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

Investigational Product Number:	MSB0010718C MDV3800, BMN 673 MEK162
Investigational Product Name:	Avelumab (MSB0010718C) Talazoparib (PF-06944076) Binimetinib (MEK162)
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Phase:	1b/2

Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 3	24 September 2019	1. The study title has been updated to reflect the updated study design. 2. Due to dose-limiting toxicities seen with the doublet of avelumab and continuous daily binimetib dosing, the study design has been updated: • The dosing schedule for binimetinib has been modified to an intermittent schedule (seven days on treatment/seven days off treatment). • Phases 1b and 2 doublet combinations have been modified to study binimetinib and talazoparib. • Estimates for total enrollment in Phases 1b and 2 were revised to reflect the updated study design. 3. Phase 2 design has been modified to remove the randomized NSCLC cohort due to enrollment concerns (ie, anticipated slow enrollment of these patients). NSCLC will instead be included as an eligible tumor type in the RAS-mutation positive 'tumor agnostic' cohort, which does not pre-specify a minimum or maximum number of any given tumor type. This tumor agnostic cohort was also increased in size from 20 to 30 patients to accommodate this change. 4. Schedule of Activities have been updated to include: • The Day 7 visit has been clarified to be Day 8, and the visit window has been removed to allow for a PK

		assessment following a single dose of binimetinib. • TNM staging and date of progression during or following each prior regimen as part of cancer history. • Pharmacokinetic (PK) sampling timepoints were revised to reflect the updated study design and to enable a C_{max} assessment for binimetinib. If indicated, an additional sample may also be drawn to investigate a potential exposure-toxicity relationship for any given patient. • Triplicate ECGs corresponding to PK sampling have been removed as this is no longer required and did not align to T_{max} at steady state for all study drugs. However, a triplicate ECG will be performed at screening and pre-dose on Cycle 1 Day 1. Single ECGs will be performed as a standard safety assessment on Day 1 of all other cycles. 5. The protocol background section has been updated: • Avelumab background information has been clarified and upated per updates included in the current Investigator's Brochure (June 2019). • Rationale has been provided for the decision to discontinue the doublet combination of avelumab and binimetinib and replace this with the doublet combination of binimetinib and talazoparib. • A preliminary summary of the available safety data for the doublet

		combination of avelumab and binimetinib has been added. • Rationale has been provided for the inclusion of the Phase 2 NSCLC patients into the 'tumor agnostic' cohort. • Rationale has been added for the change to an intermittent dosing schedule for binimetinib. • Regulatory approval information has been added for binimetinib and talazoparib. 6. Study objectives and endpoints have been updated accordingly: • The doublet combination of binimetinib and talazoparib has been added. • The NSCLC specific patient reported outcomes have been removed. • PK parameters have been updated to reflect the current design. 7. The maximum administered dose definition has been updated to reflect the intermittent schedule of binimetinib and the modified doublet combination of binimetinib and talazoparib. 8. Inclusion criteria were updated: • #1 (eligible tumor types) was updated such that NSCLC patients are only eligible for Phase 2. • #5 (tumor tissue requirements) was updated to clarify that bone lesion biopsies are not acceptable. 9. Exclusion criterion were updated:

		• #20 (concomitant medication restrictions) was revised in accordance with the current guidance relating to use of Pg-p inhibitors/inducers. • #22 (uncontrolled hypertension restriction) has been updated to clarify that patients requiring anti-hypertensive medication must be on a stable regimen for at least 2 weeks. 10. Section 5.5 has been updated to clarify the treatment administration procedures to be followed due to the updated study design. 11. The dose-limiting toxicity definitions have been updated to align with visit scheduling and the current guidance for binimetinib protocols. a. Hypertension criteria has been modified to allow 14 days for Grade 3 hypertension to be controlled to Grade ≤2 with or without ongoing medical therapy. b. The duration of Grade 3 lipase/amylase has been removed. c. Eye disorder criterion has been modified to Grade ≥3 uveitis, blurred vision, flashing lights or floaters. d. Removed criterion: Grade 3 rash that does not improve to Grade 1 within 14 days, limits self-care, or which is associated with infection. 12. The dose modification guidance has been updated to improve consistency and align with the guidance in the prescribing information and current protocol guidance for binimetinib, and the prescribing information for talazoparib and avelumab. The combined tables of dose

		modifications have been removed to simplify the instructions for investigators and to ensure consistency with the prescribing guidance's described above. 13. Section 5.8.3 has been updated to clarify requirements for use of steroids in the management of treatment-related adverse events. 14. Sections 5.8.6 and 5.8.7 have been updated based on current guidance for prohibited medications and those to be used with caution during treatment with talazoparib and binimetinib. 15. Section 6.4 has been updated to clarify that all patients are expected to enter survival follow-up, even if they discontinue short-term follow-up prior to completing the 90 day follow-up period. 16. Assessments (Section 7) have been updated: • Table 15 (required laboratory safety tests) was updated to confirm that glucose can be sampled regardless of fasting status as per standard protocol guidance, and that myoglobin may be measured in blood or urine (previously limited to urine) since some study centers do not have access to a urine myoglobin laboratory test. • 12 Lead ECG requirements have been updated per changes in the Schedule of Assessments. 17. Section 8.3 has been updated to remove Grade 0 from the 'Clinical Description of Severity' table per the current Pfizer standard protocol template. 18. The statistical sections of the protocol (Section 9) was updated to reflect the

		changes in study design, including the addition of Appendix 6. 19. References have been updated to include new information. 20. Minor editorial changes have been made for consistency and readability.
Protocol Amendment 2	05 November 2018	CCI  3. Consistent with changes implemented in the updated talazoparib Investigator's Brochure (dated August 2018), the protocol was revised to increase the duration of contraception use and concomitant medication restrictions. Requirements for male contraceptive use in relation to binimetinib was also clarified as per the current binimetinib IB (dated 20 March 2018) and regulatory guidance (Exclusion criterion #29, Section 4.1; Section 4.3; Section 5.8.6).

		4. Consistent with changes implemented in the updated talazoparib Investigator's Brochure (dated August 2018), background pharmacokinetic information was updated (Section 1.2.3.2). 5. Preliminary safety information that has become available from the B9991025 study has been added in Section 1.2.3.3. 6. Permissible highly effective methods of contraception were updated as per current protocol standard, including the addition of sexual abstinence (Section 4.3). 7. Consistent with the Avelumab Investigator's Brochure (version 8, 16May2018), the recommendation for management of Grade 1 to 2 immune-related rash was updated and Recommendations for the management of pulmonary irAEs was added as this had previously been omitted in error (Table 12, Section 5.5.7). 8. Required safety laboratory tests (Table 13, Section 7.1.4) were updated as follows: • As not all study centers have access to a complete CK isozyme panel (CK-MB, CK-MM and CK-BB) at their local laboratory, it was clarified that CK-MB is required and others (CK-MM, CK-BB) should be performed if available (Table 13, Section 7.1.4). • As many centers perform an activated partial thromboplastin time assessment (aPTT) rather than PTT, aPTT was added as an alternate coagulation test. • Given potential variation in reporting of PT results across study centers, PT has been removed as a reportable test

		result in favor of collecting the INR result alone (Table 13, Section 7.1.4). 9. Study-required ECG assessments were clarified in order to specify that single ECG procedures should be performed prior to study drug dosing (Schedule of Assessments; Section 7.1.6). 10. Avelumab PK blood sample collection requirement for Cycle 1 Day 7 was clarified (Schedule of Assessments). 11. Requirements relating to tumor biopsy procedures were clarified (Section 7.4.1.1). 12. Section 8.4.1 Protocol-Specified Serious Adverse Events was added in accordance with the standard protocol template. 13. Related editorial updates have been made for consistency and readability.

Protocol Amendment 1	05 June 2018	Revised as per request from United States Food and Drug Administration review.
		
		• Summary and Study Design sections were clarified:
		
		  • The Phase 1b portion of the study will only enroll patients with KRAS- or NRAS-mutant non-small cell lung cancer (NSCLC) and metastatic pancreatic ductal adenocarcinoma (mPDAC).
		
		  • Each dose cohort (doublet or triplet) may enroll both NSCLC and mPDAC patients without preference to tumor type (ie, separate dose cohorts by tumor type are not planned during Phase 1b).
		
		  • Example tumor types expected to be enrolled in the 'other advanced solid

		tumors' cohort in the Phase 2 portion of the study were added. • Inclusion criterion #1a was clarified that locally advanced or metastatic NSCLC includes stage IIIb and IV. • Exclusion criterion #8 was revised to exclude patients with a prior history of uveitis and iritis. • DLT definition for eye disorders revised to specify the maximum duration (ie, ≤21 days) of Grade 2 immune-related uveitis, eye pain, blurred vision or decreased visual acuity and to clarify that systemic treatment is corticosteroid based.
Original protocol	20 April 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and Rationale:

Avelumab (MSB0010718C) is a human immunoglobulin (Ig) G1 monoclonal antibody (mAb) directed against programmed death-ligand 1 (PD-L1). Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint inhibition pathway. In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first approved treatment for metastatic merkel cell carcinoma (MCC) followed by approvals in Japan, Australia, European Union, Switzerland, and Israel. In May 2017, avelumab received accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In January 2018, avelumab was approved for the same indication in Israel. Avelumab is currently being investigated as a single-agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors and various hematological malignancies.

Binimetinib (MEK162) is an oral potent small molecule mitogen-activated protein kinase kinase (MEK) 1/2 inhibitor currently being developed by Array BioPharma for the treatment of B-Raf proto-oncogene serine/threonine-protein kinase (BRAF)-mutant melanoma (in combination with encorafenib, a novel oral BRAF kinase inhibitor) and BRAF-mutant colorectal cancer (CRC) (in combination with encorafenib and cetuximab). The US FDA and European Medicines Agency approved the use of binimetinib and encorafenib for the treatment of BRAF-mutant, unresectable or metastatic melanoma on 27 June 2018 and 20 September 2018, respectively. MEK is a key protein kinase in the RAS/RAF/MEK/ERK signaling pathway, which regulates several key cellular activities including proliferation, differentiation, migration, survival and angiogenesis. Inappropriate activation of this pathway has been shown to occur in many cancers, particularly through mutations in BRAF and RAS gene family members (including Kirsten rat sarcoma viral oncogene (KRAS) and neuroblastoma RAS viral oncogene homolog (NRAS).

Talazoparib (PF-06944076) is a potent, orally bioavailable poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, which is cytotoxic to human cancer cell lines harboring gene mutations that compromise deoxyribonucleic acid (DNA) repair, an effect referred to as synthetic lethality. Talazoparib is currently being investigated as a single-agent and in combination with other anti-cancer therapies, including avelumab (Pfizer Study B9991025). In a Phase 3 trial in patients with breast cancer susceptibility gene (BRCA) ½-positive locally advanced and/or metastatic breast cancer (protocol no. 673-301 [EMBRACA]), single-agent talazoparib demonstrated superior progression-free survival (PFS) versus physician choice chemotherapy.[40] Median PFS was 8.6 months (95% confidence interval (CI): 7.2, 9.3) for patients treated with talazoparib and 5.6 months (95% CI: 4.2, 6.7) for those treated with chemotherapy [hazard ratio (HR): 0.54 (95% CI: 0.41, 0.71), p<0.0001]. Based on this study, the US FDA and European Medicines Agency approved the use of talazoparib for the treatment of adult patients with germline breast cancer susceptibility gene (gBRCA)-mutated human epidermal growth factor receptor 2

(HER2)-negative locally advanced or metastatic breast cancer on 16 October 2018 and 20 June 2019, respectively.

Combinations of avelumab, binimetinib and talazoparib are expected to produce additive or synergistic anti-tumor activity relative to each drug used as a single-agent. Studies suggest that oncogenic RAS signaling upregulates PD-L1 expression via the MEK-extracellular regulated signal kinase (ERK) pathway,[41,47] and that inhibition of MEK in combination with checkpoint blockade promotes T-cell and anti-tumor activity.[42] Consistent with this, the combination of binimetinib with an anti-PD-1 antibody improved anti-tumor activity and survival as compared to single-agent controls in a KRAS-mutant tumor model.[43] Emerging data also indicate that the combination of PARP and MEK inhibition has synergistic anti-tumor activity. Combined treatment with the PARP inhibitor talazoparib and MEK inhibitor selumetinib induces synergistic cytotoxic effects *in vitro* and *in vivo* in multiple RAS-mutant tumor models across tumor lineages where RAS mutations are prevalent.[44] The effects of the combination are independent of BRCA1/2 and p53 mutation status, suggesting that the synergistic activity is likely to be generalizable.

In conclusion, the above rationale supports the clinical investigation of combinations of PD-L1, MEK, and PARP inhibition in patients with locally advanced or metastatic KRAS- or NRAS-mutant tumors where there are few effective therapeutic options.

The primary purpose of this study is to assess the safety and early signs of efficacy of combinations of avelumab, binimetinib and talazoparib in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) and other locally advanced or metastatic KRAS- or NRAS-mutant solid tumors. The combinations to be studied include avelumab and binimetinib, binimetinib and talazoparib, and all 3 study drugs combined. The primary tumor type of interest for this study - mPDAC - was selected based on the high frequency of RAS mutations in this tumor type,[39,46] as well as an unmet medical need which is foreseen to continue into the future. Given the high frequency of KRAS mutations in pancreatic cancer (ie, over 90%),[39,46] these patients will not be preselected based on KRAS/NRAS mutation status.

Study Objectives and Endpoints:

Primary Objectives

- 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 pharmacokinetics (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]

Primary Endpoints

- Phase 1b: DLT during the primary DLT evaluation period (Cycle 1).
- Phase 2: Confirmed objective response (OR) based on Investigator assessment per RECIST v1.1.

Secondary 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.

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

- 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.

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

- 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).

- PD-L1 expression level, DDR gene alterations, and tumor mutational burden in baseline tumor tissue.

Exploratory Endpoints

[redacted]

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 and other locally advanced or metastatic KRAS- or NRAS-mutant solid tumors.

Initially, this study examined avelumab given intravenously (IV) every 2 weeks (Q2W) and binimetinib given orally 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 and talazoparib. Due to observed dose-limiting toxicities (DLTs) with continuous binimetinib dosing, the dosing schedule for binimetinib has been modified (Amendment 3) to an intermittent dosing schedule(s) which is expected to mitigate these potential toxicities.

Given that recent clinical trial results for a combination of an anti-PD-L1 and a MEK inhibitor showed limited clinical activity[69,70] and pre-clinical data support the combination of MEK and PARP inhibitors,[44,72] this trial has also been modified (Amendment 3) to explore the doublet combination of binimetinib and talazoparib in addition to the triplet combination of avelumab, binimetinib and talazoparib. This doublet combination is anticipated to have an acceptable safety profile, as seen with the combination of the MEK and PARP inhibitors, selumetinib and olaparib, respectively, which was well tolerated in an ongoing Phase 1 study.[71]

Per 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 previously enrolled during Phase 1b 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.

For Phase 1b, only patients with mPDAC will be enrolled. The doublet combination of binimetinib (BID, 7 days on/7 days off; Schedule 7d/7d) and talazoparib will be evaluated first to determine the RP2D for this combination. Upon the completion of the dose-finding for the doublet, the triplet of avelumab in combination with binimetinib and talazoparib will then be evaluated to determine the RP2D for this combination.

Guidance for Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment (number of patients to be enrolled in the next cohort) decisions will be based on a Bayesian Logistic Regression Model (BLRM). The BLRM incorporates single-agent and available combination DLT data (historical and prospectively across dose cohorts) to estimate the posterior probability of underdosing, target dosing, and overdosing, thereby reducing patient risk and increasing efficiency and precision during dose finding with combination treatments.

Phase 1b Design

The dose levels for the combination of avelumab and continuous binimetinib prior to implementation of Amendment 3 are shown in Table 1 below. The starting dose level (D0) was 800 mg avelumab IV Q2W and 45 mg binimetinib orally (PO) twice daily, which satisfied the Escalation With Overdose Control (EWOC) criterion[35] that the risk for excessive toxicity be less than 0.25. (NOTE: For the starting dose level D0, the risk of excessive toxicity was estimated to be 0.10 based on information from prior single-agent Phase 1

studies and a pharmacokinetic (PK) assessment of no potential significant drug-drug interaction between avelumab and binimetinib.)

Table 1. Avelumab and Binimetinib Dose Levels

Dose Level	Avelumab dose IV (mg Q2W)	Binimetinib dose PO (mg twice daily)
D0	800	45
D-1	800	30

D0= starting dose; D-1=reduced dose; IV= intravenous; mg= milligram; Q2W= every 2 weeks.

The potential dose levels for the combination of binimetinib and talazoparib are shown in Table 2. The starting dose level (BT0) is 45 mg binimetinib orally BID, Schedule 7d/7d, and 0.75 mg talazoparib orally once daily (QD) on a continuous dosing schedule, which satisfies the EWOC criterion[35] that the risk for excessive toxicity be less than 0.25. Of note, for BT0, the risk of excessive toxicity was estimated to be 0.189 based on the information from prior single-agent Phase 1 studies[30,9] and a PK assessment of no potential drug-drug interaction between binimetinib and talazoparib (see Appendix 6, Table 40).

Table 2. Binimetinib and Talazoparib Dose Levels

Dose Levels	Binimetinib Dose (Oral) (mg twice daily)*	Talazoparib Dose (Oral) (mg daily)
BT1	45	1.0
BT0	45	0.75
BT-1	45	0.5
BT-2	30	1.0
BT-3	30	0.75
BT-4	30	0.5

Abbreviations: mg=milligram.
*In accordance with the assigned intermittent dosing schedule (ie, 7d/7d or 5 days on/2 days off (5d/2d)).

Dose-finding for the triplet combination of avelumab, binimetinib and talazoparib will begin once the RP2D for the doublet combination (with intermittent Schedule 7d/7d binimetinib dosing) has been confirmed in at least 9 DLT-evaluable patients.

The potential dose levels for the triplet combination are listed in Table 3. The starting dose level will be determined at the completion of the dose finding for the doublet combinations based on clinical data (including but not limited to safety and PK data) from the avelumab and binimetinib and binimetinib and talazoparib doublet dose-finding portions of this study and from the combination of avelumab and talazoparib (dose-finding phase of study B9991025).

Table 3. Avelumab, Binimetinib and Talazoparib Dose Levels

Avelumab Dose IV (mg Q2W)	Binimetinib Dose PO (mg twice daily, Schedule 7d/7d)	Talazoparib Dose PO (mg once daily)
800	30	0.5
800	30	0.75
800	30	1.0
800	45	0.5
800	45	0.75
800	45	1.0

IV= intravenous; mg= milligram; Q2W= every 2 weeks; PO=oral.

If the doublet of binimetinib and talazoparib is well tolerated using Schedule 7d/7d for binimetinib with an RP2D of at least 45 mg binimetinib and 0.75 mg talazoparib, the combination of binimetinib (BID) administered on a more intensive dosing schedule (ie, 5 days on/2 days off; Schedule 5d/2d) with continuous talazoparib (QD) may also be explored in order to determine the RP2D for this combination. In this case, possible dose levels include those indicated in Table 2, with a starting dose level that will be selected based on satisfying the EWOC criterion. Patient enrollment into this doublet combination using Schedule 5d/2d for binimetinib dosing may occur in parallel with that of the triplet dose finding using Schedule 7d/7d for binimetinib dosing.

For each combination, beginning with the starting dose level, cohorts of 3-6 patients will be enrolled, treated, and monitored during the 28-day DLT evaluation period (Cycle 1). Patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of the investigational products in Cycle 1 for reasons other than treatment related toxicity are not evaluable for DLT. A minimum of 3 DLT-evaluable patients will be required; additional patients will be enrolled in the specific enrollment cohort to replace patients who are not considered DLT-evaluable, where required. When all DLT-evaluable patients treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior distribution for the risk of DLT for new patients at different dose levels for the combination of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the intervals shown below.

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

In addition to accumulating safety data and observed DLTs, decisions on further patient enrollment and dose level selection will be guided by the Escalation With Overdose Control EWOC criterion.[35] A combination dose may only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose is less than 0.25.

A dose level combination is a potential candidate for being the maximum tolerated dose (MTD) level when all the following criteria are met:

- ≥6 patients have been treated at that dose;
- Probability of target dosing >50%;
- Probability of overdosing <25%.

An RP2D below the MTD may be determined based on other safety, clinical activity, PK, and pharmacodynamic (PD) data. Before initiating the Phase 2, safety will be confirmed in at least 9 DLT-evaluable patients treated at the RP2D for each combination. Available PK data for approximately 6 patients treated with the doublet and triplet will be evaluated. If the PK profile of each drug appears to be consistent with the PK profile of each drug given individually, Phase 2 will be initiated without waiting for complete PK data.

Phase 2 Design

Once the Phase 1b part 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 with 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 of the doublet schedules 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).

In total, approximately 70 patients are expected to be treated in Phase 2.

Study Treatments:

Eligible patients will be centrally assigned to a study treatment cohort after providing informed consent and completing the screening procedures. Patients enrolled in Phase 1b prior to implementation of Amendment 3 will continue to receive the originally assigned study treatment, with subsequent dose adjustments made as allowed for study drug-related toxicity.

Avelumab will be supplied as a sterile solution (20 mg/mL) and will be administered as a 1-hour IV infusion Q2W on Days 1 and 15 of each 28-day cycle at a fixed dose of 800 mg. In order to mitigate infusion-related reactions (IRRs), patients will be premedicated with an antihistamine and paracetamol (acetaminophen) prior to the first 4 infusions of avelumab; thereafter, premedications should be administered based upon clinical judgment and the presence/severity of prior infusion reactions.

Binimetinib will be provided as 15 mg film-coated tablets for oral administration, and packaged in induction sealed, high density polyethylene bottles with child resistant caps. Patients should self-administer binimetinib, orally twice daily at the defined dose (either 30 mg or 45 mg) and schedule, with or without food. The first dose should be taken in the morning, with the second dose 12±2 hours later.

Talazoparib will be supplied as 0.25 mg and 1.0 mg capsules for oral administration, and packaged in induction sealed, high density polyethylene bottles with child resistant caps. Patients should self-administer talazoparib, orally once daily at the defined dose level (either 0.5 mg, 0.75 mg, or 1 mg), at approximately the same time each morning along with the first dose of binimetinib.

On the days when avelumab is administered, patients must be instructed **not to** administer the morning binimetinib dose and the talazoparib dose at home, but to take their medication to the clinic (ie, investigative site) on these days for administration after necessary procedures are completed.

Statistical Methods:

The primary endpoint for Phase 1b will be the occurrence of DLT during the primary DLT evaluation period (Cycle 1).

The primary endpoint for Phase 2 will be confirmed OR. OR is defined as a Complete Response (CR) or Partial Response (PR) per RECIST v1.1, occurring from the date of first dose of study treatment for non-randomized cohorts or date of randomization for randomized cohorts, until the date of first documentation of progressive disease (PD) or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR is defined as the proportion of patients with a confirmed CR or PR based on the Investigator's assessment according to RECIST v1.1. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation of response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of ORR. Within each cohort and for each combination, ORR will be estimated and the two-sided exact 95% CIs for ORR will be calculated.

In the Phase 1b dose finding, it is estimated that approximately up to 18 and 12 patients will be enrolled in the doublet and triplet combination, 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 level and at least 9 patients at the RP2D. The actual number of patients will depend on the number of DLT events, 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.

With 20 treated patients per treatment group (doublet and triplet combinations) for mPDAC, ORR can be estimated with a maximum standard error of 0.112.

- With 30 treated patients in the 'tumor agnostic' cohort of the triplet combination, ORR can be estimated with a maximum standard error of 0.091.

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

- mPDAC cohort for the doublet combination: 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 for the triplet combination: 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 for the triplet combination: 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.[49-58]

SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each assessment required for compliance with the protocol.

The Investigator may schedule visits (unplanned visits) in addition to those listed in the SOA table (Table 4) in order to conduct evaluations or assessments required to protect the well-being of the patient.

This SOA will be followed for the entire study, including all study drug combinations and schedules to be studied in Phase 1b and Phase 2. Further details can be found in Section 5, Section 6, and Section 7.

Table 4. Schedule of Activities: Safety and Efficacy Assessments

Protocol Activities	Screening	On-Treatment Period: (One Cycle =28 Days)							Post-Treatment Period		
	≤28 Days Prior to Enrollment	Cycle 1			Cycle 2		Cycles ≥3		End of Treatment[1]	Short-Term Follow-Up (Day After Last Dose 30±3, 60±3, 90±3)[2]	Long-Term Follow-Up (Every 12 Weeks ±14 days)[3]
		Day 1	Day 8 (Phase 1b ONLY)	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)				±2	±2	±2	±2	±2	+7	±3	±14
Informed Consent[4]	X										
Cancer History[5]	X										
Medical History[6]	X										
Baseline Signs and Symptoms[7]		X									
Height	X										
Weight	X	X			X		X		X		
Contraceptive Check[8]	X	X			X		X		X	X[8]	X[8]
Laboratory and Safety Assessments – Must be performed pre-dose during the Treatment Period. Note: laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review.											
Physical Examination (including skin)	X	X			X		X		X	X (30 day visit only)	
Vital Signs[9]	X	X	X	X	X	X	X	X	X	X (30 day visit only)	
ECOG Performance Status[10]	X	X			X		X		X	X (30 day visit only)	
Hematology[11]	X	X[12]	X	X	X	X	X	X	X	X (30 day visit only)	
Blood Chemistry[11]	X	X[12]	X	X	X	X	X	X	X	X (30 day visit only)	
Coagulation[11]	X	X[12]			X		X		X	X (30 day visit only)	
Cardiac Troponin (cTn)[13]	X	If CK-MB is >ULN. For new cardiac biomarker increase, see Table 14.									
Blood or Urine Myoglobin	X	If CK is Grade ≥3									
ACTH and Thyroid Function Tests[11]	X				Every 2 cycles (C2, 4 6, etc)				X	X (30 day visit only)	
Urinalysis[14]	X	As clinically indicated.									
Serum/Urine Pregnancy Test (*for women of childbearing potential only*)[15]	X	X			X		X		X		
Hepatitis B and Hepatitis C Virus tests[16]	X										

Table 4. Schedule of Activities: Safety and Efficacy Assessments

Protocol Activities	Screening	On-Treatment Period: (One Cycle =28 Days)							Post-Treatment Period		
	≤28 Days Prior to Enrollment	Cycle 1			Cycle 2		Cycles ≥3		End of Treatment[1]	Short-Term Follow-Up (Day After Last Dose 30±3, 60±3, 90±3)[2]	Long-Term Follow-Up (Every 12 Weeks ±14 days)[3]
		Day 1	Day 8 (Phase 1b ONLY)	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)				±2	±2	±2	±2	±2	+7	±3	±14
Triplicate 12-Lead ECG[17]	X	X									
Single 12-Lead ECG[17]					X		X		X		
Ophthalmic Examination	X[18]				X[18]		Every 8 weeks (±7 days) eg, Cycle 4, 6, 8 etc[18]		X	X (30 day visit only)[19]	
ECHO/MUGA (LVEF Determination)	X				X		Cycle 5 then every 12 weeks (±7 days) eg, Cycle 8, 11, 14 etc		X		
Enrollment and Treatment											
Enrollment/Treatment Assignment[20]		X									
Talazoparib Administration[21]		Continuous once daily.									
Binimetinib Administration[22]		Twice a day as per the assigned dosing schedule.									
Premedication for Avelumab[23]		X		X	X	X	Optional Administration, at PI discretion, based on presence/severity of prior infusion reactions.				
Avelumab Administration[24]		X		X	X	X	X	X			
Other Clinical Assessments											
Tumor Assessments (by RECIST for all tumor types)[25]	X	Every 8 weeks (±7 days) after C1D1. After 52 weeks from C1D1, every 16 weeks (±7 days) until progressive disease.									
Serious and Non-Serious Adverse Event Monitoring[26]	X	Monitored and recorded continually							X	X[27]	

Table 4. Schedule of Activities: Safety and Efficacy Assessments

Protocol Activities	Screening	On-Treatment Period: (One Cycle =28 Days)							Post-Treatment Period		
	≤28 Days Prior to Enrollment	Cycle 1			Cycle 2		Cycles ≥3		End of Treatment[1]	Short-Term Follow-Up (Day After Last Dose 30±3, 60±3, 90±3)[2]	Long-Term Follow-Up (Every 12 Weeks ±14 days)[3]
		Day 1	Day 8 (Phase 1b ONLY)	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)				±2	±2	±2	±2	±2	+7	±3	±14
Concomitant Treatments[28]	X	Monitored and recorded continually							X	X	
Subsequent Anti-Cancer Treatment[29]										X	X
Survival[30]										X	X
CCI [redacted]											
[redacted]											
[redacted]											

Abbreviations: ACTH=adrenocorticotropic hormone, C=Cycle; C1D1=Cycle 1 Day 1; CCI [redacted]; ECG=electrocardiogram; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; CCI [redacted]; LVEF=Left Ventricular Ejection Fraction; MUGA=multigated acquisition; PI=Principal Investigator; CCI [redacted].

Footnotes for Safety and Efficacy Assessments (Phase 1b and Phase 2) Schedule of Activities:

1. **End of Treatment:** Perform tests/procedures if not completed during the previous 7 days.
2. **Short-Term Follow-up:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment or until the start of new anti-cancer treatment, whichever occurs first. If the patient has discontinued from study treatment for a reason other than disease progression, the patient should continue to undergo tumor assessments until disease progression regardless of initiation of a subsequent anti-cancer therapy. Assessments during this period will be conducted according to the SOA or as clinically indicated. See Section 6.4 for further details.
3. **Long-Term Follow-up:** Follow-Up to continue until death unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. If the patient has withdrawn from study treatment for a reason other than disease progression, the patient should continue to undergo tumor assessments until disease progression regardless of initiation of a subsequent anti-cancer therapy. See Section 6.4 for further details.
4. **Informed Consent**: Must be obtained prior to undergoing any study-specific procedure and may be obtained >28 days prior to enrollment. Upon providing written informed consent, the site should contact the IRT system so as to register the patient and receive a centrally assigned study identification code.
5. **Cancer History:** Oncology-related history for the current malignancy under study, including information on prior regimens (duration of administration, best overall response [BOR] observed, and date of progression), current tumor, node, metastasis (TNM) stage, surgery, and radiation therapy.
6. **Medical History:** Includes history of diseases or injuries (active or resolved) and concomitant illnesses that are not considered to be the disease under study.
7. **Baseline Signs and Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to enrollment and record on the Medical History case report form (CRF) page.
8. **Contraceptive Check:** Investigator to confirm correct use of contraception, as applicable, for the duration of its required usage. See Lifestyle Guidelines and Contraceptive Check Section 7.1.2 for additional details.
9. **Vital Signs:** Record blood pressure (BP), pulse heart rate (HR), and temperature.
10. **ECOG Performance Status:** See Appendix 2 for the criteria to assign the ECOG Performance Status at each time point.

11. **Hematology, Coagulation, Blood Chemistry, ACTH and Thyroid Function Tests:** Required safety laboratory test results that must be reviewed prior to study drug administration include, at a minimum, hematology (ie, hemoglobin, platelets, and white blood cells) and chemistry (ie, ALT, AST, alkaline phosphatase, creatine kinase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, and glucose). See Section 7.1.4 for the list of required Laboratory Tests and Section 5.5.7.3 for requirements to perform additional laboratory tests to monitor toxicity related to either investigational product.
12. **Hematology, Coagulation, Blood Chemistry, and Urinalysis:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to C1D1 as part of Screening.
13. **Cardiac Troponin:** During screening, clinically significant positive results in myocardial biomarkers should be further assessed as per local standard of care to rule out concurrent cardiac conditions which could make the patient ineligible for the study per the exclusion criteria. During the study, new laboratory cardiac biomarker elevations suggestive of myocarditis should be assessed as per Table 14. Additional tests should also be performed when clinically indicated. See Section 7.1.4.
14. **Urinalysis:** Dipstick is acceptable. Perform microscopic analyses if dipstick is positive for blood or protein. See Section 7.1.4.
15. **Serum/Urine Pregnancy Test (*for women of childbearing potential only*):** Results of the pregnancy test should be available prior to dosing. See Section 4.1 for criteria defining women of childbearing potential, as those patients who require pregnancy testing. Serum or urine pregnancy tests must have a sensitivity of at least 25 mIU/mL. Additionally, perform pregnancy tests whenever one menstrual cycle is missed or when a potential pregnancy is otherwise suspected. See Section 7.1.1 for additional pregnancy testing details.
16. **Hepatitis B and Hepatitis C Virus tests:** Includes HBV surface antigen and anti-HCV antibody tests. If anti-HCV antibody test is positive, HCV RNA test must be to be performed.
17. **12-Lead ECG:** Triplicate 12-lead ECGs will be performed at Screening and pre-dose on Cycle 1 Day 1. On Day 1 of all other cycles, a single 12-lead ECG will be performed prior to any study drug dosing. The parameters to be recorded are RR, QT, QTc, PR, and QRS. See Section 7.1.6 for details regarding ECGs and the procedure to follow if QTc is prolonged (>500 msec). If the patient experiences any cardiac AE or syncope, dizziness, seizures, or stroke, triplicate ECGs should be obtained at the time of the event. See Section 7.1.6.
18. **Ophthalmic Examination:** Full ophthalmic examination, including best corrected visual acuity for distance testing, automated visual field testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially RPED, serous detachment of the retina and RVO (or associated symptoms). In the case of any suspected retinal abnormality optical coherence tomography (OCT) and/or fluorescein angiography will be performed. .
19. See Section 7.1.8.1.Only required if there was a clinically significant abnormality noted at the End of Treatment Visit.
20. **Enrollment/Treatment Assignment:** Managed by an Interactive Response Technology (IRT) system operated by Pfizer or designee. 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. See Section 5.1 for information regarding the IRT system and allocation to treatment.
21. **Talazoparib Administration:** See Section 5.5.3 for details on talazoparib administration. On Day 1 and 15 of each cycle, and also on Cycle 1 Day 8 for Phase 1b patients, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed (see Section 5.5.1 on the administration of the study combinations).
22. **Binimetinib Administration:** See Section 5.5.2 for details on binimetinib administration. On Day 1 and 15 of each cycle, the first daily dose of binimetinib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed (see Section 5.5.1 on the administration of the study combinations). Phase 1b Only: At the Cycle 1 Day 8 visit, a single dose of binimetinib will be administered in the clinic for all patients after all pre-dose procedures/assessments have been completed; where applicable per the assigned dosing schedule, the morning dose of binimetinib on Cycle 1 Day 8 should not be taken prior to the study visit.
23. **Premedication for Avelumab:** An antihistamine and paracetamol (acetaminophen) must be administered prior to the first 4 avelumab infusions (See Section 5.5.4 for further details on the premedication and Section 5.5.1 on the administration of the study combinations).
24. **Avelumab Administration:** See Section 5.5.5 for details on avelumab administration and Section 5.5.5.1 for special precautions for avelumab administration.

25. **Tumor Assessments (*for all tumor types)*:** See Section 7.6 for details on tumor assessments, including tumor assessments to confirm CR or PR using RECIST version 1.1 (See Appendix 3). Bone imaging is required at baseline for all patients. Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. Baseline scans are to be performed within 28 days prior randomization (for randomized cohorts) or start of study treatment (for non-randomized cohorts). Imaging should be performed with contrast agents unless contraindicated for medical reasons. Timing of disease assessment should follow calendar days and should not be adjusted for delays in cycle starts. Tumor assessments should also be performed whenever disease progression is suspected. Bone imaging is required at a different frequency than other imaging (every 16 weeks during the first 52 weeks of study treatment and every 24 weeks thereafter) if bone metastases are present at baseline.
26. **Serious and Non-Serious Adverse Event Monitoring:** AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 90 calendar days after the last investigational product administration. If the patient begins a new anti-cancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
27. **Safety Follow-up Serious and Non-Serious Adverse Event Monitoring:** Patients continuing to experience a study treatment-related AE following discontinuation of investigational products will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
28. **Concomitant Treatments:** Includes all medications and non-drug supportive interventions (eg, transfusions) from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new treatment is started. See Section 5.8 for additional details, Section 5.8.6 for prohibited medications, and Section 5.8.7 for drugs that should be given with caution when patients are being treated with the investigational products, which should be discussed with the patient and appropriately managed.
29. **Subsequent Anti-Cancer Treatment:** Subsequent anti-cancer therapy will be documented and recorded.
30. **Survival:** Contact patients via telephone or at the clinic for survival status independently of time of disease progression for at least 2 years after enrollment of the last patient or until death, lost-to-follow-up, patient withdrawal of consent, or study discontinued by the Sponsor, whichever comes first. For those patients without evidence of disease progression at the time of treatment discontinuation who continue to be followed with tumor assessments at Long-Term Follow-Up, survival status will be collected at the time of the scheduled tumor assessments.

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Table 5. Schedule of Activities: Tumor Tissue, Pharmacokinetic and Pharmacodynamic/Pharmacogenomic Assessments

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)							Post Treatment		
	≤28 Days Prior to Enrollment	Cycle 1			Cycle 2		Cycles ≥3		End of Treatment	Short-Term Follow-Up (Day 30, Day 60 and Day 90 after last dose)	Long-Term Follow-Up (Every 3 months)
		Day 1	Day 8 (Phase 1b ONLY)	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)				±2	±2	±2	±2	±2	+7	±3	±14
Tumor Tissue											
KRAS/NRAS Mutation Status[1]	X										
Tumor Sample/Biopsy	X[2]	Optional[3]							X[4]		
PK & Immunogenicity											
Binimetinib PK[5]		X	X	X	X		Cycle 3 only				
Talazoparib PK[6]		X	X	X	X		Cycle 3 only				
Avelumab PK[7]		X	X	X	X	X	Cycles 3, 5, 9, and 12 only				
Immunogenicity (ADA) Testing[8]		X		X	X	X	Cycles 3, 5, 9, and 12 only				
PD/PG Blood Sampling[9]											
CCI [redacted]		[redacted]									
		[redacted]									
Circulating tumor (ct)DNA[12]		X			X		Cycles 3-5 only		X		
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		
		[redacted]		[redacted]			[redacted]		[redacted]		
		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		
		[redacted]	[redacted]	[redacted]			[redacted]		[redacted]		

Abbreviations: ADA=anti-drug antibodies; DNA=deoxyribonucleic acid; PD=pharmacodynamic; PG=pharmacogenomic; PK=pharmacokinetic; CCI [redacted].

Footnotes for Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments Schedule of Activities:

Please refer to **Laboratory Manual for instructions on sample collection, processing and shipment for all Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic tests listed in Table 5.**

1. **KRAS/NRAS Mutation Status:** For NSCLC patients, as well as the patients enrolled in the 'KRAS or NRAS mutation positive' Phase 2 cohort, a positive KRAS or NRAS mutation status must have been previously documented through local laboratory testing. Any Clinical Laboratory Improvement Amendments (CLIA)-approved test (or comparable local validation) using either tumor tissue or ctDNA may have been used for this analysis. For NSCLC patients not previously tested locally or for whom the tumor mutation status is unknown, then a tumor tissue sample (specified in footnote #2) may be sent to the central laboratory to determine the KRAS and NRAS status; to allow for adequate turnaround time (~14 days), this sample may be submitted prior to the 28 day screening period but after informed consent has been obtained. See Section 7.7.
2. **Tumor Biopsy:** A mandatory tumor core needle or excisional biopsy from a locally recurrent or metastatic tumor site that is not the only RECIST v1.1 target lesion must be performed during screening to provide a FFPE tumor tissue block. If tumor tissue is available from a biopsy/surgery that was performed within 1 year prior to study enrollment and the patient did not receive any intervening systemic anti-cancer treatment, this tumor tissue may be submitted without repeating a tumor biopsy during the screening period. In all instances, if a block cannot be provided due to documented local/institutional regulations, at least 20 unstained slides are required. See Section 7.4.1.1.
3. **Tumor Biopsy during Treatment Period (Optional):** Optional biopsies are encouraged between Cycle 2 Day 1 and Cycle 3 Day 1. In addition, tumor tissue is requested for study purposes for patients who undergo tumor biopsy or resection as part of routine clinical care at any time during the treatment period. See Section 7.4.1.1.
4. **Tumor Biopsy at End of Treatment:** Every effort should be made to obtain an EOT (±14 days) biopsy if a patient discontinues study treatment due to RECIST v1.1 confirmed disease progression, except in instances where the procedure, as performed in the clinical research setting, poses an unacceptable risk to the patient. See Section 7.4.1.1.
5. **Blood Draw for Binimetinib PK:** Phase 1b Only: Blood samples (3-mL whole blood) will be collected at pre-dose, 1, 2 and 3 hours post-dose on Day 1 and Day 8 of Cycle 1. All patients (Phase 1b and Phase 2): Pre-dose on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 3 Day 1. If indicated, an additional PK sample may also be drawn with agreement between the Investigator and Sponsor (eg, to investigate a potential exposure-toxicity relationship for a particular patient). See Section 7.2.2.
6. **Blood Draw for Talazoparib PK:** Blood samples (3-mL whole blood) will be collected at pre-dose on Day 1, Day 8 (Phase 1b Only) and Day 15 of Cycle 1, and Day 1 of Cycle 2 and Cycle 3. If indicated, an additional PK sample may also be drawn with agreement between the Investigator and Sponsor (eg, to investigate a potential exposure-toxicity relationship for a particular patient). See Section 7.2.3.
7. **Blood Draw for Avelumab PK (not applicable for binimetinib and talazoparib doublet combination patients):** Blood samples (3.5-mL whole blood) will be collected at pre-dose and at the end of infusion (within 10 minutes after the avelumab infusion ends) on Day 1, and Day 15 of Cycle 1; Day 1 and Day 15 of Cycle 2; and Day 1 of Cycles 3, 5, 9 and 12. An additional single sample will also be obtained at the Cycle 1, Day 8 visit for Phase 1b patients. If indicated, an additional PK sample may also be drawn with agreement between the Investigator and Sponsor (eg, to investigate a potential exposure-toxicity relationship for a particular patient). See Section 7.2.1.
8. **Blood Draw for Avelumab Immunogenicity (ADA) Testing** (not applicable for binimetinib and talazoparib doublet combination patients)**:** Blood samples (3.5-mL whole blood) 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 Cycle 3, 5, 9, and 12. See Section 7.3.
9. **PD/PG Blood Sampling:** PD/PG time points may be adjusted based on emerging data during the course of the study; however, the total number of samples drawn during the study will not be increased.

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12. **ctDNA:** A 20-mL blood sample (for plasma preparation) will be collected prior to dosing on Day 1 of Cycles 1 through 5, and at the EOT. See Section 7.4.2.

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1. INTRODUCTION

This is a Phase 1b/2 study to assess the safety and early signs of efficacy of combinations of avelumab (MSB0010718C), binimetinib (also known as MEK162 or ARRY-438162) and talazoparib (also known as PF-06944076, BMN 673, or MDV38003) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) and other locally advanced or metastatic KRAS- or NRAS-mutant solid tumors.

1.1. Mechanism of Action/Indication

1.1.1. Avelumab

Avelumab (MSB0010718C) is a human immunoglobulin (Ig)G1 mAb directed against PD-L1. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint inhibition pathway. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[1,2] For complete details of the *in vitro* and nonclinical studies, refer to the avelumab Investigator's Brochure (IB) v9.0.[3]

In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first approved treatment for metastatic Merkel cell carcinoma (MCC) followed by approvals in Japan, Australia, European Union, Switzerland, and Israel. In May 2017, avelumab received accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic Urothelial Cancer (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In January, 2018 avelumab was approved for the same indication in Israel.

Avelumab is currently being investigated as single-agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors and various hematological malignancies.

Additional information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab Investigator Brochure (IB).[3]

1.1.2. Binimetinib

Binimetinib is an oral potent small molecule mitogen-activated protein kinase kinase (MEK) 1/2 inhibitor. In cell-free systems, binimetinib inhibits MEK1 and MEK2 with half maximal inhibitory concentrations (IC_{50}) of 12 nM and 46 nM, respectively. *In vivo*, single-agent binimetinib inhibits the growth of tumors in numerous xenograft models, including those derived from NSCLC, colorectal, pancreatic and melanoma cancers. Binimetinib is currently being developed by Array BioPharma for the treatment of B-Raf proto-oncogene serine/threonine-protein kinase (BRAF)-mutant melanoma (in combination with encorafenib, a novel oral BRAF kinase inhibitor) and BRAF-mutant CRC (in combination with encorafenib and cetuximab). The US FDA and European Medicines Agency approved the

use of binimetinib and encorafenib for the treatment of BRAF-mutant, unresectable or metastatic melanoma on 27 June 2018 and 20 September 2018, respectively.

Additional information for binimetinib may be found in the SRSD, which for this study is the binimetinib IB.[30]

1.1.3. Talazoparib

Talazoparib is a potent, orally bioavailable poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, which is cytotoxic to human cancer cell lines harboring gene mutations that compromise deoxyribonucleic acid (DNA) repair, an effect referred to as synthetic lethality, by inhibiting PARP catalytic activity and possibly by trapping PARP protein on DNA, thereby preventing DNA repair, replication, and transcription.[5,6,7] Although other PARP inhibitors also possess both activities, *in vitro* studies demonstrated that talazoparib has more potent PARP trapping activity than other PARP inhibitors in clinical development.[6,8]

DNA damage promotes inflammation via the NF-κB pathway[10] and the stimulation of interferon genes (STING) pathway,[11,12] and has been shown to increase the intrinsic immunogenicity of tumor cells via up-regulation of major histocompatibility complex (MHC), natural killer group 2 member D Ligand (NKG2DL), and inducible costimulator ligand (ICOSL).[13,14] As such, increased DNA damage via PARP inhibition is expected to enhance effective recognition and infiltration of tumors by immune cells. In keeping with this expectation, talazoparib has been shown to promote T-cell and natural killer (NK) cell infiltration and activation in a mouse model of ovarian cancer.[15] Additionally, talazoparib treatment has been shown to lead to increased expression of PD-L1 by tumor cells,[16] suggesting that this may represent a means by which tumors function to inhibit talazoparib-mediated anti-tumor immunity.

Talazoparib is currently being investigated as a single-agent and in combination with other anti-cancer therapies, including avelumab (Pfizer Study B9991025). Based on this study, the US FDA and European Medicines Agency approved the use of talazoparib for the treatment of adult patients with germline breast cancer susceptibility gene (gBRCA)-mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer on 16 October 2018 and 20 June 2019, respectively.

Additional information for talazoparib may be found in the SRSD, which for this study is the talazoparib IB.[9]

1.2. Background and Rationale

1.2.1. Avelumab Clinical Experience

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono and is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic MCC and in adult patients having UC with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Avelumab is also being studied in a wide variety of

cancers, including NSCLC, gastric cancer, renal cell carcinoma (RCC), ovarian cancer, UC, Hodgkin's Lymphoma, and relapsed or refractory diffuse B-cell lymphoma, as a single-agent or in combination with chemotherapy, tyrosine kinase inhibitors, or other immune-modulating agents.

The safety profile of avelumab administered intravenously (IV) as single-agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in MCC (N=88). Study EMR100070-001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor types.

As of 05 November 2015, 53 patients were treated in the dose escalation phase of the EMR100070-001 study, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg Q2W, respectively. According to the study protocol, the DLT assessment was performed on 19 patients who participated in the 3 + 3 dose-escalation algorithm (1 mg/kg [n = 4], 3 mg/kg [n = 3], 10 mg/kg [n = 6], and additional patients were enrolled to further assess safety and other study endpoints but without a formal DLT assessment.[4] Among the 19 patients in the DLT analysis set, none of the patients treated with doses up to 10 mg/kg experienced a DLT, and the 10 mg/kg dose of avelumab was thus considered a safe and well tolerated dose for further investigation in the dose expansion cohorts. One DLT (a Grade 3 immune-related adverse event (irAE) characterized by increased creatine kinase (CK), myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

The dose expansion phase of study EMR100070-001 included patients with NSCLC, gastric cancer, breast cancer, CRC, castration resistant prostate cancer (CRPC), adrenocortical carcinoma, melanoma, mesothelioma, UC, ovarian cancer, RCC, and squamous cell cancer of the head and neck. Study EMR100070-003 Part A was conducted in patients with MCC.

A summary of pooled safety data as of the data cutoff date of 09 June 2016 from patients treated at 10 mg/kg Q2W in studies EMR100070-001 and EMR100070-003 (N=1738) is provided here.

Treatment-emergent adverse events (TEAEs) were observed in 1697 (97.6%) patients, with the most frequent (≥10%) being fatigue (32.4%), nausea (25.1%), diarrhea (18.9%), constipation (18.4%), decreased appetite (18.4%), IRR (17.1%), weight decreased (16.6%), vomiting (16.2%), anemia (14.9%), abdominal pain (14.4%), cough (13.8%), pyrexia (13.6%), dyspnea (13.2%), edema peripheral (11.9%), back pain (11.8%), and arthralgia (10.4%).

Treatment-related TEAEs were observed in 1164 (67.0%) patients, and the most frequent (≥5%) were fatigue (17.7%), IRR (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

A total of 177 patients (10.2%) experienced Grade ≥3 treatment-related TEAEs, and the most frequent (≥0.5%) were fatigue (1.0%), increased lipase (1.0%), increased gamma-glutamyl transferase (GGT) (0.6%), IRR (0.6%), and increased aspartate aminotransferase (AST) (0.5%).

A total of 777 (44.7%) patients had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 108 (6.2%) patients, with the most frequent (≥0.2%) being IRR (0.9%), pneumonitis (0.6%), pyrexia (0.3%), adrenal insufficiency (0.3%), and hypothyroidism, diarrhea, vomiting, autoimmune disorder, autoimmune hepatitis, transaminases increased, dyspnea, and colitis (0.2% each).

There were 911 deaths (52.4%) in the pooled safety data set. The majority of deaths were due to progressive disease (744, 42.8%). There were 59 deaths (3.4%) attributed to TEAEs not related to trial treatment, and 4 deaths (0.2%) attributed to a treatment-related TEAE by the Investigator and which occurred up to 30 days after the last dose of avelumab: pneumonitis (1 case), acute liver failure (1 case), respiratory distress (in the context of sepsis) (1 case), and autoimmune hepatitis with hepatic failure (1 case). In addition, 1 patient died with acute respiratory failure (in the context of lung cancer progression) considered related to avelumab by the Investigator 37 days after the last dose of avelumab. The cause of death was marked as "other" or "unknown" in 17 (1.0%) and 83 (4.8%) cases, respectively.

A total of 244 patients (14.0%) permanently discontinued avelumab treatment due to TEAEs, including 107 patients (6.2%) discontinuing because of treatment-related TEAEs. The most frequent treatment-related TEAEs leading to treatment discontinuation were IRR (1.8%), GGT increased (0.4%), and diarrhea, fatigue, autoimmune disorder, alanine aminotransferase (ALT) increased, blood creatine phosphokinase (CPK) increased, lipase increased, arthralgia, and pneumonitis (0.2% each).

Immune-Related Adverse Events (irAEs): in the pooled safety data (N=1738), a total of 247 patients (14.2%) experienced irAEs, defined as adverse events (AEs) requiring use of corticosteroids (and/or hormonal therapy for endocrinopathies), and no clear alternate etiology. The median time to first onset of an irAE was 11.7 weeks. The most frequent irAEs were thyroid disorders including hypothyroidism (5.2%), hyperthyroidism (0.4%) and thyroiditis (0.2%), immune-related rash (5.2%), immune-related colitis (1.5%), immune-related pneumonitis (1.2%), immune-related hepatitis (0.9%), adrenal insufficiency (0.5%), and immune-related myositis (0.5%). In addition, irAEs reported in 0.1% of patients in the pooled safety dataset included: type 1 diabetes mellitus, immune-related nephritis/renal dysfunction, hypopituitarism, uveitis, and Guillain-Barre Syndrome. The majority of irAEs were Grade 1 or Grade 2 in severity, with 39 (2.2%) being of Grade ≥3 severity. Fatal outcome was reported in 1 patient (0.1%) with immune-related pneumonitis, and 2 patients (0.1%) with immune-related hepatitis. Other relevant irAEs reported with avelumab outside the pooled safety dataset as of 22 March 2019 included 12 cases of potential myocarditis (including 1 case of fatal outcome), 7 cases of potential pancreatitis (including 1 with fatal outcome), 3 cases of non-fatal graft versus host disease, and 1 case of immune thrombocytopenic purpura.

IRRs: a total of 439 patients (25.3%) experienced at least 1 IRR, defined as a TEAE coded under the preferred terms of IRR, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, and abdominal pain according to a predefined case definition. The most common preferred terms that met the definition for an IRR included: infusion-related reaction (17.0%), chills (5.4%), and pyrexia (3.6%). Most of the events were of Grade 1 or Grade 2 severity. Grade ≥3 IRRs occurred in 12 patients (0.7%) including 3 patients (0.2%) who experienced Grade 4 IRRs. No Grade 5 IRRs were reported. In most cases, the first occurrence of an IRR was related to the first infusion, with only 6 patients experiencing the first IRR at the fifth or later infusion. All Grade ≥3 IRRs occurred with the first (7 patients) or second (5 patients) infusion. Overall, 21.6% of patients had 1 IRR, 2.6% of patients had 2 IRRs, 14 patients (0.8%) had 3 IRRs, and 3 patients had >3 IRRs. IRR recurrence after the fourth infusion was rare (15 patients) and all recurrent IRRs were of Grade 1 or 2 severity. In 35 patients (2.0%), treatment was permanently discontinued because of an IRR.

Immunogenicity of avelumab in humans: immunogenicity assessment included all subjects from Studies EMR100070-001 and EMR100070-003 treated with 10 mg/kg of avelumab Q2W and who had at least one valid anti-drug antibody (ADA) result as of the data cut-off date of 09 June 2016. Of the 1738 patients treated with avelumab, 1627 were evaluable for treatment-emergent ADAs, 96 (5.9%) tested positive for ADAs and 41 (2.5%) tested positive for neutralizing antibodies. Titers were generally low across ADA ever-positive subjects, with no clear relationship between the duration of immunogenicity response and the maximum observed titer. Current data suggest there is no clinically meaningful impact of ADA positivity on the pharmacokinetics (PK), efficacy, or safety of avelumab.

Clinical Experience in mPDAC

The primary patient population of interest for this current study (B9991033) are those with pancreatic cancer. Seven patients with pancreatic cancer were enrolled in the phase 1a dose escalation phase of Study EMR100070-001, at dose levels ranging from 1 mg/kg to 20 mg/kg; no objective responses were reported among these 7 patients.[61]

1.2.1.1. Clinical Efficacy in Patients with Solid Tumors

Study EMR 100070-001 is an ongoing global, open-label Phase 1 study to investigate the safety, tolerability, pharmacokinetics (PK), and biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors. The study has various tumor type specific expansion cohorts, including NSCLC, RCC, urothelial carcinoma, gastric and gastro-esophageal junction cancer, metastatic breast cancer, colorectal cancer, castrate-resistant prostate cancer, melanoma, ovarian cancer, adrenocortical carcinoma, head and neck carcinoma, and mesothelioma. As reported in the Investigator's Brochure,[3] confirmed and unconfirmed objective response rates (ORRs) in the first-line advanced NSCLC, second-line advanced NSCLC, ovarian cancer, second-line gastric/gastroesophageal junction cancer, urothelial carcinoma, mesothelioma, and adrenocortical carcinoma expansion cohorts were 19.9% (31 of 156 patients), 14.1% (26 of 184), 7.0% (16 of 228 patients in secondary and efficacy expansion cohorts combined), 6.7% (4 of 60), 16.1% (39 of 242), 9.4% (5 of 53), and 10.5% (2 of 19), respectively.

1.2.1.2. Pharmacokinetics of Avelumab in Humans

Available PK data from Study EMR100070-001 show that the concentration at the end of the dosing interval (C_{trough}) increased more than proportionally to dose between 1 to 10 mg/kg, and proportionally to dose for doses above 10 mg/kg. The terminal half-life ($t_{1/2}$) also increased with dose; however, the geometric mean values for $t_{1/2}$ were similar for the 10 mg/kg and 20 mg/kg dose levels, at 94.6 hours (3.96 days) and 99.1 hours (4.1 days), respectively. This PK characteristic suggests that target-mediated drug disposition is involved in the clearance of avelumab, and that high PD-L1 target receptor occupancy (TO) is likely achieved throughout the dosing interval at doses of 10 mg/kg and 20 mg/kg given Q2W.

The 10 mg/kg dose Q2W achieved high TO (mean TO >90%) of PD-L1 in peripheral blood mononuclear cells (PBMC) during the entire dosing interval, as determined from *ex vivo* studies. Based on the *in vitro* TO data and the observed trough serum avelumab levels in the dose escalation cohorts of Study EMR100070-001, TO was predicted to reach or exceed 95% throughout the entire dosing interval in more subjects in the 10 mg/kg dose group than in the 3 mg/kg dose group.

Avelumab is eliminated by intracellular lysosomal proteolytic degradation throughout the entire body and therefore is not expected to be affected by small molecule drugs that are cytochrome P450 (CYP450) enzyme modulators or by transporter modulators. Furthermore, avelumab itself is not expected to interfere with either absorption or elimination of small molecule drugs that are substrates of transporters, are metabolized via CYP450, hydrolysis or conjugation, and/or are renally excreted.

Population PK analysis did not show any meaningful effects on clearance of avelumab from premedication with paracetamol (acetaminophen) or diphenhydramine, nor from concomitant medication with ibuprofen, acetylsalicylic acid, opioids, corticosteroids, and biological therapies evaluated to date.

1.2.2. Binimetinib Clinical Experience

As of 20 January 2018, a total of 2816 healthy subjects and patients have received at least 1 dose of binimetinib either as monotherapy or in combination with other agents. This includes 229 healthy subjects, 164 patients with rheumatoid arthritis, 17 patients with hepatic dysfunction, 6 patients with renal dysfunction, and 2400 patients with advanced cancer.

Binimetinib has been/is being extensively studied in combination with other targeted and standard chemotherapy agents, including targeted inhibitors of protein kinase C (PKC; sotrastaurin), cyclin dependent kinase (CDK) 4/6 (ribociclib), phosphatidylinositol-3 kinases (PI3K; BYL719, buparlisib), RAF (encorafenib), epidermal growth factor receptor (EGFR; erlotinib, cetuximab) and insulin-like growth factor (IGF)-1R (ganitumab), as well as with standard chemotherapy agents (cisplatin, gemcitabine, 5-FU/oxaliplatin, paclitaxel).

Available clinical data indicate a predictable safety profile consistent with that reported for other allosteric MEK1/2 inhibitors. The most frequent TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term in patients receiving binimetinib include rash, dermatitis acneiform, nausea, vomiting, diarrhea, peripheral edema, fatigue, and creatine kinase (CK) elevation. Other clinically relevant toxicities are retinal events, increased blood pressure, decreased cardiac ejection fraction, and noninfectious pneumonitis/interstitial lung disease, all of which should be monitored closely with appropriate diagnostic evaluations. These observed AEs are generally reversible and manageable by appropriate supportive medical care and/or dose modifications.

As of the data cutoff date of 20 January 2018, the experience of binimetinib as a single-agent in patients with advanced cancer -includes 943 patients who received at least 1 dose of binimetinib in 7 clinical studies. In the Phase 1 Study ARRAY-162-111, binimetinib doses were escalated from 30 mg to 80 mg twice daily (BID) and the recommended single-agent dose for further development was 45 mg BID.

Pooled AE data from 2 single-agent clinical studies of binimetinib in patients with metastatic melanoma (Study CMEK162X2201 and CMEK162A2301) are presented in Table 6 and provides a safety assessment of the recommended single-agent dose ("binimetinib 45 mg population;" N = 427). All 427 patients (100%) included in the analysis reported at least 1 AE, the most common (≥20.0% of patients) of which were blood CK increased (44.7%), diarrhea (42.6%), acneiform dermatitis (41.5%), peripheral edema (40.7%), rash (34.2%), nausea (30.0%), and fatigue (26.7%). Most of these events were Grade 1 or 2 in severity.

Two hundred eighty-five patients (66.7%) in the binimetinib 45 mg population experienced at least 1 Grade 3/4 AE; those reported for >2.0% of patients were blood CK increased (20.8%), hypertension (8.0%), ejection fraction decreased, fatigue and general physical health deterioration (3.5% each), rash (3.0%), dermatitis acneiform (2.6%), ALT increased and anemia (2.3% each), and AST increased and hypokalemia (2.1% each).

Table 6. Adverse Events Regardless of Causality Reported in ≥10.0% of Patients by Preferred Term (Pooled Data from Studies of Single-agent Binimetinib 45 mg BID in Patients with Melanoma)

Preferred term	45 mg BID N = 427	
	All Grades n (%)	Grade 3/4 n (%)
Any AE	427 (100)	285 (66.7)
Blood CK increased	191 (44.7)	89 (20.8)
Diarrhea	182 (42.6)	8 (1.9)
Dermatitis acneiform	177 (41.5)	11 (2.6)
Oedema peripheral	174 (40.7)	3 (0.7)
Rash	146 (34.2)	13 (3.0)
Nausea	128 (30.0)	5 (1.2)

Preferred term	45 mg BID N = 427	
	All Grades n (%)	Grade 3/4 n (%)
Fatigue	114 (26.7)	15 (3.5)
Vomiting	84 (19.7)	8 (1.9)
Constipation	65 (15.2)	2 (0.5)
Hypertension	64 (15.0)	34 (8.0)
Asthenia	60 (14.1)	8 (1.9)
AST increased	59 (13.8)	9 (2.1)
Pruritus	58 (13.6)	4 (0.9)
Decreased appetite	55 (12.9)	2 (0.5)
Pyrexia	53 (12.4)	0
Dry skin	45 (10.5)	0
Dyspnoea	44 (10.3)	6 (1.4)
Ejection fraction decreased	44 (10.3)	15 (3.5)
Retinal detachment	44 (10.3)	0

Abbreviations: AE = adverse event; AST = aspartate aminotransferase; CK = creatinine phosphokinase; mg = milligram(s); n or N = number.
Data cutoff date CMEK162A2301 18 Mar 2016; CMEK162X2201 06 Nov 2015.

One hundred three patients (24.1%) in the binimetinib 45 mg population experienced AEs that resulted in discontinuation of binimetinib treatment. The most frequently reported AEs leading to discontinuation (>1.0% of patients) were ejection fraction decreased (16 patients [3.7%]), blood CK increased (8 patients [1.9%]), retinal vein occlusion (7 patients [1.6%]), and edema peripheral, dermatitis acneiform and general physical health deterioration (5 patients [1.2%] each).

One hundred forty-one patients (33.0%) in the binimetinib 45 mg population reported at least 1 serious adverse event (SAE) on study or within 30 days of the last dose of binimetinib. The most frequently reported SAEs (>1.0% of patients) by PT were general physical health deterioration (3.7%), RVO (1.4%) and blood CK increased, diarrhea, dyspnea and vomiting (1.2% each).

In the binimetinib 45 mg population, 46 patients (10.8%) died on study or within 30 days of the last dose of binimetinib. The majority of on-treatment deaths (40 patients [9.4%]) were due to progression of malignant melanoma. Adverse events resulting in death for patients in the binimetinib 45 mg population were sepsis (2 patients) and dyspnea, embolism, euthanasia and multi-organ failure (1 patient each).

Please refer to the binimetinib IB[30] for a detailed discussion of the safety profile of binimetinib.

Clinical Experience in mPDAC

Study CMEK162X1101, conducted in Japanese patients with advanced solid tumors, included 3 with pancreatic cancer. Of these 3 patients, 1 experienced a SAE of Grade 4 CPK increased and 1 discontinued study treatment due to Grade 4 lipase increase; both of these events were considered to be related to study treatment. No objective responses (CR or PR) were observed in any of these patients.

1.2.2.1. Clinical Efficacy in Patients with Solid Tumors

Anti-tumor activity with single-agent binimetinib was demonstrated among 269 patients with NRAS-mutant melanoma enrolled in the Phase 3 NEMO study. In that study, the observed ORR was 15% (95% CI: 11, 20%) with a median duration of response of 6.9 months.[48]

Binimetinib has also demonstrated clinical activity when used in combination with encorafenib. In the Phase 3 COLUMBUS trial for the treatment of patients with BRAF-mutant advanced, unresectable or metastatic melanoma, the median progression-free survival for patients treated with the combination of encorafenib (450 mg daily) plus binimetinib (45 mg twice daily) was 14.9 months versus 7.3 months for patients treated with vemurafenib alone (960 mg twice daily) HR 0.54 (95% CI: 0.41–0.71, p<0.0001).[60]

1.2.2.2. Pharmacokinetics of Binimetinib

The pharmacokinetics (PK) of binimetinib are characterized to be a moderate to high variability drug. Increases in exposure are generally dose proportional over the dose range of 5 to 80 mg. The area under the curve (AUC) accumulation ratio was 1.31 at the 45-mg twice daily (BID) dose level in cancer patients (Study CMEK162X2201). Steady-state concentrations were reached within 15 days with an accumulation of approximately 1.5 fold with BID dosing. The median terminal half-life ($t_{1/2}$) was approximately 9 hours following a single 45 mg oral dose of ^{14}C-binimetinib in healthy male subjects (CMEK162A2102). Binimetinib and its metabolites were primarily eliminated by way of feces (62%).

The effect of food on binimetinib PK was evaluated in 2 studies, ARRAY-162- 104 and CMEK162A2103. No clinically significant food effect was observed in either study, therefore binimetinib may be administered without regard to food. Furthermore, a drug-interaction study (ARRAY-162-105) with the proton-pump inhibitor rabeprazole indicates binimetinib can be administered in the presence of stomach pH-altering agents.

Binimetinib is primarily metabolized by glucuronidation pathways (mainly via uridine diphosphate glucuronosyl transferase [UGT]1A1, 1A3 and 1A9); however, the impact of UGT1A1 inhibitors or inducers has not been clinically assessed. *In vitro* studies also demonstrated that binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but the effects of inhibitors of these transporters on the PK of binimetinib are unknown.

In vitro, binimetinib reversibly inhibits CYP2B6; however based on the inhibitory constant (Ki) and IC_{50} values for inhibition, the in vivo inhibition of CYP2B6 is not anticipated to be clinically relevant. Binimetinib has also induced CYP3A *in vitro*; however, in a drug-drug interaction study (CMEK162A2105) in healthy subjects, binimetinib did not alter the exposure of midazolam, indicating this induction is not clinically relevant.

Clinical Study CMEK162A2104 is a completed Phase 1 study investigating the PK of binimetinib in hepatic impairment subjects versus healthy subjects. Six subjects with mild hepatic impairment, 6 subjects with moderate impairment, 5 subjects with severe impairment and 10 subjects with normal hepatic function were enrolled. Data indicate that binimetinib exposure was not significantly altered in subjects with mild hepatic impairment compared to healthy subjects, but may be potentially increased up to 2-fold in subjects with moderate and severe hepatic impairment.

Clinical Study ARRAY-162-106 is a completed Phase 1 study investigating the PK of binimetinib in renal impairment subjects versus healthy subjects. The study was to be divided into 2 parts. In Part 1, a total of 12 subjects were enrolled: 6 subjects with severe renal impairment [estimated glomerular filtration rate (eGFR) ≤29 mL/min/1.73 m^2] and 6 matching healthy subjects (eGFR ≥80 mL/min/1.73 m^2). The Part 1 results indicated the exposure of binimetinib in severely impaired subjects was 20% to 30% higher compared with healthy subjects. A review of the Part 1 PK data determined Part 2 (evaluation of subjects with moderate and mild renal impairment and matching healthy subjects) was not required to be conducted since the increase in binimetinib exposure in subjects with severe renal impairment compared with the matching healthy subjects was below the protocol-specified 50% increase.

In a population PK analysis, apparent oral clearance (CL/F) and apparent volume of distribution (V/F) decreased by about 1% and 8%, respectively, in typical elderly subject in the 95th percentile of age (79 years old) on study, compared with a typical younger patient (59 years old). Binimetinib exposure has not been evaluated in adolescents or children less than 18 years of age.

For further details on the PK and metabolism of binimetinib, please refer to the current binimetinib IB.[30]

1.2.2.3. Avelumab in Combination with Binimetinib

Preliminary safety results for the doublet combination of avelumab with binimetinib that was examined within this current study (B9991033) are provided in this section. The initial Phase 1b study examined the safety of avelumab administered at a fixed dose of 800 mg Q2W in combination with binimetinib administered orally BID on a continuous daily dosing schedule. Two dose levels were studied, including a first dose level with binimetinib at 45 mg BID (Dose Level D0) and a reduced dose level with binimetinib at 30 mg BID (Dose Level D-1). As of the database cut-off date of 31 July 2019, a total of 22 patients with mPDAC received study treatment.

Initially, a total of 12 patients were treated at the starting dose of avelumab (800 mg Q2W) and binimetinib at 45 mg BID. Of these 12 patients, 11 were determined to be DLT-evaluable; 1 patient discontinued treatment prior to completing the DLT evaluation period due to disease progression and was not evaluable. Among the 11 DLT-evaluable patients, 5 experienced AEs that met DLT criteria, including 1 patient each with Grade 3 hypertension, Grade 4 increased blood creatinine phosphokinase (CPK), and Grade 3 pustular rash; 1 patient with a combination of gastrointestinal toxicities (ie, Grade 2 nausea, Grade 2 vomiting, Grade 2 abdominal pain, and Grade 1 diarrhea); and 1 patient with two DLTs, including Grade 3 retinal pigment epithelium detachment (RPED) that fully resolved following treatment discontinuation and a Grade 3 pneumonitis that was also reported as a serious adverse event (SAE). Based on these DLTs, avelumab Q2W in combination with this binimetinib dose administered on a continuous schedule was assessed as having exceeded the probability of overdosing and, therefore, enrollment proceeded at the lower dose level (D-1).

A total of 10 patients were treated at the avelumab 800mg Q2W and binimetinib 30 mg BID dose level, all of whom were determined to be DLT-evaluable. In total, 3 of the 10 patients experienced study treatment-related AEs that met DLT criteria, including 1 patient each with Grade 3 increased blood CPK, Grade 3 acneiform dermatitis, and Grade 3 mucosal inflammation (mucositis). Of these DLTs, the Grade 3 mucositis also met SAE criteria as the patient was hospitalized due to this event.

As of the database cut-off date of 31 July 2019, the most frequently reported TEAEs among all 22 patients, regardless of study drug relationship, included rash (9 patients); AST increased, acneiform dermatitis, CPK increased, and fatigue (7 patients each); ALT increased, pyrexia, diarrhea, nausea, and vomiting (6 patients each); abdominal pain, hypertension, and peripheral edema (5 patients each); and infusion-related reaction, dehydration, and pruritis (4 patients each). Most reported TEAEs were Grade 1-2 in severity, however most (18 of 22) of the patients experienced at least one Grade ≥3 TEAE, including 3 patients with Grade 5 (fatal) TEAEs of disease progression that were not related to study drug.

Although the rate of DLTs was higher than expected, the overall safety profile remained consistent with the individual study drugs and the study population. Given the observed DLT rates when avelumab was combined with either 30 or 45 mg BID continuous binimetinib, enrollment into any of the planned triplet combination dose levels (avelumab, binimetinib and talazoparib) was not feasible according to the BLRM and no further patients will be enrolled using the continuous binimetinib dosing schedule.

1.2.3. Talazoparib Clinical Experience

As of 30 November 2016, approximately 439 patients have received talazoparib in company-sponsored studies in hematologic malignancies and solid tumors. Studies in solid tumors include a Phase 1 study (PRP-001) in advanced or recurrent solid tumors, a Phase 1 study in advanced malignancies (PRP-002), a Phase 2 study (673-201) in locally advanced and/or metastatic breast cancer patients with a germline breast cancer gene (BRCA) defect, a Phase 3 study (673-301) in locally advanced or metastatic breast cancer with a germline BRCA defect, a Phase 1 hepatic impairment study (MDV3800-02), a Phase 1 absorption,

distribution, metabolism and excretion (ADME) study (MDV3800-03) and a Phase 1 study on cardiac repolarization (MDV3800-14).

As of 30 November 2016, aggregate safety data from 3 company-sponsored clinical studies evaluating talazoparib monotherapy at the recommended single-agent dose of 1 mg once daily (QD) in patients with advanced malignancies (Phase 1 studies PRP-001 and MDV3800-14 and Phase 2 study 673-201; 164 patients total) provide the basis for the most common TEAEs (occurring in ≥20% of patients), which were fatigue (47.6%), anemia (45.7%), nausea (41.5%), thrombocytopenia (26.8%), diarrhea (26.2%), alopecia (22.6%), neutropenia (22.6%), constipation (22.0%), and headache (21.3%). Study drug-related TEAEs occurring in ≥20% of patients included anemia (42.1%), fatigue (36.6%), nausea (29.3%), thrombocytopenia (25.6%), neutropenia (20.7%), and alopecia (20.1%). The most common Grade 3 or higher drug-related TEAEs occurring in ≥5% of patients were anemia (28.0%), thrombocytopenia (16.5%), and neutropenia (12.2%).

Serious adverse events (SAEs) occurred in 52 of 164 patients (31.7%) who received 1 mg QD talazoparib. Serious adverse events occurring in ≥2% of patients were pleural effusion (4.3%), anemia and dyspnea (3.7% each), and neoplasm progression and thrombocytopenia (2.4% each). Fourteen patients had SAEs considered related to talazoparib, which included anemia (3.0%); thrombocytopenia (2.4%); platelet count decreased (1.2%); and increased transaminases, neutropenic sepsis, and vomiting (0.6% each).

A total of 12 of 164 patients (18.8%) who received 1 mg QD talazoparib had a TEAE that led to death (6 associated with the underlying malignancy including 1 also associated with bronchopneumonia; 2 dyspnea; and 1 each disease progression, lung infection, hypoxia, and respiratory failure). Of these events, none were assessed as related to talazoparib.

Among the 164 patients who received 1 mg QD talazoparib, 19.5% had a TEAE that led to dose reduction and 57.3% had a TEAE that led to dose interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression.

Five of 164 patients (3.0%) treated with talazoparib at a dose of 1 mg QD permanently discontinued talazoparib due to a TEAE. The TEAEs that led to study drug discontinuation were anemia, increased ALT, increased AST, metastatic breast cancer, and dyspnea.

In the ongoing Phase 3, open-label, randomized, parallel-group study (protocol no. 673-301 [EMBRACA]), talazoparib is being evaluated in patients with germline BRCA 1/2 mutations who received no more than 3 prior chemotherapy regimens for locally advanced or metastatic breast cancer. Based on this study, a NDA for talazoparib as a treatment for this patient population was submitted to US FDA on 06 April 2018. For this submission, a pooled safety analysis for 494 patients with solid tumors in Phase 1-3 studies who received talazoparib 1 mg QD was provided, with a data cut-off date of 15 September 2017.[62] AEs reported for ≥20% of patients were anemia (49.2%), fatigue (47.6%), nausea (44.3%), headache (26.5%), neutropenia (22.9%), diarrhea (22.7%), alopecia and vomiting (22.3% each), constipation (20.6%), and decreased appetite (20.2%). The results are

consistent with the pooled safety analysis reported in the current Investigator's Brochure for talazoparib and summarized above.

Clinical Experience in mPDAC

Thirteen patients with pancreatic cancer received talazoparib in study PRP-001, including 3 patients in the dose escalation phase (Part 1) and 10 patients receiving 1.0 mg/day in a tumor expansion cohort (Part 2). Treatment-related AEs reported in 2 or more of the 13 pancreatic patients included anemia (2 patients), neutropenia (3 patients), and flatulence (2 patients). Of these events, 2 each of anemia and neutropenia were Grade 3 or 4 in severity. Six (6) patients experienced a SAE, including 1 patient each with bacteremia, malignant ovarian cyst, pancreatic carcinoma, tumor associated fever, disease progression, and hyperbilirubinemia. None of these SAEs was considered by the investigator to be related to study drug.

Among 10 patients with pancreatic cancer receiving 1.0 mg/day in the dose-expansion (Part 2) phase of study, the objective response rate was 20.0% (2 patients with a PR) and clinical benefit rate (CR, PR, or stable disease lasting at least 16 weeks) was 30.0% (3 patients). In addition, there were 3 pancreatic cancer patients treated in dose escalation (Part 1) phase of the study, including 1 enrolled at 0.025 mg/day and 2 enrolled at 0.05 mg/day; no objective response was observed among these 3 patients.

1.2.3.1. Clinical Efficacy in Patients with Advanced Solid Tumors

Talazoparib, as a single-agent, has demonstrated anti-tumor activity in patients with multiple types of solid tumors with DNA repair pathway abnormalities, particularly those associated with BRCA and phosphatase and tensin homolog gene (PTEN) dysfunction, including breast cancer, ovarian/peritoneal cancer, and pancreatic cancer in the Phase 1 Study PRP-001. In patients with advanced breast cancer, ovarian/peritoneal cancer and pancreatic cancer, ORRs of 50.0% (7 of 14), 41.7% (5 of 12) and 20% (2 of 10) were observed, respectively.[9]

In the ongoing Phase 3 EMBRACA study in patients with BRCA 1/2-positive locally advanced and/or metastatic breast cancer, single-agent talazoparib demonstrated superior PFS versus physician choice chemotherapy. Median PFS was 8.6 months (95% CI: 7.2, 9.3) for patients treated with talazoparib and 5.6 months (95% CI: 4.2, 6.7) for those treated with chemotherapy [HR: 0.54 (95% CI: 0.41, 0.71), p<0.0001].[40]

1.2.3.2. Pharmacokinetics of Talazoparib in Humans

Talazoparib plasma exposure was dose proportional in the dose range of 0.025 mg to 2 mg QD suggesting linear PK. Talazoparib absolute bioavailability is at least 54.6%. After administration of a single 1 mg dose of talazoparib to cancer patients, the median T_{max} ranged from 0.5 to 2.0 hours across studies. Administration of talazoparib with food (a high-fat, high-calorie meal) had no impact on the AUC while reduced the C_{max} by 46%. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is driven by total exposure. Therefore, talazoparib can be taken without regard of food.

Mean talazoparib binding to human plasma proteins is 74%. Population PK analysis showed that talazoparib apparent steady-state volume of distribution (V_{ss}/F) was 420 L, which is greater than total body water (42 L), indicating that talazoparib distributes to peripheral tissues.

Talazoparib undergoes minimal hepatic metabolism. Based on population PK analysis, there was no effect of mild hepatic impairment (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) on talazoparib exposure. No dose adjustment is necessary for patients with mild hepatic impairment. The effect of hepatic impairment on talazoparib PK is being investigated in the ongoing study MDV3800-02.

Talazoparib was eliminated slowly with a mean terminal plasma half-life ($t_{1/2}$) of 89.8 hours. Talazoparib accumulated after 1 mg QD dosing with a median accumulation ratio ranging from 2.33 to 5.15, consistent with its $t_{1/2}$. Population PK analysis showed that talazoparib CL/F was 6.45 L/hr. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose. Population PK analysis showed that talazoparib CL/F was reduced by 14.4% and 37.1% in patients with mild renal impairment (creatinine clearance [CrCl], 60-89 mL/min) and moderate renal impairment (30 mL/min ≤CrCl <60 mL/min), respectively, compared to that of patients with normal renal function (CrCl >90 mL/min). No dose adjustment is recommended for patients with mild renal impairment. The starting dose of talazoparib for patients with moderate renal impairment should be reduced to 0.75 mg. The effect of renal impairment on talazoparib PK is being investigated in the ongoing study MDV3800-01.

In vitro studies showed that talazoparib is a substrate for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Population PK analysis indicated that concomitant administration of strong P-gp inhibitors with talazoparib increased talazoparib exposure by 44.7% relative to talazoparib administered alone. Details of prohibited medications for this study are provided in Section 5.8.6.

1.2.3.3. Talazoparib in Combination with Avelumab (Study B9991025)

The combination of avelumab with talazoparib is currently being studied in Pfizer study B9991025 (JAVELIN Parp Medley). This Phase 1b/2 study will examine the safety and anti-tumor activity of avelumab administered at a fixed dose of 800 mg Q2W in combination with talazoparib (0.5 mg, 0.75 mg, or 1.0 mg) administered orally once daily in patients with advanced solid tumors. The starting dose level of talazoparib was 1.0 mg once daily. Preliminary safety data are available for the Phase 1b portion of this study, following evaluation of the first 12 enrolled patients. All patients had completed their first cycle with treatment of avelumab at 800 mg IV Q2W in combination with talazoparib 1 mg PO QD and were evaluable for DLT. The most frequently reported TEAEs were anemia (8 patients, 66.7%), neutropenia (7 patients, 58.3%), and chills and thrombocytopenia (both 5 patients, 41.7%). The most frequently reported Grade 3 TEAEs were thrombocytopenia (4 patients, 33.3%), anemia (3 patients 25.0%), and neutropenia (2 patients, 16.7%).

A DLT rate of 0.25 was observed with no unexpected toxicities: a total of 3 DLTs occurred that warranted dose interruption and reduction (two cases of Grade 3 thrombocytopenia and one case of Grade 3 neutropenia).[68]

The safety profile of the combination of avelumab with talazoparib at full dose remained aligned to the safety profiles for the individual monotherapies. The RP2D for talazoparib in combination with avelumab at 800 mg IV Q2W was established at 1 mg PO QD.

1.2.4. Rationale for the Study

1.2.4.1. Rationale for Combination Treatment

Based on the mechanisms of action discussed in Sections 1.1.1, 1.1.2 and 1.1.3, avelumab, binimetinib and talazoparib have the potential to produce additive or synergistic anti-tumor activity relative to each drug used as a single-agent, with (i) avelumab functioning to overcome PD-L1-mediated inhibition of anti-tumor immune response, (ii) binimetinib enhancing the antitumor activity of anti-PD-1/PD-L1 antibodies, (iii) talazoparib functioning to promote immune priming and tumor immunogenicity, and (iv) talazoparib and binimetinib having a potential synergistic cytotoxic effects when administered in combination.

The activity of avelumab depends on generation of a productive immune response, composed of effective antigen presentation, T-cell priming, infiltration of tumors, and recognition and killing of tumor cells.[18] Studies suggest that oncogenic RAS signaling upregulates PD-L1 expression via the MEK-ERK pathway,[41,47] and that inhibition of MEK in combination with checkpoint blockade promotes T-cell and anti-tumor activity.[42] Consistent with this, the combination of binimetinib with an anti-PD-1 antibody improved anti-tumor activity and survival as compared to single-agent controls in a KRAS-mutant tumor model.[43]

In addition to upregulating PD-L1, MEK has also been identified as a negative regulator of MHC-I expression in multiple cancer cell lines. As demonstrated with the MEK inhibitor (MEKi) trametinib and the V600E BRAF inhibitor vemurafenib, binimetinib also increases basal interferon (IFN)-gamma induced MHC Class I expression in NRAS-and BRAF-mutant melanoma cell lines.[33] In syngeneic CT26 CRC engrafted BALB/C mice, the MEKi trametinib + anti-PD-1 antibody inhibited tumor growth more effectively than their single-agent controls. In addition, the combination increased tumor infiltrating CD8+ T cells *in vivo*, with no significant alterations in the numbers and expression levels of CD3, CD4, CD25, CD69, and PD-1.[34]

Talazoparib, via its ability to promote increased DNA damage, has the potential to promote several key stages of the immune response that may synergize with PD-L1 blockade by avelumab. Firstly, talazoparib-mediated cell death, via either PARP trapping or via increased DNA damage, has the potential to release antigens into the tumor microenvironment, promoting effective antigen presentation; this has been described for other therapies that lead; to increased tumor cell death.[19] Secondly, DNA damage promotes inflammation via 2 alternative pathways, the first being activation of the NF-κB pathway via ataxia-telangiectasia mutated (ATM)-mediated phosphorylation of the NF-κB essential modulator (NEMO),[10] and the second being activation of the STING pathway via generation

and detection of cytosolic DNA.[11,12] Activation of these pathways leads to increased pro-inflammatory signaling that enhances effective recognition and infiltration of tumors by immune cells, and has recently been shown to be critical to the response to checkpoint inhibition in mice.[20] Finally, DNA damage has been shown to lead to upregulation of MHC, NKG:2DL, and ICOSL,[13,14] which would be expected to increase the intrinsic immunogenicity of tumor cells and enhance their recognition and killing by T -cells and NK -cells.

Emerging data also indicate that the combination of PARP and MEK inhibition has synergistic anti-tumor activity. Combined treatment with the PARP inhibitor talazoparib and MEK inhibitor selumetinib induces synergistic cytotoxic effects *in vitro* and *in vivo* in multiple RAS-mutant tumor models across tumor lineages where RAS mutations are prevalent.[44] The effects of the combination are independent of BRCA1/2 and p53 mutation status, suggesting that the synergistic activity is likely to be generalizable.

Given that recent clinical trial results for a similar combination of an anti-PD-L1 and a MEK inhibitor showed limited clinical activity[69,70] and pre-clinical data support the combination of MEK and PARP inhibitors,[44,72] this trial has been modified (Amendment 3) to explore the doublet combination of binimetinib and talazoparib in addition to the triplet combination of avelumab, binimetinib and talazoparib. This doublet combination is anticipated to have an acceptable safety profile, as seen with the combination of the MEK and PARP inhibitors, selumetinib and olaparib, respectively, which was well tolerated in an ongoing Phase 1 study.[71]

In conclusion, the above rationale supports the clinical investigation of combinations of PD-L1, MEK, and PARP inhibition in patients with locally advanced or metastatic KRAS- or NRAS-mutant tumors where there are few effective therapeutic options.

1.2.4.2. Safety Considerations and Rationale for Phase 1b BLRM Design

The relatively distinct safety profile of avelumab, binimetinib and talazoparib also supports the clinical evaluation of the doublet and triplet combinations. While there are no overlapping DLTs observed in the single-agent Phase 1 trials of these agents, common toxicities observed with all 3 agents includes fatigue, nausea, and diarrhea, however these were generally mild or moderate in severity. Additionally, the relatively short half-life of binimetinib may allow for more effective toxicity management in the context of the combination treatments.

Guidance for dosing (dose level to be evaluated in the next cohort) and enrollment (number of patients to be enrolled in the next cohort) decisions will be based on a Bayesian Logistic Regression Model (BLRM). The BLRM provides an optimal design for dose finding with combination treatments as it incorporates single-agent and available combination DLT data (historical and prospectively across dose cohorts) to estimate the posterior probability of underdosing, target dosing, and overdosing, thereby reducing patient risk and increasing efficiency and precision during dose finding with combination treatments.

1.2.4.3. Drug-Drug Interaction Assessment

Based on the characteristics of each compound, the drug-drug interaction (DDI) potential among avelumab, binimetinib, and talazoparib is considered to be minimal for the following reasons: i) the DDI between small molecules (binimetinib and talazoparib) and biologics (avelumab) is uncommon; ii) the 3 drugs do not share metabolic/elimination pathways: Avelumab is an immunoglobulin G1 (IgG1) mAb eliminated by intracellular lysosomal proteolytic degradation, binimetinib is metabolized primarily by glucoronidation, and talazoparib is mostly renally eliminated; and iii) although both binimetinib and talazoparib are substrates of P-gp and BCRP, neither drug was found to be an *in vitro* inhibitor of these transporters. Therefore, the potential of metabolic interaction between these drugs is minimal.

To assess for potential DDI, the concentrations of avelumab, binimetinib and talazoparib will be measured in all patients enrolled in this study and compared with historical PK data for each agent when administered alone, including a real time PK assessment during the Phase 1b part of the study.

1.2.5. Rationale for Patient Population

1.2.5.1. Rationale for KRAS- and NRAS-Mutant Tumors

Oncogenic RAS mutations are common drivers of cancer cell proliferation and survival, yet therapies which specifically target RAS-mutant tumors are not currently available in the clinic. While the proposed combination treatments may also have clinical utility against BRAF-mutant tumors that also activate the MEK-ERK pathway, drugs specifically targeting BRAF are currently available and/or are actively being studied; as such, BRAF-mutant tumors were not considered for inclusion in this current study.

Section 1.2.4 presents the mechanistic rationale for targeting RAS-mutant tumors with the combinations of avelumab, binimetinib and talazoparib:

- RAS mediates upregulation of PD-L1 via the MEK-ERK signaling pathway.[47]
- MEK is a negative regulator of MHC-I expression in multiple cancer cell lines.
- Concurrent PARP and MEK inhibition has synergistic anti-tumor activity in RAS-mutant tumor models.

Thus, combinations of PD-L1, MEK, and PARP inhibition may confer clinical benefit in patients with RAS-mutant tumors.

Given that different RAS proteins may potentially activate different pathways outside of MEK/ERK, as well as the small sample size planned for this study, the study population will be limited to those with KRAS- or NRAS-mutant tumors.

1.2.5.2. Rationale for Tumor Types and Prospective Patient Selection

The primary tumor type of interest for this study - mPDAC - was selected based on the high frequency of RAS mutations in this tumor type as well as an unmet medical need which is foreseen to continue into the future.

As anti-PD-1/L1 therapy is anticipated to become more commonly administered in the first- and second-line settings for patients with NSCLC, this population will be limited to those who have progressed following 1 prior treatment line with these agents in order to explore the anti-tumor activity of each combination treatment. The rationale for the combination treatment provided in Section 1.2.4.1 also supports studying this population by providing a basis for potentially overcoming resistance to immune checkpoint blockade, such as by: (i) increasing IFN-gamma induced MHC-I expression and T-cell infiltration (ie, via MEK inhibition with binimetinib), and (ii) increasing antigen presentation and pro-inflammatory signaling (ie, via PARP inhibition with talazoparib).

KRAS- and NRAS-mutations are prevalent in mPDAC, occurring at a frequency of over 90% in pancreatic cancer.[39,46] While patients with mPDAC will be enrolled in a tumor-specific cohort in the Phase 2 portion of this trial, eligible patients with advanced NSCLC will be enrolled in a 'tumor agnostic' cohort of patients bearing either KRAS- or NRAS-mutant tumors. While it was initially planned to include a tumor-specific NSCLC cohort, this was removed in Amendment 3 due to patient recruitment concerns (ie, anticipated slow enrollment of these patients). In addition to NSCLC, it is anticipated that the 'tumor agnostic' cohort will enroll patients with CRC (~50% are positive for KRAS/NRAS mutations) as well as patients with melanoma, endometrial and stomach cancers (~10 - 30% positive).[46] For this cohort, only the triplet combination of avelumab, binimetinib and talazoparib will be studied as this combination may provide clinical benefit to a broader population of patients than primarily planned for this study (ie, mPDAC).

Patients in the 'tumor agnostic' cohort must be positive for KRAS or NRAS mutations in order to be eligible for participation in this study. To facilitate patient enrollment and study conduct, previous positive test results obtained at any time for the current diagnosis under study, as well as by prospective local laboratory testing, may be used to determine patient eligibility. Given the high frequency of KRAS mutations in pancreatic cancer, these patients will not be preselected based on KRAS/NRAS mutation status. Nevertheless, tumor samples for all patients will be submitted to a central laboratory for a retrospective confirmation of RAS mutation status.

1.2.6. Rationale for the Investigational Product Doses

1.2.6.1. Avelumab 800 mg fixed Dose Q2W

To date, avelumab has been administered at the clinically active, safe, and tolerable dose of 10 mg/kg Q2W to more than 1700 patients across multiple indications. Furthermore, this 10 mg/kg Q2W avelumab dosing regimen has been approved by the FDA as the first treatment for MCC and also for the treatment of UC following platinum-containing chemotherapy.

Avelumab was originally dosed on a mg/kg basis in order to reduce inter-subject variability in drug exposure. However, emerging data for mAbs, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body-weight independent) dosing regimens.[21,22,23] Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population PK analysis was conducted based on the acquired PK data across 3 single-agent avelumab studies in patients with 14 different types of cancer. Pharmacokinetic simulations suggest that exposures to avelumab across the available range of body weights are similar with 800 mg Q2W compared with 10 mg/kg Q2W; exposures were similar near the population median weight. Low-weight subjects tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when flat dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the whole population. Furthermore, the 800 mg Q2W and every 3 weeks (Q3W) dosing regimens are expected to result in C_{trough} >1 μg/mL which is required to maintain avelumab serum concentrations at >90% TO throughout the entire dosing interval in all weight categories.

Therefore, in this clinical trial, a fixed dosing regimen of 800 mg administered as a 1-hour IV infusion Q2W will be utilized for avelumab.

1.2.6.2. Binimetinib

The dose levels of binimetinib to be evaluated in this study are supported by clinical studies in patients with advanced solid tumors. A summary of pooled safety data from 2 single-agent clinical studies of binimetinib in patients with metastatic melanoma (Study CMEK162X2201 and CMEK162A2301) treated at the recommended dose of 45 mg twice daily has demonstrated an acceptable safety profile.

As of the data cutoff date of 20 January 2018, the experience of binimetinib in combination with other targeted agents, standard chemotherapy agents or immunomodulating agents in 1457 patients with advanced cancer in 16 clinical studies. The 45 mg twice daily dose has been used in a triple combination with encorafenib and ribociclib, and has also been studied in combination with other investigational agents (RAF265, buparlisib, BEZ235, sotrastaurin and ganitumab).

Initially, this study (B9991033) examined avelumab and continuous binimetinib with the objective of identifying an RP2D for the doublet combination of avelumab and binimetinib. Due to observed DLTs, the dosing schedule for binimetinib has been modified (Amendment 3) to an intermittent schedule of 7 days on treatment/7 days off (Schedule 7d/7d). As most of the DLTs observed with the continuous binimetinib dosing schedule were consistent with binimetinib's safety profile (eg, rash, CPK increase, RPED), an intermittent dosing schedule is expected to mitigate these potential toxicities. This schedule is also supported by preclinical data that have shown that pulsatile (Schedule 7d/7d) dosing of the MEKi

selumetinib resulted in superior efficacy as compared with continuous dosing, potentially through improved activation of tumor infiltrating lymphocytes.[73]

In the event that the doublet combination of binimetinib and talazoparib is well tolerated using Schedule 7d/7d for binimetinib with an RP2D of at least 45 mg binimetinib and 0.75 mg talazoparib, the combination of binimetinib (BID) administered on a more intensive dosing schedule (ie, 5 days on treatment/2 days off treatment [Schedule 5d/2d]) with continuous talazoparib (QD) may also be explored for this doublet combination (Note: the triplet combination will only use Schedule 7d/7d binimetinib dosing). Similar intermittent dosing schedules have also been administered with other MEK inhibitors in order to reduce treatment-related toxicity, including selumetinib (4 days on treatment/3 days off treatment) and PD-0325901 (5 days on treatment/2 days off treatment).[74,75]

1.2.6.3. Talazoparib

The dose levels of talazoparib to be evaluated in this study are supported by clinical studies in patients with advanced malignancies. In the PRP-001 Phase 1 study in patients with advanced or recurrent solid tumors, talazoparib was escalated from 0.025 to 1.1 mg daily and the recommended dose for further development was determined to be 1 mg daily. Data from this study at 1 mg/day demonstrated objective responses or clinical benefit (CR, PR, or stable disease ≥24 weeks) in patients with breast, ovarian/peritoneal, pancreatic cancer, small cell lung cancer (SCLC), and Ewing sarcoma. Aggregate safety data for 164 patients enrolled in 3 open-label, company-sponsored clinical studies evaluating talazoparib monotherapy at 1 mg/day (PRP-001, 673-201, and MDV3800-14) have demonstrated an acceptable safety profile. Additionally, the dose level of 1 mg daily was used in the randomized Phase 3 study 673-301 in patients with locally advanced or metastatic breast cancer.

1.2.7. Summary of Benefit/Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

The benefit-risk relationship has been carefully considered in the planning of this trial. Responses to avelumab have been observed in a broad range of other tumor types, including NSCLC, ovarian cancer, gastric/gastroesophageal junction cancer, urothelial carcinoma, mesothelioma, adrenocortical carcinoma, gastric cancer, and merkel cell carcinoma.[3] The clinical safety data available to date with single-agent avelumab in patients with advanced solid tumors suggest an acceptable safety profile, as described in Section 1.2.1. Most of the observed AEs were either in line with those expected in patients with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with an antihistamine and acetaminophen prior to the first 4 avelumab infusions (Cycles 1-2) and as clinically indicated thereafter.

Based upon the observed anti-tumor activity as a single agent in NRAS-mutant melanoma in combination with its clinical safety profile, binimetinib continues to have a favorable benefit-risk profile to support current clinical development in patients with selected advanced/metastatic malignancies. In pooled safety data from 2 single-agent clinical studies (N=427), the most common (≥20.0% of patients) AEs were blood CK increased (44.7%), diarrhea (42.6%), dermatitis acneiform (41.5%), edema peripheral (40.7%), rash (34.2%), nausea (30.0%), and fatigue (26.7%). Anti-tumor activity with single-agent binimetinib was demonstrated among 269 patients with NRAS-mutant melanoma enrolled in the Phase 3 NEMO study. In that study, the observed ORR was 15% (95% CI: 11, 20%) with a median DR of 6.9 months.[48]

As described in Section 1.2.2.3, the overall safety profile of binimetinib administered continuously in combination with avelumab remained consistent with the individual study drugs and the study population. However, due to the DLT rate observed among patients receiving avelumab and continuous binimetinib dosing in this study, the dosing schedule for binimetinib proposed for evaluation in the doublet and triplet combinations has been modified (Amendment 3) to an intermittent dosing schedule(s) which is expected to mitigate these potential toxicities.

As described in Section 1.2.3.1, talazoparib has shown anti-tumor activity in patients with breast, ovarian, peritoneal and pancreatic cancers. The clinical safety profile of talazoparib supports its use as both a single-agent and in combination with cancer therapies. The most common TEAEs associated with single-agent talazoparib administration (>20% of patients) were myelosuppression (eg, anemia, thrombocytopenia, neutropenia), gastrointestinal toxicity (eg, nausea, diarrhea, vomiting), fatigue, alopecia, and headache; Grade ≥3 TEAEs in ≥5% of patients were associated with myelosuppression. These AEs were primarily Grade 1 or 2 severity and typically resolved with temporary dose interruptions or reductions.[9] The anti-tumor activity of single-agent talazoparib has been demonstrated in the ongoing EMBRACA study in BRCA1/2-positive patients with locally advanced and/or metastatic breast cancer, in which talazoparib provided a significantly superior ORR and PFS benefit as compared to standard chemotherapy.[40]

Based on the manageable safety profiles of avelumab, binimetinib and talazoparib administered as single-agents, the expected low incidence of overlapping severe toxicities, and the anticipated enhanced anti-tumor activity, the projected benefit-risk relationship of the proposed combinations are expected to be favorable for investigation in this population of patients with advanced solid tumors.

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2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• Phase 1b: To assess the 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 ORR of the doublet and triplet combinations based on Investigator assessment per RECIST v1.1 in patients with mPDAC and other KRAS- or NRAS-mutant advanced solid tumors.	• Phase 1b: DLT during the primary DLT evaluation period (Cycle 1). • Phase 2: Confirmed OR based on Investigator assessment per RECIST v1.1 (see Appendix 3).
Secondary Objective(s):	**Secondary Endpoint(s):**
• 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, DDR gene alterations, and TMB in baseline tumor tissue.	• Adverse Events as characterized by type, severity (as graded by NCI CTCAE v4.03), timing, seriousness, and relationship to study treatment. • Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v4.03) and timing. • PK parameters, ie, C_{trough} for avelumab, binimetinib, and talazoparib, and C_{max} for avelumab and binimetinib, at various cycles. • Avelumab ADA levels and nAb against avelumab. • Phase 1b: Confirmed OR based on Investigator assessment per RECIST v1.1. • TTR, DR, and PFS based on Investigator assessment per RECIST v1.1 and OS. • PD-L1 expression level, DDR gene alterations, and TMB in baseline tumor tissue.

Exploratory Objective(s)	Exploratory Endpoint(s)
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

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 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 and talazoparib. Due to observed DLTs with continuous binimetinib dosing, the dosing schedule for binimetinib has been modified (Amendment 3) to an intermittent dosing schedule(s) which is expected to mitigate these potential toxicities.

Per 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 previously enrolled during Phase 1b enrolled prior to implementation of 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.

For Phase 1b, only patients with mPDAC will be enrolled. The doublet combination of binimetinib BID (Schedule 7d/7d) and talazoparib will be evaluated first to determine the RP2D for this combination. Upon the completion of the dose-finding for the doublet, the triplet of avelumab in combination with binimetinib and talazoparib will then be evaluated to determine the RP2D for this combination.

Guidance for Phase 1b dosing (dose level to be evaluated in the next cohort) and enrollment (number of patients to be enrolled in the next cohort) decisions will be based on a BLRM. The BLRM incorporates single-agent and available combination DLT data (historical and prospectively across dose cohorts) to estimate the posterior probability of under-dosing, target dosing and overdosing, thereby reducing patient risk and increasing efficiency and precision during dose finding with combination treatments.

3.1.1. Phase 1b Design

The dose levels of avelumab and continuous binimetinib studied prior to implementation of Amendment 3 are included in Table 7. The starting dose level (D0) was 800 mg avelumab IV Q2W and 45 mg binimetinib orally twice daily, which satisfied the EWOC criterion[35] that the risk for excessive toxicity be less than 0.25. Of note, for the D0, the risk of excessive toxicity was estimated to be 0.10 based on the information from prior single-agent Phase 1 studies and a PK assessment of no potential drug-drug interaction between avelumab and binimetinib.

Table 7. Avelumab and Binimetinib Dose Levels

Dose Level	Avelumab dose IV (mg Q2W)	Binimetinib dose oral (mg twice daily)
D0	800	45
D-1	800	30

Abbreviations: D0= starting dose; D-1=reduced dose; IV= intravenous; mg= milligram; Q2W= every 2 weeks.

The potential dose levels for the combination of binimetinib and talazoparib are shown in Table 8. The starting dose level (BT0) is 45 mg binimetinib orally BID, Schedule 7d/7d, and talazoparib 0.75 mg orally, QD on a continuous dosing schedule, which satisfies the EWOC criterion[35] that the risk for excessive toxicity be less than 0.25. Of note, for BT0, the risk of excessive toxicity was estimated to be 0.189 based on the information from prior single-agent Phase 1 studies[30,9] and a PK assessment of no potential drug-drug interaction between binimetinib and talazoparib (see Appendix 6 Table 40).

Table 8. Binimetinib and Talazoparib Dose Levels

Dose Levels	Binimetinib Dose (Oral) (mg twice daily)*	Talazoparib Dose (Oral) (mg daily)
BT1	45	1.0
BT0	45	0.75
BT-1	45	0.5
BT-2	30	1.0
BT-3	30	0.75
BT-4	30	0.5

Abbreviations: mg= milligram.
*In accordance with the assigned intermittent dosing schedule (ie, Schedule 7d/7d or 5d/2d).

Dose-finding for the triplet of avelumab, binimetinib and talazoparib will begin once the RP2D for the doublet combination (Schedule 7d/7d binimetinib dosing) has been confirmed in at least 9 DLT-evaluable patients (see Section 9.1.3).

The potential dose levels for the triplet combination of avelumab, binimetinib, and talazoparib are listed in Table 9. The starting dose level for the triplet will be determined at the completion of the dose finding for the doublet combinations based on all available clinical data (including but not limited to safety and PK data) from the avelumab and binimetinib and binimetinib and talazoparib doublet dose-finding portions of this study and from the combination of avelumab and talazoparib (dose-finding component of study B9991025).

Table 9. Avelumab, Binimetinib and Talazoparib Dose Levels

Avelumab Dose (IV) (mg Q2W)	Binimetinib Dose (Oral) (mg twice daily, Schedule 7d/7d)	Talazoparib Dose (Oral) (mg daily)
800	30	0.5
800	30	0.75
800	30	1.0
800	45	0.5
800	45	0.75
800	45	1.0

Abbreviations: IV= intravenous; mg= milligram; Q2W= every 2 weeks.

If the doublet of binimetinib and talazoparib is well tolerated using Schedule 7d/7d for binimetinib with an RP2D of at least 45 mg binimetinib and 0.75 mg talazoparib, the combination of binimetinib (BID) administered on a more intensive dosing schedule (ie, 5 days on/2 days off; Schedule 5d/2d) with continuous talazoparib (QD) may also be explored in order to determine the RP2D for this combination. In this case, possible dose

levels include those indicated in Table 8, with a starting dose level that will be selected based on satisfying the EWOC criterion. Patient enrollment into this doublet combination using Schedule 5d/2d for binimetinib dosing may occur in parallel with that of the triplet dose finding using Schedule 7d/7d for binimetinib dosing.

For each combination, beginning with the starting dose level, cohorts of 3-6 patients will be enrolled, treated, and monitored during the 28 day DLT evaluation period (Cycle 1). Patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of the investigational products in Cycle 1 for reasons other than treatment related toxicity are not evaluable for DLT. A minimum of 3 DLT-evaluable patients will be required; additional patients will be enrolled in the specific enrollment cohort to replace patients who are not considered DLT-evaluable, where required. When all DLT-evaluable patients treated in a given enrollment cohort have completed the DLT observation period or experienced a DLT, whichever occurs first, the posterior distribution for the risk of DLT for new patients at different dose levels for the combination of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the intervals shown below:

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

In addition to accumulating safety data and observed DLTs, decisions on further patient enrollment and dose level selection will be guided by the EWOC criterion.[35] A combination dose may only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose is less than 25% (0.25).

Available PK data for approximately 6 patients treated with the doublet and triplet combinations will be evaluated. If the PK profile of each drug appears to be consistent with the PK profile of each drug given individually, Phase 2 will be initiated without waiting for complete PK data.

Before expanding into Phase 2, available PK data will be reviewed and safety will be confirmed in at least 9 DLT-evaluable patients treated at the RP2D for each combination.

3.1.2. Phase 2 Design

Once the Phase 1b part 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 drug combination. Up to 40 patients with mPDAC will be randomized in a 1:1 ratio to the doublet and triplet combinations, respectively (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).

In total, approximately 70 patients are expected to be treated in Phase 2.

3.2. Dose-Limiting Toxicity Definition

The study drug combinations will be administered in 28 day cycles and the DLT evaluation period will be 28 days after treatment start (ie, Cycle 1). The severity of AEs will be graded according to CTCAE v 4.03. For the purpose of dose finding, any of the following AEs occurring in the first cycle of treatment which are attributable to any or all agents in the combination will be classified as DLTs:

3.2.1. 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).

3.2.2. 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.

3.2.3. 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.

3.2.4. 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.

3.2.5. Respiratory Disorders

- Interstitial lung disease/pneumonitis Grade ≥2.
- Bronchospasm Grade 3.

3.2.6. 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.

3.2.7. 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.

3.2.8. Dose Reductions

- Any AE that results in a dose reduction of talazoparib or binimetinib during the first cycle of treatment as per Section 5.5.7.2 and Section 5.5.7.3.

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.

3.3. Maximum Tolerated Dose Definition

A dose level combination is a potential candidate for being the maximum tolerated dose (MTD) level when all the following criteria are met:

- ≥6 patients have been treated at that dose;
- Probability of target dosing >50%; and
- Probability of overdosing <25%.

3.4. Maximum Administered Dose Definition

The maximum administered dose (MAD) is the highest dose level of the combination administered. In this clinical study, the MAD for the doublet combination will not exceed binimetinib 45 mg orally twice daily and talazoparib 1mg orally once daily. The MAD for the triplet will not exceed avelumab 800 mg IV Q2W in combination with binimetinib 45 mg orally twice daily (Schedule 7d/7d) and talazoparib 1 mg orally once daily.

3.5. RP2D Definition

The RP2D is the dose level of the combination that will be chosen for further clinical development and for evaluation in Phase 2.

A RP2D below the MTD may be determined based on other safety, clinical activity, PK and PD data.

4. PATIENT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

For the purposes of determining patient eligibility, the date of treatment assignment will be considered the "date of enrollment" (see Section 5.1).

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Prior to Independent Ethics Committee/Institutional Review Board (IEC/IRB) approval of Amendment 3: Histological diagnosis of locally advanced (primary or recurrent) or metastatic solid tumors that are not amenable for treatment with curative intent as follows:

    a. Stage IIIb/IV NSCLC with documented positive KRAS or NRAS mutation status as determined using a validated test performed in a College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (or other comparable local or regional certification); or

    b. Metastatic pancreatic ductal adenocarcinoma; or

    c. Phase 2 only: other advanced solid tumors with documented positive KRAS or NRAS mutation as determined using a validated test performed in a CAP/CLIA-certified laboratory (or other comparable local or regional certification).

Post IEC/IRB approval of Amendment 3: Histological diagnosis of locally advanced (primary or recurrent) or metastatic solid tumors that are not amenable for treatment with curative intent as follows:

    a. Metastatic pancreatic ductal adenocarcinoma; or

    b. Phase 2 only: Stage IIIb/IV NSCLC or other advanced solid tumors with documented positive KRAS or NRAS mutation as determined using a validated test performed in a CAP/CLIA-certified laboratory (or other comparable local or regional certification).

2. Have had disease progression during or following at least 1 and not more than 2 prior lines of treatment for advanced or metastatic disease.

3. Patients with NSCLC must have previously received treatment with an anti-PD-1 or anti-PD-L1 agent for advanced disease.

4. Measurable disease as per RECIST v1.1 criteria (Appendix 3) with at least 1 target lesion.

5. Provision of a Baseline Tumor sample:

   Mandatory primary or metastatic tumor biopsy to be performed within 28 days (45 days for patients requiring prospective biomarker testing for eligibility evaluation) prior to study enrollment to allow formalin-fixed paraffin-embedded (FFPE) tissue to be submitted for protocol-required testing. Core needle or excisional biopsies are required, as fine needle aspirations will not yield enough tissue for protocol-specified testing. Bone lesion biopsies are not acceptable.

   Exception: If an archival tumor tissue sample is available from a biopsy/surgery that was performed within 1 year prior to study enrollment and the patient did not receive any subsequent systemic anti-cancer treatment, the tumor tissue may be submitted without repeating a tumor biopsy during the screening period.

6. Age ≥18 years (except in Japan, where patients must be ≥20 years old).

7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.

8. Adequate Bone Marrow Function (without hematopoietic growth factor or transfusion support within 14 days prior to study enrollment), including:

   a. ANC ≥1,500/mm3 or ≥1.5 x 109/L;

   b. Platelets ≥100,000/mm3 or ≥100 x 109/L;

   c. Hemoglobin ≥9 g/dL (≥5.6 mmol/L).

9. Adequate renal function defined by an estimated creatinine clearance (CL_{CR}) ≥60 mL/min according to the Cockcroft-Gault formula or by 24 hour urine collection for CL_{CR}, or according to local institutional standard method.

10. Adequate Liver Function, including:

    a. Total serum bilirubin ≤1.5 × ULN;

    b. AST and ALT ≤2.5 × ULN.

11. Adequate Cardiac Function including:

    a. Left ventricular ejection fraction (LVEF) ≥50% or above institutional normal value as determined by a multigated acquisition (MUGA) scan or echocardiography;

    b. QTc ≤480 msec (mean from triplicate electrocardiograms [ECGs]).

12. Female patients of childbearing potential must have negative serum pregnancy or urine pregnancy test at screening. Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure.
    - All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

13. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

14. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Prior treatment with avelumab, a PARP inhibitor or MEK inhibitor.

2. Prior systemic anti-cancer therapy within 2 weeks prior to study enrollment.

3. Persisting toxicity related to prior therapy NCI CTCAE v4.0 Grade >1; however, alopecia, sensory neuropathy Grade ≤2, or other Grade ≤2 adverse events not constituting a safety risk based on the investigator's judgment are acceptable.

4. Prior radiation therapy within 2 weeks prior to enrollment. Exception: Prior palliative radiotherapy is permitted, provided it has been completed at least 2 days prior to study enrollment and no clinically significant toxicities are expected (eg, mucositis, esophagitis).

5. Major surgery within 4 weeks prior to study enrollment.

6. Current use of immunosuppressive medication at the time of study enrollment, EXCEPT for the following permitted steroids (see Section 5.8.3):

    a. Intranasal, inhaled, topical steroids, eye drops or local steroid injection (eg, intra-articular injection);

b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;

c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography (CT) scan premedication).

7. Known prior severe hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥3).

8. Known history of immune-mediated colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis, uveitis or iritis.

9. Active or prior autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

10. Prior organ transplantation including allogenic stem-cell transplantation.

11. Vaccination within 4 weeks of study enrollment and while on trials is prohibited except for administration of inactivated vaccines.

12. Diagnosis of Myelodysplastic Syndrome (MDS).

13. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study enrollment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

14. Participation in other studies involving investigational drug(s) within 4 weeks prior to study enrollment.

15. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immune deficiency syndrome (AIDS).

16. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).

17. Active infection requiring systemic therapy.

18. Clinically significant (ie, active) cardiovascular disease: myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II) or a serious cardiac arrhythmia requiring medication.

19. History of thromboembolic or cerebrovascular events ≤6 months prior to study enrollment, including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli.

20. Prior to IEC/IRB approval of Amendment 3: Current or anticipated use of a P-gp inhibitor (amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir , itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil), P-gp inducer (avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort), or inhibitor of breast cancer resistance protein (BCRP) (curcumin, cyclosporine, elacridar [GF120918], and eltrombopag).

    Post IEC/IRB approval of Amendment 3: Current or anticipated use of strong P-gp inhibitor(s) and/or inducer(s) within 7 days prior to randomization. For a list of strong P-gp inhibitors/inducers, refer to Section 5.8.6.

21. Inability to swallow or administer whole capsules or tablets, known intolerance to talazoparib or binimetinib or its excipients, known malabsorption syndrome, or other condition that may impair absorption of talazoparib or binimetinib.

22. Prior to IEC/IRB approval of Amendment 3: Uncontrolled hypertension defined as persistent systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg despite current therapy.

    Post IEC/IRB approval of Amendment 3: uncontrolled hypertension defined as persistent systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg despite current therapy. Patients requiring anti-hypertensive therapy must be on a stable regimen for ≥2 weeks prior to commencing study treatment.

23. Concurrent neuromuscular disorder that is associated with the potential of elevated CK (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

24. Known history of Gilbert's syndrome.

25. History or current evidence of retinal degenerative disease, RVO or current risk factors for RVO (eg, uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).

26. Bisphosphonate or denosumab dosage that was not stable (ie, not the same) for at least 2 weeks before study enrollment for patients receiving these therapies.

27. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

28. Diagnosis of any other malignancy within 2 years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the breast, bladder or of the cervix, and low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation, or castration) or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms is allowed.

29. Pregnant female patients; breastfeeding female patients; female patients of childbearing potential who are unwilling or unable to use a method of highly effective contraception as outlined in this protocol during treatment and for at least 30 days after the last dose of avelumab or binimetinib and 7 months after the last dose of talazoparib; fertile male patients with female partners of reproductive potential or pregnant partners, unwilling to use a condom (even after vasectomy) during treatment and for at least 30 days after the last dose of binimetinib and 4 months after the last dose of talazoparib.

30. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4.3. Lifestyle Guidelines

In this study, all patients will receive avelumab for which the teratogenic risk is currently unknown, in combination with binimetinib, which has been associated with teratogenic risk, with or without talazoparib, which has been associated with genotoxic and teratogenic risk.

All female patients of childbearing potential who are, in the opinion of the Investigator, sexually active and at risk for pregnancy must agree to use highly effective contraception, preferably with low user dependency, during treatment and for at least 30 days after the last dose of avelumab or binimetinib and at least 7 months after the last dose of talazoparib.

Fertile male patients with female partners of reproductive potential or pregnant partners, must agree to use a condom (even after vasectomy) during treatment and for at least 30 days after the last dose of binimetinib and for 4 months after the last dose of talazoparib. Female partners of reproductive potential should use an additional highly effective contraceptive method for at least 4 months after the patient's last dose of talazoparib.

The Investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected an appropriate method of contraception for the individual patient from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the SOA, the

Investigator or designee will inform the patient of the need to use highly effective contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart (patients need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the Investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner.

Contraception methods

Highly Effective Methods That Have Low User Dependency include:

1. Implantable progestogen only hormone contraception associated with inhibition of ovulation.

2. Intra-uterine device (IUD).

3. Intra-uterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of child-bearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Highly Effective Methods That Are User Dependent Include:

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal;

    - Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;

    - Injectable.

3. Sexual abstinence. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are avelumab, binimetinib and talazoparib.

5.1. Allocation to Treatment

Eligible patients will be centrally assigned to a treatment cohort after providing a written informed consent and completing the screening procedures. For the purposes of determining patient eligibility, the date of treatment assignment will be considered the "date of enrollment."

For the doublet combination (avelumab and binimetinib) in Phase 1b, mPDAC patients were treated with avelumab 800 mg Q2W and binimetinib 45 mg or 30 mg twice daily (continuous). Patients enrolled in Phase 1b prior to the implementation of Amendment 3 will continue to receive the originally assigned study treatment, with subsequent dose adjustments made as allowed for study drug-related toxicity.

Per Amendment #3, the doublet combination of binimetinib and talazoparib will first be evaluated in Phase 1b with a starting dose level (BT0) of binimetinib 45 mg twice daily, Schedule 7d/7d, and talazoparib 0.75 mg once daily.

Once the RP2D is established for the doublet combination (binimetinib and talazoparib), patients will be enrolled into the triplet Phase 1b to receive avelumab 800 mg Q2W, binimetinib (Schedule 7d/7d) and talazoparib at a starting dose level guided by the BLRM. In the case that a more intensive dosing schedule of binimetinib (ie, Schedule 5d/2d) is studied for the doublet of binimetinib and talazoparib, enrollment into this doublet and the triplet will occur in parallel by alternating enrollment of a complete cohort of patients to the doublet or triplet (ie, only a single dose level cohort will be open to enrollment at any given time).

In the Phase 2 part, patients will be treated at the RP2Ds determined during Phase 1b. If RP2Ds are established for both the doublet and triplet combinations, mPDAC patients will be randomized in a 1:1 ratio to either the doublet or triplet combination. The ‘tumor agnostic’ KRAS- or NRAS- mutant solid tumor cohort will be enrolled into the triplet combination only.

Assignment of patient number, patient enrollment (for Phase 1b patients and Phase 2 ‘tumor agnostic’ patients), and allocation of study treatment by dose level (Phase 1b) and randomization (for mPDAC patients) into cohorts at the RP2D (Phase 2) will be managed by an Interactive Response Technology (IRT) system. At the time that a patient has signed informed consent and entered screening, the site should contact the IRT system to obtain the patient identification number. Once a patient has met all eligibility criteria, the site then contacts the IRT system to enroll the patient and to obtain the study treatment allocation information (including randomization where applicable). Study treatment should be initiated no later than 3 days after enrollment.

At the time of enrollment (for Phase 1b patients and Phase 2 ‘tumor agnostic’ cohort patients) or randomization (for Phase 2 mPDAC patients), site personnel (study coordinator or specified designee) will be required to enter into or select information from the IRT system including but not limited to the user’s identification (ID) and password, the protocol number, the patient number, and the date of birth of the patient (in accordance with local data protection regulations and practices). The IRT system will then provide a treatment assignment and dispensable unit (DU) or vial number. The IRT system will also provide a confirmation report containing the patient number and DU or vial number assigned. The confirmation report must be stored in the site’s files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Treatment Duration

Patients will continue to receive study treatment until objective disease progression assessed by Investigator (see Section 5.5.8 for guidance on treatment beyond progression), patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, or other withdrawal criteria are met (see Section 6.3).

If the study was to be prematurely terminated, when patients may still derive benefit from the treatment under study, a roll over study or early access program will allow the patient to continue receiving study drug treatment until disease progression, or unacceptable toxicity or up to 2 years, whichever occurs first.

5.3. Patient Compliance

The information related to each trial drug administration, including the date, time, and dose of study drug, will be recorded in the case report form (CRF). The Investigator will make sure that the information entered into the CRF regarding drug administration is accurate for each patient. Any reason for noncompliance should be documented.

5.3.1. Avelumab Patient Compliance

All doses of avelumab will be administered at the investigational site by well-trained medical staff. The start and stop times of the avelumab infusion, along with the total volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in rate of avelumab infusion will also need to be recorded in the patients' medical records. The vials of avelumab that are assigned and prepared for patients will be recorded in the pharmacy records. These records will all be available for Sponsor representatives to verify compliance.

The site will complete the required dosage Preparation Record located in the Investigational Product manual (IP manual) for avelumab. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the avelumab dose, including date of infusion, total dose administered, start and stop times of the infusion, and any reasons that a dose other than the protocol-specified dose or dosing schedule was administered. This may be used in place of the Preparation Record after approval from the Sponsor and/or designee.

Noncompliance is defined as a patient missing >1 infusion of avelumab for non-medical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for non-medical reasons, then the patient would also be considered noncompliant.

5.3.2. Binimetinib and Talazoparib Patient Compliance

Patients will be required to return all unused binimetinib tablets and talazoparib capsules (if applicable) every cycle. The number of tablets or capsules returned by the patient will be counted, documented, and recorded by site personnel in the patient's medical record and reconciled with the patient's dosing diary to support the binimetinib/talazoparib accountability process. Study site personnel must make reasonable efforts to obtain study drug packaging and any unused tablets or capsules from patients who do not routinely return them at study site visits.

Additionally, a patient dosing diary will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed binimetinib/talazoparib doses. The time of each binimetinib/talazoparib dose administration and the total dose of binimetinib/talazoparib taken each day will be recorded in the dosing diary. Patients will be required to return the completed patient dosing diary on Day 1 and 15 of every cycle for timely review by site personnel and discussion of missed doses and/or compliance issues to ensure accurate data entry for the Dosing CRF. On days when the patient's binimetinib/talazoparib dose is given at the clinic due to scheduled PK sample collection, the time of binimetinib/talazoparib dose administration and the total dose of binimetinib/talazoparib taken will be recorded in the patient's dosing records that are included in the medical chart.

Treatment compliance (reported as a percent) will be defined as the number of tablets or capsules taken during the study divided by the expected number of tablets or capsules, for binimetinib and talazoparib respectively multiplied by 100%.

5.4. Investigational Product Supplies

Avelumab, binimetinib and talazoparib will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational products in accordance with the protocol and any applicable laws and regulations.

5.4.1. Dosage Forms and Packaging

Packaging and labeling for all study drugs will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. The information on each study drug will be in accordance with approved submission documents.

5.4.1.1. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented at a concentration of 20 mg/mL in 10-mL glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each vial is intended for single use only.

Avelumab will be packed in boxes each containing 1 vial.

Avelumab will be shipped under refrigerated conditions (2°C to 8°C) that are monitored with temperature control monitoring devices.

5.4.1.2. Binimetinib

Binimetinib will be provided as 15 mg film-coated tablets for oral administration, packaged in induction sealed, high-density polyethylene bottles with child-resistant caps. Each bottle will contain 60 tablets and will be appropriately labeled according to local regulatory requirements.

5.4.1.3. Talazoparib

Talazoparib will be provided as capsules for oral administration. The 0.25 mg (opaque white, size 4) and 1.0 mg (opaque pale-pink, size 4) capsules will be supplied in separate bottles and labeled according to local regulatory requirements. Talazoparib is packaged in induction sealed, high-density polyethylene bottles with child-resistant caps with 30 capsules of a single strength per bottle.

5.4.2. Preparation and Dispensing

Investigational products must not be used for any purpose other than the trial. The administration of study treatment to patients who have not been enrolled into the trial is not covered by the trial insurance.

5.4.2.1. Avelumab

For administration in this trial, 4 vials of avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) to a volume of 250 mL. See the IP manual for instructions on how to prepare avelumab for administration. Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the IP Manual.

Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Any unused portion of the avelumab solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

5.4.2.2. Binimetinib

Binimetinib should be dispensed on the Day 1 Visit of every cycle. A qualified staff member will dispense the investigational product in the bottles provided, in quantities of 60 tablets per bottle. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site on the Day 1 Visit of every cycle.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the dispensing, handling, and safe disposal of binimetinib. Patients should be advised that oral anti-cancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

5.4.2.3. Talazoparib

Talazoparib should be dispensed on the Day 1 Visit of every cycle. A qualified staff member will dispense the investigational product in the bottles provided, in quantities of 30 capsules per bottle. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site on the Day 1 Visit of every cycle.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the dispensing, handling, and safe disposal of talazoparib. Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment.[24] Patients should be advised that oral anti-cancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

5.5. Administration

5.5.1. Combination Therapy Administration

5.5.1.1. Avelumab and Binimetinib (doublet)

Binimetinib will be self-administered by the patient at home as per Section 5.5.2. On the days when avelumab is administered, patients must be instructed **not to** administer the morning binimetinib dose at home, **but to take their medication to the clinic on these days for administration after necessary procedures are completed**.

On Days 1 and 15 of each cycle, when both avelumab and binimetinib are administered at the clinic, the following must occur in the order specified:

1. All required tests and assessments will be performed, as per the SOA and pre-dose blood will be drawn for PK and ADA assessments (when scheduled);

2. Binimetinib will be administered to the patient 30-60 minutes prior to the avelumab infusion by the qualified site personnel;

3. Avelumab premedication will be administered, as described below in Section 5.5.4;

4. Avelumab infusion will start after the avelumab premedications have been administered and after dosing with binimetinib; and

5. Blood will be drawn for PK assessments (when scheduled) prior to the avelumab infusion and immediately after the end of the avelumab infusion.

The exact dose administration date/time for both drugs should be documented in the patient's notes and CRF.

5.5.1.2. Binimetinib and Talazoparib (doublet)

Binimetinib and talazoparib will be self-administered by the patient at home as per Section 5.5.2 and 5.5.3. On the days when study drug dosing is required at the clinic per the SOA, patients must be instructed **not to** administer the morning binimetinib and the talazoparib dose at home, **but to take their medication to the clinic on these days for administration after necessary procedures are completed**.

On the applicable days, when both binimetinib and talazoparib are administered at the clinic, the following must occur in the order specified:

1. All required tests and assessments will be performed, as per the SOA and pre-dose blood will be drawn for PK assessments (when scheduled);

2. Binimetinib and talazoparib will be administered to the patient by the qualified site personnel;

3. Blood will be drawn for PK assessments (when scheduled).

4. The exact dose administration date/time for both drugs should be documented in the patient's notes and CRF.

5.5.1.3. Avelumab, Binimetinib & Talazoparib (Triplet)

Binimetinib and talazoparib will be self-administered by the patient at home as per Section 5.5.2 and 5.5.3. On the days when study drug dosing is required at the clinic per the SOA, patients must be instructed **not to** administer the morning binimetinib dose and the talazoparib dose at home, **but to take their medication to the clinic on these days for administration after necessary procedures are completed**.

On Days 1 and 15 of each cycle, when avelumab, binimetinib and talazoparib are administered at the clinic, the following must occur:

1. All required tests and assessments will be performed, as per the SOA and pre-dose blood will be drawn for PK and ADA assessments (when scheduled);

2. Talazoparib and binimetinib will be co-administered to the patient prior to the avelumab infusion by the qualified site personnel. Of note, on Cycle 1 Day 1, talazoparib and binimetinib should be administered 30-60 minutes prior to the start of the avelumab infusion;

3. Avelumab premedications will be administered as described in Section 5.5.4;

4. Avelumab infusion will start after avelumab premedications have been administered and after dosing with binimetinib and talazoparib; and

5. Blood will be drawn for PK assessments (when scheduled) immediately after the end of the avelumab infusion.

The exact dose administration date/time for all three drugs should be documented in the patient's notes and CRF.

5.5.2. Binimetinib Administration

Binimetinib will be taken twice daily at the defined dose (either 30 mg or 45 mg) starting on Cycle 1 Day 1 (C1D1) in accordance with the assigned treatment schedule (eg, Schedule 7d/7d) and treatment should continue until the 'End of Treatment' (EOT) visit. On Days 1 and 15 of each cycle, when the patient returns to the clinic for safety assessments and avelumab administration (if applicable), and on Cycle 1 Day 8 for Phase 1b patients, the patients must be reminded to take the medication to the clinic with them. The first daily dose of binimetinib should **NOT** be taken prior to the study visit and will be taken **at the clinic, after all procedures/assessments have been completed** and before the avelumab infusion (if applicable). In addition to the dosing schedule outlined, at the Cycle 1 Day 8 visit for Phase 1b patients, a single morning dose will be administered at the clinic and subsequent blood samples will be collected for PK.

Patients should self-administer binimetinib orally twice daily in accordance with the assigned treatment schedule, with or without food. The first dose should be taken in the morning, with the second dose 12±2 hours later. The tablets should be swallowed whole with a glass of water without chewing or dissolving them prior to swallowing.

Patients should be instructed to take each dose of binimetinib in the morning and evening at approximately the same time each day and to not take more than the prescribed dose at any time.

The oral dose of talazoparib (if applicable) should be taken at the same time as the binimetinib morning dose.

If a patient misses a dose or vomits any time after taking a dose, he/she must be advised that study drug should not be re-administered (patient should not "make it up") but to resume subsequent doses either in the evening if a morning dose is affected, or, on the next morning as prescribed, if an evening dose is affected.

Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment, a dose, or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every visit.

5.5.3. Talazoparib Administration

Talazoparib will be taken once daily at the defined dose level (either 0.5 mg, 0.75 mg, or 1 mg) starting on Cycle 1 Day 1 (C1D1) and treatment should continue until the EOT visit. On Days 1 and 15 of each cycle, when the patient returns to the clinic for safety assessments and avelumab administration (if applicable), and also on Cycle 1 Day 8 for Phase 1b patients, patients must be reminded to take the medication to the clinic with them. The daily dose of talazoparib should **NOT** be taken prior to the study visit and will be taken **at the clinic, after all procedures/assessments have been completed** and before the avelumab infusion (if applicable).

Patients should self-administer talazoparib orally once daily, in the morning, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening them prior to swallowing.

Patients should be instructed to take talazoparib at approximately the same time each morning along with the first dose of binimetinib (if applicable according to the dosing schedule) and to not take more than the prescribed dose at any time.

If a patient misses a day of treatment or vomits any time after taking a dose, he/she must be advised that study drug should not be re-administered (patient should not "make it up") but to resume subsequent doses the next day as prescribed.

Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every visit.

5.5.4. Avelumab Premedication

In order to mitigate IRRs, premedication with an antihistamine and with paracetamol (acetaminophen) prior to the first 4 infusions of avelumab is mandatory. Premedication should be administered for subsequent avelumab doses based on clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate. Prophylactic corticosteroids are not permitted.

When avelumab and binimetinib (and talazoparib where applicable) are administered on the same day, premedications may be given either prior to, at the same time as, or after binimetinib (and talazoparib where applicable). However, the avelumab infusion will start after the avelumab premedication is administered and after binimetinib and talazoparib administration (where applicable).

5.5.5. Avelumab Administration

Avelumab will be administered at 800 mg as a 1-hour IV infusion (-10/+20 minutes) starting after the binimetinib and talazoparib (where applicable) is administered, as per Section 5.5.4, at the investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. The schedule for avelumab should be maintained: if avelumab cannot be given during the allowed visit window for any reason, the infusion should be skipped, and all other assessments should be completed for that visit as usual. Investigational sites should make every effort to target the timing of the avelumab infusion to be as close to 1 hour as possible. The exact duration of infusion should be recorded in both the source documents and the CRFs. Additionally, the start and stop times of any interruptions to infusion and/or changes in rate of avelumab infusion will also need to be recorded in source documents.

After Cycle 1 Day 1, avelumab may be administered up to 2 days before or after the scheduled treatment day of each cycle for administrative reasons.

5.5.5.1. Special Precautions for Avelumab Administration

As with all mAb therapies, there is a risk of allergic reactions, including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. If a hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. In order to mitigate avelumab IRRs, patients have to be premedicated, according to guidance in Section 5.5.4.

Following the infusions of avelumab, patients must be observed for at least 30 minutes post-infusion for potential infusion-related reactions.

Symptoms of avelumab infusion-related reactions include, but are not limited to, fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Management of avelumab IRRs is described in Table 13. Patients should be instructed to immediately report to the Investigator any delayed reactions that may occur after they leave the clinic.

5.5.6. Food Requirements

The investigational products may be administered without regard to food.

5.5.7. Recommended Dose Modifications

Every effort should be made to administer each investigational product at the planned dose and schedule.

In the event of study treatment toxicity, dosing may be interrupted, delayed and/or reduced, only as described for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed (CTCAE v4.03) and/or the most conservative recommendation for any given toxicity. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Treatment/dose modifications may occur independently for each investigational product in the combination based on the observed toxicity and the general guidance, as follows:

- Avelumab: No dose reductions are permitted, but the next infusion may be omitted based on persisting toxicity.
- Talazoparib: Dose modifications (dose interruptions or dose reductions) may be implemented to manage toxicities.
- Binimetinib: Dose modifications (dose interruptions or dose reductions) may be implemented to manage toxicities.

See Section 5.5.7.3 for details regarding the specific protocol-permitted modifications for each investigational product.

All dose modifications must be clearly documented in the patient's medical chart and in the CRF. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

In addition to dose modifications, Investigators are encouraged to employ best supportive care according to local institutional clinical practices.

5.5.7.1. Dosing Interruptions

Guidelines for study treatment modifications for patients experiencing adverse events are provided in Section 5.5.7.3.

Dose interruptions for study treatment-related AEs are allowed as per the recommendations provided in Section 5.5.7.3. Doses of any investigational product that were not administered due to toxicity will not be replaced within the same cycle. In addition to dose interruption, the need for a dose reduction for binimetinib or talazoparib at the time of treatment resumption should also be considered based on recommendations provided in Section 5.5.7.3.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) for >7 consecutive days, treatment resumption will be decided in consultation with the Sponsor.

Dose interruptions due to treatment-related adverse events of more than 28 days for talazoparib or 21 days for binimetinib are not allowed and will result in permanent discontinuation unless resuming treatment is judged by the Investigator and the Sponsor to be in the best interest of the patient.

5.5.7.2. Dose Reductions - Binimetinib and Talazoparib

Following dosing interruption due to toxicity, the binimetinib or talazoparib dose may need to be resumed at a reduced dose as per the recommendations provided in Section 5.5.7.3.

Available dose levels for binimetinib are 45 and 30 mg twice daily per the assigned dosing schedule.

Available dose levels for talazoparib are 1, 0.75 and 0.5 mg once daily. Dose reduction of talazoparib by 1 dose level at a time will be allowed depending on the starting dose. If a talazoparib dose reduction is required, the patient may need to return to the clinic to receive a new drug supply since dosage strengths of the capsules may be different.

Once the dose of binimetinib or talazoparib has been reduced for a given patient, all subsequent cycles should be administered at that dose level. Intra-patient dose re-escalation is not allowed.

Site personnel must ensure the patient is instructed how to take the reduced dose and that the patient has the correct dosage strength for the reduced dose.

5.5.7.3. Toxicity Related Treatment Modifications

Recommended dose modifications are presented in this section as follows:

- Section A: Treatment Modifications for Talazoparib-Related Toxicity;
- Section B: Treatment Modifications for Binimetinib-Related Toxicity;
- Section C: Treatment Modifications for Avelumab-Related Toxicity.

The instructions should be followed in the table(s) regarding the investigational product(s) that toxicity is attributed to. Patients who interrupt or permanently discontinue any of the investigational products due to toxicity may continue treatment with the investigational product(s) not considered to be responsible for the toxicity observed. For patients receiving avelumab, any AE suspected to be immune-related should be managed according to the guidance for irAEs management (Table 12: Immune-Related Adverse Events Toxicity Management). In addition, for suspected immune-related toxicities due to avelumab that require withholding avelumab or discontinuation (except for endocrinopathies), talazoparib and binimetinib should also be placed on hold until the toxicity is Grade ≤1 or baseline. For toxicities attributed to talazoparib and/or binimetinib that require dosing interruption, avelumab may also be withheld until the toxicity is Grade ≤1 or baseline.

5.5.7.4. Section A: Study Treatment Modifications for Talazoparib Drug-Related Toxicity

General treatment modifications in case of talazoparib related toxicity are shown in Table 10.

Table 10. Treatment Modifications for Talazoparib Drug-Related Toxicity

Drug-related Adverse Reactions	Withhold Talazoparib until levels resolve to	Dose modification
Hemoglobin <8 g/dL	≥9 g/dL	Resume talazoparib at 1 reduced dose level
Platelet count <50,000/µL	≥75,000/µL	
Neutrophil count <1,000/µL	≥1500/µL	
Non-hematologic Grade 3 or Grade 4	≤Grade 1	Consider resuming talazoparib at a reduced dose or discontinue

5.5.7.5. Section B: Treatment Modifications for Binimetinib-Related Adverse Events

For cutaneous reactions, interstitial lung disease, cardiac events, rhabdomyolysis/CPK elevation, and liver toxicity that could represent an immune-related toxicity, the guidance for irAE management should also be followed for avelumab (Table 14: Management of Immune-Related Adverse Events). If avelumab should be placed on hold or discontinued for a suspected irAE, binimetinib and talazoparib should also be placed on hold until the toxicity resolves to Grade ≤1 or baseline. Treatment modifications for binimetinib related toxicity are shown below in Table 11.

Table 11. Treatment Modifications for Binimetinib Drug-Related Toxicity

Dermatologic	
Grade 2	• If no improvement within 2 weeks, withhold until Grade ≤1. • Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	• Interrupt dosing of binimetinib until resolved to Grade ≤1. • Then resume at current dose level for 1st occurrence or at reduced dose if recurrent.
Grade 4	• Permanently discontinue binimetinib.
Ocular Events: Serous Retinopathy	
Symptomatic serous retinopathy/Retinal pigment epithelial detachments	• Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume treatment at current dose level. • If not improved, resume treatment at 1 reduced dose level or permanently discontinue binimetinib.

Ocular Events: Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue binimetinib.
Grade 4	Permanently discontinue binimetinib.
Ocular Events: Retinal Vein Occlusion	
Any Grade	Permanently discontinue binimetinib.
Other Eye Disorders: (ie, Non-retinal, Non-Uveitis Events)	
Grade 1-2	Maintain dose level of binimetinib and increase frequency of ophthalmic monitoring to at least every 2 weeks until stabilization or resolution.
Grade 3	Interrupt dosing of binimetinib and refer patient to ophthalmologist within 1 week: • If resolved to Grade ≤1 in ≤3 weeks, resume treatment at 1 reduced dose level. • If not resolved to Grade ≤1 in ≤3 weeks, permanently discontinue and ensure close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue binimetinib and ensure immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Cardiac Events: Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of greater than 10% from	Withhold binimetinib for up to 4 weeks and evaluate LVEF every 2 weeks.

baseline that is also below the lower limit of normal (LLN)	Resume treatment at 1 reduced dose level if the following are present: • LVEF is at or above the LLN; and • Absolute decrease from baseline in 10% or less; and • Patient is asymptomatic. • If the LVEF does not recover within ≤4 weeks permanently discontinue binimetinib.
Grade 3-4 (Symptomatic congestive heart failure or absolute decrease in LVEF of > 20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Venous Thromboembolism	
Uncomplicated Deep Venous Thrombosis or Pulmonary Embolism	Withhold binimetinib. • If improves to Grade ≤1, resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Life threatening Pulmonary Embolism	• Permanently discontinue binimetinib.
Interstitial Lung Disease	
Grade 2	Withhold binimetinib for up to 4 weeks. • If improved to Grade ≤1, resume treatment at 1 reduced level. • If not resolved within 4 weeks, permanently discontinue binimetinib.
Grade 3-4	• Permanently discontinue binimetinib.

Hepatotoxicity	
Grade 2 AST or ALT increased	• Maintain dose level of binimetinib. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade ≤1 or to pretreatment/baseline levels, then resume at the same dose.
Grade 3 or 4 AST or ALT increased	• See Other Adverse Reactions.
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
Grade 4 asymptomatic CPK elevation or any Grade CPK elevation with symptoms or with renal impairment	Interrupt dosing of binimetinib for up to 4 weeks. • If resolved to Grade ≤1, resume treatment at 1 reduced dose level. • If not resolved in ≤4 weeks, permanently discontinue binimetinib.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of binimetinib. Promptly institute antiemetic measures.
Grade 3	Interrupt dosing of binimetinib until resolved to Grade ≤1. • Then resume treatment at 1 reduced dose level of binimetinib. • Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of binimetinib for Grade ≥3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).

Grade 4	• Permanently discontinue binimetinib.
All Other Adverse Events (Including Hemorrhage)	
Recurrent Grade 2 or first occurrence of any Grade 3	Withhold binimetinib for up to 4 weeks. • If improves to Grade ≤1 or to pretreatment/baseline levels, resume at 1 reduced dose level. • If no improvement, permanently discontinue binimetinib.
First occurrence of any Grade 4	Permanently discontinue or interrupt dosing for up to 4 weeks. • If resolved to Grade ≤1 or baseline then resume at 1 reduced dose level. • If no improvement, permanently discontinue binimetinib.
Recurrent Grade 3	• Consider permanently discontinuing binimetinib.
Recurrent Grade 4	• Permanently discontinue binimetinib.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK= Creatine Phosphokinase; LLN=lower limit of normal; LVEF=Left Ventricular Ejection Fraction

5.5.7.6. Section C: Treatment Modifications for Avelumab-Related Toxicity

Recommended treatment modifications for avelumab-related toxicity are shown in Table 12.

Recommended treatment modifications in case of avelumab IRRs are shown in Table 13.

For patients receiving avelumab, any AE suspected to be immune-related (ie, an irAE) should be managed according to the guidance for management of irAEs (see Table 14).

Table 12. Treatment Modification for Avelumab Drug-Related Toxicity

	NCI CTCAE Severity Grade	Avelumab Treatment Modification
Drug-related adverse reactions (excluding infusion-related reaction/hypersensitivity and immune-related AE)	Grade 1	Continue as per schedule.
	Grade 2	Continue as per schedule.
	Grade 3	Withhold until recovery to Grade ≤1 or baseline. Permanently discontinue if toxicities do not resolve to Grade ≤1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs. Exceptions are: Laboratory abnormalities that do not have any clinical correlate.
	Grade 4	Permanently discontinue Exceptions are: Laboratory abnormalities that do not have any clinical correlate.

Table 13. Treatment Modification for Symptoms of IRRs Associated with Avelumab

NCI CTCAE Severity Grade	Treatment Modification
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	Temporarily discontinue avelumab infusion. Resume avelumab infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect infusion tubing from the patient. Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

If avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.
Abbreviations: NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous.

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated above (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed. At the next dose, the Investigator may consider the addition of H2 blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic corticosteroids are not permitted.

Table 14. Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over Baseline. Colitis: asymptomatic	Continue avelumab therapy. Symptomatic treatment (eg, loperamide).	Close monitoring for worsening symptoms. Educate patient to report worsening immediately. If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool.	Withhold avelumab therapy. Symptomatic treatment.	If improves to Grade ≤1: Resume avelumab therapy. If persists >5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation.	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area.	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids).	If Grade 2 persists >1 to 2 weeks or recurs: Withhold avelumab therapy. Consider skin biopsy. Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume

Table 14. Management of Immune-Related Adverse Events

		avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences.	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy. Dermatology consult. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only.	Consider withholding avelumab therapy. Monitor for symptoms every 2 to 3 days. Consider Pulmonary and Infectious Disease consults.	Re-assess at least every 3 weeks. If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms.	Withhold avelumab therapy. Pulmonary and Infectious Disease consults. Monitor symptoms daily; consider hospitalization. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper. If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening.	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent.	If improves to Grade ≤1: Taper steroids over at least 1 month. If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV

Table 14. Management of Immune-Related Adverse Events

	Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT >ULN to 3.0 x ULN and/or Total bilirubin >ULN to 1.5 x ULN.	Continue avelumab therapy.	Continue liver function monitoring. If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN.	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days.	If returns to Grade ≤1: Resume routine monitoring; resume avelumab therapy. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN.	Permanently discontinue avelumab therapy. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤1: Taper steroids over at least 1 month. If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 **Creatinine increased >ULN to 1.5 x ULN.**	Continue avelumab therapy.	Continue renal function monitoring. If worsens: **Treat as Grade 2 to 3 or 4.**
Grade 2 to 3	Withhold avelumab therapy.	If returns to Grade ≤1:

Table 14. Management of Immune-Related Adverse Events

Creatinine increased >1.5 and ≤6 x ULN.	Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN.	Permanently discontinue avelumab therapy. Monitor creatinine daily. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis.	Permanently discontinue avelumab.	Once improving, taper steroids over at least 1 month.

Table 14. Management of Immune-Related Adverse Events

	Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus).	Continue avelumab therapy. Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie hypopituitarism/ hypophysitis).	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus).	Withhold avelumab therapy. Consider hospitalization. Endocrinology consult. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie,	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Table 14. Management of Immune-Related Adverse Events

	hypopituitarism/ hypophysitis).	
Hypopituitarism/Hypophysitis (secondary endocrinopathies).	If secondary thyroid and/or adrenal insufficiency is confirmed (ie subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). • Hormone replacement/suppressive therapy as appropriate. • Perform pituitary MRI and visual field examination as indicated. **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month. • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Table 14. Management of Immune-Related Adverse Events

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE.	Withhold avelumab therapy pending clinical investigation.	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy. If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE.	Withhold avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs.	Permanently discontinue avelumab therapy. to 2.0 mg/kg/day. prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4.	Permanently discontinue avelumab therapy. to 2.0 mg/kg/day. prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month.

Table 14. Management of Immune-Related Adverse Events

Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency. Persistent Grade 2 or 3 irAE lasting 12 weeks or longer.	Permanently discontinue avelumab therapy. Specialty consult.	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

5.5.8. Treatment After Initial Evidence of Radiological Disease Progression

Immunotherapeutic agents such as avelumab, may produce antitumor effects by potentiating cancer-specific immune responses. Following immunotherapy, a clinical response may occur later than would typically be expected following treatment with a cytotoxic agent. In addition, this response may occur after an initial increase in tumor burden or even after the appearance of new lesions.

If radiologic imaging shows disease progression, after discussion between the Sponsor and Investigator, patients may continue to receive investigational products at the investigators discretion if the following criteria are met:

- No decline in ECOG performance status;
- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

Before continuation of treatment after initial PD, the patient must be re-consented via informed consent addendum and informed that, by continuing to receive investigational products, the patient may be foregoing approved or investigational therapies with possible clinical benefit(s).

If the patient is subsequently found to have further disease progression at a subsequent tumor assessment, either radiologically according to RECIST v1.1 or clinically, then treatment with investigational products should be permanently discontinued.

5.6. Investigational Product Storage

The Investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. Any storage conditions stated in the SRSD, will be superseded by the storage conditions stated on the product labels.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Receipt of materials, door opening and closing, and other routine handling operations where the investigational products are briefly out of the temperature range described in the labeling are not considered excursions.

Specific details regarding information the site should report for each excursion will be provided to the site in the Investigational Product Manual.

5.6.1. Avelumab Storage

Avelumab must be stored in the refrigerator at 2°–8°C (36°–46°F). Do not freeze. Protect from light. Do not shake vigorously. See the Investigational Product Manual for storage conditions of avelumab once diluted.

5.6.2. Talazoparib Storage

Talazoparib is stored at room temperature (15°C–30°C; 59°F–86°F) or per approved local label.

Site staff will instruct patients on the proper storage requirements for take home investigational product, as talazoparib will be self-administered at home by patients.

5.6.3. Binimetinib Storage

Binimetinib – do not store above 25ºC (77ºF).

Site staff will instruct patients on the proper storage requirements for take home investigational product, as binimetinib will be self-administered at home by patients.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All unused binimetinib and talazoparib (where applicable) must be returned to the Investigator or designated investigative site personnel by each patient on Day 1 of every cycle and at the end of the trial in order to perform and document drug accountability.

5.7.1. Destruction of Investigational Product Supplies

The Sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

Concomitant treatment considered necessary for the patient's well-being may be given at the discretion of the treating physician.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment(s) and up to 90 days after the last dose of study treatment(s). All concomitant medications should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, as well as non-drug supportive interventions (eg, transfusions).

Given that recording of non-serious AEs ends when a patient begins a new anti-cancer therapy (Section 8.1.4.2 Recording Non-serious AEs and SAEs on the CRF), recording of concomitant medications associated with these non-serious AEs should also end. However, given that SAEs (Section 8.1.4.2) must continue to be recorded up to 90 days after the last dose of study treatment(s) even if the patient begins a new anti-cancer therapy, concomitant medications associated with these SAEs must also be recorded.

Concurrent anti-cancer therapy with agents other than study treatments is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Recommended medications to treat IRRs, hypersensitivity reactions, and immune-related adverse events are reported in Table 13 and Table 14, respectively.

5.8.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/Vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 14 Management of Immune-Related Adverse Events.

Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the DLT observation period (eg, Cycle 1). These factors may be used at any time to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[25]

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines.

Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.8.2. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered, as needed, assuming the drug is not included in the Prohibited Concomitant Medications and Treatments section (Section 5.8.6).

5.8.3. Corticosteroids

Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[26,27] Furthermore, as for all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives, such as steroids, will counteract the intended benefit of avelumab. However, studies with anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) compounds indicate that short-term use of steroids can be employed without compromising clinical outcomes.[27] Therefore, the use of steroids during this trial is restricted as follows while on avelumab treatment:

- Therapeutic use: steroids are permitted for the treatment of adverse drug reactions, IRRs, and irAEs.
- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- Intranasal, inhaled topical steroids, eye drops, or local steroid injection (eg, intra-articular injection) are permitted.

5.8.4. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping investigational products temporarily is recommended in case of a

surgical procedure. Postoperatively, the decision to reinitiate treatment with investigational products should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.8.5. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline; otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression. Study treatment should be withheld for the entire duration of palliative radiotherapy and can be restarted upon recovery from any radiotherapy-related toxicities, but no sooner than 48 hours after radiotherapy completion.

5.8.6. Prohibited Concomitant Medications and Therapies

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than investigational products.
- Radiation therapy (with the exception noted above in Section 5.8.5).
- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine), except for administration of inactivated vaccines.
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Bisphosphonate or denosumab treatment unless it has been initiated more than 14 days prior to enrollment.
- Strong P-gp inhibitors that result in ≥ 2-fold increase in the exposure of an in vivo probe P-gp substrate according to the FDA website (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2) and University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/) (eg, amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir/pibrentasvir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir/velpatasvir/voxilaprevir, telaprevir, tipranavir, valspodar, and verapamil) are not recommended while on binimetinib/talazoparib treatment.

- Note: local topical treatments (eg, topical erythromycin) are permitted where systemic absorption is minimal.

- Strong P-gp inducers (eg, avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort) while on binimetinib treatment.

- Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of treatment assignment are excluded. Inhaled or topical steroids, and adrenal replacement steroid doses ≤10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

If there is a clinical indication for one of the medications or vaccinations specifically prohibited during the trial, discontinuation from study treatment may be required. The Investigator should consult with the Sponsor about individual cases.

There are no prohibited therapies during the Short-Term and Long-Term Follow-up Phases.

5.8.7. Cautionary Use of Other Medication During Treatment With Binimetinib

The following inhibitors and inducers of UGT1A1 are to be used with caution while being treated on study with binimetinib:

- **UGT1A1 inhibitors**: eg, Atazanavir, erlotinib, flunitrazepam, gemfibrozil, indinavir, ketoconazole, nilotinib, pazopanib, propofol, regorafenib, sorafenib;

- **UGT1A1 inducers:** eg, Carbamazepine, nicotine, rifampicin, testosterone propionate.

- P-gp and BCRP inhibitors/inducers: Caution and monitoring for potential increased adverse reactions should be used upon concomitant use of P-gp or BCRP transporter inhibitors with talazoparib and binimetinib including the following: atorvastatin, azithromycin, conivaptan, curcumin, cyclosporine, diltiazem, diosmin, eliglustat, elacridar [GF120918], eltrombopag, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract.

- A list inhibitors/inducers can be found according to the FDA website (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2) and University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/).

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the SOA and Section 7. All screening activities must take place within 28 days prior to enrollment into the study, unless otherwise noted.

Upon providing written informed consent, the site should contact the IRT system so as to register the patient and receive a centrally assigned study identification code.

6.2. Treatment Period/ End of Treatment

Once screening procedures have been completed, eligible patients may then be assigned to a treatment cohort as described in Section 5.1 Allocation to Treatment.

For the treatment period procedures, see the SOA and Section 7.

For the treatment period, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following prioritization of events should be adhered to, where possible:

- Pharmacokinetic blood specimens – obtain at the scheduled time.
- ECGs – obtain as close as possible to the scheduled time, but prior to pharmacokinetic blood specimen collection and within 30 minutes of the nominal time. (See Section 7.1.6).
- Assessments noted in the SOA table for End of Treatment do not need to be repeated if completed in the prior 7 days.

6.3. Patient Withdrawal

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety (see also Section 8.1.3) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.5.8 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two investigational products, the Investigator may continue treatment with the other investigational product;

- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from the study may include:

- Study terminated by Sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request that the patient return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.4. Follow-up and Long-term Follow-up

For follow-up procedures, see the SOA and Section 7.

In follow-up, all patients should be evaluated for safety and followed for survival through 90 days (at 30, 60 and 90 days) after the last dose of investigational product(s) or until the initiation of a new anti-cancer therapy, whichever occurs first. Follow-up beyond 30 days and up to and including 90 days after last dose of investigational product(s) may be performed either via a clinic visit or by remote contact (eg, telephone), with subsequent in-clinic visits requested if any concerns are noted during the telephone call.

Following early discontinuation or completion of the initial 90 day Follow-up period, all patients will continue to be followed in Long-term Follow-up for survival and for subsequent anti-cancer treatments every 12 weeks (±14 days) until death, end of the study, or patient withdrawal of consent, whichever comes first. These visits may be conducted in-clinic or by remote contact.

Patients whose disease has not progressed at the time of the End of Treatment visit will continue to undergo disease assessments every 8 weeks for 52 weeks from the start of study treatment and then every 16 weeks thereafter until documented disease progression regardless of initiation of subsequent anti-cancer therapy.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Safety Assessments

Safety assessments will include, but are not limited to, collection of AEs, SAEs, vital signs, physical examination, 12-lead electrocardiogram (ECG), ophthalmology examination, echocardiogram (ECHO)/multigated acquisition (MUGA) scan, and laboratory assessments, including pregnancy tests, and verification of concomitant treatments. See the following sections regarding the specific safety assessments.

7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL human chorionic gonadotropin (hCG) and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving study treatment (1 negative pregnancy test at screening and one at the baseline (Cycle 1 Day 1) visit immediately before study treatment administration).

Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy result will then be required at the baseline (Cycle 1 Day 1) visit before the patient may receive the study treatment. Pregnancy tests will also be repeated on Day 1 of every cycle prior to dosing of either study drug during the active treatment period and at the End of Treatment visit- to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is

missed and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational products but should remain in the study for Short-Term and Long-Term Follow-up (see Sections 8.4.3 and 8.4.3.1 for required pregnancy follow-up and safety reporting requirements and the SOA for Short-Term and Long-Term Follow-Up procedures).

7.1.2. Contraceptive Check

The Investigator or his or her designee will discuss with and confirm that any female patient of childbearing potential, who, in the opinion of the investigator, is sexually active and at risk for pregnancy is correctly and consistently using contraception (see Lifestyle Guidelines section). This discussion will be documented in the patient's chart. These patients must continue to use appropriate contraception for 30 days after the last dose of avelumab or binimetinib and 7 months after the last talazoparib dose for female patients. Fertile male patients with female partners of reproductive potential or pregnant partners, must agree to use a condom (even after vasectomy) during treatment and for at least 30 days after the last dose of binimetinib and for 4 months after the last dose of talazoparib. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. See also SOA for timing of contraceptive check.

7.1.3. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by NCI CTCAE v 4.03), timing, seriousness, and relatedness.

7.1.4. Laboratory Safety Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the SOA and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory(ies) for each study center.

Prior to study drug administration on Days 1 and 15 of each treatment cycle, hematology (ie, hemoglobin, platelets, and white blood cells) and chemistry (ie, ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, and glucose) tests must be performed and results reviewed by the treating physician prior to study drug administration. When applicable, results from pregnancy tests must also be available for review prior to dosing.

The required safety laboratory tests are listed in Table 15.

Table 15. Required Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis (Dipstick is acceptable)	Pregnancy Test
Hemoglobin	ALT	INR	Urine dipstick for urine protein: If positive collect a microscopic sample (Reflex Testing).	For female patients of childbearing potential, serum or urine with a sensitivity of at least 25 mIU/mL.
Platelets	AST	PTT or aPTT		
WBC	Alkaline Phosphatase			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic sample (Reflex Testing).	
	Chloride			
	Total Calcium			
	Total Bilirubin[a]			
Thyroid Function Tests:	BUN or Urea			
TSH, Free T4	Creatinine			
	Uric Acid			
	Glucose (fasting not required)			
Other Tests:	Albumin			
ACTH	Phosphorus or Phosphate			
HBV surface antigen	Total Protein			
Anti-HCV antibody	Amylase			
If Anti-HCV antibody test positive, then HCV RNA	Gamma Glutamyl Transferase (GGT)			
	Creatine Kinase			
	C-reactive Protein (CRP)			

Table 15. Required Safety Laboratory Tests

	Lactate Dehydrogenase (LDH)			
	Lipase			
	CK isozymes (CK-MM, CK-MB, CK-BB)[b]			
	Other Tests:			
	Cardiac Troponin T and/or I[c]			
	Myoglobin (blood or urine)			

Abbreviations: ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PTT=partial thromboplastin time, RNA=ribonucleic acid, TSH=thyroid-stimulating hormone, WBC=white blood cell.

a. For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

b. Measurement of CK-MB is required. Measurement of CK-MM and CK-BB should also be performed if available at the local laboratory.

c. Measurement of both troponin T and I is preferred where available at the local laboratory; in case where both are not available, then the same subunit measured during screening should be measured consistently throughout the study for any given patient.

7.1.5. Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems (including skin), vital signs, assessment of ECOG performance status (see Appendix 2), weight and height (height will be measured at screening only) at the time points described in the SOA.

Vital signs, to include blood pressure, pulse rate and temperature will be also recorded at the time points described in the SOA. Vital signs should be taken prior to administration of any investigational products at the visit.

7.1.6. (12-Lead) Electrocardiograms

Triplicate ECGs will be performed at screening and pre-dose on Day 1 of Cycle 1. All patients require a single ECG measurement on Day 1 of all other Cycles prior to any study drug dosing, and at the EOT visit. See the SOA for the ECG collection time points. The parameters to be recorded are RR, QT, QTc, PR, and QRS. A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. If, during a single measurement, the QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then a triplicate ECG will be collected to confirm the original measurement. Pre-dose ECG results should be reviewed prior to any study drug dosing.

Triplicate ECGs

For triplicate measurements, 3 consecutive ECGs will be performed approximately 2 minutes apart to determine mean QTc interval.

If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed, as appropriate. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the Investigator(s) and Sponsor is determined to be due to cause(s) other than investigational products, treatment may be continued with regular ECG monitoring as clinically indicated. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to ≤500 msec. Patients will then restart the investigational product at the next lowest dose level or the dose will be withheld as appropriate for the specific investigational product. If the QTc interval has still not decreased to <500 msec after 2 weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be permanently discontinued from study treatment. Additional triplicate ECGs may be performed as clinically indicated.

Each episode of prolongation of the QTc interval will be evaluated by a specialist to determine if it is due to the investigational product or due to other potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance).

If patient experiences any cardiac AE or neurologic AEs (especially syncope, dizziness, seizures, or stroke) an ECG in triplicate should be obtained at time of the event.

Triplicate ECG collections should be started within 30 minutes prior to the PK sampling time, except when coinciding with the end of avelumab infusion time, in which case ECG collection should be started within up to 10 minutes post infusion. If the infusion of avelumab is interrupted due to a non-cardiac or neurological AE, any ECG scheduled during the time the AE is occurring is not required.

7.1.7. Echocardiogram/Multigated Acquisition Scan

LVEF will be assessed by transthoracic ECHO or MUGA performed as indicated in the SOA.

Whichever modality was used at baseline should be used consistently throughout the study.

The assessment may be performed up to 7 days prior to the clinic visit to enable results to be available for review.

7.1.8. Ophthalmic Assessments

A full ophthalmic examination will be performed at the time points described in the SOA, and will include best corrected visual acuity for distance testing, automated visual field testing, slit lamp examination, intraocular pressure and dilated fundoscopy with attention to retinal abnormalities, especially retinal pigment epithelial detachment (RPED), serous detachment of the retina and RVO (or associated symptoms).

OCT and fluorescein angiography will be performed for any non-vascular/vascular abnormality, respectively as indicated in the SOA.

All ophthalmology assessments may be conducted up to 7 days prior to the clinic visit to enable results to be available for review.

7.1.8.1. Additional Ophthalmology Assessments

Patients with clinical suspicion of retinal abnormalities (ie, RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity, etc.), **must** complete at least one of the following additional assessments:

- For non-vascular abnormalities: OCT of the macula (spectral domain OCT recommended);
- For vascular abnormalities: fluorescein angiography of the central 30 degree.

Images/results of the ophthalmic examinations (at a minimum, OCT and/or fluorescein angiography) should be sent to the study site and be maintained in the patient's source document file. These images/results may be requested to be sent to the Sponsor or designee.

7.2. Pharmacokinetic Assessments

All efforts should be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor. PK sampling schedule may be modified based on emerging PK data.

PK samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

Details regarding the collection, processing, storage and shipping of the PK blood samples will be provided to the investigator site prior to initiation of the trial. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling

procedure that resulted in compromised sample integrity will be considered a protocol deviation.

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7.2.1. Blood for PK Analysis of Avelumab

Blood samples (3.5 mL whole blood at each time point) will be collected for PK analysis of avelumab, as outlined in the SOA. Blood for PK samples will be drawn from the contralateral arm of the drug infusion. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

7.2.2. Blood for PK Analysis of Binimetinib

Blood samples (3 mL whole blood at each time point) will be collected for PK analysis of binimetinib and the metabolite AR00426032 as outlined in the SOA. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

7.2.3. Blood for PK analysis of Talazoparib

Blood samples (3 mL whole blood at each time point) will be collected for PK analysis of talazoparib as outlined in the SOA. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

7.3. Immunogenicity Assessments

Blood samples (3.5 mL whole blood) will be collected for assessment of avelumab ADAs and nAb, as outlined in the SOA. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

For all patients, blood for ADA samples will be drawn from the contralateral arm of the avelumab infusion.

Immunogenicity blood samples will be assayed for ADA using a validated assay in compliance with Pfizer standard operating procedures. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination.

Samples tested positive for ADA will be further analyzed for nAb using a validated assay in compliance with Pfizer standard operating procedures.

Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Laboratory Manual to maintain sample integrity.

Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case by case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure that resulted in compromised sample integrity will be considered a protocol deviation.

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7.4. Biomarker and Pharmacodynamic Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers in tissue and blood that may have predictive value in identifying those patients who are most likely to benefit from treatment with the combination of avelumab and binimetinib or avelumab, binimetinib and talazoparib. In addition, analyses of sequentially obtained blood biomarkers will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the EOT visit may help provide some understanding on potential acquired mechanisms of resistance to the drug combination.

Information about PD-L1 expression will be collected at Screening, as part of patient's cancer history, for all patients with prior available results.

7.4.1. Tumor Biospecimens and *De Novo* Tumor Biopsies

Tumor tissue samples and tissue from biopsies of the primary and/or metastatic lesion(s) performed during the study will be used to analyze candidate DNA, RNA, or protein markers, or a relevant signature of markers, for their ability to identify those patients who are most likely to benefit from treatment with the avelumab and binimetinib or avelumab, binimetinib and talazoparib combination.

Candidate markers of interest include, but may not be limited to:

- CCI [redacted].
- PD-L1 expression on tumor and infiltrating immune cells measured by immunohistochemistry (IHC).
- Presence of DDR gene alterations.
- CCI [redacted]
- Tumor mutational burden (TMB).
- CCI [redacted]
- [redacted]

[redacted]

[redacted].

7.4.1.1. Tumor Biospecimens

Tumor biospecimens to be collected for study purposes include:

- Mandatory Screening *De Novo* Tumor Biopsy/Recent Tumor Tissue Sample:

  A mandatory *de novo* (ie, fresh) tumor core needle or excisional biopsy (that can yield at least 20 unstained slides) from a locally recurrent or metastatic tumor site that is not the only RECIST v1.1 target lesion must be performed during the 28 day screening period to provide a FFPE tumor tissue block. For patients with NSCLC who require prospective testing of RAS mutation status for eligibility determination, the biopsy may be performed within 45 days prior to enrollment.

  Exception: If an archival tumor tissue sample (that can yield at least 20 unstained slides) is available from a biopsy/surgery that was performed within 1 year prior to study enrollment and the patient did not receive any subsequent systemic anti-cancer treatment, this tumor tissue sample may be submitted without repeating a tumor biopsy during the screening period.

- Optional On-Treatment Tumor Sample(s):

  Optional biopsies are encouraged between Cycle 2 Day 1 and Cycle 3 Day 1. In addition, tumor tissue is requested for study purposes for patients who undergo tumor biopsy or resection as part of routine clinical care at any time during the treatment period.

- End of Treatment Tumor Biopsy:

  A biopsy at EOT is requested except in instances where the procedure poses unacceptable risks per Investigator documentation. The EOT tumor biopsy should be performed before initiation of subsequent anti-cancer therapy and preferably no later than ±14 days after the End of Treatment visit.

For any sample of tumor tissue, one FFPE tissue block should be provided if available and permitted by local laws and policies. If one or more blocks cannot be provided for these reasons, then sections must be freshly cut (ie, cut no more than 30 days prior to shipment to the central laboratory), 4-5 µm thick and mounted on positively-charged microscope slides (SuperFrost Plus glass slides are recommended). A minimum of 20 slides should be provided per timepoint.

A minimum 18 gauge core needle (or per institutional practice) should be used in biopsies in order to maximize the quality and value of obtained tissue; a minimum of 3 separate cores is requested for each biopsy procedure. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted.

Guidance for Selection of Biopsy Site: Where possible, the biopsied lesion must be distinct from the target lesion(s) being followed for measurable disease. Most importantly, the biopsied lesion must be one that can be accessed safely. In cases where only a primary lesion is present or accessible, a biopsy should only be collected following determination that the procedure will not confound subsequent disease assessments. Biopsies from bone lesions should not be submitted.

See the Laboratory Manual for additional details on the handling of these samples including processing, storage, and shipment.

7.4.2. Peripheral Blood Samples

As described in the SOA, the following blood samples and subsequent analyses will be conducted:

- [redacted]
- Blood sample (20 mL whole blood) will be collected as outlined in the SOA for processing to circulating tumor DNA (ctDNA) [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

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[redacted]

CCI [redacted]

[redacted]

[redacted]

7.6. Tumor Response Assessment

The decision for body areas to be scanned will depend on the disease under study and the extent of disease. Tumor assessments must include all known or suspected disease sites. The minimum recommended body areas to be scanned depending upon malignancy are detailed in the Imaging Manual. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline (within 28 days prior to randomization (for randomized cohorts) or start of study treatment (for non-randomized cohorts)), then every 8 weeks for 52 weeks from Cycle 1 Day 1, and then every 16 weeks thereafter until disease progression regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities: Safety and Efficacy Assessments. In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (eg, symptomatic deterioration) or when clinically indicated.

The schedule of tumor assessments should be fixed according to the calendar, starting with enrollment/randomization, regardless of treatment schedule or treatment interruptions due to toxicity.

Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans and other anatomy such as head or neck, as clinically indicated or protocol required.

Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

Whole body bone imaging using bone scan (bone scintigraphy) or other methods considered standard of care locally such as 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET), ^{18}-F-sodium fluoride-PET (^{18}F-NaF-PET), PET/CT, or MRI is required at baseline. Bone lesion(s) identified at baseline by bone scintigraphy, ^{18}F-FDG-PET, ^{18}F-NaF-PET, or PET/CT will be further assessed at baseline by correlative imaging, such as diagnostic CT or MRI and subsequently re-assessed by diagnostic CT or MRI as per the tumor assessment schedule (every 8 weeks during the first 52 weeks of study treatment and then every 16 weeks thereafter). Only for those patients with bone lesions present at

baseline, whole body bone imaging should be repeated at every other tumor assessment visit (ie, every 16 weeks during the first 52 weeks of study treatment and every 24 weeks thereafter) and at the time of confirmation of CR. For all patients, whole body bone imaging may be repeated during study as clinically indicated (ie, patient has new or worsening bone pain, increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases).

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Assessment of response will be made using RECIST v1.1 (Appendix 3). Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless progression of such lesions has been observed following completion of radiation therapy.

In case CR or PR is observed, tumor assessments must be confirmed on repeated imaging at least 4 weeks after initial documentation.

The allowable time window for tumor assessments is ±7 days.

All patients' files and radiologic images must be available for source verification and for potential peer review. All radiographic images will be collected and stored by an independent third-party imaging laboratory, according to instructions provided in the Imaging Manual.

7.7. Tumor RAS Mutation Status

For patients enrolled in the Phase 2 'tumor agnostic' cohort, documentation of a positive KRAS or NRAS mutation status must have been previously obtained through local laboratory testing. Any Clinical Laboratory Improvement Amendments (CLIA) -approved test (or comparable local validation) using either tumor tissue or ctDNA may have been used for this analysis.

For NSCLC patients who have not previously been tested locally and/or the status is unknown, then the mandatory screening tumor tissue sample (Section 7.4.1.1) may be sent to the central laboratory to determine the mutation status. To allow for adequate turnaround time (~14 days), this sample may be submitted prior to the 28 day screening period but after informed consent has been obtained.

Enrollment rates will be reviewed on an ongoing basis and if appropriate, KRAS/NRAS testing may be extended to other tumor types on a case by case basis.

All patients will have centralized testing performed to confirm the tumor KRAS/NRAS mutation status.

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[redacted]

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8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of suspected causal relationship to the investigational product will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the Investigator **are to be reported regardless of whether the event is determined by the Investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the Investigator does not become immediately aware of the occurrence of an event, the Investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the Investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the Investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE

Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The Investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Patient Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 90 calendar days after the last administration of the investigational product.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety if the Investigator becomes aware of them; at a minimum, all SAEs that the Investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the Investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

If a patient begins a new anti-cancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Pfizer concurs with that assessment.

If a patient begins a new anti-cancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.1.5. Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the Investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor. If the Investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to

progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST **OR** ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST **OR** ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the Sponsor.

The patient should return to the Investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of Investigator awareness.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the Investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the Investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the Investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the Investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the Investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.
- Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.
- In the event of medication dosing error, the Sponsor should be notified immediately.

- Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint or their analyses will also be reflected in a protocol amendment.

This section describes the statistical methodology for the analysis of the pre-specified endpoints to address the objectives of the study.

Prior to implementation of Amendment 3, this study examined avelumab 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 and talazoparib. However, due to observed DLTs with continuous binimetinib dosing, the schedule for binimetinib has been modified (Amendment 3) to an intermittent dosing schedule(s) which is anticipated to mitigate these potential toxicities.

9.1. Analysis Sets

9.1.1. Full Analysis Set

For Phase 1b and the non-randomized cohort in Phase 2, the full analysis set includes all enrolled patients who receive at least 1 dose of study treatment. Patients will be classified according to the study treatment actually received.

For the randomized cohort in Phase 2, the full analysis set includes all randomized patients. Patients will be classified according to the treatment assigned at randomization.

9.1.2. Safety Analysis Set

The safety analysis set includes all enrolled patients who receive at least 1 dose of study treatment.

9.1.3. DLT-evaluable Analysis 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. Additional patients will be enrolled in the specific cohort to replace patients who are not considered DLT-evaluable.

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9.1.5. Pharmacokinetics/Immunogenicity Analysis Set

9.1.5.1. Pharmacokinetics Analysis Set

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least 1 concentration for avelumab, binimetinib or talazoparib.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least 1 of the PK parameters of interest for avelumab, binimetinib or talazoparib.

9.1.5.2. 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 sample collected for avelumab.

9.1.5.3. Biomarker Analysis (BA) 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.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose Finding: BLRM

Identification of a recommended 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 Amendment 3, the doublet of avelumab in combination with binimetinib was evaluated first to determine the RP2D. Per Amendment 3, the doublet combination of binimetinib and talazoparib will be evaluated to determine the RP2D. Upon the completion of the dose finding of the doublet combinations, the triplet combinations will then be evaluated to determine the RP2D for this combination.

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.[38]

a. Doublet combination model:

Prior to implementation of Amendment 3:

For the doublet combination of avelumab and binimetinib, the Bayesian model[38] consists of three parts, representing:

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

Per Amendment 3:

For the doublet combination of talazoparib and binimetinib, the Bayesian model[38] 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[38] 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 avelumab and binimetinib;
- Triple interaction among talazoparib, binimetinib 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 5 (prior to implementation of Amendment 3) and Appendix 6 (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.[35] 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.[36,37,38] 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 5 (prior to implementation of Amendment 3) and Appendix 6 (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 5 (prior to implementation of Amendment 3) and Appendix 6 (Amendment 3).

Starting dose levels

Prior to implementation of Amendment 3, the starting dose for the doublet combination was D0 (800 mg avelumab IV Q2W, and 45 mg binimetinib orally twice daily). For this dose the prior risk of excessive toxicity was 0.10, which satisfies the EWOC criterion.

Per 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. For this dose the prior risk of excessive toxicity is 0.189, which satisfies the EWOC criterion.

A full assessment of the prior risk to patients is given in Appendix 5 (prior to implementation of Amendment 3) and Appendix 6 (Amendment 3).

The starting dose for the triplet will be determined based on all available data after completion of the dose finding for the doublet. A full assessment of the prior risk to patients is given in Appendix 5 (prior to implementation of Amendment 3) and Appendix 6 (Amendment 3).

9.3. Sample Size Determination

During the Phase 1b dose finding, prior to implementation of Amendment 3, it was estimated that approximately up to 12 and 15 patients will be enrolled and assigned to treatment with either the doublet or the triplet combinations. Per Amendment 3, it is estimated that approximately up to 18 and 12 patients will be enrolled and assigned to treatment with either the doublet or the triplet combinations (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 level and at least 9 patients at the RP2D. The actual number of patients will depend on the number of DLT events, 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.

- With 20 treated patients per treatment group (doublet and triplet combinations) for mPDAC, ORR can be estimated with a maximum standard error of 0.112.
- With 30 treated patients in the 'tumor agnostic' cohort of the triplet combination, ORR can be estimated with a maximum standard error of 0.091.
- Further, assuming a beta-binomial distribution for the ORR and a beta (0.5, 0.5) prior.
- mPDAC cohort for the doublet combination: 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 for the triplet combination: 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 for the triplet combination: 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.[49-58]

9.4. Efficacy Analysis

In the sections that follow, 'start date' refers to date of randomization for randomized cohorts and first dose of study treatment for non-randomized cohorts. All efficacy analyses will be performed based on the full analysis set, separately by treatment combination and:

- For Phase 1b: by dose level and for all dose levels combined;
- For Phase 2: by cohort and the assessment of efficacy will be based on Phase 2 (not Phase 1b unless the triplet combination does not move forward, in which case the Phase 1b patients treated at the RP2D will be combined with Phase 2 for the mPDAC cohort).

9.4.1. Analysis of the Primary Endpoint

The primary endpoint for Phase 2 is confirmed OR.

OR is defined as a CR or PR per RECIST v1.1 from 'start date' until the date of first documentation of PD or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR is defined as the proportion of patients with a confirmed CR or PR based on the Investigator's assessment according to RECIST v1.1. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation of response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of ORR. Within each cohort and for each combination, ORR will be estimated and the two-sided exact 95% CIs for ORR will be calculated. ORR for Phase 1b will be summarized by dose level and for all dose levels combined using simple descriptive statistics.

9.4.2. Analysis of the Secondary Endpoints

PFS is defined as the time from 'start date' to the date of PD by RECIST v1.1 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 new anti-cancer treatment prior to an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have any adequate post-baseline tumor assessments will be censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

- 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.

- 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.

- OS is defined as the time from time from the 'start date' to the date of death due to any cause. Patients without an event (death) will be censored at the date of last contact.

- TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods. Point estimates will be presented with 95% CIs.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics of Investigational Products

Pharmacokinetic analyses will include pre-dose and post-dose sampling for serum avelumab concentrations on Days 1 and 15 of Cycle 1; Days 1 and 15 of Cycle 2; and Day 1 of Cycles 3, 5, 9, and 12. An additional single avelumab PK sample will also be obtained at the Cycle 1 Day 8 visit. For binimetinib and talazoparib, PK samples will be collected at pre-dose on Days 1, 8 and 15 of Cycle 1, and on Day 1 of Cycles 2 and 3. In addition, PK samples collected at 1, 2 and 3 hours post-binimetinib dosing will be collected for binimetinib (and metabolites, if analyzed) on Day 1 and Day 8 of Cycle 1. If indicated, an additional unplanned PK sample may also be drawn with agreement between the Investigator and Sponsor (eg, to investigate a potential exposure-toxicity relationship for a particular patient). PK analyses will include descriptive summary statistics of the post-infusion concentration for avelumab and pre-dose/trough (C_{trough}) concentrations for avelumab, binimetinib and talazoparib for each planned sampling occasion by dose level in Phase 1b and by cohort in Phase 2, as applicable.

Other PK parameters (eg, C_{max}, T_{max}) may be determined, as appropriate.

The summary data will be compared with the historical data of avelumab, binimetinib and talazoparib as single-agents and to assess the potential drug-drug interaction effect of co-administration of the study drugs.

9.5.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/Pharmacodynamic) Modeling

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 study drug exposure and biomarkers, efficacy or significant safety endpoints. If performed, the details of these analyses will be outlined in a separate pharmacometric analysis plan (PMAP). The results of these analyses, if performed, may be reported separately.

9.5.3. Analysis of Immunogenicity Data of Avelumab

ADA/nAb data for avelumab will be listed and summarized for each sampling occasion per the schedule of assessments.

The percentage of patients with positive ADA and nAbs will each be summarized by treatment group and for all treatment groups combined. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on avelumab concentrations and pharmacokinetics may be evaluated, if data permit. A comparison of safety and efficacy endpoints between avelumab ADA and nAb positive vs. negative patients may be performed, if data permit.

9.6. Analysis of Biomarker Secondary[redacted]

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.

Appropriate change from baseline measurements will be provided.

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

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as Fisher's exact test, Kaplan-Meier estimates, and linear regression as appropriate. The statistical approaches will explore the correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy, such as tumor response and progression free survival.

[redacted]

9.7. Safety Analysis

9.7.1. Analysis of the Primary Endpoint in Phase 1b

DLT during the primary DLT evaluation period (Cycle 1) is the primary endpoint for Phase 1b.

Analyses of DLT are based on the DLT-evaluable analysis set. The occurrence of DLTs and AEs constituting DLTs will be summarized and listed for each combination per dose level, overall and by dose level for patients enrolled in Phase 1b.

9.7.2. Adverse Events

AEs will be graded by the Investigator according to the CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on TEAEs, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades.

9.7.3. Laboratory Test Abnormalities

The laboratory results will be graded according to the CTCAE v4.03 severity grade whenever applicable. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Shift tables will be provided to examine the distribution of laboratory toxicities.

9.7.4. Electrocardiogram

Baseline ECG measurements and changes from baseline will be summarized by cohort and visit. Interval measurements from clinically indicated on treatment ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS, and QTc.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval.

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9.9. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label phase 1b/2 study, the Sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-finding decisions, facilitating PK/Pharmacodynamic modeling, or to support clinical development.

9.10. Data Monitoring Committee

An external independent Data Safety Monitoring Committee will not be established for the study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines;
- Discussions between the Investigators and the Sponsor of AEs and laboratory tests alterations seen at each dose level will be performed in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the Investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The Investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with Pfizer or its agents to prepare the Investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The Investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the Investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the Investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The Investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject, or his or her legally acceptable representative, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the Investigator will inform Pfizer immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application (CTA) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of avelumab and/or talazoparib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD)

for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (CSR synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the Principal Investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The Investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the Investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations and Definitions of Terms

The following is a list of abbreviations that are used in the protocol.

ACTH	Adrenocorticotropic Hormone
ADA	Anti-Drug Antibody
ADME	Absorption, Distribution, Metabolism, and Excretion
ADP	Adenosine Diphosphate
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATM	Ataxia-Telangiectasia Mutated
ATR	Ataxia-Telangiectasia and Rad3-Related
AUC	Area Under the Curve
BA	Biomarker Analysis
CCI	[redacted]
BID	Twice daily
BLRM	Bayesian Logistic Regression Model
BCRP	Breast Cancer Resistance Protein
BNP	B-type natriuretic peptide
BOR	Best Overall Response
BP	Blood Pressure
BT0	Starting dose level for binimetinib and talazoparib
BRAF	B-Raf proto-oncogene serine/threonine-protein kinase
BRCA	Breast Cancer Susceptibility Gene
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CAP	College of American Pathologists
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CK	Creatine Kinase
CL	Clearance
CL_{CR}	Creatinine Clearance
CL/F	Apparent Oral Clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
CRPC	Castration Resistant Prostate Cancer
CRC	Colorectal Cancer
CPK	Creatine Phosphokinase
C_{trough}	Lowest Mean Plasma Trough Concentration

CR	Complete Response
CRF	Case Report Form
CRP	C-Reactive Protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Clinical Trial
CT	Computed Tomography
CTA	Clinical Trial Application
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
CV	Coefficient of Variation
CYP450	Cytochrome P450
D	Dose
DDI	Drug-Drug Interaction
DDR	DNA Damage Repair
DILI	Drug-Induced Liver Injury
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
DU	Dispensable Unit
E	Escalation/ Re-Escalation
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure During Pregnancy
EDTA	Ethylene Diamene Tetra-acetic Acid
EGFR	Epidermal Growth Factor Receptor
eGFR	Estimated Glomerular Filtration Rate
CCI [redacted]	[redacted]
EOT	End of Treatment
CCI [redacted]	[redacted]
ER	Estrogen Receptor
ERK	Extracellular regulated signal kinase
EWOC	Escalation With Overdose Control
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FANC	Fanconi Anemia Complementation
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed Paraffin-Embedded
FSFV	First Subject First Visit
FSH	Follicle Stimulating Hormone
gBRCA	germline Breast Cancer Susceptibility gene

GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GITR	Glucocorticoid Induced TNF Receptor
GnRH	Gonadotropin-Releasing Hormone
GMP	Good Manufacturing Practice
GVHD	Graft Versus Host Disease
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HER2	Human Epidermal Growth Factor Receptor 2
HFSR	Hand Foot Skin Reaction
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentrations
ICH	International Council for Harmonisation
ICOSL	Inducible Costimulator Ligand
ID	Identification
IDO	Indoleamine 2,3-Dioxygenase
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
IFN	Interferon
Ig	Immunoglobulin
IgF	Immunoglobulin F
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
IV	Intravenous
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLQ	Lower Limit of Quantitation
LOH	Loss of Heterozygosity
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody

MAD	Maximum Administered Dose
MAP	Meta-Analytic-Predictive
MCC	Merkel Cell Carcinoma
MCMC	Markov Chain Monte Carlo
M-CSF	Macrophage-Colony Stimulating Factor
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MEKi	MEK Inhibitor
MHC	Major Histocompatibility Complex
mPDAC	Metastatic Pancreatic Ductal Adenocarcinoma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
MUGA	Multigated Acquisition
NA	North America
N/A	Not Applicable
Nab	Neutralizing Antibody
NCI	National Cancer Institute
CCI [redacted]	[redacted]
NDA	New Drug Application
NE	Not Estimable
NEMO	NF-κB essential modulator
NK	Natural Killer
NKG2DL	Natural Killer Group 2 Member D Ligand
NRAS	NRAS proto-oncogene, GTPase
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
OCT	Optical Coherence Tomography
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PBMC	Peripheral Blood Mononuclear Cell
PCD	Primary Completion Date
PD	Pharmacodynamic
PD	Progressive Disease
PDAC	Pancreatic Ductal Adeno Carcinoma
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PET	Positron Emission Tomography
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI	Principal Investigator

PI3K	Phosphatidylinositol-3 kinase
PK	Pharmacokinetics
PKC	Protein Kinase C
PMAP	Pharmacometric analysis plan
PO	Orally
PR	Partial Response
CCI	[redacted]
PS	Performance Status
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog Gene
PTT	Partial Thromboplastin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QD	Once Daily
QLQ	Quality of Life Questionnaire
RCC	Renal Cell Carcinoma
RE	Re-escalation
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic Acid
RPED	Retinal Pigment Epithelial Detachment
RP2D	Recommended Phase 2 Dose
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SD	Standard Deviation
SD	Stable Disease
SE	Standard Error
SOA	Schedule of Assessments
SOPs	Standard Operating Procedures
SRSD	Single Reference Safety Document
STING	Stimulation of Interferon Genes
$t_{1/2}$	Terminal Half-Life
TBili	Total Bilirubin
TCR	T-cell Receptor
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Maximum Plasma Concentration
TMB	Tumor Mutational Burden
TNM	Tumor, Node, Metastasis
TNBC	Triple-Negative Breast Cancer
TO	Target Occupancy
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
TTR	Time-to-Tumor Response
UC	Urothelial Cancer
UGT	Uridine Diphosphate Glucuronosyl Transferase

ULN	Upper Limit of Normal
UPM	Unit Probability Mass
US	United States
VEGF	Vascular Endothelial Growth Factor
V/F	Apparent Volume of Distribution
V_{ss}/F	Apparent Steady-State Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
5d/2d	5 days on/2 days off
7d/7d	7 days on/7 days off

Appendix 2. ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

From: Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649–655.[28]

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228-247.[29]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to randomization (for randomized cohorts) or start of study treatment (for non-randomized cohorts) and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed post-baseline.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target Disease

- All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE (ie, Not Evaluable), PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case should be discussed with the radiologist and the Sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Not evaluable (NE): Progression has not been documented, and

    - one or more target lesions have not been assessed; or

    - assessment methods used were inconsistent with those used at baseline; or

    - one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or

    - one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels (if being followed). All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level (if being followed) above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Not evaluable (NE): Progression has not been determined and one or more non-target lesion sites have not been assessed or assessment methods used were inconsistent with those used at baseline or one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images) or one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document PD even after discontinuation of study treatment.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in the following table.

Table 16. Objective Response Status at Each Assessment for Patients with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non-PD includes CR and Non-CR/Non-PD
** New lesions must be unequivocal

Determination of Best Overall Response

The best overall response is the best response recorded from randomization (for randomized cohorts) or the start of the treatment (for non-randomized cohorts) until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment at a minimum interval of 6 weeks.

Appendix 4. Cockroft-Gault Formula

[(140-Age) * Mass (in kg)]/[72 * Serum creatinine (in mg/dL)].

If the patient is female, multiply the above by 0.85.

Appendix 5. Detailed Dose Escalation/De-escalation Scheme for BLRM Design – prior to implementation of 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.

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 (see Section 1.2.6.1).

A.5.1. 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.5.1.1. 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: $\text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$

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

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(>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

A.5.1.2. 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:

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

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

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.5.2. 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.5.2.1. 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.5.2.1.1. 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:

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

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

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

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

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.5.2.1.2. Single Agent Avelumab

Dose-DLT data in the avelumab IB[4] (Section 5.3.1.1.1.7) from study EMR100070-001 as presented in Table 17 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 17. Historical Dose Limiting Toxicity Data from Study EMR100070-001

Avelumab dose (mg/kg Q2W)	Number of patients	Number of patient 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).[38]

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 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.5.2.1.3. Single Agent Binimetinib

Dose-DLT data in the binimetinib IB[30] (section 5.2.3.1.1) from studies ARRAY-162-111 and CMEK162X11 as presented in Table 19 are used to derive the prior of the single agent logistic parameters for binimetinib.

Table 19. 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 20 below.

Table 20. 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.5.2.1.4 Single Agent Talazoparib

Dose-DLT data from study PRP-001 (C3441007) (de Bono et al. 2017)[59] presented in Table 21 are used to derive the prior of the single agent logistic parameters for talazoparib.

Table 21. 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 22. 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.5.2.2. 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.5.2.3. Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 23. Table 24 and Table 25 illustrates the resulting prior distribution of DLT rate derived from the prior given in Table 23 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 23. 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 24. 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 25: in absence of doublet combination 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 is available. Some hypothetical examples for the starting dose of the triplet are shown in Table 27.

Table 25. 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.5.3 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 26 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 26. Doublet Combination: Data Scenarios, Next Dose Recommendation, and the Interval Probability of Target Toxicity and Overdosing at Next Dose.

	Dose Evaluated				Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
Scenarios	Ave (mg/kg Q2W)	Bini (mg BID)	Tala mg (QD)	D/N*	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 27 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 27. 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; QD=once daily; Q2W=every 2 weeks.

Table 28 shows data scenarios for the triplet combination and the corresponding recommendations for the next dose.

Table 28. 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				Next Dose (ND)			Pr(TT) at ND	Pr(OD) at ND
Scenarios	Ave (mg/kg Q2W)	Bini (mg BID)	Tala (mg QD)	D/N*	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 26 and Table 28, the recommended next dose is adequate for all considered scenarios.

A.5.4. 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.5.4.1) and in each scenario 1000 trials were simulated, with results summarized in A.5.4.3.

A.5.4.1. 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 29 and Table 30, respectively. Scenario 4 in Table 30 represents a true toxicity profile with dose combinations in both under-dose and over-dose regions.

Table 29. 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 30. 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.5.4.2. 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($0.16 \leq \pi_{\tilde{d}} < 0.33$)≥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 (fixed), 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($0.16 \leq \pi_{\tilde{d}} < 0.33$)≥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.5.4.3. Simulation Results

Operating characteristics for the doublet and the triplet combinations are presented in Table 31 and Table 32, 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 31. 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	00	14.3	9
3. Higher dose level is overly toxic	48.6	51.4	0	0.674	0	00	32.6	11

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

Table 32. 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 6. Detailed Dose Escalation/De-escalation Scheme for BLRM Design - 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 (see Section 1.2.6.1).

A.6.1. Statistical Model

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

A.6.1.1. 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.6.1.2. 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:

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

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

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 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 of talazoparib and binimetinib combination (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.6.2. 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.6.2.1. 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.6.2.1.1. 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:

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

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

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

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

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.6.2.1.2. Single Agent Talazoparib

Dose-DLT data from study PRP-001 (C3441007) (de Bono et al. 2017)[59] presented in Table 33 are used to derive the prior of the single agent logistic parameters for talazoparib.

Table 33. 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 34 below.

Table 34. 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.6.2.1.3. Single Agent Binimetinib

A.6.2.1.3.1. 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

Meta-analysis predictive prior using continuous regimen data for binimetinib

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

A.6.2.1.3.1. Single Agent Binimetinib (Continuous Dosing)

Dose-DLT data in the binimetinib IB[30] from studies ARRAY-162-111 and CMEK162X11 (continuous dosing schedule) as presented in Table 35 are used to derive the MAP priors of the single agent logistic parameters for continuous binimetinib.

Table 35. 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 36 below.

Table 36. 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.6.2.1.3.2. 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.6.2.1.4. Single Agent Avelumab

Dose-DLT data in the avelumab IB[4] from study EMR100070-001 as presented in Table 37 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 37. Historical Dose Limiting Toxicity Data from Study EMR100070-001

Avelumab dose (mg/kg Q2W)	Number of patients	Number of patient 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).[38]

The prior distributions for the model used for deriving the MAP priors are specified in Table 38 below.

Table 38. 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.6.2.2. 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.6.2.3. 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.6.2.3. Summary of Prior Distributions

The prior distributions of the model parameters are provided in Table 39.

Table 39. 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 40 and Table 41 illustrate the resulting prior distribution of DLT rate derived from the prior given in Table 39 for the doublet and the triplet combinations, respectively. The probability of overdosing for the proposed starting dose level for the doublet with binimetinib 45 mg (7d/7d) and talazoparib 0.75 mg is 0.189, which satisfies the EWOC criteria.

Table 40. Summary of Prior Distribution of Dose Limiting Toxicity Rates for the Binimetinib (7d/7d) + Talazoparib Doublet

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 41, 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 43.

Table 41. Summary of Prior Distribution of DLT Rates for the Avelumab + Binimetinib + Talazoparib Triplet

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.6.3. 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 42 shows some hypothetical dose escalation data scenarios for the binimetinib (7d/7d) + talazoparib doublet combination and the corresponding recommendations for the next dose.

Table 42. Binimetinib (7d/7d) + Talazoparib Doublet: 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.

Table 43 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 43. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet: 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	45	0.75	3/6	No feasible starting dose for the triplet				

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)		
	0 0	30 30	0.5 0.75	1/5 3/12					
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 44 shows data scenarios for the triplet and the corresponding recommendations for the next dose.

Table 44. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet: 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)				

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)		
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 (10)	45 45 30	0.75 1.0 0.75	1/6 2/12 1/6	(10)	30 45	1.0 0.75	0.614 0.512	0.239 0.209
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.6.4. 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.6.4.1) and in each scenario 1000 trials were simulated, with results summarized in A.6.4.3.

A.6.4.1. Simulation Scenarios

The true DLT rates under different scenarios for doublet and triplet combinations are shown in Table 45 and Table 46, 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 45 represents a true toxicity profile with dose combinations in both under-dose and over-dose regions.

Table 45. Binimetinib (7d/7d) + Talazoparib Doublet: 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 46. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet: 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.6.4.2. 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:

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.6.4.3. Simulation Results

Operating characteristics for the doublet and the triplet combinations are presented in Table 47 and Table 48 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 47. Binimetinib + Talazoparib (7d/7d) Doublet Combination: Operating Characteristics

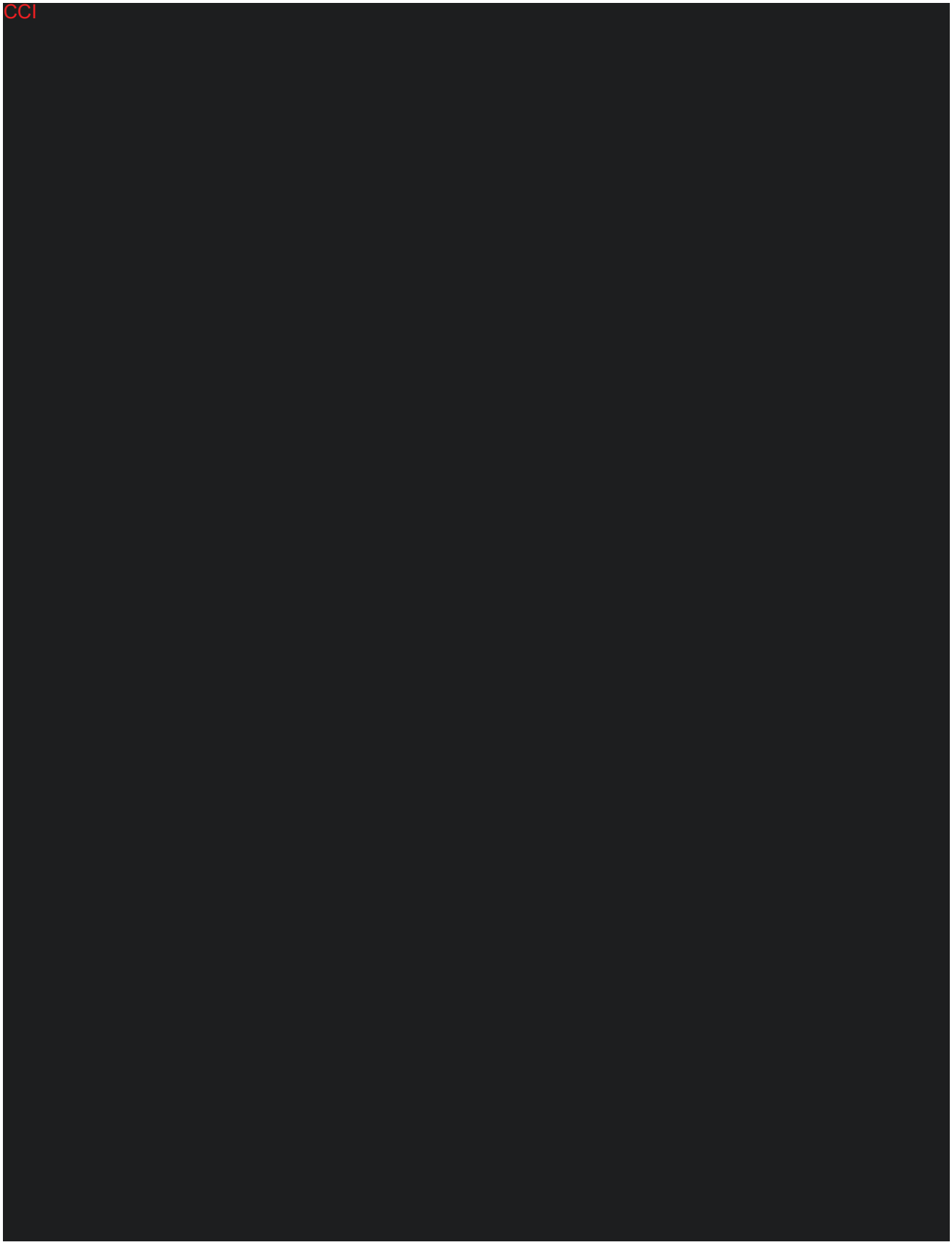
True DLT Scenarios	% Patient allocation			% declare MTD			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
1. Prior means	97.2	0	2.8	85.2	0	0	14.8	10
2. 25% more toxic than prior means	88.8	11.2	0	77.3	0	0	22.7	10
3. 40% more toxic than prior means	82.5	17.5	0	59.0	0	00	41.0	11
4. With underdose 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 48. Avelumab + Binimetinib (7d/7d) + Talazoparib Triplet: Operating Characteristics

True DLT Scenarios	% Patient allocation			%declare MTD			% stop (no MTD)	Average sample size
	TT	OD	UD	TT	OD	UD		
Prior means	90.5	9.5	0	60.8	0	0	39.2	11
10% more toxic than prior means	91.6	8.4	0	56.4	0	0	43.6	9
10% less toxic than prior means	100	0	0	65.4	0	0	34.6	12
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.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