), \log(\beta_s))$'s using the available single agent dose-DLT information via a MAP approach.

A.4.2.1.1 Description of the Meta-Analytic-Predictive Approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies. Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s $(s = 1, \ldots, \langle S \rangle)$. The corresponding probability of a DLT is π_{ds}. The model specifications are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi_{g(s)} \sim \text{BVN}\left(\mu, \psi_{g(s)}\right), \qquad s = 1, \ldots, \langle S \rangle$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi_{g(*)} \sim \text{BVN}\left(\mu, \psi_{g(*)}\right)$$

The historical trials are partitioned into $\langle G \rangle$ exchangeability groups, with the exchangeability group membership of historical trial s being represented by $g(s)$. The new trial is assigned to exchangeability group $g(*)$. The parameter $\mu = (\mu_1, \mu_2)$ is the mean for the logistic parameters, and ψ_g is the between-trial covariance matrix for exchangeability group $g = 1, \ldots, \langle G \rangle$. Covariance matrix ψ_g is defined by the standard deviations $(\tau_{g1},\ \tau_{g2})$, and correlation ρ (a common value for ρ is used across all groups). The parameters τ_{g1} and τ_{g2} quantify the degree of between trial heterogeneity for exchangeability group g. With different prior distributions for the parameter sets $\left(\tau_{g1}, \tau_{g2}\right)$ it is possible to allow for differential discounting for the historical strata. In this way the quality and relevance of historical data can be accounted for in the meta-analysis. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_{g1} and τ_{g2}, and
- a uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $\left(log(\alpha^*), log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, \langle S \rangle)$$

Since the predictive distribution is not available analytically, the Markov chain Monte Carlo (MCMC) method is used to simulate values from this distribution. This is implemented using JAGS version 4.0.

A.4.2.1.2 Single Agent Talazoparib

Dose-DLT data from study PRP-001 (C3441007) (de Bono et al. 2017)[6] presented in Table 31 are used to derive the prior of the single agent logistic parameters for talazoparib.

Table 31. Historical Dose Limiting Toxicity data from study NCT01286987

Talazoparib dose (mg QD)	Number of patients	Number of patients with DLTs
0.025	3	0
0.05	3	0
0.1	3	0
0.2	3	0
0.4	3	0
0.6	6	0
0.9	6	1
1.0	6	0
1.1	6	2

Abbreviations: DLT=dose-limiting toxicity; QD=once daily; mg=milligram.

Weakly informative normal priors are assumed for μ_{1t} and μ_{2t}, with means corresponding to a 50% chance of DLT at talazoparib=1.0 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1t} and τ_{2t} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations. The prior distributions for the model used for deriving the MAP priors for talazoparib are specified in Table 32 below.

Table 32. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Talazoparib Model Parameters

Parameter	Prior distribution
μ_{1t}	N(mean = 0, sd = 2)
μ_{2t}	N(mean = 0, sd=1)
τ_{1t}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2t}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_t	uniform(-1,1)

A.4.2.1.3. Single Agent Binimetinib

A.4.2.1.3.1. Single Agent Binimetinib (Intermittent Dosing)

No prior Dose-DLT data are available for an intermittent binimetinib dosing schedule. Therefore, a mixture of bivariate normal prior is used for $(\log(\alpha_2), \log(\beta_2)$. The components are:

a. Meta-analysis predictive prior using continuous regimen data for binimetinib.

b. Weakly informative prior considering higher toxicity that has been observed in the continuous regimen.

A.4.2.1.3.1. Single Agent Binimetinib (Continuous Dosing)

Dose-DLT data in the binimetinib IB[2] from studies ARRAY-162-111 and CMEK162X11 (continuous dosing schedule) as presented in Table 33 are used to derive the MAP priors of the single agent logistic parameters for continuous binimetinib.

Table 33. Historical Dose Limiting Toxicity Data from Studies ARRAY-162-111 and CMEK162X1101

	Study ARRAY-162-111*		Study CMEK162X1101*	
Binimetinib dose (mg BID)	**Number of patients**	**Number of patients with DLTs**	**Number of patients**	**Number of patients with DLTs**
30	4	0	6	0
45	44	2	15	2
60	41	2		
80	4	2		

Abbreviations: BID=twice a day; DLT=dose-limiting toxicity; mg=milligram.

Weakly informative normal priors are assumed for μ_{1b} and μ_{2b}, with means corresponding to a 50% chance of DLT at binimetinib=45 mg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. The priors for between-trial heterogeneity parameters are set in the following way:

- Priors for τ_{11b} and τ_{12b} (ARRAY-162-111) are assigned such that (1) their medians correspond to moderate between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

- Priors for τ_{21b} and τ_{22b} (CMEK162X1101) are assigned such that (1) their medians correspond to large between-trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations.

Study ARRAY-162-111 is a phase 1 study conducted in advanced or metastatic cancer patients the United States. Study CMEK162X1101 is a study in Japanese patients with advanced solid tumors whose disease has progressed despite standard therapy or for whom no standard therapy exists. The patient population in study CMEK162X1101 is less similar to study B9991033 and hence large between trial heterogeneity is assumed.

The prior distributions for the model used for deriving the MAP priors for binimetinib are specified in Table 34 below.

Table 34. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Binimetinib Model Parameters

Parameter	Prior distribution
μ_{1b}	N(mean = 0, sd =2)
μ_{2b}	N(mean = 0, sd=1)
τ_{11b}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{12b}	log-normal(mean = log(0.125), sd = log(2)/1.96)
τ_{21b}	log-normal(mean = log(1), sd = log(2)/1.96)
τ_{22b}	log-normal(mean = log(0.5), sd = log(2)/1.96)
ρ_b	uniform(-1,1)

(τ_{11b}, τ_{12b}) = the degree of between trial heterogeneity for Study ARRAY-162-111; (τ_{21b}, τ_{22b}) = the degree of between-trial heterogeneity for Study CMEK162X1101.

A.4.2.1.3.2. Weakly Informative Prior for Binimetinib (7d/7d) Regimen

Higher DLT rates were observed in the avelumab + binimetinib doublet combination than that observed in historical binimetinib studies. To account for uncertainty, mixture priors of the MAP prior and a weakly informative prior were used for the binimetinib 7d/7d regimen single agent model parameters. The default weakly informative multivariate normal (MVN) prior of (log(α) and log(β)) is used where (mean$_1$, mean$_2$, standard deviation$_1$, standard deviation$_2$, correlation) = (logit(p*), 0, 2, 1, 0). Where p* is the anticipated DLT rate at the scaling dose 45 mg. Based on historical continuous binimetinib data, the apriori probability of DLT at the reference dose 45 mg is exp(-2.795)/(1+exp(-2.795)) ~= 6%. We used a prior of doubling the DLT rate (12%) at the reference dose, ie. (mean$_1$, mean$_2$, standard deviation$_1$, standard deviation$_2$, correlation) =(logit(0.12), 0, 2, 1, 0) = (-1.992, 0, 2, 1, 0).

Apriori 50% weights are assigned to MAP prior and weakly informative priors respectively.

A.4.2.1.4. Single Agent Avelumab

Dose-DLT data in the avelumab IB[8] from study EMR100070-001 as presented in Table 35 are used to derive the prior of the single agent logistic parameters for avelumab. Based on clinical review, the population of the current study is moderately similar to study EMR100070-001.

Table 35. Historical Dose Limiting Toxicity Data from Study EMR100070-001

Avelumab dose (mg/kg Q2W)	Number of patients	Number of patients with DLTs
1	4	0
3	3	0
10	6	0
20	6	1

Abbreviations: mg=milligram: DLT=dose-limiting toxicity; Q2W=every 2 weeks.

Weakly informative normal priors are assumed for μ_{1a} and μ_{2a}, with means corresponding to a 50% chance of DLT at avelumab=10 mg/kg, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_{1a} and τ_{2a} are assigned such that (1) their medians correspond to moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014).

The prior distributions for the model used for deriving the MAP priors are specified in Table 36 below.

Table 36. Prior Distributions for the Parameters of the MAP Model Used to Derive the Prior for the Single-Agent Avelumab Model Parameters

Parameter	Prior distribution
μ_{1a}	N(mean = 0, sd = 2)
μ_{2a}	N(mean = 0, sd=1)
τ_{1a}	log-normal(mean = log(0.25), sd = log(2)/1.96)
τ_{2a}	log-normal(mean = log(0.125), sd = log(2)/1.96)
ρ_a	uniform(-1,1)

A.4.2.2. Prior Distribution for the Interaction Parameters

Normal priors for the log-odds multipliers $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are used. Based on pharmacometrics assessment, no drug-drug interaction between avelumab and talazoparib and between binimetinib and talazoparib, or three-way drug-drug interaction is expected, although uncertainty remains. The priors for these interactions are centered on an assumption of no drug-drug interaction, but with appropriate uncertainty that allows for both synergistic and antagonistic toxicity. Based on the data from continuous binimetinib and avelumab doublet combination in B9991033, synergistic interaction between these two drugs is expected. The prior for $\eta_{12}, \eta_{13}, \eta_{23}, \eta_{123}$ are specified as percentiles of increase in the odds of DLT due to possible interaction in combination therapy at reference doses;

η_{12} is normally distributed, with mean 0 and sd 0.207 (corresponds to no increase in DLT odds at median and 1.5 fold increase in DLTs at 97.5th percentile).

η_{13} is normally distributed, with mean 0 and sd 0.207 (corresponds to no increase in DLT odds at median and 1.5 fold increase in DLTs at 97.5th percentile).

η_{23} is normally distributed, with mean 0.140 and sd 0.636 (corresponds to 15% increase in DLT odds at median and 4-fold increase in DLTs at 97.5th percentile)η_{123} is normally distributed, with mean 0 and sd 0.025 (corresponds to no increase in DLT odds at median and 1.05 fold increase in DLTs at 97.5th percentile).

η_{12}: Two-way interaction between talazoparib and binimetinib;

η_{13}: Two-way interaction between talazoparib and avelumab;

η_{23}: Two-way interaction between binimetinib and avelumab;

η_{123}: Three-way interaction among talazoparib, binimetinib and avelumab.

A.4.2.3. Use of Dose-DLT Data from B9991025 Study

In this appendix, data from study B9991025 for the combination of avelumab and talazoparib was incorporated in the prior distribution of the DLT, feasible starting dose assessment, data scenarios and simulations for the avelumab + binimetinib (7d/7d) + talazoparib triplet.

Based on the preliminary data from the Phase 1b portion of study B9991025, a total of 12 patients were enrolled at the starting dose level of 800 mg avelumab Q2W in combination with talazoparib at 1.0 mg once daily. All 12 patients were DLT-evaluable with a DLT rate of 3/12. This information was incorporated using a direct down-weighting approach. The weight is calculated using the formula below:

$$w = \frac{1}{1 + \frac{2\tau^2}{\sigma^2} N}$$

where N=12 (total number of patients enrolled in the Phase 1b of study B9991025)

σ =2 (population standard deviation)

τ = 0.25 (moderate heterogeneity between populations in the Phase 1b of study B9991025 and the triplet of this study in terms of DLT).

A.4.2.3 Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 37.

Table 37. Prior Distribution for the Model Parameters

Parameter	Mean	Standard deviations	Correlation
Talazoparib single agent parameters: BVN MAP Prior			
$(\log(\alpha_1), \log(\beta_1))$	-1.757, 0.657	0.727, 0.888	0.191
Binimetinib single agent parameters: BVN MAP Prior			
$(\log(\alpha_2), \log(\beta_2))$	-2.795, 0.313	0.578, 0.854	-0.313
Binimetinib single agent parameters: Weakly Informative Prior			
$(\log(\alpha_2), \log(\beta_2))$	-1.992, 0	2, 1	0
Avelumab single agent parameters*: BVN MAP Prior			
$(\log(\alpha_3), \log(\beta_3))$	-2.665,-0.056	0.961, 0.825	-0.234
Interaction parameters: Normal prior			
η_{12}	0	0.207	
η_{13}	0	0.207	
η_{23}	0.140	0.636	
η_{123}	0	0.0249	

η_{12}: Two-way interaction between talazoparib and binimetinib;
η_{13}: Two-way interaction between talazoparib and avelumab;
η_{23}: Two-way interaction between binimetinib and avelumab;
η_{123}: Three-way interaction between avelumab, binimetinib and talazoparib.
Abbreviations: BVN=bivariate normal; MAP=meta-analytic-predictive.

Table 38 and Table 39 illustrate the resulting prior distribution of DLT rate derived from the prior given in Table 37 for the doublet and the triplet combinations, respectively. The probability of overdosing for the proposed starting dose level for the doublet combination with binimetinib 45 mg (7d/7d) and talazoparib 0.75 mg is 0.189, which satisfies the EWOC criteria.

Table 38. Summary of Prior Distribution of Dose Limiting Toxicity Rates for the Binimetinib (7d/7d) + Talazoparib Doublet Combination

Bini dose (mg BID)	Tala dose (mg QD)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
30	0.5	0.719	0.171	0.11	0.153	0.17	0.011	0.096	0.717
30	0.75	0.581	0.283	0.137	0.191	0.168	0.029	0.139	0.732
30	1.0	0.323	0.443	0.234	0.257	0.169	0.064	0.211	0.756
45	0.5	0.625	0.219	0.156	0.193	0.193	0.023	0.124	0.805
45	0.75	0.475	0.336	0.189	0.23	0.19	0.042	0.167	0.815
45	1.0	0.243	0.457	0.3	0.293	0.188	0.076	0.24	0.833

Abbreviations: Bini=binimetinib; mg=milligram; tala=talazoparib; BID=twice daily; OD=once daily; DLT=dose-limiting toxicity; SD=standard deviation.

From Table 39, in absence of the binimetinib (7d/7d) doublet combination data, avelumab= 10mg/kg, binimetinib= 30 mg (7d/7d) and talazoparib= 0.5 mg is an acceptable starting dose for the triplet. However, the final starting dose for the triplet will be determined after the dose-DLT data for the binimetinib (7d/7d) + talazoparib doublet is available. Some hypothetical examples for the starting dose of the triplet are shown in Table 41.

Table 39. Summary of Prior Distribution of DLT Rates for the Avelumab + Binimetinib + Talazoparib Triplet Combination

Bini dose (mg BID)	Tala dose (mg QD)	Prior probabilities that DLT rate is in the interval:			Mean	SD	Quantiles		
		[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
30	0.5	0.379	0.394	0.227	0.246	0.178	0.044	0.198	0.766
30	0.75	0.257	0.447	0.296	0.283	0.176	0.064	0.24	0.778
30	1.0	0.114	0.431	0.454	0.345	0.175	0.101	0.311	0.801
45	0.5	0.301	0.361	0.338	0.298	0.21	0.046	0.241	0.858
45	0.75	0.217	0.371	0.412	0.333	0.209	0.061	0.283	0.867
45	1.0	0.118	0.335	0.547	0.391	0.208	0.088	0.355	0.883

Avelumab dose fixed at 10 mg/kg every 2 weeks.
Abbreviation: Bini=binimetinib; mg=milligram; tala=talazoparib; BID=twice daily; OD=once daily; DLT=dose-limiting toxicity; SD=standard deviation.

A.4.3 Hypothetical on-Study Data Scenarios

To illustrate the performance of the Bayesian model used to guide dose finding, hypothetical dose finding scenarios following the provisional dose levels specified in the protocol are displayed. In each case, the possible recommended dose that can be used in the next cohort of patients is shown. These recommended doses are determined using the model-based assessment of the risk of DLT in future patients, EWOC criteria and maximum amount of escalation allows (100% of current dose). In practice, the dose recommended by the adaptive Bayesian logistic model may be regarded as guidance. The final recommendation will be based on overall safety profile and PK data.

Table 40 shows some hypothetical dose escalation data scenarios for the binimetinib (7d/7d) + talazoparib doublet combination and the corresponding recommendations for the next dose.

Table 40. Binimetinib (7d/7d) + Talazoparib Doublet Combination: Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

Scenarios	Dose Evaluated			D/N*	Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
	Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		
1	0	45	0.75	1/5	0	45	1	0.548	0.224
2	0	45	0.75	1/6	0	45	1	0.561	0.186
3	0	45	0.75	2/6	0	45	0.75	0.513	0.202
4	0	45	0.75	3/6	0	30	0.5	0.380	0.245
5	0 0	45 45	0.75 1	1/6 2/12	0	45	1	0.639	0.058
6	0 0	45 45	0.75 1	1/6 3/12	0	45	1	0.705	0.131
7	0 0	45 45	0.75 0.75	2/6 1/6	0 0	45 30	0.75 1.0	0.574 0.594	0.099 0.191
8	0 0	45 45	0.75 0.75	2/6 2/6	0	45	0.75	0.599	0.243
9	0 0	45 45	0.75 0.5	3/6 1/5	0 0	30 30	0.75 0.5	0.576 0.476	0.247 0.150

Abbreviations: Ave=avelumab; BID=twice a day; Bini=Binimetinib; mg=milligrams; mg/kg=milligrams per kilogram; *D=number of patients with DLT, N=number of DLT-evaluable patients; ND=next dose; tala=talazoparib.

Table 41 shows the plausible starting dose level(s) for the avelumab + binimetinib (7d/7d) + talazoparib triplet given hypothetical data from the binimetinib (7d/7d) + talazoparib doublet.

Table 41. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet Combination: Clinically Meaningful Starting Dose Given Hypothetical Data from the Doublet, and the Interval Probability of Target Toxicity and Overdosing at Starting Dose.

Scenarios	Doublet Dose			D/N*	Triplet starting dose (SD)			Pr(TT) at SD	Pr(OD) at SD
	Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		
1	0 0	45 45	0.75 1.0	1/6 2/12	(10) (10)	30 45	0.75 0.5	0.525 0.424	0.168 0.215
2	0 0	45 45	0.75 1.0	1/6 3/12	(10) (10)	30 45	0.75 0.5	0.530 0.424	0.204 0.245
3	0 0	45 45	0.75 1.0	0/6 1/12	(10) (10)	30 45	1.0 0.75	0.548 0.381	0.209 0.198
4	0	45	0.75	3/12	(10)	30	0.5	0.486	0.180
5	0	45	0.75	4/12	No feasible starting dose for the triplet				

6	0 0	45 30	0.75 0.5	3/6 3/12	No feasible starting dose for the triplet				
7	0 0 0	45 30 30	0.75 0.5 0.75	3/6 1/5 3/12	No feasible starting dose for the triplet				
8	0 0	45 45	0.75 1.0	0/6 0/12	(10) (10)	30 45	1.0 0.75	0.526 0.409	0.164 0.173
9	0 0 0	45 30 45	0.75 0.5 0.5	3/6 0/4 3/12	No feasible starting dose for the triplet				

Abbreviations: Ave=avelumab; BID=twice a day; Bini=Binimetinib; mg=milligrams; mg/kg=milligrams per kilogram;*D=number of patients with DLT, N=number of DLT-evaluable patients; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Tala=Talazoparib; QD=once daily; Q2W=every 2 weeks.

Table 42 shows data scenarios for the triplet and the corresponding recommendations for the next dose.

Table 42. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet Combination: Data Scenarios (Given Hypothetical Doublet Data), Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

Scenarios	Dose evaluated			D/N*	Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
	Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)		
1	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 2/12 0/6	(10)	45	1.0	0.510	0.175
2	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 2/12 1/6	(10)	45	0.75	0.544	0.186
3	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 2/12 2/6	(10)	30	0.75	0.641	0.207
4	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 2/12 3/6	Stop (all doses are overdosing)				
5	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 3/12 0/6	(10)	45	1.0	0.517	0.229
6	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 3/12 1/6	(10)	45	0.75	0.548	0.215
7	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 3/12 2/6	(10)	30	0.75	0.633	0.240
8	0 0 (10)	45 45 45	0.75 1.0 0.5	1/6 3/12 3/6	Stop (all doses are overdosing)				
9	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 2/12 0/6	(10)	45	1.0	0.498	0.210
10	0 0	45 45	0.75 1.0	1/6 2/12	(10)	30 45	1.0 0.75	0.614 0.512	0.239 0.209

	(10)	30	0.75	1/6					
11	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 2/12 2/6	(10)	30	0.75	0.620	0.215
12	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 2/12 3/6	Stop (all doses are overdosing)				
13	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 3/12 0/6	(10)	30 45	1.0 0.75	0.609 0.445	0.167 0.113
14	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 3/12 1/6	(10)	30 45	0.75 0.75	0.590 0.513	0.111 0.237
15	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 3/12 2/6	(10) (10)	30 30	0.75 0.5	0.614 0.565	0.248 0.144
16	0 0 (10)	45 45 30	0.75 1.0 0.75	1/6 3/12 3/6	Stop (all doses are overdosing)				

Abbreviations: Ave=avelumab; BID=twice a day; Bini=Binimetinib; mg=milligrams; mg/kg=milligrams per kilogram; *D=number of patients with DLT, N=number of DLT-evaluable patients; ND=next dose; Pr(TT)=probability of target toxicity; Pr(OD)=probability of overdosing; Tala=Talazoparib; QD=once daily; Q2W=every 2 weeks.

A.4.4. Operating Characteristics

A simulation study is used to illustrate the properties of the dose finding model guided by BLRM. Several example scenarios were investigated (A.4.4.1) and in each scenario 1000 trials were simulated, with results summarized in A.4.4.3.

A.4.4.1 Simulation Scenarios

The true DLT rates under different scenarios for doublet and triplet combinations are shown in Table 43 and Table 44, respectively. Several scenarios are considered: Scenario 1 represents the case when the distribution of DLT coincides with prior, ie, the true DLT probability equals to mean of prior DLT. Scenarios 2-3 represent a proportionally increased/decreased DLT rate compared to Scenario 1. Scenario 4 in Table 43 represents a true toxicity profile with dose combinations in both under-dose and over-dose regions.

Table 43. Binimetinib (7d/7d) + Talazoparib Doublet Combination: True Dose Limiting Toxicity Rate Scenarios

Binimetinib (mg BID)	Talazoparib (mg QD)					
	0.5	**0.75**	**1.0**	**0.5**	**0.75**	**1.0**
	Scenario 1. prior means of DLT rate			Scenario 2. 25% more toxic than prior means		
30	0.153	0.191	0.257	0.192	0.239	0.321
45	0.193	0.23	0.293	0.242	0.287	0.366
	Scenario 3. 40% more toxic than prior means			Scenario 4. With underdose and overdose		
30	0.215	0.268	0.360	0.100	0.200	0.300
45	0.271	0.322	0.410	0.150	0.250	0.450

Abbreviations: BID=twice a day; DLT=dose-limiting toxicity; QD=once daily; mg=milligram.

Table 44. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet Combination: True Dose Limiting Toxicity Rate Scenarios

Binimetinib (mg BID)	Talazoparib (mg QD)					
	0.5	**0.75**	**1.0**	**0.5**	**0.75**	**1.0**
	Scenario 1. prior means of DLT rate			Scenario 2. 10% more toxic than prior means		
30	0.246	0.283	0.345	0.271	0.311	0.379
45	0.298	0.333	0.391	0.328	0.366	0.430
	Scenario 3. 10% less toxic than prior means			Scenario 4. With underdose and overdose		
30	0.222	0.254	0.310	0.100	0.250	0.350
45	0.269	0.300	0.352	0.200	0.300	0.450

Avelumab dose fixed at 10 mg/kg every 2 weeks; Abbreviations: BID=twice a day; DLT=dose-limiting toxicity; mg=milligram; QD=once daily.

A.4.4.2 Simulation Details

Simulations were performed using R version 3.3.5 (The R-project for Statistical Computing. https://www.r-project.org/), and JAGS 4.8 to perform the MCMC analyses.

For each scenario, data for 1000 trials were generated, with a cohort size of 3. At any time during the course of dose finding, escalation to doses where the risk of overdose exceeds 0.25 is not permitted. The 'next dose recommendation' is the dose with maximum probability of overdose among all dose levels that meet the EWOC criteria.

For the doublet, the starting dose was binimetinib 45 mg and talazoparib 0.75 mg. For the triplet, the starting dose is the lowest dose of avelumab 10 mg/kg, binimetinib 30 mg, and talazoparib 0.5 mg. No on-trial binimetinib + talazoparib doublet combination data is considered in this exercise. The maximum number of patients per trial was set to 60. The trial was stopped when the following criteria were met:

- At least 6 patients have been treated at the recommended MTD $\tilde{d}$.
- The dose $\tilde{d}$ satisfies one of the following conditions:
  - The probability of target toxicity at dose $\tilde{d}$ exceeds 50%, ie, $\Pr(0.16 \leq \pi_{\tilde{d}} < 0.33) \geq 50\%$;
  - A minimum of 15 patients have been treated in the trial.

The following metrics were assessed in the simulations:

- Percentage of patients receiving dose combination(s) in the target toxicity interval;
- Percentage of patients receiving an overdose;
- Percentage of patients receiving an underdose;
- Probability that recommended MTD at the end of the trial is in the target toxicity interval;
- Probability that recommended MTD is an overdose;
- Probability that recommended MTD is an underdose;
- Percentage of trials stopped without MTD declaration;
- Average sample size.

A.4.4.3 Simulation Results

Operating characteristics for the doublet and the triplet combinations are presented in Table 45 and Table 46 respectively. The percentage of trials with a correctly identified MTD ranges from 67.4% to 99% is reasonable and the percentage of patients treated at overly toxic doses is well controlled for most of the scenarios. The average sample size for the doublet combination is between 10 and 11 patients, and the average sample size for the triplet is between 9 to 15 patients.

Table 45. Binimetinib + Talazoparib (7d/7d) Doublet Combination: Operating Characteristics

True DLT Scenarios	% Patient allocation			% declare MTD			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	97.2	0	2.8	85.2	0	0	14.8	10
2. 25% more toxic than prior means	88.8	11.2	0	77.3	0	0	22.7	10
3. 40% more toxic than prior means	82.5	17.5	0	59.0	0	00	41.0	11
4. With underdose and overdose	83.9	12.9	3.2	88.0	0	00	12.0	10

Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose: OD=overdose; TT=target toxicity; UD=underdose.

Table 46. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet Combination: Operating Characteristics

True DLT Scenarios	% Patient allocation			%declare MTD			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	90.5	9.5	0	60.8	0	0	39.2	11
2. 10% more toxic than 3. prior means	91.6	8.4	0	56.4	0	0	43.6	9
4. 10% less toxic than prior means	100	0	0	65.4	0	0	34.6	12
5. With underdose and overdose	53.0	3.8	43.2	68.4	0	17.1	14.5	15

Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose; OD=overdose; TT=target toxicity; UD=underdose.