Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase Ib Safety Run-in and Randomized Phase II, Open-label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of M6620 in Combination with Avelumab and Carboplatin in Comparison to Standard of Care Therapy in Participants with PARPi-resistant Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Study Number:	MS201943-0029
Amendment Number	Amendment 2
Merck Compound Number:	G.20194301
Short Title:	Phase Ib/II Study of Carboplatin + M6620 + Avelumab in PARPi-resistant Ovarian Cancer
Coordinating Investigator:	PPD Telephone PPD : PPD Telephone PPD : PPD

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Medical Monitor Name and Contact Information:	PPD PPD (mobile) PPD (landline) mailto: PPD

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	24 Jul 2018
1.1-BEL	Local Protocol Amendment	06 Nov 2018
2.0	Global Protocol Amendment	30 Nov 2018

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

In general, this global amendment incorporates clarifications and changes to allow investigative sites additional ease in enrolling and adhering to the protocol.

Section # and Name	Description of Change	Brief Rationale
Title Page	"Phase 1b Safety Run-in" was added to the study title	The title now reflects the Part A, Phase 1b Safety Run-in portion of the trial which was previously not included.
Throughout, where applicable	The order of study drugs was modified where applicable to carboplatin + M6620 + avelumab therapy. Avelumab maintenance therapy compared to the standard of care (SoC) now includes optional bevacizumab (that is platinum-containing chemotherapy with optional bevacizumab).	To establish consistent study intervention naming conventions throughout the document, where applicable.
Synopsis and Section 3: Objectives and Endpoints (Parts A and B)	Deleted irRECIST for response assessment.	Assessment by CA-125 and RECIST is relevant for ovarian cancer and irRECIST was not necessary given that prior trials with avelumab do not identify any clinically relevant differences in irRECIST compared to RECIST v1.1.
Synopsis and Section 3: Objectives and Endpoints (Part A only)	Deleted secondary objective to characterize immunogenicity.	Part A is expected to have as few as 3 participants and up to 18 participants; given the low rate of immunogenicity observed in other avelumab trials, it is unlikely to reliably characterize immunogenicity from only Part A participants. The Part B objective to characterize immunogenicity will include all participants treated with avelumab from both Parts A or B.
Tables 1, 2, and 3: Schedule of Assessments	Added clarifying language for evaluating progression as per GCIG guidelines.	To provide clarification of guidelines for response/progression.
Synopsis Study Intervention Groups and Section 6	Clarification that after a completion of 6 cycles, participants will continue in maintenance treatment with avelumab (800 mg every 2 weeks as monotherapy) until PD, unacceptable toxicity, withdrawal of consent, death, or a minimum of 12 months of treatment following confirmed CR.	For consistency with other avelumab monotherapy protocols.

Section # and Name	Description of Change	Brief Rationale
Synopsis Study Intervention Groups and Section 6	Added SoC option: carboplatin AUC 5 on Day 1 + pegylated liposomal doxorubicin (PLD) 30 mg/m^2 every 4 weeks for up to 6 cycles with or without bevacizumab.	To address the concern that participants may not be eligible to receive paclitaxel or gemcitabine as part of a 3rd line or later carboplatin combination therapy, given that participants may have received these other agents earlier.
Synopsis Study Intervention Groups and Section 6	Added that the recommended dosage for the SoC regimen may be adapted per Investigator discretion and in accordance to the local institutional guidelines.	To provide allowance for the Investigator to adjust the starting dose of either the carboplatin or combination chemotherapy agent, given that some participants may not be able to tolerate the usual recommended dose if they have previously received the agents.
Section 5.1: Inclusion Criteria	Reduced minimum time of prior PARPi treatment from at least 6 to 4 months.	Following discussions with investigators, it was recommended to reduce the minimum time of PARPi treatment to at least 4 months as sufficient minimum treatment to evaluate PARP resistance and to reduce screen failures due to PARP treatment time without impacting ability to evaluate treatment in patients with PARP resistance aligned with the rationale for the combination treatment.
Section 5.1: Inclusion Criteria	Made the Part A two (2) paired biopsies optional instead of mandatory.	Feedback from clinical sites reported feasibility of paired biopsies to be very low and could result in difficulty recruiting participants to Part A of trial, given that pharmacodynamics is a tertiary objective and safety is the primary determinant to accept the dose
Section 5.1: Inclusion Criteria and Appendix 3	Contraception criteria was changed to: Contraception from 1 menstrual cycle before the cycle preceding the start of the first dose during the study intervention period (Parts A and B), and for at least 6 months after the last dose of carboplatin, M6620 or the defined SoC combination treatments, or at least 60 days after the last dose of maintenance with avelumab or bevacizumab, whichever is later.	To bring the protocol into alignment with the SmPC for carboplatin and defined SoC combination treatments, as well as the M6620 IB, which specify to continue contraception for at least 6 months after the last treatment.
Section 5.3.1: Meals and Dietary Restrictions	Deleted restrictions on food and beverages and specified no restrictions on meals or diet.	Deleted food and beverage restrictions because M6620 is administered intravenously and will not be affected by food and beverages.
Section 6.3.2: Blinding	Added the following sentence: However, any aggregate summary of data, if required, will be provided only in a blinded way during the study, to limit bias in the conduct of the study.	To further protect study integrity.
Section 6.6.1: Definition of Dose-limiting Toxicity	The definition of a DLT was clarified to:	To provide clarification of when an IRR is a DLT.

Section # and Name	Description of Change	Brief Rationale
	"…any death not clearly due to the underlying disease or extraneous causes or any ≥ Grade 3 nonhematologic or ≥ Grade 4 hematologic toxicity that is possibly, probably, or definitely related to any of the study interventions…except for any of the following: - Grade 3 infusion-related reaction resolving within 6 hours from the end of infusion and controlled with medical management.	
Section 6.11: Management of Adverse Events of Interest (Avelumab)	Clarified that infusion-related reactions and irAEs should be handled according to the 2018 ASCO guidelines.	To clarify source of current guidance for management of infusion-related reactions and irAEs.
Section 8.2.5: Safety and Data Monitoring Committees	Added: "For Part B, a data monitoring committee (IDMC) will be constituted by Sponsor's members independent from the project team and if needed may include external medical expert to regularly review the data in Part B of the study to ensure safety of the participants as well validity and integrity of the study. The participants, data reporting details and specific working procedures will be defined in the DMC charter prior to start of enrollment in Part B."	To ensure integrity of the trial data by including a Data Monitoring Committee consisting of internal Sponsor staff not associated with the clinical study to review data during Part B of the study.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

[redacted]

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase Ib Safety Run-in and Randomized Phase II, Open-label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of M6620 in Combination with Avelumab and Carboplatin in Comparison to Standard of Care Therapy in Participants with PARPi-resistant Recurrent Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Short Title: Phase Ib/ II Study of Carboplatin + M6620 + Avelumab in PARPi-resistant Ovarian Cancer

Rationale: The purpose of Study MS201943-0029 is to evaluate the safety of the recommended Phase II dose (RP2D) of carboplatin +M6620 (doublet) when used in combination with avelumab (Part A; triplet) and the efficacy and safety of carboplatin + M6620 + avelumab therapy with avelumab maintenance compared to the standard of care (SoC; platinum-containing doublet chemotherapy with optional bevacizumab) (Part B) in participants with recurrent ovarian, primary peritoneal, or fallopian tube cancer who have progressed on a poly (ADP-ribose) polymerase inhibitor (PARPi). Given that PARPi-resistant recurrent ovarian cancer with expected platinum sensitivity is associated with a high mutational load and homologous recombination deficiency, the combination treatment of a deoxyribonucleic acid (DNA)-damaging agent (carboplatin) with a DNA damage response inhibitor (DDRi; M6620) and an immune checkpoint inhibitor (avelumab) is expected to synergize and lead to insufficient DNA repair, increased DNA mutations, immunologic cell death, and an increase in potential immunological targets within the tumor.

Objectives and Endpoints:

Part A (Safety Run-in Period)

Objectives (Part A)	Endpoints (Outcome Measures)
Primary	
To evaluate a safe, tolerable RP2D of carboplatin + M6620 in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	Occurrence of dose-limiting toxicities (DLTs) during the DLT observation period
Secondary	
To evaluate the safety and tolerability of carboplatin + M6620 at the RP2D when used in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	Occurrence of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Objectives (Part A)	Endpoints (Outcome Measures)
To evaluate the antitumor activity of carboplatin + M6620 at the RP2D in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	• Confirmed best overall response (BOR) • Progression-free survival (PFS) from date of first dose of study intervention until progressive disease (PD) or death • Duration of response (DOR) as assessed from complete response (CR) or partial response (PR) until PD, death, or last tumor assessment • Time to progression (TTP) from first dose of study intervention until PD All the above by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and/or cancer antigen 125 (CA-125) response (Gynecologic Cancer Intergroup [GCIG] criteria), as assessed by the Investigator. • Time to first subsequent therapy (TFST)
To characterize the pharmacokinetic (PK) profiles of avelumab and M6620 when given in combination with carboplatin	• PK parameter estimates for M6620 • PK summary statistics for avelumab

Part B (Randomized Treatment Period)

Objectives (Part B)	Endpoints (Outcome Measures)
Primary	
To evaluate antitumor activity of carboplatin + M6620 in combination with avelumab compared with the standard of care treatment in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	PFS according to RECIST v1.1 as assessed by the Investigator
Secondary	
To evaluate the safety and tolerability of carboplatin + M6620 at the RP2D in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	Occurrence of TEAEs and treatment-related AEs and immune-related adverse events (irAEs) according to NCI-CTCAE
To further evaluate antitumor activity of carboplatin + M6620 in combination with avelumab compared with the standard of care treatment	• PFS according to GCIG CA-125 as assessed by the Investigator • Confirmed BOR according to RECIST v1.1 and GCIG CA-125 • DOR assessed from CR or PR until PD, death, or last tumor assessment • TTP • TFST
To characterize the PK of avelumab and M6620 when given in combination with carboplatin	• PK parameter estimates for M6620 • PK summary statistics for avelumab
To characterize the immunogenicity of avelumab in combination with M6620 + carboplatin	Immunogenicity of avelumab in combination therapy as measured by ADA assay from all participants treated with carboplatin + M6620 + avelumab in Part A and Part B

Overall Design: This Phase Ib / II study is an open-label, randomized, controlled study consisting of 2 parts. Part A is a safety run-in dose de-escalation to identify a safe dose of carboplatin + M6620 in combination with avelumab for Part B. In Part B, participants will be randomly assigned to receive open-label treatment with either the triplet combination (carboplatin + M6620 + avelumab) or SoC (platinum-based doublet therapy with optional bevacizumab). Participants will be randomized (stratified by BRCA [breast cancer gene] status) to one of the treatment arms.

Number of Participants: During Part A of the study, approximately 3 to 18 participants are expected to be enrolled to evaluate the safe dose for the triplet combination (a modified 3 + 3 design, but dose reductions will be considered only if necessary).

In Part B, a total of approximately 72 participants will be enrolled. Based on 50 events for progression-free survival (PFS), the probability to observe a hazard ratio (HR) of 0.6 or lower is 74% under the assumption of a true HR of 0.5; whereas, if the true HR is 0.75 (a nonrelevant effect regarding further development of this combination therapy for such an indication), the probability to observe a HR of 0.6 or lower is 21.5%, and if there is no effect (i.e., if the true HR = 1), the probability for an observed HR of 0.6 is 3.5%. To observe 50 PFS events, a sample size of N = 72 (with a 1:1 randomization, stratified by BRCA status) has been chosen.

Study Intervention Groups and Duration: During Part A, participants will receive the triplet combination at starting doses of area under the concentration-time curve (AUC) 5 for carboplatin, 90 mg/m^2 for M6620, and 1600 mg for avelumab, for up to six 3-week cycles. The M6620 dose may be de-escalated to 60 mg/m^2, 40 mg/m^2, or another dose level upon recommendations by the Safety Monitoring Committee. After completion of the 6-cycles participants will continue in the maintenance treatment with avelumab, (800 mg every 2 weeks as monotherapy) until PD, unacceptable toxicity, withdrawal of consent, death, or a minimum of 12 months of treatment following confirmed CR.

During Part B, participants will be randomly assigned to receive either carboplatin + M6620 (at the RP2D evaluated in Part A) in combination with avelumab or SoC treatment for up to 6 cycles. The SoC regimen is to be chosen by the Investigator among the following options:

- Carboplatin AUC 5 + paclitaxel 175 mg/m^2 on Day 1; every 3 weeks for up to 6 cycles with or without bevacizumab, or
- Carboplatin AUC 4 on Day 1 + Gemcitabine 1000 mg/m^2 on Days 1 and 8; every 3 weeks for up to 6 cycles, with or without bevacizumab, or
- Carboplatin AUC 5 on Day 1 + pegylated liposomal doxorubicin (PLD) 30 mg/m^2; every 4 weeks for up to 6 cycles, with or without bevacizumab.

Recommended dosage for the SoC regimen may be adapted per Investigator discretion and in accordance to the local institutional guidelines.

Thereafter, for those who were randomized to receive triplet study intervention (carboplatin + M6620 + avelumab), avelumab will be administered as maintenance therapy (800 mg every 2 weeks as monotherapy) until PD, unacceptable toxicity, withdrawal of consent, death, or minimum 12 months therapy after confirmed CR if agreed to by the participant.

For participants in either part (Part A and Part B), the study periods consist of a 28-day Screening Period, an up to 6 cycle Treatment Period (six 3-week cycles or six 4-week cycles), an avelumab or optional bevacizumab Maintenance Treatment Period until PD, 30-day and 90-day Safety Follow-up Periods after last dose of study drug, and survival follow-up.

Involvement of Special Committee(s): Safety Monitoring Committee and Data Monitoring Committee.

1.2 Schema

Figure 1 Overall Study Design Schema

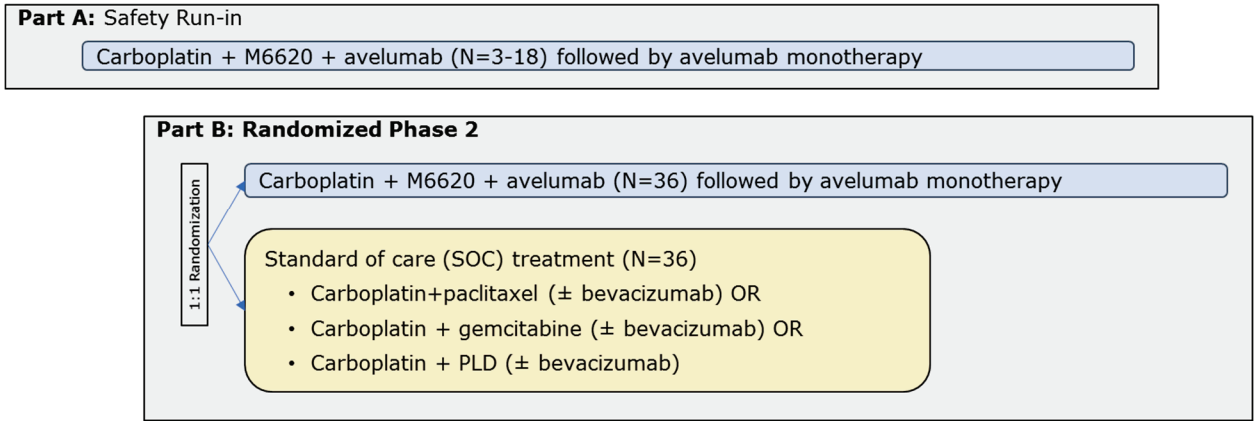
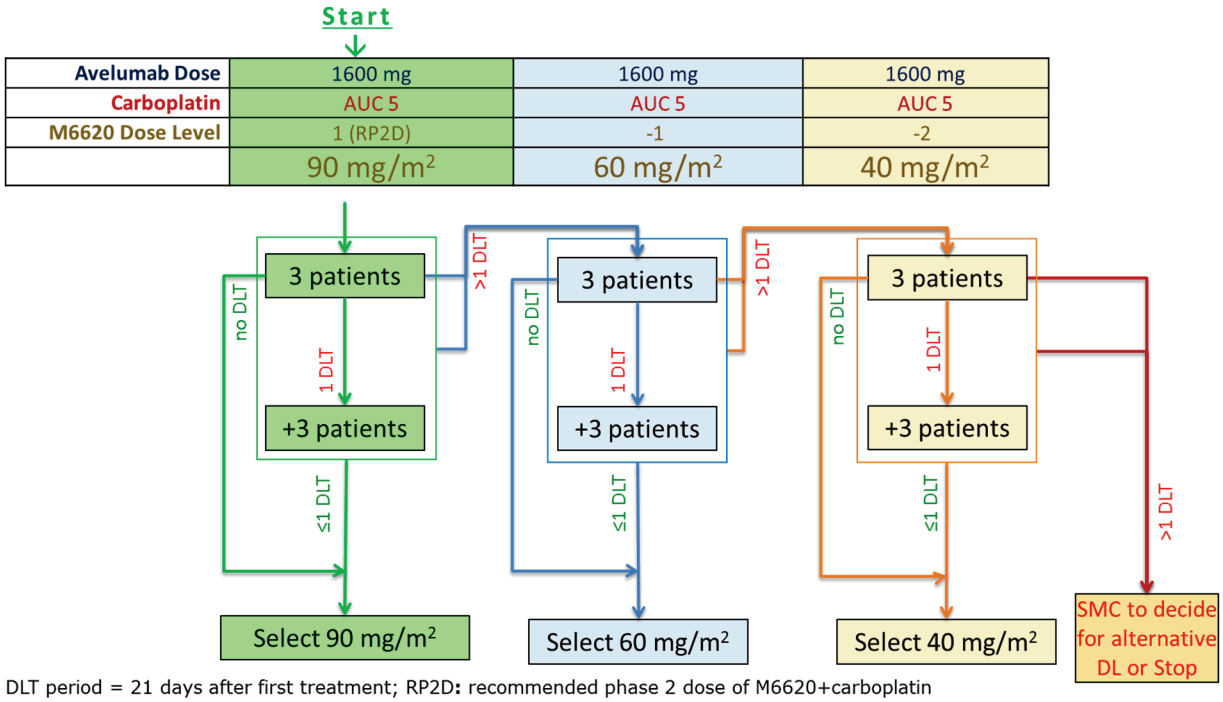
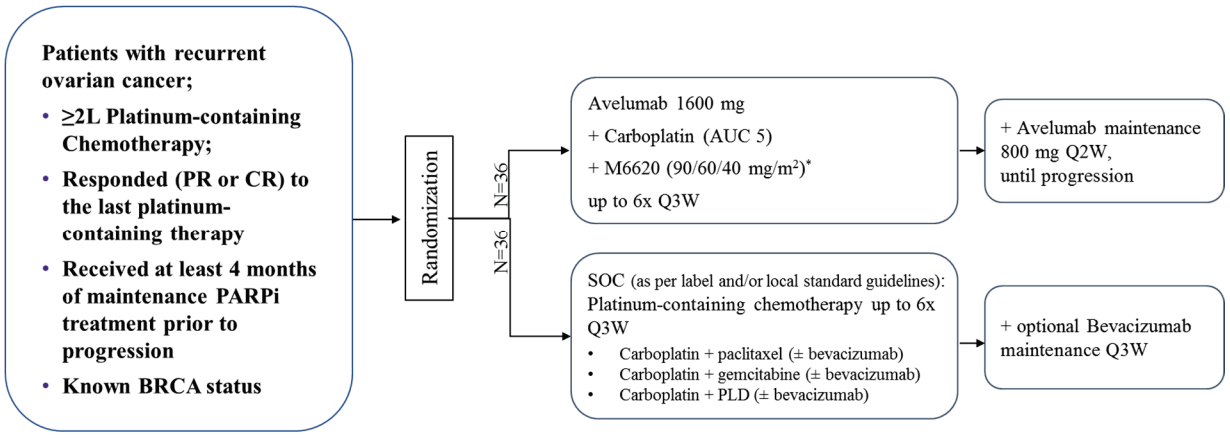


Figure 2 Part A: Safety Run-in



AUC=area under the concentration-time curve; DL=dose level; DLT=dose-limiting toxicity; RP2D=recommended Phase II dose; SMC=Safety Monitoring Committee.

Figure 3 Part B: Randomized Study Intervention Versus Standard of Care



BRCA=breast cancer gene (BRCA1, BRCA2); CR=complete response; PARPi=poly (ADP-ribose) polymerase inhibitor; PR=partial response; Q2W=every 2 weeks; Q3W=every 3 weeks; SoC=standard of care; see Section 6.1 for permitted regimens.

1.3 Schedule of Activities

A detailed schedule of study procedures and assessments are provided in Table 1 for the 6 cycles of combination study intervention in Parts A and B; in Table 2 for avelumab maintenance treatment, end of treatment, and safety follow-up in Parts A and B; and in Table 3 for SoC treatment, end of treatment, and safety follow-up in Part B.

All Part A and Part B procedures are permitted to be performed up to 3 days before or 1 day after the scheduled visit, except as otherwise noted. The treatment schedule should be strictly adhered to, returning to the target date for Day 1 even if the previous treatment was off schedule.

All participants discontinuing study intervention for any reason will undergo an End of Treatment (EoT) Visit within 7 days after the decision to discontinue study intervention, but (if possible) before any new antineoplastic therapy is started.

The 30-day Safety Follow-up Visit (± 5 days) and 90-day Safety Follow-up Phone Call (± 5 days) should be conducted, if possible, prior to the start of any new antineoplastic therapy.

Participants without PD at the EoT Visit will be followed for disease progression (CT/MRI scans every 9 weeks, and after 6 months from randomization, every 12 weeks) or start of subsequent anticancer therapy, whichever comes first.

Follow-up post study treatment discontinuation includes collection of subsequent anticancer treatment information and long-term survival status. Survival follow-up information will be documented every 12 weeks until participant's death or end of study. Progression and survival follow-up will continue until end of study defined as 1 year after the last participant has received the last dose or dies, whichever comes first.

Re-initiation of avelumab is possible for participants who experience a CR, discontinue treatment, progress, and later re-initiate treatment. The re-initiation Schedule of Activities (SoA) is presented in Table 2, without M6620 and carboplatin treatment.

Table 1 Schedule of Study Procedures/Assessments (Parts A and B) – Carboplatin- + M6620 + Avelumab (Every 3 Weeks Up to 6 Cycles)

Assessments and Procedures Avelumab + M6620+ Carboplatin	Screening	Parts A and B				Notes
		Cycles C1 up to C6 (Q3W)				
	Day -28 to -1	Day 1 (-3/+1)	Day 2 (±0)	Day 4 (± 1)	Day 8 (± 1)	
Informed consent	X					Confirm also the additional pharmacogenetics consent (Section 8.7)
Inclusion and exclusion criteria	X					No deviations or waivers are permitted
Demography	X					Age, date of birth, gender
Medical history	X					Medical history, cancer history, prior anticancer therapy (surgery, medications, radiation, etc.) and their corresponding response assessments.
Concomitant medications and procedures	X	X	X	X (Cycle 1 only)	X	Verify if any prohibited medications are given. If systemic steroids are used, confirm indication is for irAEs. Otherwise this is a deviation. Confirm any steroids for irAEs have documented tapered dosing over a minimum of 4 weeks. Document all biopsies, excisions or aspirations with procedure name and date. If indicated for suspected recurrences, ensure pathology or cytology reports are available and document results in the eCRF.
Physical examination	X	X			X	Screening and Day 1 (window = Day -3 to Day 1) of each cycle should include a full physical examination prior to study intervention administration. A PE after study intervention is a deviation All other visits should have a symptom-oriented physical examination with emphasis on irAEs.
ECOG PS	X	X				Performed prior to study intervention administration.
Height	X					
Weight	X	X				
Vital signs	X	X	X	X (Cycle 1 only)	X	Assess vital signs (blood pressure and pulse, respiratory rate, temperature) preceded by at least 5 minutes of rest and taken sitting at the following timepoints: predose (within 15 minutes prior to BOI of any study intervention administration at a given visit), at EOI (+ 15 minutes), and 1 hour after EOI (± 15 minutes).

Assessments and Procedures Avelumab + M6620+ Carboplatin	Screening	Parts A and B				Notes
		Cycles C1 up to C6 (Q3W)				
	Day -28 to -1	Day 1 (-3/+1)	Day 2 (±0)	Day 4 (± 1)	Day 8 (± 1)	
12-lead ECG	X	X	X	X (Cycle 1 only)		All participants require a single ECG measurement at Screening. Perform on-treatment ECGs on Day 1 predose (within 4 hours before avelumab infusion and before carboplatin dose) and on Day 2 (before M6620 administration) of Cycles 1 and 2. Collect ECGs matched to PK time points as follows: • Cycle 1, Day 2: predose, and 1, 2, 3, 6, and 47 hours (Day 4) after M6620 EOI. • Cycle 2, Day 2: predose and M6620 EOI. For ECGs matched to PK time points: perform 3 consecutive 12-lead ECGs (triplicates) approximately 2 minutes apart to determine mean QTc (average of triplicates) with digital upload for centralized analysis. Perform ECG assessment within 10 minutes prior to PK blood sample collection, such that the blood sample is collected at the nominal time. If ECG measurement is not feasible before PK collection, then perform ECG 10 minutes after sample collection to allow participants to recover to normal heart rate. See Section 8.2.3 for ECG assessment details in case of concurrent cardiac or neurologic AEs.
Tumor evaluation	X	Q9W				Radiologic imaging and CA-125 assessment at Screening should be performed within 4 weeks of Cycle 1, Day 1, and; should be performed every 9 weeks for the first 3 assessments, i.e., at the end of Weeks 9, 18, and 27, and then every 12 weeks thereafter (Weeks 39, 51, etc.) with a time window of up to 5 days prior to original scheduled D1 of next cycle, until PD according to RECIST v1.1. Timing of imaging/CA-125 assessment is independent from treatment delays. See Section 8.1.1 for procedures for tumor evaluation to confirm tumor response and after initial assessment of PD.
Brain CT scan/MRI, bone scan/imaging	X					Brain CT/MRI scan (either, with contrast preferred) is required at Screening unless previously done within 6 weeks prior to the Screening visit. Thereafter, brain imaging should be done only if clinically indicated. A bone scan should be done for clinically indicated tumors at Screening. Bone metastases detected at Screening need to be followed at subsequent tumor evaluation visits.
CA-125	X	X				Screening: To evaluate for response as per GCIG guidelines: if baseline CA-125 is 2 × ULN and >2 weeks prior to dosing, then collect a repeat CA-125 to obtain required pretreatment value.

Assessments and Procedures Avelumab + M6620+ Carboplatin	Screening	Parts A and B				Notes
		Cycles C1 up to C6 (Q3W)				
	Day -28 to -1	Day 1 (-3/+1)	Day 2 (±0)	Day 4 (± 1)	Day 8 (± 1)	
						Treatment and Follow-up: Collect CA-125 on Day 1 (unless performed within 7 days prior) for each of the 6 treatment cycles, and at every tumor evaluation visit or more frequently as clinically indicated. If at any time the CA-125 values decrease by at least 50% from pretreatment value, then repeat CA-125 at least 28 days later to confirm response by CA-125. To evaluate for progression as per GCIG guidelines: (1) if pretreatment CA-125 value is elevated, and during treatment CA-125 normalizes, and later elevates to at least 2 × ULN, then collect repeat CA-125 at least 7 days later to confirm progression by CA-125. (2) If pretreatment CA-125 value is elevated, and during treatment CA-125 never normalizes, then elevates to 2 x the nadir value, then collect repeat CA-125 at least 7 days later to confirm progression by CA-125 (3) If pretreatment CA-125 value is normal, and during treatment or later elevates to 2 × ULN then collect repeat CA-125 at least 7 days later to confirm progression by CA-125.
Patient-reported outcomes **(Part B only)**	(X)	X				Baseline assessments should be completed at Screening prior to any intervention. Otherwise they may be done at Visit 1 (Day 1). All subsequent assessments should be completed on Day 1 of each cycle prior to any intervention.
Documentation of AEs	X	X	X	X (Cycle 1 only)	X	Any SAE assessed as related to study intervention must be reported within 24 hours of learning of the event regardless of the time elapsed since the last administration of study intervention(s).
Study Interventions (Experimental Treatment)						
Prophylactic medication for carboplatin		X				Premedication for carboplatin (e.g., antiemetics, etc.) according to the local institutional guidelines.
Carboplatin		X				Administered on D1; up to a maximum of 6 cycles
Prophylactic medication for avelumab		X				Premedication, with the following approximately 30 to 60 minutes prior to the first 4 doses of avelumab, is mandatory: • Antihistamines (e.g., either 10 mg of chlorphenamine or 25 mg of diphenhydramine iv) • Paracetamol (acetaminophen) 500-650 mg.

Assessments and Procedures Avelumab + M6620+ Carboplatin	Screening	Parts A and B				Notes
		Cycles C1 up to C6 (Q3W)				
	Day -28 to -1	Day 1 (-3/+1)	Day 2 (±0)	Day 4 (± 1)	Day 8 (± 1)	
Avelumab		X				For Cycles 1 through 6 (triplet therapy Q3W regimen), avelumab administered on D1 at 1600 mg dose given iv immediately after completion of carboplatin administration.
Prophylactic medication for M6620			X			Premedication with the following drugs should be given to participants who have developed acute hypersensitivity or pruritus with M6620 infusion and who continue to receive treatment with M6620: • Antihistamines (e.g., either 10 mg of chlorphenamine or 25 mg of diphenhydramine iv) approximately 30-60 minutes before the infusions • 100-200 mg hydrocortisone iv approximately 60 minutes (± 15 minutes) before M6620 infusion
M6620			X			On D2 of each cycle up to maximum of 6 cycles by iv or central line administration;
Laboratory Studies						
HBV, HCV	X					Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM. Hepatitis C screening: HCVAb with reflex to HCV RNA.
Hematology	X	X			X	Hematology results must be available and reviewed by a study Investigator at least prior to D1 dose administration for every Cycle, and weekly during Cycle 1 (i.e., Day 8, Day 15, and Day 22 [which is C2D1, if treatment not delayed]).
Full serum chemistry	X	X				Full serum chemistry results must be available and reviewed by a study Investigator prior to D1 dose administration. Full serum chemistries include core chemistries in addition to: direct bilirubin, amylase, lipase, creatine kinase, LDH.
Core serum chemistry					X	Core serum chemistry results must be available and reviewed by a study Investigator on D8. Core serum chemistries include: Na^+, K^+, Cl^-, BUN, creatinine, glucose, calcium, magnesium, phosphorus, AST, ALT, alkaline phosphatase. and total bilirubin.
Urinalysis	X	X				Microscopic (sediment) examination at Screening, End of Treatment Visit, and if urinalysis is positive for protein or blood. Urinalysis results must be available and reviewed by a study Investigator prior to D1 dose administration.
β-hCG pregnancy test (if applicable)	X	X				Pregnancy tests are performed for WOCBP. Serum pregnancy test is done at Screening only. Urine pregnancy tests are done at Day 1 of each cycle, and results must be available prior to dosing at any given visit.

Assessments and Procedures Avelumab + M6620+ Carboplatin	Screening	Parts A and B				Notes
		Cycles C1 up to C6 (Q3W)				
	Day -28 to -1	Day 1 (-3/+1)	Day 2 (±0)	Day 4 (± 1)	Day 8 (± 1)	
Free T4, TSH	X	X				Every 6 weeks
M6620 plasma PK collection			X	X (Cycle 1 only)		• Cycle 1, Day 2: predose (before BOI), and at 0 (EOI), 1, 2, 3, and 6 hours after EOI of M6620. • Cycle 1, Day 4: 47 hours after EOI of M6620. • Cycle 2, Day 2: predose (before BOI), and at 0 (EOI) hours after EOI of M6620.
Avelumab serum PK collection		X				Collect predose within 2 hours prior to avelumab BOI on Day 1 of every cycle at Weeks 1, 4, 7, 10, 13, and 16. If carboplatin+M6620+avelumab is discontinued before completing the 6 cycles (i.e. before Week 16), then collect serum for PK every 12 weeks from date of first maintenance dose through Week 49. EOI: Weeks 1, 4, and 13.
Avelumab serum ADA collection		X				Collect predose within 2 hours prior to avelumab BOI on Day 1 of every cycle every 3 weeks during 6 treatment cycles at Weeks 1, 4, 7, 10, 13, 16, and then during maintenance at Week 19, 25, 37, and 49. If carboplatin+M6620+ avelumab is discontinued before completing the 6 cycles, then collect serum ADA every 12 weeks from date of first maintenance dose.
Paired FFPE tumor biopsies, optional (**Part A only**) **(Not applicable for Part B)**			X			**Part A only: Optional** paired tumor biopsies are collected at Cycle 1, Day 2, before (within 2 h before M6620 BOI) and after (1-3 h after M6620 EOI) M6620 administration. The collection is permitted on Cycle 2, Day 2, if not feasible to collect the post infusion biopsy or if neither biopsy collected in Cycle 1. If available, additional archival tissue samples from previous biopsy or surgical procedures (pre-PARPi) should also be provided for exploratory CCI analysis.
FFPE tumor biopsy and archival tissue (Required for Part B)	X (FFPE biopsy and archival tissue)	X End of Cycle 3 at Week 9 only				**Screening sample:** **Part B required for all participants** Availability of fresh FFPE tumor biopsy or archival biopsy is accepted if obtained after latest progression on PARPi. Otherwise, a fresh biopsy is required. For FFPE samples, either block or sections (> 15 slides) may be provided.

Assessments and Procedures Avelumab + M6620+ Carboplatin	Screening	Parts A and B				Notes
		Cycles C1 up to C6 (Q3W)				
	Day -28 to -1	Day 1 (-3/+1)	Day 2 (±0)	Day 4 (± 1)	Day 8 (± 1)	
		(FFPE biopsy)				If available, additional archival tissue samples from previous biopsy or surgical procedures (pre-PARPi) should also be provided for exploratory CCI analysis. **On-treatment biopsy Week 9:** FFPE tumor biopsy of a lesion at the time of the first tumor assessment (Week 9), can be from the same lesion as for the screening biopsy if possible.
CCI						

ADA=antidrug antibody; AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; BOI=beginning of infusion; BUN=blood urea nitrogen; CT=computed tomography; DC=discontinue; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; eCRF= electronic case report form; EOI=end of infusion; FFPE=formalin-fixed, paraffin-embedded; GCIG=gynecologic cancer intergroup; HBV=hepatitis B virus; HCV=hepatitis C virus; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCVAb=hepatitis C virus antibody; IgG=immunoglobulin G; IgM=immunoglobulin M; irAE=immune-related adverse event; iv=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PARPi=poly (ADP-ribose) polymerase inhibitor; PD=progressive disease; PK=pharmacokinetics; Q3W=every 3 weeks; Q9W=every 9 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse event; T4=thyroxine; TSH=thyroid-stimulating hormone; Tx=treatment; WOCBP=women of childbearing potential.

Table 2 Schedule of Study Procedures/Assessments (Parts A and B) – Avelumab Maintenance Period (Every 2 Weeks Starting After the Last Cycle of Carboplatin-+ M6620 + Avelumab), End of Treatment, and Follow-up

Assessments & Procedures Avelumab Maintenance	Parts A and B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
	Maintenance doses (M1 to Mx) until PD Q2W	Within 7 Days of Decision to Discontinue	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	Maintenance period begins after the end of the last cycle of the carboplatin + M6620 + avelumab regimen (3 weeks after last dose)
Concomitant medications and procedures	X	X	X		X	Verify if any prohibited medications given, if systemic steroids are used confirm indication for irAEs otherwise deviation; confirm any steroids for irAE have documented dosing taper over minimum 4 weeks. Document all biopsies or excisions or aspirations procedure name, date and if indicated for suspected recurrences ensure pathology or cytology reports available with results documented in eCRF.
Physical examination	X	X	X			A symptom-oriented physical examination with emphasis on irAEs should be done on Day 1 of each 2-week cycle with full physical examination at least every 12 weeks or as clinically indicated. End of Treatment and Safety Follow-up Visits should include a full physical examination.
ECOG PS	X	X	X			Performed prior to avelumab administration.
Vital signs	X	X	X			Vital signs (after 5 min seated rest - blood pressure, pulse, respiratory rate, temperature) should be assessed predose (within 15 minutes prior to BOI), at EOI (+ 15 minutes), and 1 hour after EOI (± 15 minutes).
12-lead ECG	Q8W to Q12W	X	X			ECGs will be performed on first maintenance dose and may be performed as clinically indicated. See Section 8.2.3 for ECG assessment details in case of concurrent cardiac or neurologic AEs.

Assessments & Procedures Avelumab Maintenance	Parts A and B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
	Maintenance doses (M1 to Mx) until PD Q2W	Within 7 Days of Decision to Discontinue	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	Maintenance period begins after the end of the last cycle of the carboplatin + M6620 + avelumab regimen (3 weeks after last dose)
Tumor evaluation	Q9W to Q12W				X	During avelumab maintenance therapy, tumor evaluations, should continue according to the initial schedule regardless of when avelumab maintenance was started and independent of treatment delays (every 9 weeks for the first 3 assessments, i.e., at the end of Weeks 9, 18, and 27), and then every 12 weeks thereafter (Weeks 39, 51, etc.) until PD according to RECIST v1.1. See Section 8.1.1 for procedures for tumor evaluation to confirm tumor response and after initial assessment of PD.
Brain CT scan/MRI, bone scan/imaging	If clinically indicated					A bone scan should be done for clinically indicated tumors at Screening. Bone metastases detected at Screening must be followed at subsequent tumor evaluation visits.

Assessments & Procedures Avelumab Maintenance	Parts A and B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
	Maintenance doses (M1 to Mx) until PD Q2W	Within 7 Days of Decision to Discontinue	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	Maintenance period begins after the end of the last cycle of the carboplatin + M6620 + avelumab regimen (3 weeks after last dose)
CA-125	X (Wk 27 and Q12W)	X				Follow-up: Collect CA-125 at every tumor evaluation visit and more frequently as clinically indicated. If at any time the CA-125 value decreases by at least 50% from pretreatment value, then repeat CA-125 at least 28 days later to confirm response by CA-125. To evaluate for progression as per GCIG guidelines: (1) if pretreatment CA-125 value is elevated, and during treatment CA-125 normalizes, and later elevates to at least 2 × ULN, then collect repeat CA-125 at least 7 days later to confirm progression by CA-125. (2) If pretreatment CA-125 value is elevated, and during treatment CA-125 never normalizes, then elevates to 2 × the nadir value, then collect repeat CA-125 at least 7 days later to confirm progression by CA-125 (3) If pretreatment CA-125 value is normal, and during treatment or later elevates to 2 × ULN then collect repeat CA-125 at least 7 days later to confirm progression by CA-125
Overall survival					X	
CCI [redacted]						

Assessments & Procedures Avelumab Maintenance	Parts A and B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
	Maintenance doses (M1 to Mx) until PD Q2W	Within 7 Days of Decision to Discontinue	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	Maintenance period begins after the end of the last cycle of the carboplatin + M6620 + avelumab regimen (3 weeks after last dose)
Documentation of AEs	X	X	X	X	X (as applicable)	After the 30-day Safety Follow-up Visit, all SAEs, AESIs, and treatment-related nonserious AEs must be documented until the 90-day Safety Follow-up Phone Call. Participants with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be followed by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up." Any SAE assessed as related to study intervention must be reported within 24 hours of learning of the event, regardless of the time elapsed since the last administration of study intervention(s).
Prophylactic medication for avelumab	X					Optional premedication 30 to 60 minutes before the infusion after the 4th dose, should be administered based upon clinical judgement and presence/severity of prior infusion-related reactions). with: • Antihistamines (e.g., either 10 mg of chlorphenamine or 25 mg of diphenhydramine iv) • Paracetamol (acetaminophen) 500-650 mg
Avelumab monotherapy	X					After completion of the last chemotherapy combination treatment cycle, avelumab will be administered as maintenance monotherapy at 800 mg Q2W until PD or unacceptable toxicity or minimum 12 months of therapy following a confirmed CR without recurrence.
Hematology	X	X	X			Hematology results must be available and reviewed by a study Investigator prior to dose administration.
Full serum chemistry		X	X			Full (and core) serum chemistry results must be available and reviewed prior to dose administration by a study Investigator. Full serum chemistries include core chemistries in addition to direct bilirubin, amylase, lipase, creatine kinase, and LDH.

Assessments & Procedures Avelumab Maintenance	Parts A and B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
	Maintenance doses (M1 to Mx) until PD Q2W	Within 7 Days of Decision to Discontinue	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	Maintenance period begins after the end of the last cycle of the carboplatin + M6620 + avelumab regimen (3 weeks after last dose)
Core serum chemistry	X					Core serum chemistries include Na^+, K^+, Cl^-, BUN, creatinine, glucose, calcium, magnesium, phosphorus, AST, ALT, alk phos, and total bilirubin.
Urinalysis	X	X	X			Microscopic (sediment) examination at Screening, End of Treatment, 30-day Safety Follow-up Visit, and if urinalysis is positive for protein or blood. Urinalysis results must be available and reviewed by a study Investigator prior to dose administration.
β-hCG pregnancy test (if applicable)	Q4W		X			Pregnancy tests are performed for WOCBP. Urine pregnancy test on Day 1 of every other cycle (once per month) during maintenance. Results of urine pregnancy test must be available prior to dosing at any given visit. Urine pregnancy test must be performed at 30 days after last dose safety follow-up.
Free T4, TSH	Q6W		X			
Avelumab serum PK collection	X (see Notes)		X (see Notes)			Collect predose, within 2 hours prior to avelumab BOI, at Weeks 1, 4, 7, 10, 13, and 16 and at start of avelumab maintenance at Weeks 19, 25, 37, and 49. Collect EOI at Weeks 1, 4, and 13. If avelumab maintenance starts earlier, collect the BOI every 12 weeks through Week 49. At the 30-day Safety Follow-up Visit, samples will be collected only from participants whose last treatment is on Week 49 or earlier.
Avelumab serum ADA collection	X (see Notes)		X (see Notes)			Collect predose, within 2 hours prior to avelumab BOI, at Weeks 1, 4, 7, 10, 13, and 16 and at start of avelumab maintenance on Week 19, 25, 37, and 49. If avelumab maintenance starts earlier, collect every 12 weeks through Week 49.

Assessments & Procedures	Parts A and B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
Avelumab Maintenance	**Maintenance doses (M1 to Mx) until PD** **Q2W**	**Within 7 Days of Decision to Discontinue**	**Visit: 30 D (± 5) after Last Tx**	**Phone Call: 90 D (± 5) after Last Tx**	**Every 12 Wks (± 1) after Last Tx**	**Maintenance period begins after the end of the last cycle of the carboplatin + M6620 + avelumab regimen (3 weeks after last dose)**
						At the 30-day Safety Follow-up Visit, samples will be collected only from participants whose last treatment is on Week 49 or earlier.
CCI						

ADA=antidrug antibody; AE=adverse events; AESI=adverse event of special interest; alk phos=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=β-human chorionic gonadotropin; BOI=beginning of infusion; BUN=blood urea nitrogen; CT=computed tomography; D=Day(s); DC=discontinue; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOI=end of infusion; iv=intravenous; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetics; Q2W=every 2 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse event; T4=thyroxine; TSH=thyroid-stimulating hormone; Tx=treatment; WOCBP=women of childbearing potential.

Table 3 Schedule of Study Procedures/Assessments (Part B) – Standard of Care (Every 3 or 4 Weeks for the First 6 Cycles), End of Treatment, and Follow-up

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
	Day -28 to -1	Cycles C1 to C6 (Q3W/Q4W) Day 1 (-3/+1)	Optional bevacizumab (M1 to Mx) to PD Q3W	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
Informed consent	X							
Inclusion and exclusion criteria	X							
Demography	X							
Medical history	X							Medical history, cancer history, prior anticancer therapy (surgery, medications, radiation, etc.)
Concomitant medications and procedures	X	X	X	X	X	X	X	
Physical examination	X	X		X	X			Screening, Day 1 of each cycle, End of Treatment Visits, and Safety Visits should include a full physical examination prior to any study intervention administration.
ECOG PS	X	X		X	X			Performed prior to study intervention administration.
Height	X							
Weight	X	X						

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
Vital signs	X	X		X	X			Assess vital signs (blood pressure, pulse, respiratory rate, temperature) predose (within 15 minutes prior to BOI of any study intervention administration at a given visit), at EOI (+ 15 minutes), and 1 hour after EOI (± 15 minutes).
12-lead ECG	X	X		X				All participants require a single ECG measurement at Screening. On-treatment triplicate ECGs will be performed on Day 1 of each cycle after chemotherapy infusions within 15 minutes of EOI. See Section 8.2.3 for ECG assessment details in case of concurrent cardiac or neurologic AEs.
Tumor evaluation	X	Q9W	Q9W until Wk 27 then Q12W until PD				X	Radiologic imaging and CA-125 assessment each have a time window of up to 5 days prior to Day 1 dosing and should be performed at Screening and every 9 weeks for the first 3 assessments (i.e., at the end of Weeks 9, 18, and 27), and then every 12 weeks thereafter (Weeks 39, 51, etc.) until PD per RECIST v1.1. See Section 8.1.1 for procedures for tumor evaluation to confirm tumor response and after initial assessment of PD.

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
Brain CT scan/MRI, bone scan/imaging	X							Brain CT/MRI scan (either, with contrast preferred) is required at Screening unless previously done within 6 weeks prior to start of Screening. Thereafter, brain imaging should be done only if clinically indicated. A bone scan should be done for clinically indicated tumors at Screening. Bone metastasis detected at Screening need to be followed at subsequent tumor evaluation visits.
CA-125	X	X	X (Wk 27 and Q12W)	X				Screening: To evaluate for response as per GCIG guidelines: if baseline CA-125 is 2 × ULN and >2 weeks prior to dosing, then collect a repeat CA-125 to obtain required pretreatment value. Treatment and Follow-up: Collect CA-125 on Day 1 for each of the 6 treatment cycles, at every tumor evaluation visit and more frequently as clinically indicated. If at any time the CA-125 value decreases by at least 50% from pretreatment value, then repeat CA-125 at least 28 days later to confirm response by CA-125. To evaluate for progression as per GCIG guidelines:

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
								(1) if pretreatment CA-125 value is elevated, and during treatment CA-125 normalizes, and later elevates to at least 2 × ULN, then collect repeat CA-125 at least 7 days later to confirm progression by CA-125. (2) If pretreatment CA-125 value is elevated, and during treatment CA-125 never normalizes, then elevates to 2 x the nadir value, then collect repeat CA-125 at least 7 days later to confirm progression by CA-125 (3) If pretreatment CA-125 value is normal, and during treatment or later elevates to 2 × ULN then collect repeat CA-125 at least 7 days later to confirm progression by CA-125
Overall survival							X	
CCI								

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
Documentation of AEs	X	X		X	X	X	X (as applicable)	After the 30-day Safety Follow-up Visit, all SAEs and all treatment-related nonserious AEs must be documented until the 90-day Safety Follow-up Phone Call. Participants with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be followed by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up." Any SAE assessed as related to study intervention must be reported within 24 hours of learning of the event, regardless of the time elapsed since the last administration of study intervention(s).
Standard of Care Treatment								
Prophylactic medication		X						Depending on the regimen and according to the local institutional guidelines.
Platinum-containing chemotherapy-with or without bevacizumab		X	X					Up to a maximum of 6 cycles; depending on SoC agent combined with platinum schedule is either every 3-week cycle or every 4-week cycle

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
Laboratory Studies								
HBV, HCV	X							Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM. Hepatitis C screening: HCVAb with reflex to HCV RNA.
Hematology	X	X		X	X			Hematology results must be available and reviewed prior to dose administration by a study Investigator. Additional assessments must be performed as clinically indicated and results collected
Full serum chemistry	X	X		X	X			Full (and core) serum chemistry results must be available and reviewed prior to dose administration by a study Investigator. Full serum chemistries include core chemistries in addition to direct bilirubin, amylase, lipase, creatine kinase, and LDH.
Urinalysis	X	X		X	X			Microscopic (sediment) examination at Screening, End of Treatment Visit, 30-day Safety Follow-up Visit, and if urinalysis is positive for protein or blood. Urinalysis results must be available and reviewed prior to dose administration by a study Investigator.

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
β-hCG pregnancy test (if applicable)	X	X			X			Serum pregnancy test is done at Screening only; urine pregnancy tests are done at Day 1 of each cycle, and at the 30 days after last dose safety follow-up
Free T4, TSH	X	X			X			Every 6 weeks only

Assessments & Procedures SoC	Screening	Part B	Part B	End of Treatment Visit	Safety Follow-up Visits		Long-term Follow-up	Notes
		Cycles C1 to C6 (Q3W/Q4W)	Optional bevacizumab (M1 to Mx) to PD	Within 7 Days of Decision to DC	Visit: 30 D (± 5) after Last Tx	Phone Call: 90 D (± 5) after Last Tx	Every 12 Wks (± 1) after Last Tx	
	Day -28 to -1	Day 1 (-3/+1)	Q3W					
FFPE Tumor biopsy and archival tissue (Required for Part B)	X (FFPE biopsy and archival tissue)	X End of Cycle 3 at Week 9 only (FFPE biopsy) (optional for SOC)						**Part B required for all participants;** **Screening sample:** Availability of fresh FFPE tumor biopsy or archival biopsy is accepted if obtained after the most recent progression prior to study entry. For FFPE samples, either block or sections (> 15 slides) may be provided. If available, additional archival tissue samples from previous biopsy or surgical procedures (pre-PARPi) should also be provided for exploratory CCI analysis. **On-treatment biopsy Week 9:** **Optional** for SOC arm; on-treatment biopsy of a lesion at the time of the first tumor assessment (Week 9), can be from the same lesion of the baseline biopsy if possible.
CCI								

AE=adverse events; β-hCG=β-human chorionic gonadotropin; BOI=beginning of infusion; CT=computed tomography; D=Day(s); DC=discontinue; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOI=end of infusion; FFPE=formalin-fixed, paraffin-embedded; HCV=hepatitis C virus; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCVAb=hepatitis C virus antibody; IgG=immunoglobulin G; IgM=immunoglobulin M; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PD=progressive disease; Q3W=every 3 weeks; Q4W=every 4 weeks; Q9W=every 9 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; RNA=ribonucleic acid; SAE=serious adverse event; T4=thyroxine; TSH=thyroid-stimulating hormone; Tx=treatment.

2 Introduction

Avelumab is an intravenously administered programmed death ligand 1 (PD-L1)-blocking human antibody. M6620 is a novel, intravenously administered ataxia telangiectasia and Rad3-related (ATR) inhibitor (ATRi). This study will investigate carboplatin + M6620 in combination with avelumab in the treatment of participants with recurrent ovarian, primary peritoneal, or fallopian tube cancer who have progressed on a maintenance treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi).

Complete information on the chemistry, pharmacology, efficacy, and safety of avelumab and M6620 is in the respective Investigator's Brochures (IBs).

2.1 Study Rationale

The purpose of this study is to evaluate the safe RP2D of carboplatin + M6620 in combination with avelumab (Part A) and to evaluate the efficacy and safety of carboplatin + M6620 + avelumab compared with the standard of care (SoC; platinum-containing chemotherapy) (Part B) in participants with recurrent ovarian, primary peritoneal, or fallopian tube cancer who have progressed with a PARPi. Given that PARPi-resistant recurrent ovarian cancer and expected platinum sensitivity is associated with a high mutational load and homologous recombination deficiency (HRD) (Parmar 2003), the combination treatment of a DNA-damaging agent (carboplatin) with a deoxyribonucleic acid (DNA) damage response inhibitor (DDRi; M6620) and an immune checkpoint inhibitor (avelumab) is expected to synergize and lead to insufficient DNA repair, increased DNA mutations, immunologic cell death, and an increase in potential immunological targets within the tumor.

For discussion of the scientific rationale for the study design, see Section 4.2, and for justification for dose, see Section 4.3.

2.2 Background

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. Although many patients achieve complete remission after primary treatment with cytoreductive surgery and platinum- and taxane-based chemotherapy, up to 80% of patients experience disease recurrence (Herzog 2017). Patients with recurrent platinum-sensitive ovarian cancer may undergo second-line therapy with platinum-containing regimens. In such patients, typically a median PFS time of around 9 months and a median overall survival (OS) time of around 30 months (ICON 4 [Parmar 2003], CALYPSO [Pujade-Lauraine 2010], and OCEANS [Aghajanian 2012] studies) is observed. For most patients, the benefit from treatment with platinum salts (carboplatin and cisplatin) is limited due to highly proficient cellular processes that can detect and repair damaged DNA. Nonclinical and clinical studies have shown that concurrent inhibition of DNA damage repair pathways enhances the cytotoxic effect of platinum compounds (Sundar 2017, Martin 2008, Hosoya 2014, Reaper 2011).

Alterations in genes of the DNA repair pathway involving homologous recombination have been observed in approximately 50% of high-grade serous ovarian cancer (the most common histology)

(Murai 2017). These include 25% to 30% of mutations in BRCA1/2 genes that lead to HRD, resulting in loss of heterozygosity (loss of entire genes and surrounding chromosomal regions) (Dockery 2017). DNA is repaired by multiple, partially redundant pathways with BRCA1/2 involved in error-free double-stranded DNA (dsDNA) break repair by homologous recombination (Vanderstichele 2017).

The presence of HRD is associated with favorable prognosis due to an enhanced sensitivity to platinum-based therapies as well as treatment with a DNA damage response inhibitor (DDRi), including PARPi (Ventriglia 2017). PARP repairs single-strand DNA breaks, which if left unrepaired, lead to dsDNA breaks during replication. When treated with PARPi, homologous recombination-deficient ovarian cancer cells rely on error-prone dsDNA repair systems and accumulate mutations or chromosomal changes, leading to cell death and substantial antitumor efficacy (Dockery 2017, Vanderstichele 2017, George 2017) Maintenance therapy with PARP inhibitors (olaparib [SOLO2; Pujade-Lauraine 2017], niraparib [NOVA; Mirza 2016), and rucaparib (ARIEL3; Coleman 2017]) has been shown to significantly prolong PFS compared to placebo following response to platinum-based chemotherapy in women with platinum-sensitive epithelial ovarian cancer. Some patients continue maintenance therapy for more than 5 years. However, apart from some patients with primary resistance, the majority of patients eventually develop resistance to PARP inhibition. The optimal treatment following progression on a PARPi is not currently known. There is limited literature on treatment following PARPi progression in clinical practice. The majority of patients are re-challenged with platinum-based chemotherapy if the time of progression from last dose of platinum is greater than 6 months. The median time for PFS in participants who have received treatment with platinum-containing chemotherapy after failure to PARPi maintenance treatment has been reported to be approximately 6 months (Ang 2013), depending on prior lines of treatment and the platinum-free interval. Multiple potential mechanisms of PARP inhibitor resistance have been reported (Konstantinopoulos 2015). For example, based on preclinical experiments, PARPi-resistant, BRCA1-deficient cells are increasingly dependent on the ATR pathway for survival. ATR inhibitors (ATRi) disrupt BRCA1-independent RAD51 loading to DNA DSBs in PARPi-resistant, BRCA1-deficient cells, overcoming such resistance mechanisms (Yazinski 2017). ATRi may therefore potentially overcome PARPi-resistance in BRCA-deficient cancers. As another mechanism, PARPi treatment upregulates tumor cell PD-L1 expression, which attenuates PARPi efficacy via cancer-associated immunosuppression (Jiao 2017). This provides a rationale for combined treatment with a DDRi and a PD-L1-targeting agent.

Avelumab is an intravenously administered PD-L1-blocking human antibody. PD-L1 is a ligand of programmed death 1 (PD-1), a negative regulator of T cell activity that limits the activity of T cells at a variety of stages of the immune response (Ishida 1992, Keir 2006, Freeman 2000). When engaged by a ligand, PD-1 inhibits pathways that normally lead to T cell activation. Blocking PD-1, for example with a PD-L1 antibody, thus can restore an inhibited T cell activation and lead to effective tumor reduction. Furthermore, PD-L1-blocking antibodies such as avelumab also enhance the function of tumor-infiltrating lymphocytes (TILs), which augments antitumor immunity within the tumor microenvironment. Thus, PD-1+ TILs have been shown to be indicators of response to immune checkpoint blockade, and a lack of TILs may be a predictive marker for lack of response to PD-1/L1 blockade (Curran 2010, Huang 2011, Herbst 2014). A

number of antibodies that disrupt the PD-1 axis are approved and/or are in clinical development for several tumor indications.

Avelumab is currently being evaluated in monotherapy or in combination with several chemotherapies in a number of clinical studies, including a Phase III study in combination with carboplatin/paclitaxel versus carboplatin/paclitaxel alone in previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100; NCT02718417). A total of 951 participants are planned for enrollment. As of 11 December 2017, 790 participants had received treatment. Another Phase III study is exploring avelumab alone or in combination with PEGylated liposomal doxorubicin versus PEGylated liposomal doxorubicin alone in patients with platinum resistant/refractory ovarian cancer (JAVELIN Ovarian 200; NCT02580058). In total, 546 participants (550 planned) were dosed as of the data cutoff date of 11 December 2017 (current avelumab Investigator's Brochure [IB]). The preliminary safety data from these and other studies with different tumor types suggest an acceptable safety profile of the compound as expected in participants with advanced tumor disease or in line with class effects of mAb blocking the PD 1/PD L1 axis (Avelumab IB version 8, 16 May 2018).

Inhibition of DNA damage response (DDR) is expected to synergize with PD-L1-targeting agents such as avelumab, because insufficient DNA repair may lead to increased DNA mutations, resulting in an increase in potential immunological targets ("neoantigens") within the tumor. This could increase the antitumor efficacy of a treatment acting by improving a patient's immune response toward a tumor.

Furthermore, the synthetic lethality observed after ATR inhibition in tumors with additional DDR-gene deficiencies in situations of replicative stress may result in the induction of immunogenic cell death. This is expected to synergize with PD-L1-directed activation of the patient's immune response against the tumor and result in clinical benefit. In the Phase I Study VX13-970-002, participants with advanced solid tumors received treatment with different doses of M6620 + DNA-damaging chemotherapy, including carboplatin. Among participants who received M6620 (90 mg/m^2) and carboplatin AUC 5:

- 1 participant had a RECIST v1.1 partial response (PR) of advanced BRCA mutant high-grade serous ovarian cancer with a TP53 mutation. This participant had previously progressed through multiple lines of chemotherapies and targeted agents, including a PARPi twice, and was platinum refractory.
- 8 other participants had a best response of RECIST v1.1 disease stabilization (median duration 16 weeks [range: 5 to 33 weeks]) (Sundar 2017).

In preclinical studies, chemotherapy agents that induce DNA damage have been shown to promote immune antitumor activity in addition to inducing direct cytotoxic activity (Zhao 2017, Ursic 2018) and, as a result, are expected to synergize with immunotherapies, such as avelumab. Consistent with these observations, the combination of avelumab with DNA-damaging agents results in robust synergistic antitumor activity in murine models.

The cytotoxic activity of DNA-damaging agents, including carboplatin, can be further enhanced in vivo when combined with M6620. M6620 also enhances in vitro immunogenic cell death induced by DNA-damaging agents. In addition, the combination of chemotherapy with M6620 is

hypothesized to increase neoantigen load in tumors, thereby sensitizing cancer cells to immunotherapies, such as avelumab (Mouw 2017).

Finally, it has been reported that combining DNA-damaging agents with DDR inhibitors results in greater and more persistent DNA damage, and it is expected that such combination may promote stimulator of interferon genes (STING) pathway activation and expression of Th1 cytokines (Hartlova 2015, Chen 2016). Altogether, these data support the rationale of combining avelumab with a DNA-damaging chemotherapy agent and M6620.

2.3 Benefit/Risk Assessment

The combination of carboplatin (area under the concentration-time curve [AUC] 5) + M6620 at the dose of 90 mg/m^2 has shown an acceptable safety profile and early signs of efficacy in the first-in-human clinical studies. With an established safety and efficacy profile, avelumab is currently approved in several countries for the treatment of metastatic Merkel cell carcinoma and in the United States and Israel for locally advanced or metastatic urothelial carcinoma. Additional indications (e.g., non-small cell lung, gastric, and ovarian cancers) are currently being evaluated in several ongoing Phase III studies. Based on the mechanisms of action and the available nonclinical information, and except for potential infusion-related reactions, no synergistic toxicities for the triplet combination that includes avelumab are expected. The proposed study intervention provides the possibility of substantial antitumor efficacy in ovarian cancer patients who are resistant to PARP inhibition and thus have limited treatment options. Together with the safety profile of the compounds, this results in a positive benefit-risk ratio in these patients.

Specific risks associated with the use of avelumab as a monoclonal antibody have been observed. The primary risks of exposure to avelumab include:

- infusion-related reactions
- immune-related adverse events (irAEs).

Specific risks associated with the use of M6620 with platinum therapy have been observed. The primary risks of exposure to carboplatin + M6620 include:

- infusion-related reactions
- enhanced myelosuppressive effect of carboplatin (especially thrombocytopenia, neutropenia, and anemia).

Currently, no safety data on the doublet combination of avelumab and M6620 are available; however, apart from infusion-related reactions that have been observed for both avelumab and M6620 and that are considered to be manageable by premedication and nonparallel infusions, no synergistic toxicity for this combination is expected. This is further indirectly supported by published data on the combination of the ATRi AZD6738 with the anti-PD-L1 antibody durvalumab (MEDI4736) (Yap 2016, Sundar 2017), which reported the combination was well tolerated. Nonetheless, the triplet combination of carboplatin, M6620, and avelumab at the RP2D for carboplatin + M6620 will be evaluated during a Safety Run-in Period (Part A) prior to the start of the Randomized Treatment Period (Part B) of the study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of avelumab and M6620 may be found in Section 4.2 (Scientific Rationale for Study Design) and the respective IBs.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable from a benefit/risk perspective.

3 Objectives and Endpoints

The objectives and endpoints are defined in Table 4 for Part A and in Table 5 for Part B. See Section 9.4 for statistical aspects of the endpoints.

3.1 Part A

Table 4 Part A Objectives and Endpoints – Carboplatin + M6620 + Avelumab in Recurrent PARPi-resistant Ovarian Cancer

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

Objectives (Part A)	Endpoints (Outcome Measures)
CCI	

ADA=antidrug antibody; ADME=absorption, distribution, metabolism, and excretion; AE=adverse event; BOR=best overall response; CA-125=cancer antigen 125; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; DLT=dose-limiting toxicity; DOR=duration of response; FcγR=Fc receptor of IgG; ir=immune response; mRNA=messenger ribonucleic acid; NCI=National Cancer Institute; PD=progressive disease; PGt=pharmacogenetics; PK=pharmacokinetics; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase II dose; SNP=single nucleotide polymorphism; SoA=Schedule of Activities; TEAE=treatment-emergent adverse event.

3.2 Part B

Table 5 Part B Objectives and Endpoints – Carboplatin + M6620 + Avelumab in Recurrent PARPi-resistant Ovarian Cancer

Objectives	Endpoints (Outcome Measures)
Primary	
To evaluate antitumor activity of carboplatin + M6620 + avelumab compared with the standard of care treatment in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	PFS according to RECIST v1.1 as assessed by the Investigator
Secondary	
To evaluate the safety and tolerability of carboplatin + M6620 at the RP2D in combination with avelumab in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer	Occurrence of TEAEs and treatment-related AEs and immune-related adverse events (irAEs) according to NCI-CTCAE
To further evaluate antitumor activity of carboplatin + M6620 + avelumab compared with the standard of care treatment	• PFS according to GCIG CA-125 as assessed by the Investigator • Confirmed BOR according to RECIST v1.1 and GCIG CA-125 • DOR assessed from CR or PR until PD, death, or last tumor assessment • TTP • TFST
To characterize the PK profiles of M6620 and avelumab when given in combination with carboplatin	• PK parameter estimates for M6620 • PK summary statistics for avelumab.
To characterize the immunogenicity of avelumab in combination with carboplatin + M6620	Immunogenicity of avelumab in combination therapy, as measured by ADA assay from all participants treated with carboplatin+M6620+avelumab in Part A and Part B.

Objectives	Endpoints (Outcome Measures)
Tertiary/Exploratory	
CCI	

ADA=antidrug antibodies; ADME=absorption, distribution, metabolism, and excretion; AE=adverse event; BOR=best overall response; CA-125=Cancer Antigen 125; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; DLT=dose-limiting toxicity; DOR=duration of response; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-OV28=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer; GCIG=Gynecologic Cancer Intergroup; mRNA=messenger ribonucleic acid; NCI=National Cancer Institute; PD=progressive disease; PFS=progression-free survival; PGIS=Patient Global Impression of Severity; PGt=pharmacogenetics; PK=pharmacokinetics; PR=partial response; PRO=patient-reported outcome; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase II dose; SNP=single nucleotide polymorphism; SoA=Schedule of Activities; TEAE=treatment-emergent adverse event; TFST=time to first subsequent therapy; TMB=tumor mutation burden.

4 Study Design

4.1 Overall Design

This is a 2-part (Part A: safety run-in; Part B: randomized), open-label, controlled, Phase II study to evaluate the efficacy and safety of avelumab in combination with carboplatin + M6620 in participants with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer.

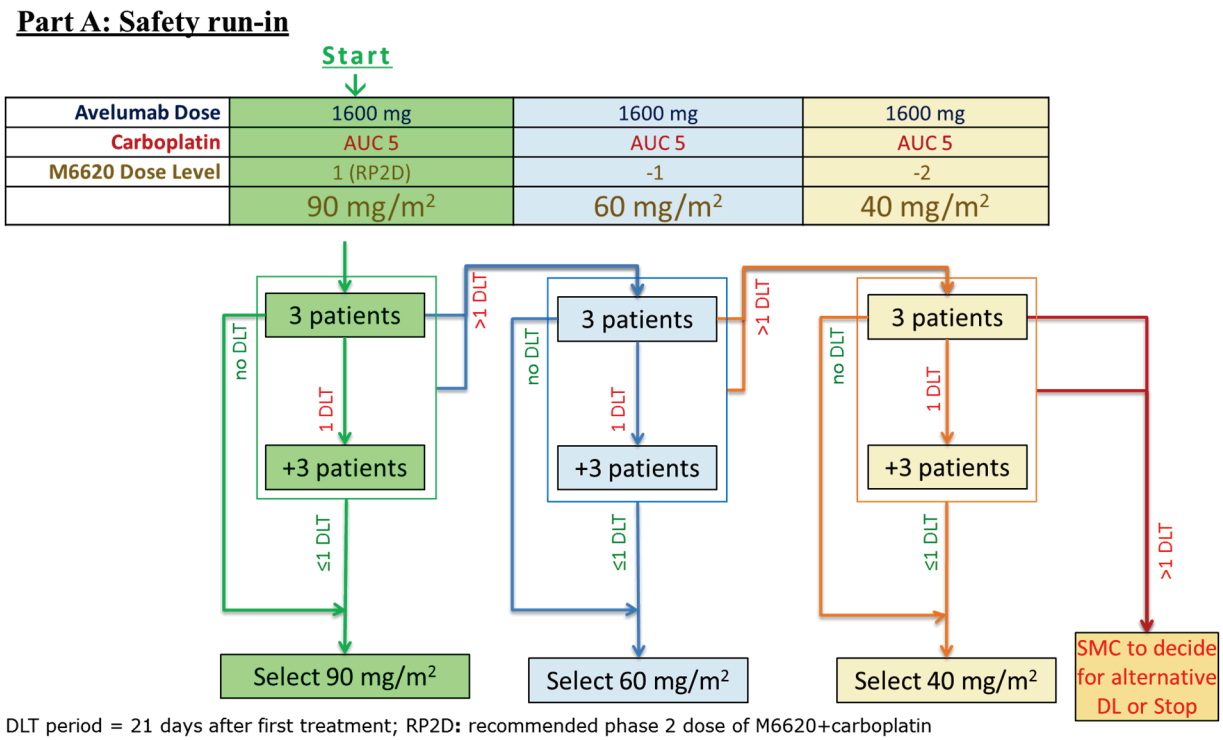
Part A is a safety run-in that will evaluate a safe RP2D dose of the triplet combination (carboplatin + M6620 + avelumab). Participants will be enrolled following a modified 3 + 3 design starting with the established doses of avelumab and the carboplatin + M6620 combination with de-escalation of M6620 doses if needed.

Participants in Part A will receive carboplatin + M6620 + avelumab every 3 weeks for 6 cycles. Treatment with avelumab will continue beyond carboplatin + M6620. Participants will be monitored for dose-limiting toxicities (DLTs) (defined in Section 6.6.1) by a Safety Monitoring Committee (SMC) (see Section 8.2.5). The DLT observation period is defined as 21 days inclusive of the day of first treatment. If at any time ≥ 2 DLTs are observed, treatment with the corresponding dose will be stopped and the next lower dose will be considered, as shown in the Part A Schema (

Figure 2). Participants are considered evaluable for dose de-escalation decisions when they have received the first planned full doses of M6620, avelumab, and carboplatin (including premedication) and completed all planned safety assessments in Cycle 1 or received any treatment and experience a DLT. Participants who do not complete the DLT observation period for reasons other than a DLT will be replaced.

Upon selection of a safe RP2D of the triplet combination in Part A, any participants who are receiving the triplet combination at a dose level higher than the RP2D will be de-escalated to the safe RP2D for the remaining every-3-week cycles, for a total of 6 infusions of the triplet combination. After receiving 6 infusions of the triplet combination during Part A, participants with ongoing treatment will receive avelumab maintenance therapy every 2 weeks until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or death.

In Part B of the study, to investigate the efficacy of the recommended triplet combination dose (as established in Part A), 72 participants (N = 36/treatment arm) will be stratified by BRCA status and randomized (1:1) to receive either the study intervention, (a treatment regimen of carboplatin + M6620 + avelumab for 6 cycles) or SoC (a treatment regimen with Investigator choice of platinum-based doublet treatment for 6 cycles) (



AUC=area under the concentration-time curve; DL=dose level; DLT=dose-limiting toxicity; RP2D=recommended Phase II dose; SMC=Safety Monitoring Committee.

Figure 3). Standard of care consisting of Investigator choice among the following platinum containing doublet therapies: carboplatin + paclitaxel, carboplatin + gemcitabine, and carboplatin + pegylated lipid doxorubicin with or without bevacizumab (see Section 6.1 for details). For participants in the study intervention triplet combination arm only, after M6620 and carboplatin

treatment has been discontinued, avelumab will be administered as maintenance therapy (every 2 weeks) until PD, unacceptable toxicity, withdrawal of consent, or death.

For participants in the SoC arm of Part B, the treatment cycle duration is 3 or 4 weeks depending on the chemotherapy agents administered with platinum as the chosen doublet combination. A total of 6 cycles will be administered as the planned treatment regimen. Bevacizumab may be administered with the SoC doublet combination as clinically indicated per discretion of the Investigator.

For participants in either Part A or Part B, the study consists of:

- a 4-week Screening Period
- a Treatment Period including for the study intervention triplet combination, is 18 weeks based on six 3-week cycles; for the SoC treatment 6 cycle for a total of to 18 weeks if 3-week cycles or 24 weeks if 4-week cycles, depending on chemotherapy agents administered;
- an avelumab Maintenance Treatment Period for the study intervention arm until PD or other reason for discontinuation; for the SoC treatment arm,
- a 7-day End of Treatment, 30-day Safety and 90-day Safety Follow-up Period,
- a Survival follow-up including collection of subsequent treatments and response data and survival status up to 1 year after last patient last treatment).

The study design schema is presented in Section 1.2, and the SoA is presented in Section 1.3. See Section 6.7 for details on study intervention after the end of the study.

4.2 Scientific Rationale for Study Design

The RP2D of M6620 in combination with carboplatin has previously been established. Because no overlapping toxicity, except for potential infusion-related reactions, with addition of avelumab is expected, the same RP2D has been selected as the starting dose in Part A and will be confirmed, or, if required, de-escalated to lower dose levels for M6620.

See Section 2 for a discussion of the relevance of mode of action for the target disease, preclinical and clinical data supporting potential activity for the study.

The study population consists of participants with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have progressed on maintenance treatment with a PARPi. The scientific rationale for the study population is provided in Section 2.

See Section 5.1 and Section 5.2 for detailed inclusion and exclusion criteria, respectively.

A randomized, controlled design comparing investigational versus SoC treatment has been selected for Part B of the study because no prospectively assessed historical data exist for the clinical endpoints to be evaluated in PARPi-resistant ovarian cancer upon treatment with SoC.

The primary objective of Part B of the study is to evaluate the antitumor activity of the investigational triplet combination regimen (carboplatin + M6620 + avelumab) compared with

SoC treatment. In recurrent ovarian cancer, PFS reported by Investigator according to RECIST v1.1 is considered an appropriate and feasible endpoint for this Phase II proof-of-concept study.

Secondary endpoints relating to safety, PK, confirmed best overall response (BOR), time to progression (TTP), and duration of response (DOR) as assessed by the Investigator using RECIST v1.1 as well as CA-125 according to the Gynecologic Cancer Intergroup (GCIG) criteria are also standard measurements.

The patient-reported outcome (PRO) assessments were selected based on the hypothesized symptoms and functional impacts associated with ovarian cancer. These will contribute to the understanding of how the participant is feeling and functioning.

The exploratory CCI assessments were selected based on the hypothesized mechanism of action and effects of M6620 and are relevant to the response, CCI . These will contribute to the understanding of AEs and help in the determination of the RP2D of M6620 in combination with avelumab and carboplatin.

4.3 Justification for Dose

4.3.1 M6620

In a M6620 monotherapy dose escalation study, no participants experienced any DLTs with a maximum administered dose of 480 mg/m^2 (O'Carrigan 2016). M6620 was generally well tolerated as a single agent, with few AEs leading to study drug discontinuation.

The RP2D of M6620 in combination with carboplatin (AUC 5) has been established at 90 mg/m^2 from Phase I studies of M6620 (refer to the M6620 IB for additional details). Among participants treated at this dose level (M6620 90 mg/m^2 + carboplatin AUC 5), 1 DLT of Grade 3 febrile neutropenia was reported (Study MS201923-0002 Part B1). The combination treatment was otherwise well tolerated (O'Carrigan 2016). Table 6 provides a summary of relevant data from the studies VX12-970-001/MS201923-0001 (Part C3) and VX13-970-002 (Parts B1 and C).

Table 6 Summary of Safety Information for Carboplatin + M6620

Combination of Carboplatin + M6620 (Study, Part, N)	VX12-970-001, Part C3 (N=10)	VX13-970-002, Part B1 (N=23)	VX13-970-002, Part C (N=11)	Total (N=44)
Dose range of M6620	90 mg/m^2	60-240 mg/m^2	90 mg/m^2	
Dose of carboplatin	AUC 5	AUC 4 or AUC 5	AUC 5	
Participants with at least one AE	8 (80.0%)	23 (100%)	11 (100%)	42 (95.5%)
AEs Grade ≥ 3	6 (60.0%)[a]	11 (47.8%)[b]	7 (63.6%)[c]	24 (54.6%)
Discontinuation due to an AE	1 (10.0%)	4 (17.4%)	4 (36.4%)[d]	9 (20.5%)
Deaths due to an AE	0	0	1 (9.1%)[e]	1 (2.3%)

[a] AEs Grade ≥ 3 occurring in ≥ 2 participants: Thrombocytopenia, neutropenia, anemia, platelet count decreased.
[b] Neutropenia was the only Grade ≥ 3 AE that occurred in more than 10% of participants.

[c] AEs Grade ≥ 3 occurring in ≥ 2 participants: Thrombocytopenia, neutropenia and anemia.
[d] Discontinuation due to AE included 2 participants with serious infusion-related reactions.
[e] One participant had a fatal AE of bronchitis.
AE=adverse event; AUC=area under the concentration-time curve.
Reference: M6620 IB 2017.

4.3.1.1 Evidence of Pharmacodynamic Effects of M6620 in Combination with Carboplatin

DNA damage, such as that induced by carboplatin, results in ATR-dependent phosphorylation of Checkpoint kinase 1 (Chk1). In preclinical studies, ATR inhibition was shown to inhibit Chk1 phosphorylation following DNA-damaging chemotherapy. Inhibition of Chk1 phosphorylation following ATR inhibitor treatment, as assessed by immunohistochemistry, was also observed in the clinical Study VX-12-970-002/MS201923-0002. In this study, paired biopsies were obtained before and after administration of M6620 in 12 participants who received carboplatin followed by M6620. Of these 5 participants had detectable levels of phospho-Chk1 prior to administration of M6620, 5 participants receiving 90 mg/m^2 of M6620 had decreases of phospho-Chk1 of 29%, 73%, and 73%, while 1 participant at 90 mg/m^2 had a 69% increase in phospho-Chk1. One participant at 120 mg/m^2 had a 94% decrease in phospho-Chk1. However, 120 mg/m^2 of M6620 was determined to be above the RP2D in combination with carboplatin. Collectively, these data support the selection of the 90-mg/m^2 dose of M6620 in combination with carboplatin and avelumab.

4.3.2 Avelumab

Avelumab has been studied and shown to be well tolerated from 1 to 20 mg/kg every 2 weeks in Phase I dose escalation study where maximum tolerated dose was not reached. The clinically active dose of 10 mg/kg every 2 weeks has shown a tolerable and manageable safety profile in more than 1700 participants across multiple tumor types. The avelumab dosing regimen of 10 mg/kg every 2 weeks has been approved by the US FDA, the EMA, and other regulatory authorities for treatment of patients with metastatic Merkel cell carcinoma, and by the US FDA for urothelial carcinoma that have progressed following platinum-containing chemotherapy.

Avelumab was originally dosed on a mg/kg basis with the aim of reducing interparticipant variability in drug exposure. However, modeling and simulation of a large body of avelumab PK data indicate that a flat dose (i.e., body weight independent) would lead to slightly less variability compared with body weight-based dosing due to a modest effect of body weight on avelumab clearance. A similar phenomenon has also been reported with other antibody drugs, which include the marketed anti-PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab (Wang 2009, Freshwater 2017, Zhao 2017, Stroh 2017). Given this finding, a flat-dose regimen is considered a favorable option which can also offer other advantages such as fewer dispensing errors, less drug wastage, shorter dose preparation times, and greater ease of administration.

Consequently, a flat dose of avelumab of 800 mg every 2 weeks has been proposed as a regimen comparable to 10 mg/kg every 2 weeks based on the following considerations. The introduction of 800 mg every 2 weeks was based on population PK analysis, with data across 3 single-agent

avelumab studies in 1827 participants with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are less variable, with 800 mg every 2 weeks compared with 10 mg/kg every 2 weeks; exposures were similar near the population median weight. Low-weight participants tended toward 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 entire population. Furthermore, the dosing regimen of 800 mg every 2 weeks is expected to result in C_{trough} > 1 µg/mL required to maintain avelumab serum concentrations at > 95% target occupancy (TO) throughout the entire 2-week dosing interval in all weight categories.

However, in the situation where avelumab is to be combined with chemotherapy that has a 3-week treatment cycle, avelumab dosing once every 3 weeks is expected to further improve convenience and compliance. For this purpose, exposures of different dose levels of avelumab given every 3 weeks were simulated. The results showed that 1600 mg every 3 weeks dosing would maintain avelumab exposure within the range demonstrated to provide high TO and meaningful antitumor activity. Specifically, avelumab concentration at 1600 mg every 3 weeks would remain above the C_{trough} of 10 mg/kg every 2 weeks for 18.2 days out of 21 days (the cycle duration) and would be 10-fold higher than the concentration (1 µg/mL) required to achieve > 95% TO in peripheral blood mononuclear cells (based on in vitro TO experiments) for the whole 21-day duration. The simulated median AUC at 1600 mg every 3 weeks is 47% higher than that obtained with a 10-mg/kg dose every 2 weeks. The simulated median C_{max} at 1600 mg every 3 weeks is comparable to that from a 20-mg/kg dose every 2 weeks, previously studied in the Phase I study, which did not show any safety concerns.

In this study, the 2 regimens of avelumab (800 mg every 2 weeks and 1600 mg every 3 weeks) will be employed. The regimen of 1600 mg every 3 weeks was chosen for evaluation in the carboplatin + M6620 + avelumab combination to align with the 3-week treatment cycle for chemotherapy and M6620 administration. During the avelumab maintenance phase, avelumab will be administered as a monotherapy using a regimen of 800 mg every 2 weeks, as synchronization with the M6620 and carboplatin regimens will no longer be necessary.

4.3.3 Reference Treatment: Standard of Care

In accordance with the current clinical practice guidelines, participants randomized to the reference treatment will receive 1 of the defined SoC treatment regimens with a platinum-containing doublet chemotherapy at the recommended dosages. The regimen will be selected by the Investigator among the allowable options defined in Section 6.1.

4.4 End of Study Definition

A participant has completed the study once all assessments have been completed, including the 90-day Safety Follow-up Phone Call post study drug discontinuation and tumor assessments to confirmed progression and or survival status reported death and the last scheduled procedure shown in Section 1.3 (SoA).

The end of the study is defined as the date of 1 year after the last participant received the last dose or dies, whichever comes first. This clinical study protocol will be closed only if the following criteria are met:

- All participants have discontinued study drug treatment regimen and maintenance therapy.
- All protocol specified end of treatment and safety follow-up visits after last participant discontinues study drug are completed.
- All protocol required procedures or interventions are completed.
- The Post-treatment Follow-up Period (including survival), defined above, has been reached.

The Sponsor may terminate the study at any time for any reason, and there may be allowance for participants to enter a rollover study, or other mechanism for avelumab access for Part A or Part B participants if randomized to that treatment, as appropriate.

5 Study Population

The study population consists of participants with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is resistant to maintenance treatment with a PARPi.

The criteria in Section 5.1 (Inclusion Criteria) and Section 5.2 (Exclusion Criteria) are designed to enroll only participants who are appropriate for the study, thereby ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥ 18 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Female participants with recurrent epithelial ovarian cancer who have disease progression following maintenance treatment with a PARPi as defined below:

    a. Participant must have histologically diagnosed epithelial ovarian, primary peritoneal, or fallopian tube cancer, with nonmucinous histology

    b. Participants must have completed at least 2 previous courses of platinum-containing therapy (e.g., carboplatin or cisplatin) and had documented response (complete response [CR] or partial response [PR]) to the last platinum-based treatment prior to treatment with a PARPi

    c. Participant has received the last dose of platinum-containing treatment at least 6 months prior to study enrollment

    d. Participant has documented disease progression (radiological) after at least 4 months of maintenance treatment with PARPi following a response to platinum-based chemotherapy.

3. Confirmed BRCA 1/2 mutation status or agree to its testing on samples collected in the study.

4. Available formalin-fixed, paraffin-embedded (FFPE) tumor biopsies.

    a. Part A: Optional - Two (2) paired on-treatment biopsies on Day 2 of Cycle 1 (first biopsy) and Day 2 of Cycle 1 or Cycle 2 (second biopsy), before and after M6620 administration, respectively, if assessed as feasible at low risk by the interventional radiologist.

    b. Part B: Histological tissue specimen (tissue block or 8 to 10 unstained slides) must be available. An archival tumor biopsy is acceptable if obtained after the last progression on PARPi treatment and is less than 6 months old. Otherwise, participants must be willing to undergo mandatory biopsy during the Screening Period to obtain sufficient tissue for histological assessment. Participants need to have an attempted biopsy. However, participants who have measurable disease documented by a radiologist as not feasible or safe to be biopsied are eligible to enter the study.

5. Measurable disease according to RECIST v1.1.

6. Greater than 28 days from and recovered from prior radiation therapy or surgery.

7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 at study entry at Screening.

8. Adequate hematological function as defined below:

    a. White blood cell count ≥ 3.0×10^9/L

    b. Absolute neutrophil count ≥ 1.5×10^9/L

    c. Lymphocyte count ≥ 0.5×10^9/L

    d. Platelet count ≥ 100×10^9/L

    e. Hemoglobin > 9 g/dL.

9. Adequate hepatic function as defined below:

    a. A total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range. Participants with documented Gilbert disease are allowed if total bilirubin > 1.5, but less than 3 × ULN

    b. Aspartate aminotransferase (AST) levels ≤ 3.0 × ULN (≤ 5 × ULN in case of liver metastases)

    c. Alanine aminotransferase (ALT) levels ≤ 3.0 × ULN (≤ 5 × ULN in case of liver metastases)

    d. Serum albumin concentrations ≥ 35 g/L (3.5 g/dL).

10. Adequate renal function defined by an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula.

Contraception Use

11. A female participant is eligible if she is not pregnant (i.e., after a confirmed menstrual period and a negative serum pregnancy test), not breastfeeding, and at least 1 of the following conditions applies to her:

    a. Is **not** a woman of childbearing potential (WOCBP), as defined in Appendix 3.

    OR

    b. Is a WOCBP who agrees to use a highly effective contraceptive method (i.e., has a failure rate of less than 1% per year), as listed in Appendix 3 from 1 menstrual cycle before the cycle preceding the start of the first dose of study intervention (as appropriate), during the study intervention period (Parts A and B), and for at least 6 months after the last dose of carboplatin, M6620, or the defined SoC combination treatments, or at least 60 days after the last dose of maintenance with avelumab or bevacizumab, whichever is later.

Informed Consent

12. Can give signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. All participants with brain metastases, except those meeting the following criteria:
    a. Brain metastases that have been treated locally and are clinically stable for at least 4 weeks prior to randomization
    b. No ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable)
    c. Participants must not be taking steroids.
2. Prior organ transplantation, including allogeneic stem cell transplantation.
3. Previous malignant disease (other than the indication for this study) within the last 5 years (except adequately treated nonmelanoma skin cancers or carcinoma in situ of any of the following tissues: skin, bladder, cervix, colon/rectum, or breast) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the participant was deemed to have been cured with no additional therapy required or anticipated to be required.
4. Active infection requiring systemic therapy:
    a. Known history of human immunodeficiency virus or known acquired immunodeficiency syndrome
    b. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at Screening (positive HBV surface antigen or HCV ribonucleic acids [RNAs] if anti-HCV antibody screening test positive).
5. Active or history of autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Participants with type I diabetes mellitus, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
6. Known severe hypersensitivity reactions to fully human monoclonal antibodies (Grade ≥ 3 National Cancer Institute [NCI]-Common Terminology Criteria for Adverse Events

[CTCAE]) or to any components of the DDRi- or DNA-damaging anticancer therapy to be tested as well as known hypersensitivity to any of excipients.

7. Uncontrolled asthma

8. Persisting toxicity related to prior therapy (NCI-CTCAE Grade > 1); however, alopecia Grade ≤ 2, or other Grade ≤ 2 AEs not constituting a safety risk based on Investigator's judgment are acceptable.

9. Uncontrolled intercurrent illness including, but not limited to:

    a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)

    b. Uncontrolled active infection

    c. Uncontrolled diabetes (e.g., glycosylated hemoglobin ≥ 8%).

10. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident or stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class ≥ II), or serious cardiac arrhythmia requiring medication.

11. Known history of inflammatory colitis, inflammatory bowel disease, pneumonitis/interstitial lung disease, or pulmonary fibrosis.

12. Other severe acute or chronic medical conditions; psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for entry into this study.

13. Any participant with intercurrent bone fracture that may be at risk of delayed healing due to protocol therapy.

14. History of tumor bleeding.

15. History of congenital or active immunodeficiency, except for acquired treatment-related hypogammaglobulinemia requiring periodic intravenous immunoglobulin infusion.

16. Participants who have been diagnosed with Li-Fraumeni syndrome or ataxia telangiectasia.

Prior/Concomitant Therapy

17. Treatment with a nonpermitted drug/intervention as listed below:

    a. Concurrent anticancer treatment (e.g., cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, or targeted small molecule

therapy) or any study intervention within 4 weeks prior to start of study intervention, or not recovered from AEs related to such therapies, with the following exceptions:

i. Hormonal therapies acting on the hypothalamic-pituitary-gonadal axis are permitted (i.e., luteinizing hormone-releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.

ii. Investigational DNA-damaging treatment or chemotherapy as defined for the specific cohort in this study.

b. For prior chemotherapy with platinum-containing agents:

i. History of prior dose reductions or dose interruptions while receiving cisplatin or carboplatin due to toxicity from the platinum or intolerance to either agent, unless discussed with and approved by the Sponsor Medical Monitor.

c. Major surgery (as deemed by Investigator) for any reason, except diagnostic biopsy, within 28 days prior to start of study intervention, or not fully recovered from surgery within 4 weeks prior to start of study intervention.

d. Prior treatment with a PD-1/PD-L1 targeting agent.

18. Current use of the following medications at the time of enrollment:

a. Immunotherapy or immunosuppressive drugs (e.g., chemotherapy or systemic corticosteroids) EXCEPT for the following:

i. Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection)

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

iii. Steroids as premedication for hypersensitivity reactions (e.g., computed tomography [CT] scan premedication).

b. Growth factors (e.g., granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) EXCEPT where indicated for treatment of study intervention-related myelosuppression and for prophylaxis of repeat myelosuppression after initial occurrence.

c. Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

d. Other DNA damage repair inhibitors (except PARPi) (e.g., inhibitors of ATR, ataxia telangiectasia mutated [ATM] kinase, DNA-dependent protein kinase [DNA-PK], or Wee kinases).

19. Administration of a live vaccine within 30 days prior to study enrollment.
20. Participants receiving treatment with ototoxic or nephrotoxic medications that cannot be discontinued at least 7 days before first dose of carboplatin as part of the study intervention and for the duration of the study.
21. Participants receiving treatment with medications that are known to be strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) that cannot be discontinued for at least 1 week before the start of treatment and for the duration of the study (see Section 6.5.3).

Other Exclusions

22. Known alcohol or drug abuse as deemed by the Investigator.
23. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or that would limit compliance with study requirements.
24. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

No restrictions on meals or diet.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions on caffeine, alcohol, or tobacco use are required during the study.

5.3.3 Sun/UV Light Exposure

Nonclinical data indicate that M6620 has phototoxic potential. Thus, it is recommended that participants should avoid unnecessary direct or prolonged skin exposure to sunlight or artificial ultraviolet rays (e.g., sunray lamp, solarium) during treatment and for 10 days following treatment discontinuation in order to prevent photosensitization. The use of protective clothing and eyewear and the application of a high-protection sunscreen formulation are recommended prior to and during sunlight exposure.

5.3.4 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened and will be assigned a new participant number.

If a participant is rescreened within the 28 days (4-week) Screening Period, the initial screening assessments may still be used. In such cases, only lab assessments for hematologic, hepatic, and renal function may need to be repeated (see Inclusion Criteria 7, 8, and 9 in Section 5.1).

6 Study Interventions

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Interventions Administration

Table 7 Overview of Study Interventions Formulation, Dosing, and Administration

Study Intervention Name	Carboplatin	Avelumab	M6620
Dose Formulation	Refer to carboplatin SmPC or Package Insert for more information.	Sterile, clear, colorless to slightly yellow concentrate for solution for infusion	Sterile, clear, slightly yellow to yellow concentrate for solution for infusion
Unit Dose Strength(s)/ Dosage Level(s)	Refer to carboplatin SmPC or Package Insert for more information.	20 mg/mL in single-use glass vials	20 mg/mL in single-use glass vials
Route of Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion
Dosing Instructions	AUC 5 on Day 1 of each Q3W cycle for a maximum of 6 cycles. Administered before avelumab. See Appendix 4 (Carboplatin dosing) for additional information.	**During combination treatment with carboplatin and M6620 6 cycles:** Infusion of 1600 mg over 1 hour on Day 1 of each Q3W cycle for a maximum 6 cycles. Administered after carboplatin following flushing of the intravenous line. **After the last cycle of carboplatin with or without M6620: Initiate maintenance monotherapy:** 800 mg over 1 hour Q2W.	Starting dose: 90 mg/m^2 (RP2D of the doublet carboplatin + M6620) across 60 minutes (± 10 minutes) on Day 2 of each Q3W cycle for a maximum of 6 cycles, only if carboplatin was administered on the prior Day 1. De-escalated dose (if required): 60 mg/m^2 or 40 mg/m^2
	See also Section 6.6 (Dose Selection and Modification).		
Supplier/ Manufacturer	Carboplatin will be sourced from the local hospital pharmacy or central pharmacy.	Avelumab will be supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.	M6620 will be supplied by the Sponsor and packaged, labeled, and distributed for clinical studies by a suitable service provider and finally released by a Sponsor qualified person under Good Manufacturing Practice conditions.

Study Intervention Name	Carboplatin	Avelumab	M6620
Packaging and Labeling	Refer to carboplatin SmPC or Package Insert for more information.	Avelumab is formulated as a 20.0 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice guidelines. The information on the label will be in accordance with approved submission documents. Additional details of packaging and labeling of the study intervention will be defined in the separate Manual of Procedure.	M6620 is formulated as a 20 mg/mL solution and is supplied by the Sponsor in single-use glass vials, closed with a rubber stopper and sealed with an aluminum polypropylene flip-off seal. Each vial will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice guidelines. The information on the label will be in accordance with approved submission documents. Additional details of packaging and labeling of the study intervention will be defined in the separate Manual of Procedure.

AUC=area under the concentration-time curve; RP2D=recommended Phase II dose; Q2W=every 2 weeks; Q3W=every 3 weeks; SmPC=Summary of Product Characteristics.

Participants who are randomized to reference treatment will receive SoC platinum-containing chemotherapy consisting of 1 of the following options to be chosen by the Investigator:

- Carboplatin AUC 5 + Paclitaxel 175 mg/m^2 on Day 1; every 3 weeks for 6 cycles, with or without bevacizumab
- Carboplatin AUC 4 on Day 1 + Gemcitabine 1000 mg/m^2 (on Days 1 and 8); every 3 weeks for 6 cycles, with or without bevacizumab.
- Carboplatin AUC 5 on Day 1 + Pegylated liposomal doxorubicin (PLD) 30 mg/m^2; every 4 weeks for up to 6 cycles with or without bevacizumab.

Recommended dosage for the SoC regimen may be adapted per Investigator discretion and in accordance to the local institutional guidelines. See Table 8 for further details.

Table 8 Overview of Standard of Care Treatments Formulation, Dosing, and Administration

Study Intervention Name	Carboplatin	Paclitaxel	Gemcitabine	Bevacizumab	Pegylated Liposomal Doxorubicin (PLD)
Dose Formulation	Refer to corresponding SmPCs or Package Inserts for more information.				
Unit Dose Strength(s)/ Dosage Level(s)	Refer to corresponding SmPCs or Package Inserts for more information.				

Study Intervention Name	Carboplatin	Paclitaxel	Gemcitabine	Bevacizumab	Pegylated Liposomal Doxorubicin (PLD)
Route of Administration	Intravenous infusion				
Dosing Instructions (may be adapted in accordance to the local institutional guidelines.)	As defined by corresponding SmPCs and applicable guidelines for recurrent ovarian cancer, for example:				
	AUC 5 (+ paclitaxel or PLD) or AUC 4 (+ gemcitabine) on Day 1 of each Q3W or Q4W cycle for a maximum of 6 cycles. See Appendix 4 (Carboplatin dosing) for additional information.	175 mg/m^2 on Day 1 of each Q3W cycle in combination with carboplatin for a maximum of 6 cycles, or as clinically indicated by Investigator discretion	1000 mg/m^2 on Days 1 and 8 of each Q3W cycle in combination with carboplatin for a maximum of 6 cycles	15 mg/kg on Day 1 of each Q3W cycle in combination with carboplatin/ paclitaxel or carboplatin/ gemcitabine followed by bevacizumab monotherapy until disease progression.	30 mg/m^2 intravenously over 60 minutes each Q4W (28 days) cycle in combination with Carboplatin for a maximum of 6 cycles.
Supplier/ Manufacturer	SoC will be sourced from the local hospital pharmacy or central pharmacy.				
Packaging and Labeling	Refer to corresponding SmPCs or Package Inserts for more information.				

AUC=area under the concentration-time curve; Q3W=every 3 weeks; Q4W=every 4 weeks; SmPC=Summary of Product Characteristics.

Toxicities and dose reductions for the reference treatment arm (SoC) will be managed according to the Summaries of Product Characteristics (SmPCs) of the individual drugs and the local institutional standards.

6.2 Study Interventions Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study interventions, the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.
- Only participants enrolled in the study may receive study interventions and only authorized site staff may supply or administer it. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.

- Study interventions accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range
  - The inventory provided for the clinical study and prepared at the site
  - The dose(s) each participant used during the study
  - The disposition (including return, if applicable) of any unused study intervention(s)
  - Dates, quantities, batch numbers, container numbers, expiry dates, formulations for study interventions prepared at the site, and the participant numbers.
- The Investigator site will maintain records, which adequately document that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the current study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study interventions accountability forms.
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Avelumab

Avelumab is formulated as a 20.0 mg/mL solution and is supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Avelumab must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each study site must be stored carefully, safely, and separately from other drugs.

Avelumab stored at room temperature (23°C to 27°C) or at elevated temperatures (38°C to 42°C) for extended periods is subject to degradation. Avelumab must not be frozen. Rough shaking of avelumab must be avoided.

For application in this study, avelumab must be diluted with 0.9% saline solution (sodium chloride injection) or as indicated in the Pharmacy Manual. 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 Pharmacy Manual.

Avelumab must not be used for any purpose other than this study. The administration of avelumab provided for the purpose of this study to anyone who has not been enrolled is not covered by the study insurance.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration. Storage, handling, preparation, and disposal of study interventions should be according to local institutional guidelines.

6.2.2 M6620

M6620 will be supplied as a 20 mg/mL sterile solution provided in 20% betadex sulfobutyl ether sodium (w/v) and 86 mM acetate buffer to be diluted in 5% dextrose solution in water before intravenous infusion.

Additional instructions for the preparation, handling, storage, and disposal of M6620 will be provided in the Manual of Procedure.

6.2.3 Carboplatin

Carboplatin will be sourced from the local hospital pharmacy or central pharmacy.

Refer to the SmPC or Package Insert for additional instructions for preparation, handling, storage, and disposal of carboplatin.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

- After confirmation of a participant's eligibility, the Interactive Web Response System (IWRS) will be used to assign unique participant numbers.
- After confirmation of a participant's eligibility for Part B of the study and prior to study intervention administration in Part B, participants will be centrally allocated to either study intervention (carboplatin + M6620 + avelumab) or SoC treatment in a 1:1 ratio, stratified by BRCA status, using IWRS and per a computer-generated randomization list. The Investigator should choose and document the potential SoC treatment option for the individual participant prior to randomization.
- Before the study is initiated, the telephone number and call-in directions for the IWRS and/or the log-in information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each participant. The site will record the study intervention assignment in the applicable electronic case report form (eCRF).

6.3.2 Blinding

This is an open-label study. Therefore, study interventions are not blinded. However, any aggregate summary of data, if required, will be provided only in a blinded way during the study, to limit bias in the conduct of the study.

6.4 Study Intervention Compliance

In this study, participants will receive study interventions at the investigational site. Well-trained medical staff will monitor and perform the administration of study interventions. The information of each study intervention administration including the date, time, and dose of study intervention will be recorded on the eCRF. The Investigator will ensure that the information entered into the eCRF regarding study intervention administration is accurate for each participant. Any reason for noncompliance should be documented.

Noncompliance is defined as a participant missing > 1 consecutive cycle of study intervention for nonmedical reasons and barring any extenuating circumstances in the opinion of the Investigator. If 1 cycle was missed and the interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well. Continuation of treatment should be discussed with the Medical Monitor under consideration of scientific integrity of the data, potential benefits and risks of study interventions and any alternative options.

Noncompliance may lead to discontinuation of study interventions as described in Section 7.1. In case of overdose, see Section 8.4. Noncompliant participants may be replaced.

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

Rescue medications may be administered due to adverse reactions or emergency situations.

Immediate access to an intensive care unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available for use in the treatment of infusion-related reactions.

If hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Participants should be instructed to report any delayed reactions to the Investigator immediately. In addition, all hypersensitivity reactions are to be reported in a timely manner.

6.5.2 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) or as short-term premedication for study interventions are acceptable.

6.5.2.1 Prophylactic Medications and Treatments

Table 9 lists the prophylactic medications that should be administered prior to the administrations of avelumab and/or M6620.

Table 9 Prophylactic Medications Administered Prior to Avelumab and/or M6620

	Avelumab	M6620	Comment
Antihistamine	X	X	e.g., either 10 mg of chlorphenamine or 25 mg of diphenhydramine iv approximately 30 to 60 minutes before the infusions, or alternative drugs as per local guidelines
Corticosteroids		X	100 mg to 200 mg hydrocortisone iv approximately 60 minutes (± 15 minutes) before M6620 infusion
Acetaminophen (paracetamol)	X		500-650 mg approximately 30 to 60 minutes before the infusions.

iv=intravenous.

For avelumab, premedication is mandatory prior to the first 4 doses, and thereafter is based upon clinical judgment and presence/severity of prior infusion reactions. Standard prophylactic premedication with corticosteroids is not recommended; however, prophylactic steroids to prevent recurrence of infusion-related reaction are not prohibited, based on the Investigator's clinical judgment.

Premedication with a corticosteroid and an antihistamine should be given to participants who have developed acute hypersensitivity or pruritus with M6620 infusion and who continue to receive treatment with M6620.

For carboplatin and other SoC treatments, premedications (e.g., antiemetics, corticosteroids, etc.) should be administered according to the local institutional treatment standards.

Premedications and their regimens may be modified based on local treatment standards and guidelines as appropriate.

6.5.3 Prohibited Medicines

Prohibited medicines are as listed in the exclusion criteria (see Section 5.2).

The following treatments must not be administered during the study:

1. Immunotherapy or immunosuppressive drugs (i.e., chemotherapy other than assigned study intervention or systemic corticosteroids) except:

    a. When required for the treatment of irAEs, infusion-related reactions, or hypersensitivity to any of the study interventions

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

    c. Systemic corticosteroids for management of participants with allergy to CT intravenous radiographic contrast media.

2. Administration of a live vaccine within 30 days prior to study intervention.

3. Growth factors (e.g., granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Growth factors are allowed for treatment of study intervention-related myelosuppression and for prophylaxis of repeat myelosuppression after initial occurrence.
4. Hematopoietic growth factors within 14 days before the first dose of study intervention. During Cycle 1 in the Part A, hematopoietic growth factors may not be used prophylactically. These may be used to specifically address participant symptoms.

5. Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

6. Strong CYP3A inhibitors or inducers as listed in Appendix 5 from 14 days before the start of study intervention until 7 days after discontinuation of M6620.

If a participant receives prohibited medication that is considered medically necessary, the participant may be withdrawn from the study at the discretion of the Investigator in case potential risks of continuation of allocated treatment are deemed to outweigh potential benefits (see Section 7).

The Investigator should refer to the carboplatin SmPC or Package Insert for guidance on prohibited mediations during treatment.

6.5.4 Other Interventions

The following **nondrug therapy must not be administered** during the study (and within 28 days before the start of study intervention):

- Radiotherapy, with the exception of palliative short course, limited field (i.e., ≤ 10 fractions and ≤ 30% bone marrow involvement or per institutional standard) radiotherapy, which may be administered during the study. However, as M6620 and other DDRi are expected to synergize with radiotherapy both on the efficacy and the safety end, M6620 dosing must be suspended at

least 5 days prior to the start of radiotherapy and must not be resumed until at least 5 days after the last radiotherapy fraction. Note: The assessment of PD will be made according to RECIST v1.1 (Eisenhauer 2009) and not based on the necessity for palliative radiotherapy.

6.6 Dose Selection and Modification

An overview of the intended study interventions dose and timing of treatments is provided in Table 10. Participants will receive carboplatin + M6620 + avelumab or SoC as per the initial treatment assignment until the criteria are met as outlined in Section 4.4 (End of Study Definition) and Section 6.7 (Study Interventions After the End of the Study).

Table 10 Overview of Intended Study Interventions Dose and Timing of Treatments

Study Intervention	Administration Days for Each Cycle	Dose	Administration
Carboplatin	On Day 1 of each Q3W cycle for a maximum of 6 cycles	AUC 5 (for 6 cycles)	Carboplatin will be administered before avelumab. (Guidance on premedication is given in Section 6.5.2.)
Avelumab	On Day 1 of each Q3W cycle	1600 mg Q3W in combination with carboplatin + M6620 for up to 6 cycles 800 mg Q2W as monotherapy following discontinuation of carboplatin + M6620 until PD or discontinuation after minimum 12 months of maintenance after a confirmed CR per RECIST v1.1	Avelumab will be administered after carboplatin following flush of the iv line. (Guidance on premedication is given in Section 6.5.2.)
M6620	On Day 2 of a Q3W cycle for a maximum of 6 cycles (only with prior carboplatin administration)	Starting dose: 90 mg/m^2 (RP2D) of the doublet carboplatin + M6620 De-escalated dose (if required) to 60 mg/m^2 or 40 mg/m^2	(Guidance on premedication is given in Section 6.5.2.)

AUC=area under the concentration-time curve; iv=intravenous; Q2W=every 2 weeks; Q3W=every 3 weeks; PD=progressive disease; RP2D=recommended Phase II dose.

No intraparticipant dose modifications of avelumab will be allowed during this study. Modifications of the infusion rate due to infusion-related reactions, as well as for other reasons, are permitted as described in Section 6.11.1.

In the case of occurrence of an AE attributed to M6620, treatment may be interrupted and may resume when all toxicities have returned to Grade 2 or less, at the discretion of the Investigator. In case a dose reduction is necessary, M6620 will be administered as described in Section 6.11.2.

No dose modifications of carboplatin are allowed prior to occurrence of a DLT. In case a dose reduction is necessary, carboplatin will be administered as described in Section 6.11.3.

Justification for dose is presented in Section 4.3.

As described in Appendix 2, the SMC will review the safety data on a regular basis throughout this clinical study. For the Safety Run-in Period (Part A), the SMC will regularly review the safety of participants enrolled in this study (at least after each applicable dose level), will decide on relevant DLTs based on criteria defined in the protocol (see Section 6.6.1) and by consensus on dose de-escalation, or suspension of enrollment and/or recommendation of the safe dose of carboplatin + M6620 in combination with avelumab.

6.6.1 Definition of Dose-limiting Toxicity

A DLT is specifically defined as any death not clearly due to the underlying disease or extraneous causes or any Grade ≥ 3 nonhematologic or Grade ≥ 4 hematologic toxicity that is possibly, probably, or definitely related to any of the study interventions (carboplatin, M6620, or avelumab) or the combination (as assessed by the Investigator and/or Sponsor) that occurs during the 3-week DLT observation period, **except** for any of the following:

- Grade 3 infusion-related reaction resolving within 6 hours from the end of infusion and controlled with medical management.
- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 72 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1 with medical management.
- Grade 3 diarrhea, Grade 3 skin toxicity, or Grade 3 liver function test increase (ALT or AST) that resolves to Grade ≤ 1 in less than 3 days after medical management (e.g., immunosuppressant or antidiarrheal treatment) has been initiated. EXCEPTION: Grade 3 liver function test increases that are assessed as irAEs will still be considered a DLT.
- Single laboratory values out of normal range that, according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor that resolve to Grade ≤ 2 within 3 days.
- Neutropenia (Grade 3 or 4) less than 7 days not associated with any infection (clinically or microbiologically). NOTE: Grade 3 or 4 neutropenia with clinical signs/symptoms (e.g., febrile neutropenia) is a DLT.

- Grade 3 thrombocytopenia for less than 7 days without clinically significant bleeding and not requiring platelet transfusion.
- Symptomatic thyroid dysfunction that is manageable with adequate treatment and resolves to Grade ≤ 2 within 6 days.

6.7 Study Intervention Beyond Progression

6.7.1 Treatment Beyond Initial Progression

Participants will receive study interventions as outlined in the SoA with avelumab administered until disease progression. Study interventions may continue past the initial determination of disease progression according to RECIST v1.1 as long as the following criteria are met:

- Participant was allocated to receive avelumab, and treatment with avelumab is ongoing
- No new unacceptable treatment or disease-related toxicity
- Tolerance of study interventions
- Stable ECOG PS
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (for example, central nervous system metastases).

A radiographic assessment should be performed within 4 to 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with study intervention(s).

6.7.2 Treatment Beyond Confirmed Progression

After confirmed PD, if the Investigator feels that the participant continues to achieve clinical benefit by continuing treatment with avelumab, with or without carboplatin and M6620, the participant should remain on the study and continue to receive monitoring according to the SoA. The decision to continue treatment beyond confirmed PD should be discussed with the Medical Monitor and documented in the study records.

Participants receiving avelumab who continue beyond progression will be evaluated for further tumor response as per the protocol schedule. Treatment should be discontinued permanently upon documentation of further, unequivocal disease progression unless there are no alternative therapeutic options and the benefit-risk assessment is favorable in consultation between the Investigator and the Medical Monitor. In case of continuation of treatment beyond PD, treatment will be discontinued once any other criteria for withdrawal are met (see Section 7.1).

6.8 Continuation of Study Intervention After Local Treatment of Disease Progression

If disease progression is due to brain metastasis, participants may continue study interventions after the local treatment of the brain lesions provided that the above criteria are met in addition to the following:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1 prior to the procedure.
- Brain metastases have been treated locally and are clinically stable for at least 2 weeks prior to re-initiation of study interventions.
- There are no ongoing neurological symptoms that are related to the brain localization of the disease (sequelae that are a consequence of the treatment of the brain metastases are acceptable).
- Participants must be either off steroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

In addition, if disease progression is mainly due to a metastatic lesion that in the opinion of the Investigator may be surgically removed, participants may continue study interventions after the local treatment of such a lesion, provided that:

- Tumor assessment showing disease progression has been performed and was documented according to RECIST v1.1 prior to the procedure.
- It has been at least 2 weeks and the participant has fully recovered from the surgery.
- Benefit-risk assessment to continue study intervention is favorable under consideration of any alternative treatment options as assessed by the Investigator.

6.9 Study Intervention After the End of the Study

After a participant has completed the study or has withdrawn early, usual treatment will be administered, if required, in accordance with the investigational site's SoC, generally accepted medical practice, and depending on the participant's individual medical needs. The Sponsor will not provide any additional care to participants who have discontinued the study because such care should not differ from what is normally expected for participants with advanced malignancies.

Upon withdrawal from the study, participants may receive whatever care they and their physicians agree upon.

Survival follow-up will continue for participants until up to 1 year after the last participant has received the last dose or the last participant dies, whichever comes first. The Sponsor may terminate the study at any time and there may be allowance for participants to enter a rollover study, or other mechanism for avelumab access for Part A or Part B participants if randomized to that treatment, as appropriate.

6.10 Special Precautions

6.10.1 Avelumab

As a routine precaution, participants enrolled in this study must be observed for 1 hour post infusion for the first 4 infusions, and then according to clinical signs and symptoms, in an area with resuscitation equipment and emergency agents. At all times during investigational treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. Treatment for possible hypersensitivity reactions (e.g., dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents) should always be available along with equipment for assisted ventilation.

Prophylactic medications and treatments are outlined in Section 6.5.2. The treatment recommendations for infusion-related reactions are outlined in Section 6.11.

Investigators should also monitor participants closely for potential irAEs, which may occur at any time during treatment. Such events include, but are not limited to, pneumonitis, hepatitis, colitis, endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus), myocarditis, myositis, and rash. See Section 6.11 for details on the management of irAEs.

If a hypersensitivity reaction occurs, the participant must be treated according to the best available medical practice. Participants should be instructed to report any delayed reactions to the Investigator immediately.

6.10.2 M6620

To minimize the possibility of phlebitis, M6620 should be administered through a large-bore catheter into a large-caliber peripheral vein or central line if clinically indicated. The intravenous infusion site should be monitored closely for the development of erythema, induration, purulence, tenderness, or warmth.

If any participant develops phlebitis, or signs or symptoms of inflammation that may progress to phlebitis or that the participant cannot tolerate, standard measures should be employed to ameliorate these symptoms (including removal of the infusion catheter and resumption of infusion through a different vein). If standard procedures to limit symptoms of injection site reaction, or pruritus or acute hypersensitivity are insufficient, then the infusion time may be extended beyond 60 minutes, but no more than 90 minutes.

Based on the observation of acute hypersensitivity in 3 participants at various doses of M6620 and of pruritus in 2 participants at 480 mg/m^2 of M6620, premedication with a corticosteroid and an antihistamine may be considered for all participants receiving M6620 (as prophylaxis against possible acute hypersensitivity). In addition, corticosteroids and antihistamine should be used for treatment of participants who develop acute hypersensitivity or pruritus after M6620 infusion, and should be used prophylactically as premedication for all participants who develop acute hypersensitivity or pruritus with M6620 infusion and who continue to receive treatment with M6620 (see Section 6.5.2).

6.10.3 Carboplatin

Refer to the carboplatin SmPC or Package Insert for information regarding precautions.

6.10.4 Standard of Care Treatment

Refer to the respective SmPCs or Package Inserts for information regarding precautions.

6.11 Management of Adverse Events of Interest

6.11.1 Avelumab

The following adverse drug reactions (ADRs) (defined as an AE that is thought to potentially be related to study intervention) require permanent treatment discontinuation or treatment modification of avelumab:

- Any Grade 4 ADRs: permanently discontinue avelumab except for laboratory values out of normal range that do not have any clinical correlate.
- Any Grade 3 ADRs:
  - Withhold avelumab except for laboratory values out of normal range that do not have any clinical correlate.
  - Permanently discontinue avelumab if toxicity does not resolve to Grade ≤ 1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs (consider consult with the Medical Monitor before permanently discontinuing the treatment).

If dosing is delayed more than 4 weeks, treatment may be resumed after consultation with the study Medical Monitor. Any delay in dosing in excess of 12 weeks due to ADRs is not permitted.

Infusion-related reactions and irAEs should be handled according to the following guidelines (see Appendix 6) and consistent with the 2018 ASCO guidelines.

Infusion-related Reactions

To mitigate infusion-related reactions, participants must be premedicated as described in Section 6.5.2.

Management of infusion-related reactions should follow the guidelines presented in Table 11.

Table 11 Treatment Modification for Symptoms of Infusion-related Reactions Associated with Avelumab

NCI-CTCAE Grade	Treatment Modification for Avelumab
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 (e.g., antihistamines, NSAIDs, narcotics, iv fluids); prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion. • Resume 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 (e.g., 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 participant. • Participants must be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

CTCAE=Common Terminology Criteria for Adverse Events; iv=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.

Immune-related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids and increase the frequency of monitoring
- Grade 1 to 2 (persistent): manage similar to high-grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high-dose corticosteroids.

Treatment of irAEs should follow the guidelines presented in Appendix 6 (Management of irAEs).

6.11.2 M6620

In the case of occurrence of an AE attributed to M6620, treatment may be interrupted and may resume when all toxicities have returned to Grade 2 or less, at the discretion of the Investigator.

Except for participants in Part A during the DLT observation period, doses of M6620 may be reduced after occurrence of a related AE using the following guidelines:

- For Grade 4 hematologic toxicity: the dose of M6620 will be reduced by 25%
- For Grade 3 nonhematologic toxicity: the dose of M6620 will be reduced by 25%
- For Grade 4 nonhematologic toxicity: the dose of M6620 will be reduced by 50%.

Guidelines for dose modification for toxicity are provided below. The final dose reduction or delay for each participant may be determined by the Investigator and Sponsor. However, these guidelines provide the minimum dose reduction or delay criteria. Additionally, if a participant who is responding to treatment experiences toxicity even after 2 dose reductions, the participant may continue to receive treatment if in the judgment of the Investigator it is in the best interest of the participant. In this case the dose of M6620 will further be reduced by at least 25%.

- In case of M6620 Grade 3 or higher toxicity (excluding fatigue or nausea/vomiting/diarrhea adequately managed by supportive care), treatment will be interrupted and may be resumed when all toxicities have returned to Grade 2 or lower, at the discretion of the Investigator.
- For the following hematologic toxicities, once the toxicity has returned to Grade 2 or lower, dosing can be resumed with 1 dose level reduction (Table 12). If, after 1 dose level reduction, any of the below drug-related hematologic toxicities are subsequently observed, then dosing may be resumed with 2 dose level reductions (Table 12):
  - Grade 4 thrombocytopenia
  - Febrile neutropenia (growth factor support, per site protocol, may be used in lieu of dose reduction) except during the DLT assessment period prior to occurrence of a DLT. Once a DLT has occurred, it is acceptable to use growth factor support even during the DLT period.
  - Grade 4 neutropenia lasting more than 7 days.
- If any of the drug-related toxicity listed below is subsequently observed, the M6620 dose will be reduced by 1 dose level (Table 12).
  - Grade 3 nonhematologic toxicity (except for fatigue or nausea, vomiting, or diarrhea adequately controlled by medication). For infusion reactions, hypersensitivity, or allergic reactions related or possibly related to M6620, see Section 6.10.2 for additional guidelines for management.
  - Any Grade 2 or lower nonhematologic toxicity requiring dose delay of more than 2 weeks.
- For Grade 4 nonhematologic toxicity, treatment will be interrupted and may be resumed with 2 dose level reductions (Table 12) when toxicity has returned to Grade 2 or lower.

If any toxicity not described above results in a delay in dosing during any part of the study and the participant may be benefitting from therapy, then the doses of M6620 may be reduced by 1 dose level at the discretion of the Investigator.

Table 12 Guidelines for M6620 Dose Modification for Toxicity in Combination with Avelumab and Carboplatin

Dose Level	M6620 (mg/m^2)	Carboplatin (mg·min/mL)
1	90	AUC 5
-1	60	AUC 5
-2	40	AUC 5

AUC=area under the concentration-time curve.

6.11.3 Carboplatin

No dose modifications of carboplatin are allowed prior to occurrence of a DLT.

See Table 12 for dose level modification guidelines for toxicity when administering carboplatin with M6620 + avelumab.

6.11.4 Standard of Care Treatment

Sites should refer to institutional standards for management of ADRs for SoC platinum chemotherapy.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Interventions

Participants must be withdrawn from study interventions if any of the following occurs:

- Participants meeting the definition of confirmed PD while on treatment based on RECIST v1.1. Participants who experience PD may continue treatment with study interventions under conditions described in Section 6.7 if the Investigator believes the participant will experience clinical benefit from the treatment and there is no unacceptable toxicity resulting from the treatment. Such participants will be withdrawn from the treatment if any other criteria for withdrawal are met or if alternative treatment options are available and indicated.
  - In case of premature withdrawal from the study interventions for reasons other than PD, participants will be asked to attend scheduled visits, including tumor assessment and other assessments as planned, until confirmed PD, end of study, or death.
- Significant clinical deterioration (clinical progression), defined as new symptoms that are deemed by the Investigator to be clinically significant or significant worsening of existing symptoms.
- Unacceptable toxicity.
- Withdrawal of consent from further treatment or from further study participation. In case of selective withdrawal from study intervention, other study-related procedures and assessments should be continued as planned.
- Occurrence of an exclusion criterion, which is clinically relevant and affects the participant's safety, if study intervention discontinuation is considered necessary by the Investigator and/or Sponsor.
- Therapeutic failure requiring urgent additional drug (if applicable).
- Occurrence of any Grade 4 ADRs (defined as an AE that is thought to potentially be related to study interventions) (see Section 6.11).
- Occurrence of AEs resulting in the discontinuation of the study interventions being desired or considered necessary by the Investigator and/or the participant.

- Occurrence of irAEs requiring discontinuation of study interventions as described in Appendix 6.
- Occurrence of pregnancy.
- Use of a prohibited concomitant drug, as defined in Section 6.5.3, where the predefined consequence is withdrawal from the study intervention if considered necessary by the Investigator or the Sponsor.
- Noncompliance if the benefit-risk assessment for continuation of treatment is negative according to Investigator assessment.
- Participation in another interventional clinical study.

For study group assigned to carboplatin + M6620 + avelumab, if confirmed CR by RECIST v1.1 followed by minimum 12 months of maintenance therapy then may discontinue treatment if participant and Investigator agree.

Investigator should consult with Medical Monitor if early discontinuation of 1 of the 3 drugs in the study intervention to discuss plan for completing the 6 cycles as per the following options;

- If participant discontinues carboplatin early for any reason, then must also discontinue M6620 and proceed into the avelumab maintenance.
- If participant discontinues M6620 early for any reason, but clinically can continue to receive carboplatin, then may complete the 6 cycles of treatment and proceed into the avelumab maintenance.
- If participant discontinues avelumab early for any reason prior to completing the 6 cycles, but clinically can continue carboplatin + M6620 or carboplatin alone to complete the 6 cycles and then proceed to End of Treatment visit.

Participants who prematurely discontinue treatment in this study or who are withdrawn from the study for any reason will be asked to return to the clinical site for an End of Treatment Visit within 7 days, and Safety Follow-up Visits at 30 days (in office) and 90 days (phone call) after their last dose of study intervention. As applicable, participants who have no evidence of PD at discontinuation, will also be asked to return for follow-up tumor scans according to the SoA (Section 1.3). Participants will be followed every 12 weeks for survival and documentation of anticancer treatment, for which participants may come to the study site or may be contacted by phone.

The SoA (Section 1.3) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Temporary Discontinuation

See Section 6.11 for instructions for temporary discontinuation of study interventions in response to Grade 2 infusion-related reactions or toxicity events. See Section 6.5 for temporary discontinuation due to administration of prohibited medicines or interventions.

Instructions for temporary discontinuation of study interventions in the management of irAEs are presented in Appendix 6 (Management of irAEs).

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent), and without giving a reason. Withdrawal of consent will be considered withdrawal from the study unless the participant agrees to participate in further study-related assessments and/or agrees to be followed for survival, which may include verification of medical records. Participants should be explicitly asked at the time of withdrawal of consent if they would allow further study-related assessments, especially tumor assessment, safety-related assessments, documentation of subsequent anticancer therapy, or collection of survival information including verification of medical/public records or contact of the participant's primary physician or family as permitted by local regulations. These responses should accordingly be captured in the eCRF.
- The participant may be withdrawn by the Investigator due to participation in another clinical study; however, participants will continue to be followed for survival and documentation of anticancer treatment.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed. In case of participant withdrawal from the study, the appropriate End of Study page must be completed.
- If a participant fails to attend scheduled study assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible.
- In Part A, if a participant is withdrawn prior to the end of the DLT observation period (for any reason except for a DLT), the participant may be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up," the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (Section 1.3).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- **Order of Procedures:**
  - Patient-reported outcomes assessments should be completed by the participant prior to a health care intervention of any nature, regardless of whether it is study-related. A protocol deviation occurs only when study-related interventions occur prior to PRO assessments, other than vital signs, demographics, and clinical history information.
  - Electrocardiogram assessments should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. However, at the PK time points where the acceptable window of sample collection is within 5 minutes, the ECG should be performed 10 minutes after sample collection to allow participants to recover to normal heart rate.

8.1 Efficacy Assessments and Procedures

8.1.1 Tumor Response Assessment

Computed tomography or magnetic resonance imaging (MRI) scans will be performed and collected until confirmed PD is assessed by the Investigator according to RECIST v1.1 (Eisenhauer 2009) or until start of new anticancer therapy in case of continuation of avelumab beyond PD, according to the SoA (Section 1.3).

For participants receiving avelumab, a subsequent scan 4 to 6 weeks after the initial assessment of PD should be collected if clinically feasible to confirm PD.

Radiographic images and physical findings (physical assessments) will be used by the Investigator for the local determination of PD and participant's treatment decisions.

For each participant, tumor response assessment will be performed by CT scan or MRI (if MRI is used, chest CT is mandatory) imaging of the chest/abdomen/pelvis (plus other regions as specifically required) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual participant. All scans performed at Screening and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Screening need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each participant, the Investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the study period will be considered. The most appropriate measures to evaluate the tumor status of a participant should be used. The measure(s) to be chosen for sequential evaluation during the study must correspond to the measures used to document the progressive tumor status that qualifies the participant for enrollment. The tumor response assessment will be assessed and listed according to the SoA (Section 1.3).

Treatment decisions will be made by the Investigator based on the Investigator's assessment of disease status. Investigator's assessment of objective tumor response to treatment will be performed according to RECIST v1.1 (all measurements should be recorded in metric notation, as described in RECIST v1.1).

- At Baseline, tumor lesions will be categorized in target and nontarget lesions as described in RECIST v1.1.
- Results for these evaluations will be recorded with as much specificity as possible so that pretreatment and post-treatment results will provide the best opportunity for evaluating tumor response.
- Any CR or PR should be confirmed, preferably at the next subsequent scheduled imaging interval, but no sooner than 6 weeks after the initial documentation of CR or PR. Confirmation of PR can be confirmed at an assessment later than the next assessment after the initial documentation of PR.
- The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if the Investigator suspects PD. Participants who withdraw from the investigational treatment for clinical or symptomatic deterioration before objective documentation of PD or who discontinue from investigational treatment for reasons other than objective PD will be requested to continue appropriate imaging according to the study schedule until determination of confirmed PD or discontinuation of the study, whichever occurs earlier. Every effort should be made to confirm a clinical diagnosis of PD by imaging.

8.1.2 Response Evaluation Based on CA-125 According to Gynecologic Cancer Intergroup Recommendations

Tumor response evaluation based on cancer antigen 125 (CA-125) will be assessed according to the SoA (Section 1.3).

According to the GCIG criteria, response based on CA-125 is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Participants can be evaluated according to CA-125 only if they have a pretreatment sample that is ≥ 2 × ULN and within 2 weeks prior to starting treatment (Rustin 2011).

According to the GCIG criteria progression based on CA-125 is defined as progression by RECIST v1.1 OR progression by CA-125.

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria:

1. Participants with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart, OR

2. Participants with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart, OR

3. Participants with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Participants are not evaluable by CA-125 if there has been medical and/or surgical interference with their peritoneum or pleura (e.g., paracentesis) during the previous 28 days.

A Participant may be declared to have PD on the basis of either the objective RECIST v1.1 criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

8.1.3 Survival Follow-up

Participants without PD according to RECIST v1.1 at the End of Treatment Visit will be followed up for disease progression (CT/MRI scans according to the schedule indicated in the SoA [Section 1.3], using the same procedures and review as while on treatment) until PD. In the case of PD with discontinuation of treatment, any subsequent local tumor assessments should be documented. Any subsequent anticancer therapies and the date of any response and subsequent progression should be captured in the eCRF.

Participants will be followed every 12 weeks (± 1 week) for survival (including assessment of any further antitumor therapy). The survival follow-up will continue until 1 year after the last participant receives the last dose of study intervention, or the last participant dies, whichever occurs first. Under some circumstances, participants may not be followed for 1 year for survival in this study; e.g., participants may be offered to enroll into a rollover study, or the Sponsor may terminate the study early.

8.1.4 Patient-reported Outcomes

Patient-reported outcomes will be distributed in paper form, accompanied by the instructions on how to complete them, exclusively for Part B participants and according to the SoA (Section 1.3).

If the participant is illiterate, blind, or too ill to complete PRO measures, the study staff (e.g., Study Coordinator, Investigator, or Subinvestigator) may obtain the participant's responses by reading aloud each question followed by the corresponding response categories and recording the participant's response. No help should be provided to the participant by any person other than the designated study staff. The designated study staff should not influence the participant's responses by any means, such as commenting, agreeing, or disagreeing with responses, either verbally or nonverbally. The designated study staff cannot translate the question into simpler language, and questions must be read verbatim. Any content may be repeated and/or read more slowly for clarification upon participant request. These instances must be documented as notes to file and included in the study site file.

The baseline assessments should be completed at Screening; if this does not occur, they can be done at Visit 1 (Day 1).

Whenever possible, the PRO assessments should be completed by the participant prior to a health care intervention of any nature, regardless of whether it is study-related or not. This sequencing is important to reduce measurement bias as the participant's assessment should reflect the participant's impressions up to a given visit; any intervention administered on that visit would be captured in the subsequent assessment. Any intervention on a given visit may bias the participant's responses positively or negatively and may no longer be an accurate reflection of the participant's impressions leading up to that visit. A protocol deviation occurs only when study-related interventions are done prior to PRO assessments, other than vital signs, demographics and clinical history information.

Data will be collected by the contract research organization (CRO) and housed in a database. Analysis of the questionnaires will be described in the Integrated Analysis Plan (IAP).

8.1.4.1 EORTC QLQ-30

The EORTC QLQ-C30 is a cancer-specific health-related quality-of-life questionnaire that has been widely used in clinical studies and investigations using PROs for individual participant management (Fayers 2001). It includes 5 function domains (physical, emotional, social, role, cognitive), 8 symptoms (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life and financial impact. Participants respond on a 4-point scale from "not at all" to "very much" for most items. Most items use a "past

week" recall period. Raw scores can be linearly converted to a 0–100 scale with higher scores reflecting higher levels of function and higher levels of symptom burden. A subset of items from the QLQ-C30 will be used in this study; namely, fatigue (3 items), appetite loss (1 item), overall quality of life (QoL) (1 item), and physical function (5 items).

8.1.4.2 EORTC QLQ-OV28

The EORTC QLQ-OV28 is a 28-item PRO questionnaire created to measure the cardinal symptoms of ovarian cancer (Greimel 2003). Items measure pain, bloating, bowel habit, flatulence, early satiety, dyspepsia, neuropathy, sensory problems, and frequent urination. Each of these items is rated on a 4-point scale from "not at all" to "very much," using the past week as the recall period. The QLQ-OV28 is scored similarly to the QLQ-C30, with raw scores linearly transformed to a 0-100 scale, with higher scores higher levels of symptom burden. A subset of items from the QLQ-OV28 will be used in this study; namely, pain (1 item), bloating (1 item), early satiety (1 item), indigestion (1 item), and urinary frequency (1 item).

8.1.4.3 Patient Global Impression of Severity

The Patient Global Impression of Severity (PGIS) is a single, global item assessing the participant's perception of overall symptom severity (Yalcin 2003; Tinchello 2013). The PGIS provides a method for classifying participants as having improved, declined, or not having changed for use in exploratory and psychometric analysis, and to evaluate the sensitivity and responsiveness of individual symptom items and interpret scores on the PRO instruments.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, ECGs, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. Assessments are performed at each visit prior to administration of any medications. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). Due to the combined administration of treatments in this study, it is important that the Investigator carefully review and attempt to differentiate causality of AEs (for carboplatin, M6620, or avelumab) to ensure appropriate toxicity treatment recommendations.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of general appearance and dermatological, pulmonary, cardiovascular, gastrointestinal, genitourinary, lymphatic, neurologic and musculoskeletal systems, head/neck, extremities, eyes, ears, nose, throat, and cognitive status. Height (at Screening) and weight will also be measured and

recorded according to the SoA (Section 1.3). If Screening physical examination is done within 3 days of Visit 1 (Day 1), it does not have to be repeated at Visit 1.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and should be a focused physical examination with attention paid to irAEs.
- Investigators should pay special attention to clinical signs related to previous serious illnesses. All newly diagnosed or worsening conditions, signs, and symptoms observed from Screening, whether related to study intervention or not, are to be reported as AEs.
- The ECOG PS will be documented during Screening and at each visit according to the SoA (Section 1.3) and document in the eCRF. If the Screening ECOG PS was performed within 3 days prior to Day 1, it does not have to be repeated at Day 1.

8.2.2 Vital Signs

- Oral or tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of seated rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests; see SoA in Section 1.3) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

Scheduled 12-lead electrocardiograms (ECGs) will be recorded after the participant has been in a supine position breathing quietly for 5 minutes.

Electrocardiogram assessments should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. However, at the PK time points where the acceptable window of sample collection is within 5 minutes, the ECG should be performed 10 minutes after sample collection to allow participants to recover to normal heart rate.

- Triplicate or single 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. See Section 7 (Discontinuation of Study Intervention and Participant/ Withdrawal) for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

- ECG recordings will be obtained after the participant has been in a supine position breathing quietly for 5 minutes. The ECG results will be used to evaluate the heart rate, atrial ventricular conduction, QR and QT intervals, and possible arrhythmias.
- All participants require a single ECG measurement at Screening.
- On-treatment ECGs will be performed predose (within 4 hours) on Day 1 (before avelumab and carboplatin administration) and on Day 2 (before M6620 administration) of Cycles 1 and 2. On those days, 3 consecutive 12-lead ECGs (triplicate) will be performed at each PK time point for M6620, approximately 2 minutes apart to determine mean QTc (average of triplicates) with digital upload for centralized analysis.
- PK-matched digital ECGs will be collected to evaluate if there is any relationship between treatment exposure and cardiovascular toxicity (e.g., QTc prolongation). These will be performed in triplicate in order to reduce the variability and improve the reliability of the measured QTc intervals.
- If a participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at the time of the event. If the mean QTc is prolonged (> 500 msec), the ECGs should be re-evaluated by a qualified person at the study site for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 7, at the time points listed in the SoA (Section 1.3). All samples should be clearly identified.
- Thyroid-stimulating hormone, thyroxine, and urinalysis will be assessed at the time points defined in the SoA (Section 1.3). If confirmation of a participant's postmenopausal status is necessary, measurement of follicle-stimulating hormone (FSH) levels will also be performed at Screening.
- For WOCBP, serum and urine β-human chorionic gonadotropin pregnancy tests will be performed as indicated in the SoA (Section 1.3).
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory.
- The Sponsor must receive a list of the local laboratory normal ranges before shipment of study interventions. Any changes to the ranges during the study must be forwarded to the Sponsor or designated organization.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.5 Safety and Data Monitoring Committees

A Safety Monitoring Committee (SMC) consists of permanent members from the Sponsor and/or CRO (clinical development lead, medical responsible, biostatistician, and global patient safety representative), the Coordinating Investigator, and other optional members with expertise in relevant areas (e.g., immune-oncology, DDR, clinical pharmacology) as well as treating Investigators, as required.

For the Safety Run-in Period (Part A), the SMC will regularly review the safety of participants enrolled in this study (at least after each applicable dose level) and will decide on relevant DLTs based on criteria defined in this protocol and by consensus on dose de-escalation, or suspension of enrollment and/or recommendation of the safe dose of M6620 in combination with carboplatin and avelumab.

In the absence of prior human experience with the triplet combination investigated here, a conservative approach (i.e., toxicities are assessed as related to combination treatment unless the opposite is proven) will be adopted in ascribing the relevance of the treatment-related toxicity to study interventions (carboplatin, M6620, avelumab). Treatment-related AEs will be ascribed as related to the individual study interventions or their combination, except where a clear relationship to the underlying disease or recognized co-morbidities is evident.

The SMC decision to de-escalate to the next dose level will be guided by the following rules:

- Assessment of individual DLTs according to criteria outlined in Section 6.6.1.
- If 1 DLT is observed among the first 3 participants of the Safety Run-in cohort, an additional 3 participants will be enrolled and treated.
- At any time if ≥ 2 DLTs are observed, treatment with the corresponding dose will be stopped and the next dose level will be considered as shown in the Part A Schema (Section 1.2).
- Should a M6620 dose lower than 40 mg/m^2 be required or at any other time, the SMC may recommend another dose level or to stop the study.

The specific working procedures will be described in an SMC Charter, which will be established prior to the start of recruitment.

For Part B, a data monitoring committee (DMC) will be constituted by Sponsor members independent from the project team and if needed may include external medical expert to regularly review the data in Part B of the study to ensure safety of the participants as well validity and integrity of the study. The participants, data reporting details and specific working procedures will be defined in the DMC charter prior to start of enrollment in Part B.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a Serious Adverse Event (SAE) are in Appendix 8.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the 90-day Safety Follow-up Phone Call.

After the 30-day Safety Follow-up Visit, all SAEs, AESIs, and treatment-related nonserious AEs need to be documented until the 90-day Safety Follow-up Phone Call. Participants with an ongoing SAE at the 90-day Safety Follow-up Phone Call must be followed by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up."

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 8, whenever it occurs, irrespective of the time elapsed since the last administration of study interventions.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 8.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate SAE Report Form as specified in Appendix 8.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the 30-day Safety Follow-up Visit and 90-day Safety Follow-up Phone Call. All SAEs (related and unrelated to study intervention), nonserious AEs classified as related to interventions by the Investigator, and AESIs that are ongoing at the 90-day Safety Follow-up Phone Call must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up." Reasonable attempts to obtain this information must be made and documented.

It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 8.

8.3.3.1 Monitoring of Specific Adverse Events

Infusion-related reactions, including drug hypersensitivity reactions and immune-related adverse reaction(s) (immune-related pneumonitis, immune-related colitis, immune-related hepatitis), immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new-onset type I diabetes mellitus, pituitary disorders), immune-related nephritis and renal dysfunction, and other irAEs (myositis, myocarditis, Guillain-Barré syndrome, uveitis) have been identified as AESIs for avelumab (see Section 6.11 and Appendix 6).

Any AE that is suspected to be a potential immune-related adverse reaction or infusion-related reaction will be considered an AESI. These AESIs do not require expedited reporting unless they are serious. Should the AESI be serious, an SAE Report Form should be completed, and the reporting process for SAEs should be followed.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) must be recorded in the AE page/section of the eCRF for pregnancies in female participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 8, section on Reporting Serious Adverse Events, Adverse Events of Special Interest, and DLTs.

Investigators must actively follow-up, document, and report on the outcome of all these pregnancies, even if the participants are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose of avelumab greater than 10% above the planned dose for a particular administration will be considered an overdose.

For this study, any dose of M6620 greater than 10% above the dose identified in Part A (starting with RP2D of the doublet [90 mg/m^2]) within a 24-hour time period will be considered an overdose.

For this study, any dose of carboplatin greater than 10% above the planned dose for a particular administration within a 24-hour time period will be considered an overdose.

For this study, any dose of SoC chemotherapy greater than 10% above the planned dose for a particular administration within a 24-hour time period will be considered an overdose.

Even if it is not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to the Sponsor's Global Patient Safety Department in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 8, section on Reporting Serious Adverse Events, Adverse Events of Special Interest, and DLTs.

The Sponsor does not recommend specific treatment for an overdose. There are no known symptoms of avelumab overdose to date. Based on available clinical data, overdose of M6620 may

increase severity and/or toxicity of carboplatin therapy. The Investigator should use his or her clinical judgment when treating an overdose of the study interventions.

8.5 Pharmacokinetics

The following PK parameters will be calculated for M6620, when appropriate (Table 13).

Table 13 Pharmacokinetics Parameters

Symbol	Definition
AUC_{0-t}	The area under the concentration-time curve (AUC) from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down).
$AUC_{0-\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last,}$ as estimated using the linear regression from λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\ \lambda_z$
AUC_τ	The area under the concentration-time curve (AUC) over the dosing interval from T_1=0 h to T_2=τ h. Calculated using the mixed log linear trapezoidal rule (linear up, log down). For single dose, AUC_τ is calculated as a partial area with the defined time range. In multiple dose profiles AUC_τ is calculated at steady state from 1 predose time point to the dosing interval time. In cases where the actual observation time is not equal to the scheduled observation time AUC_τ will be calculated based on the estimated concentration at τ hours, and not the concentration at the actual observation time.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration during a complete dosing interval
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent terminal half-life. $t_{1/2}$ = ln (2)/λ_z

- Pharmacokinetics of avelumab for all the participants will be assessed using a sparse sampling approach. Serum concentrations from sparse PK sampling for avelumab will allow population PK analyses. The population PK report will be a separate document and will not be included in the clinical study report (CSR).
- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of M6620, as specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.
- The quantification of M6620 in plasma will be performed using a validated analytical method. Concentrations will be used to evaluate the PK of M6620. The M6620 plasma samples may also be used for evaluations of metabolites of M6620, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used by or affected by M6620.
- Whole blood samples of approximately 3.5 mL will be collected for measurement of serum concentrations of avelumab, as specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded.

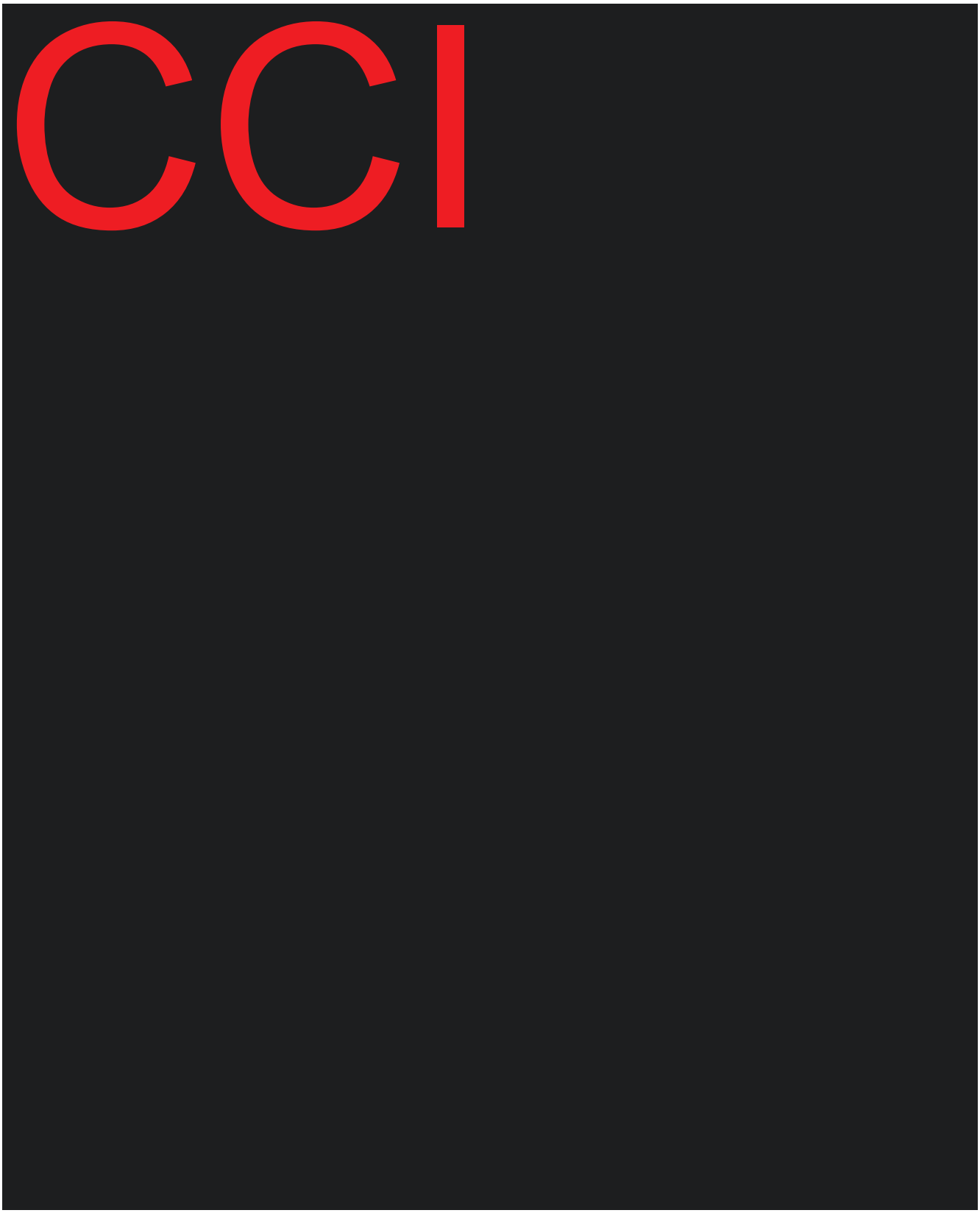
- The quantification of avelumab in serum will be performed using a validated immunoassay method. Concentrations will be used to evaluate the PK of avelumab.
- Remaining samples collected for analysis of avelumab serum concentration may also be used to evaluate immunogenicity and safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection, processing, handling, storage and shipment of these samples will be provided in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- The PK sampling schedule may be modified upon agreement of the clinical pharmacologist and Investigators to optimize the sampling time for M6620 disposition but will not increase the total number of PK blood draws. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. The exact sampling time should be recorded. Acceptable PK sampling windows are presented in Table 14. However, only cases in which no sample is collected are considered as protocol deviations.

Table 14 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time from Scheduled Sampling Allowed
Before BOI	- 120 minutes
EOI	± 5 minutes for M6620, ± 15 minutes for avelumab
0.5 to 2 hours after EOI	± 5 minutes
> 2 and ≤ 7 hours after EOI	± 20 minutes
> 7 and ≤ 23 hours after EOI	± 60 minutes
> 23 hours after EOI	± 120 minutes

BOI=beginning of infusion, EOI=end of infusion.

- For participants undergoing paired tumor biopsies on Day 2 of Cycle 1 or Cycle 2, blood samples for M6620 PK at 1, 2, and/or 3 hours may be optional only if they cannot be feasibly collected. At minimum, a blood sample should be collected for M6620 PK as close to the time of post-M6620 biopsy as is feasible, and the time recorded.
- No PK sampling will be performed for participants receiving treatment with SoC.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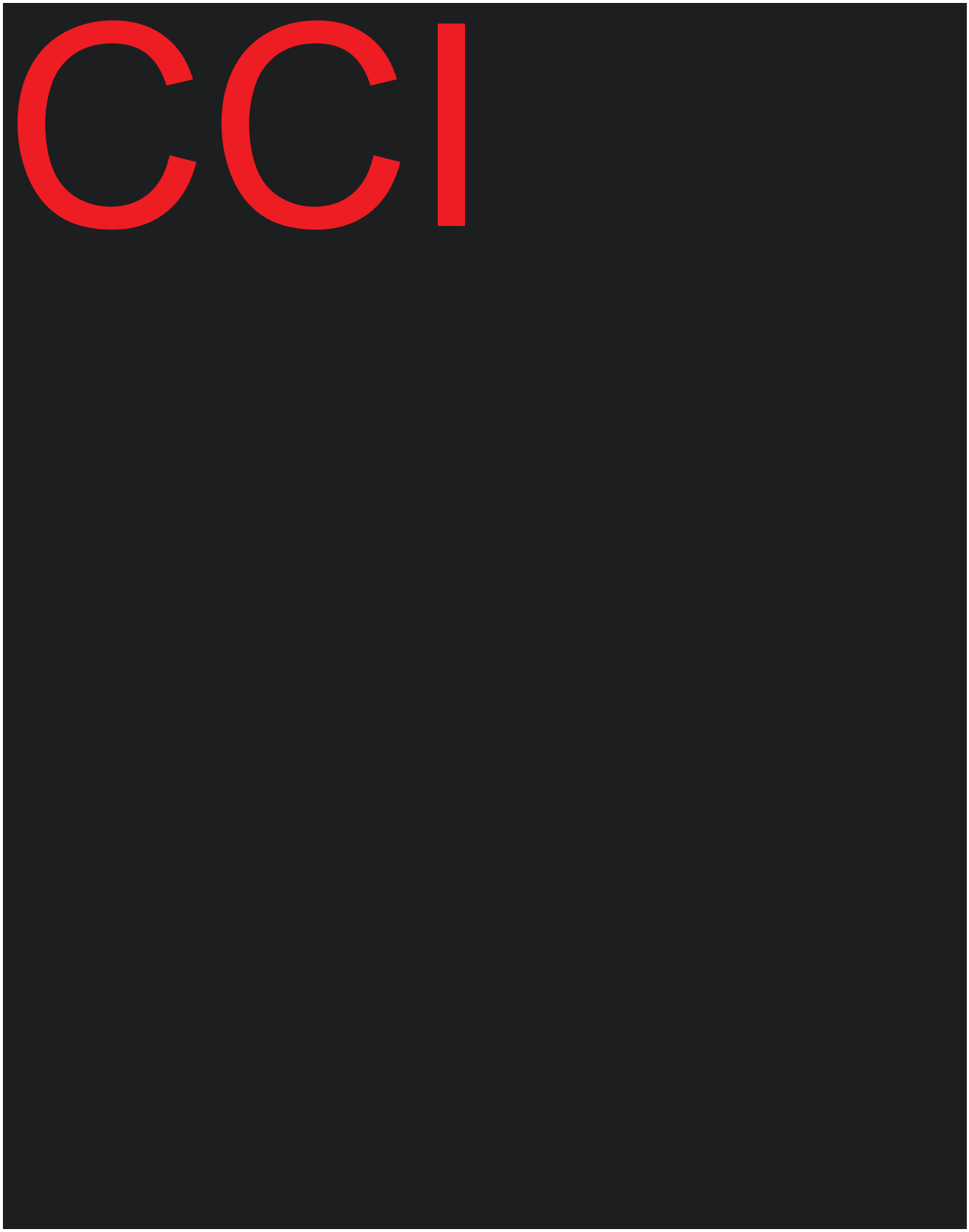
CCI

8.9 Medical Resource Utilization and Health Economics

Not applicable.

8.10 Immunogenicity Assessments

- Whole blood samples of approximately 3.5 mL will be collected for detection of antibodies against avelumab in serum, as specified in the SoA. Samples will be collected prior to any avelumab administration on the same Study Day.
- The detection of antibodies to avelumab will be performed using a validated assay method with tiered testing of screening, confirmatory, and titration. Confirmed positive antibodies may be tested for the presence of neutralizing antibodies and may be further characterized.

- Details on processes for collection and shipment of these samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

9 Statistical Considerations

All analyses will be described in detail in the IAP.

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

9.2 Sample Size Determination

Part A

During Part A of the study, approximately 3 to 18 participants are expected to be enrolled to evaluate the safe dose for the triplet combination (modified 3 + 3 design, but only dose reductions will be considered if necessary).

Part B

After confirmation of the safe target dose, approximately 72 participants will be randomly assigned to 1 of 2 treatment groups in Part B of the study (36 participants per arm; 1:1 randomization, stratified by BRCA status). The median time for PFS in participants who have received treatment with platinum-containing chemotherapy after failure to PARPi maintenance treatment has been reported to be approximately 6 months (Ang 2013), depending on prior lines of treatment and platinum-free interval.

A sample size of 36 participants in each treatment group is chosen based on the following assumptions: Based on 50 events for PFS, the probability to observe a hazard ratio (HR) of 0.6 or lower is 74% under the assumption of a true HR of 0.5; whereas, if the true HR is 0.75 (a nonrelevant effect regarding further development of this combination therapy for such an indication), the probability to observe a HR of 0.6 or lower is 21.5%, and if there is no effect (i.e., if the true HR = 1), the probability for an observed HR of 0.6 is 3.5%.

It is assumed that the accrual period will be approximately 12 months, followed by a follow-up period of 15 months (assuming median PFS time of 12 months in the triplet combination arm and 6 months in the SoC arm). The predicted drop-out rate (participants without any information about PFS event) is 10% in total.

9.3 Populations for Analyses

The analysis populations are specified in Table 16. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock.

Table 16 Population Analysis Sets

Analysis Population	Description
Enrolled (Parts A + B)	All participants who provided informed consent
DLT Analysis Set (Part A only)	All evaluable participants with data used for implementing the dose-escalation schedule. These participants will have received at least 1 study intervention administration of each avelumab, M6620, and/or chemotherapy in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period
FAS (Full Analysis Set) (Part B only)	All participants who were randomized. Participants will be classified according to the treatment assigned at randomization as per the intent-to-treat principle.
SAF Analysis Set (Parts A + B)	All participants who receive at least 1 dose of any study intervention. The SAF Analysis Set will be also used for the efficacy analyses of Part A.
QoL Analysis Set	The QoL Analysis Set will include all randomized participants who complete PRO assessments at Baseline.
PK Analysis Sets	PK Analysis Set Avelumab All participants who receive at least 1 dose of avelumab, have no clinically important protocol deviations or important events affecting PK, and provide at least 1 measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses for avelumab will be based on this analysis set. PK Analysis Set M6620 All participants who receive at least one dose of M6620, have no clinically important protocol deviations or important events affecting PK, and provide at least 1 measurable postdose concentration. Participants will be analyzed according to the actual treatment they received. All PK analyses for M6620 will be based on this analysis set.
Immunogenicity Analysis Set	All participants who have received at least 1 dose of avelumab and M6620 and have at least 1 valid ADA result.
CCI	

ADA=antidrug antibody; CCI ; DLT=dose-limiting toxicity; DNA=deoxyribose nucleic acid; CCI ; PK=pharmacokinetic; PRO=patient-reported outcomes; QoL=quality of life; SAF=Safety.

9.4 Statistical Analyses

There is no formal significance level for this study, and all analyses are considered descriptive.

In general, continuous variables will be summarized using number of participants (n); mean, standard deviation; median; 25th percentile to 75th percentile (Q1 to Q3); minimum; and maximum. If there are fewer than 5 observations available, only the mean and the observed data will be given.

Categorical variables will be summarized using frequency counts and percentages.

The calculation of proportions will be based on the number of participants in the analysis set of interest, unless otherwise specified in the IAP.

Only tumor assessments performed before the start of any further anticancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented PD.

Baseline

In general, the last nonmissing measurement prior to the first study intervention will serve as the baseline measurement. If no such a value is available, the last measurement prior to the first study intervention administration will be used as the baseline measurement with the exception of pre-randomization assessments used for the derivation of efficacy endpoints (e.g., tumor assessment at Baseline, which will be set to missing, if not done prior to randomization).

The last available assessment prior to the start of study intervention is defined as "baseline" value or "baseline" assessment for safety.

On Treatment

The on-treatment period is defined as the time from the first dose of study intervention through minimum (30 days + last dose of study intervention, start day of new anticancer therapy – 1 day), unless otherwise stated.

9.4.1 Efficacy Analyses

Analysis of Primary Endpoint (Part B: Randomized-controlled Period)

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

The HR (including 95% confidence interval) will be calculated by Cox's proportional hazards model (Table 17). A stratified analysis by BRCA status will be performed if sufficient number of participants in each stratum is available. The Full Analysis Set will be used for all efficacy analyses in Part B.

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

- For participants who do not have an event (PD or death)
- For participants who start a new anticancer therapy prior to an event
- For participants with an event after 2 or more missing tumor assessments.

Participants who do not have a baseline tumor assessment or who do not have any postbaseline tumor assessments will be censored on the date of randomization, unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

Subgroup analyses (for PD-L1 expression levels for instance) may be performed. Details will be available in the Integrated Analysis Plan.

Table 17 Statistical Analysis Methods for Efficacy Endpoints, Part B

Endpoint	Statistical Analysis Methods
Primary	Cox's proportional hazards model – Full Analysis Set
Secondary	Descriptive statistics: • Continuous variables: number of participants; mean, standard deviation; median, Q1 to Q3, minimum, and maximum • Categorical variables: frequency counts and percentages
CCI	

Q1=25th percentile; Q3=75th percentile.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety analyses will include the examination of vital signs, 12-lead ECGs, physical examination findings, and clinical laboratory tests (including hematology, blood chemistry, and urinalysis), and AEs. All safety parameters will be summarized using descriptive statistics (Table 18).

Table 18 Statistical Analysis Methods for Safety Endpoints

Endpoint	Statistical Analysis Methods
Secondary	Descriptive statistics: • Continuous variables: number of participants; mean, standard deviation; median, Q1 to Q3, minimum, and maximum • Categorical variables: frequency counts and percentages

Q1=25th percentile; Q3=75th percentile.

9.4.2.1 Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded using the NCI-CTCAE toxicity grading scale.

Treatment-emergent adverse events (TEAEs) are defined as events with onset dates occurring on treatment, or events which worsen on-treatment (see Appendix 8, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

The frequency of participants experiencing TEAEs, regardless of relatedness to study interventions, will be summarized by system organ class and preferred term for each treatment arm. Similar summaries will also be provided for serious TEAEs, TEAEs leading to permanent discontinuation of study interventions, TEAEs by maximum severity, TEAEs related to study intervention, TEAEs with fatal outcome, and treatment-emergent AESIs, such as irAEs. A listing of AEs meeting DLT definition will be provided.

9.4.2.2 Laboratory Values

Laboratory results will be classified by grade according to NCI-CTCAE. The worst on-treatment grades for chemistry and hematology laboratory results will be summarized. Shifts in toxicity grading from Baseline to highest grade during the on-treatment period will be displayed. For laboratory tests without an NCI-CTCAE grade definition, results will be presented categorically (e.g., below, within, or above normal limits).

9.4.3 Other Analyses

9.4.3.1 Baseline Characteristics

Analyses of participant disposition, treatment/study discontinuations, demographics, and other baseline characteristics will be described in the IAP.

PK, immunogenicity, PD, and biomarker exploratory analyses will be specified in the Integrated Analysis Plan finalized before database lock. Integrated analyses across studies, such as the population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

9.4.3.2 Estimation of Individual PK Parameters

Pharmacokinetic parameters for M6620 will be calculated by the PK/CCI Data Processing Group of QPD, Merck, Darmstadt, Germany, or by a CRO selected by the Sponsor, using standard noncompartmental methods and the actual administered dose. Pharmacokinetic parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the Statistical Analysis System (SAS®) format Best12. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

Noncompartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.3, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

The statistical software SAS® (SAS-Institute, Cary, NC, USA, Windows version 9.1 or higher) may be used to produce tables, listings, and figures and in the calculation of PK parameters if appropriate.

Pharmacokinetic parameters to be calculated are presented in Section 8.5. The calculation of the AUCs will be performed using the mixed log-linear trapezoidal method (linear up, log down). Extrapolated areas will always be computed using the predicted last concentration that is estimated using the linear regression from terminal rate constant determination. Pharmacokinetics of avelumab for all participants will be assessed using a sparse sampling approach. Plasma concentrations from sparse PK sampling for avelumab will allow population PK analyses. The population PK report will be a separate document and not be included in the CSR.

Pharmacokinetic concentrations below the lower limit of quantification (LLOQ) are taken as zero for descriptive statistics for M6620 and avelumab. M6620 PK concentrations below LLOQ, which are before the last quantifiable data point, will be taken as zero for calculating the AUC. The PK parameters will be summarized using descriptive statistics. Individual as well as mean concentration-time plots will be depicted.

9.4.3.3 Immunogenicity Analysis

Participants will be categorized based on the onset and duration of the ADA response. Tables will be prepared for incidence and listings will be prepared for characterization of the ADA response and potential association with PK, safety, and efficacy.

9.4.4 Sequence of Analyses

This is an exploratory study. Available data will be evaluated during the study by the SMC during part A and the DMC during part B.

No formal interim analyses are planned; however, unplanned interim analyses may be performed.

The SMC and DMC will be formed to review the safety data on a regular basis throughout this clinical study and is described in Section 8.2.5. For Part B, no formal statistical stopping rule will be used for the DMC. Refer to the DMC Charter for additional details.

The main analysis will be performed approximately 15 months after the last participant's first visit.

The analyses will be performed based on the IAP, which will be finalized prior to database lock.

10 References

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11 Appendices

Appendix 1 Abbreviations

ADA	Antidrug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATR	Ataxia telangiectasia and Rad3-related
ATRi	Ataxia telangiectasia and Rad3-related inhibitor
AUC	Area under the concentration-time curve
BOI	Beginning of infusion
BOR	Best overall response
BRCA	Breast cancer gene (BRCA1, BRCA2)
CA-125	Cancer antigen 125
Chk1	Checkpoint kinase 1
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribose nucleic acids
CYP3A4	Cytochrome P450 3A4
DDR	DNA damage response
DDRi	DNA damage response inhibitor
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
dsDNA	Double-stranded DNA
ECG	Electrocardiogram

ECOG PS	Eastern Cooperative Oncology Group Performance Status
(e)CRF	(Electronic) Case Report Form
EOI	End of infusion
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EORTC QLQ-OV28	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer
FFPE	Formalin-fixed, paraffin-embedded
FSH	Follicle-stimulating hormone
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
HRD	Homologous recombination deficiency
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
irAE	Immune-related adverse event
IRB	Institutional Review Board
iv	Intravenous
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PARPi	Poly (ADP-ribose) polymerase inhibitor
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease

PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcomes
QoL	Quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
CCI	[redacted]
RP2D	Recommended Phase II dose
SAS	Statistical Analysis System
SAE	Serious adverse event
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocyte
CCI	[redacted]
CCI	[redacted]
TO	Target occupancy
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative (defined as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure[s] involved in the research) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be reconsented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.
- As this study includes optional CCI examinations, including collection and storage of biological samples, a separate CCI ICF will be required. At selected sites, optional blood samples for immune cell subset by flow cytometry analyses will be collected under a separate required ICF.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.
- The Investigator will complete the participant registration form using IWRS (see Section 6.3.1). At Screening, the participant will receive a screening identification number. If the participant meets all inclusion criteria and does not meet any of the exclusion criteria, the participant will be registered by IWRS.

Study Administrative

The Sponsor of this clinical study is EMD Serono Research & Development Institute, Inc. (EMD Serono R&D), Billerica, MA, in the United States, and Merck KGaA, Darmstadt, Germany, for sites outside the United States.

The study will be conducted at approximately 35 study sites in the European Union and the United States. Approximately 24 sites will be in the United States. Sites will be a mixture of academic centers and inpatient clinics.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the CSR.

The study will appear in the following clinical studies registries: ClinicalTrials.gov, EudraCT, and all other required registries.

An SMC in Part A and a DMC in Part B will review the safety data on a regular basis throughout this clinical study (see Section 8.2.5).

The Sponsor will coordinate the study and will utilize the support of CROs (e.g., PPD), for some activities of the study. The Sponsor will perform oversight of the activities performed by the CROs. Monitoring and data management will be performed by PPD and the Sponsor will be responsible for regulatory submission.

The Clinical Trial Supplies department of the Sponsor will supply the study interventions of avelumab and M6620. The study interventions will be packaged, labeled, and distributed by a designated contract manufacturing organization.

Safety laboratory assessments will be performed locally by each investigational site. Pharmacokinetics and exploratory biomarker analyses will be performed under the responsibility and/or supervision of the Sponsor.

The Sponsor's Global Patient Safety Department, Merck KGaA, Darmstadt, Germany, or its designated representative will supervise drug safety and the timely reporting of AEs and SAEs.

Quality assurance of the study conduct will be performed by the Sponsor's Development Quality Assurance Department, Merck KGaA, Darmstadt, Germany.

A CRO (e.g., PPD) will write the study IAP, perform the statistical analyses, and will provide the outputs from the statistical analyses; the Sponsor will provide oversight.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Study Leader.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, IB, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
  - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the

participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Posting of data on Clintrials.gov, EudraCT, and all other required registries is planned and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for

verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Manual of Operations.

- For PRO data (e.g., QoL and pain assessments), ePRO will be used.
- The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs

- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Study Monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator, countersigned by the Study Monitor, and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the eCRF guidelines.

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate recruitment of participants by the Investigator.
  - Discontinuation of further development of the Sponsor's compound.

Appendix 3 Contraception

Woman of Childbearing Potential (WOCBP)

A woman is of childbearing potential (i.e., fertile), following menarche and until either:

1) becoming postmenopausal; or,
2) is permanently sterile by means of a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Highly Effective Contraceptive Methods

Highly effective methods are those with a failure rate of less than 1% per year when used consistently and correctly.

These methods are further classified into user-independent and user-dependent methods. Because user-independent methods do not depend on the participant's ability to use them consistently and correctly, they are preferred when contraception is introduced as a condition for study participation.

Caution should be taken for hormonal contraception, as it may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraception method. In this case, a second highly effective method of contraception should be used during the treatment period and for at least 6 months after the last dose of carboplatin, M6620, or the defined SoC combination treatments, or at least 60 days after the last dose of maintenance with avelumab or bevacizumab, whichever is later.

User-Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable

User-Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: This is a highly effective contraception method only if the partner is the sole sexual partner of the WOCBP and he has received medical assessment of the surgical success.
- Sexual abstinence: This is a highly effective method only if the WOCBP refrains from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable Contraceptive Method

Allowed only under certain situations, as specified in the Clinical Trial Facilitation Group recommendations, because they have a failure rate of **more than** 1% per year and therefore are not considered to be highly effective methods.

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Combination of a male condom with cap, diaphragm or sponge with spermicide (i.e., double barrier method)

Appendix 4 Carboplatin Dosing

Calvert Equation

Carboplatin dose (mg) = Target area under the curve (AUC mg·min/mL) x (GFR* + 25)
*GFR (glomerular filtration rate) estimated by calculated creatinine clearance (CrCl) using Cockcroft-Gault Equation (see below).

Cockcroft-Gault Equation

$$\text{CrCl}\left(\text{male};\frac{\text{mL}}{\text{min}}\right)=\frac{(140-\text{age})\text{ x (weight in kg)}}{72\text{ x serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)};\ \text{CrCl (female)}=0.85\text{ x CrCl (male)}$$

Maximum Carboplatin Dose Calculation

Consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function.

Based on target AUC (mg min/mL), the maximum dose can be calculated according to the Calvert formula as:

Maximum carboplatin dose (mg) = Target AUC (mg·min/mL) x (125 mL/min + 25)
For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg

Additional Considerations

- Overweight or obese patients (BMI ≥ 25 kg/m^2): Consider using an adjusted body weight.

  Adjusted body weight (kg) =

  ideal body weight (IBW) + 0.4 x (total body weight [TBW] – IBW)

- Patients with abnormally low serum creatinine (Cr), including elderly or cachectic patients: Consider using a minimum Cr of 0.7 mg/dL to avoid overestimation of CrCl.

For more details refer to the following reference:
https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf (last updated: 12 February 2018)

Appendix 5 List of Selected Cytochrome P450 3A4 Inducers and Inhibitors

In vitro drug metabolism studies suggest that M6620 is a substrate of CYP3A and its systemic exposure may be affected by co-medications that are strong CYP3A inhibitors and inducers (listed below). Based upon in vitro data, M6620 is not a potent inhibitor or inducer of human CYP enzymes in isolated enzyme systems, and its probability to interact with other medications that are substrates of CYP metabolism is expected to be low. However, Investigators should use standard precautions when prescribing co-medications, as with any novel therapeutic for which there is limited clinical experience.

Inhibitors of CYP3A4

Ketoconazole, itraconazole
Ritonavir, indinavir, saquinavir, nelfinavir
Clarithromycin, telithromycin, chloramphenicol

Inducers of CYP3A4

Phenytoin, carbamazepine, topiramate
Phenobarbital
St John's Wort (*Hypericum perforatum*)
Modafinil
Nevirapine
Rifabutin, rifampicin, rifapentin

Appendix 6 Management of Immune-related Adverse Events

Table 19 Management of Immune-related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., loperamide)	Close monitoring for worsening symptoms Educate participant 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 to 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 hours; 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 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (e.g., antihistamines, topical steroids)	If Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 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 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)	**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, or for recurrent Grade 2: 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 Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (e.g., infliximab, cyclophosphamide, iv 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 × ULN and/or Total bilirubin > ULN to 1.5 × 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 × ULN and/or total bilirubin > 1.5 to ≤ 3 × 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 × ULN and/or total bilirubin > 3 × 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 1.5 × baseline, or creatinine increased > ULN to 1.5 × ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased 1.5 × baseline and ≤ 6 × ULN, or creatinine increased > 1.5 and ≤ 6 × ULN	Withhold avelumab therapy 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	If returns to Grade ≤ 1: 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 × 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 (e.g., 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-related myocarditis. Guideline-based supportive treatment as per cardiology consult. * Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related etiology is ruled out, restart avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related myocarditis.
Immune-related myocarditis	Permanently discontinue avelumab. 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.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A).
*Local guidelines, or e.g., 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 (i.e., 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 (i.e., hypopituitarism/hypophysitis)	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.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	Withhold avelumab therapy If secondary thyroid and/or adrenal insufficiency is confirmed (i.e., subnormal serum free T4 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 as appropriate • Perform pituitary MRI and visual field examination as indicated	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.

	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.	
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 restarting 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 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.
Grade 4	Permanently discontinue avelumab therapy 1.0 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

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; AHA=American Heart Association; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; ESC=European Society of Cardiology; 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=National Cancer Institute; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

Appendix 7 Clinical Laboratory Tests

Table 20 Protocol-required Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit		RBC Indices: • MCV • MCH • % Reticulocytes	WBC Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Core Clinical Chemistry	BUN/total urea	Potassium	AST/SGOT	Total bilirubin
	Creatinine	Sodium	ALT/SGPT	Magnesium
	Glucose	Chloride	Phosphorus	Alk Phos
	Calcium			
Included in Full Clinical Chemistry	Amylase		Direct bilirubin	
	LDH	Lipase	Creatine kinase	
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 (Discontinuation of Study Intervention) and Appendix 8 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, macroscopic appearance, bilirubin, color, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (at Screening and End of Treatment Visit, or if blood or protein is abnormal).			
Hemostaseology	aPTT		Prothrombin time/INR	
Thyroid Function	TSH and Free T4			
Antidrug Antibodies	Totality of binding ADA			
Other Screening Tests	• FSH (as needed in women of nonchildbearing potential **only**) • Serum and urine βhCG pregnancy test (as needed for women of childbearing potential). • Serology: Hepatitis B screening: HBsAg, HBsAb, HBcAb IgG and IgM. Hepatitis C screening: HCVAb with reflex to HCV RNA.			

ADA=antidrug antibody; ALT=alanine aminotransferase; Alk Phos = alkaline phosphatase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; βhCG=β-human chorionic gonadotropin; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle-stimulating hormone; HCV=hepatitis C virus; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCVAb=hepatitis C virus antibody; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; RBC=red blood cell; RNA=ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

Appendix 8 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators will reference the NCI-CTCAE, version 5.0 (publication date: 27 November 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other nonstudy interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study interventions include, but may not be limited to, temporal relationship between the AE and the study interventions, known side effects of study interventions, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. The AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. The AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs, AESIs, and DLTs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the participant's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.2 (Method of Detecting Adverse Events and Serious Adverse Events).

Adverse Events of Special Interest for Safety Monitoring

Any AE that is suspected to be a potential irAE or an infusion-related reaction will be considered an AESI.

Other Adverse Events to be Reported Following a Specialized Procedure

Dose-limiting toxicities are defined in Section 6.6.1.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. If an AE constitutes a DLT, this is documented accordingly.

Specific guidance is in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events, Adverse Events of Special Interest, and Dose-limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the SAE Report Form in the eCRF following specific completion instructions.

Reporting of SAEs via paper report form is required as a back-up method only in the case of electronic data capture (EDC) failure. Names, addresses, and telephone and fax numbers will be included on the paper report form. All information reported via paper form must be transcribed into the eCRF as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an SAE Report Form must be completed immediately thereafter in the eCRF.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

Serious AESIs must be reported in an expedited manner as SAEs as outlined above. Nonserious AESI are not required to be reported in an expedited manner.

Reporting of nonserious AESIs via paper report form is required as a back-up method only in the case of EDC failure. Names, addresses, and telephone and fax numbers will be included on the paper report form. All information reported via paper form must be transcribed into the eCRF as soon as the system becomes available.

Dose-limiting Toxicities

Each event meeting the criteria of a DLT, as specified in Section 6.6.1, must be recorded in the eCRF within 24 HOURS after becoming aware of the event. Serious DLTs must be reported in an expedited manner as SAEs, as outlined above.


CCI

Appendix 10 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Version	Description of Change	Brief Rationale
Version 1.1-BEL	Table 2 and Table 3 (Schedule of Assessments): Added urine pregnancy test at Visit 30 Days (± 5) after Last Treatment and a notation that urine pregnancy tests are to be performed at 30 days after the last dose safety follow-up.	To bring the protocol into alignment with the CTFG recommendations for contraception and pregnancy testing in clinical trials.
	Section 5.1 Inclusion Criteria 11b and Appendix 3 Contraception: Added that contraception for Parts A and B would continue for at least 6 months after the last dose of carboplatin, M6620, or the defined SOC combination treatments, or at least 60 days after the last dose of maintenance with avelumab, whichever is later.	To bring the protocol into alignment with the SmPC for carboplatin and defined SoC combination treatments, as well as the M6620 IB, which specify to continue contraception for at least 6 months after the last treatment.
Version 1.0	Original Protocol	Not applicable

Appendix 11 Sponsor Signature Page

Study Title:	A Phase Ib Safety Run-in and Randomized Phase II, Open-label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of M6620 in Combination with Avelumab and Carboplatin in Comparison to Standard of Care Therapy in Participants with PARPi-resistant Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Regulatory Agency Identifying Numbers:	EudraCT # 2018-001534-17 US IND # CCI
Clinical Study Protocol Version:	30 Nov 2018/Version 2.0

I approve the design of the clinical study:

PPD

Signature

PPD

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	Merck KGaA
Address:	Frankfurter Str. 250 64293 Darmstadt Germany Post code: F135/202
Telephone number:	PPD
Fax number:	
E-mail address:	

Appendix 12 Coordinating Investigator Signature Page

Study Title:	A Phase Ib Safety Run-in and Randomized Phase II, Open-label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of M6620 in Combination with Avelumab and Carboplatin in Comparison to Standard of Care Therapy in Participants with PARPi-resistant Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Regulatory Agency Identifying Numbers:	EudraCT # 2018-001534-17 US IND # CCI
Clinical Study Protocol Version:	30 Nov 2018/Version 2.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 13 Principal Investigator Signature Page

Study Title:	A Phase Ib Safety Run-in and Randomized Phase II, Open-label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of M6620 in Combination with Avelumab and Carboplatin in Comparison to Standard of Care Therapy in Participants with PARPi-resistant Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Regulatory Agency Identifying Numbers:	EudraCT # 2018-001534-17 US IND # CCI
Clinical Study Protocol Version:	30 Nov 2018/Version 2.0
Site Number:	

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: