Clinical trial results:
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

Summary

EudraCT number	2018-001534-17
Trial protocol	GB BE IT
Global end of trial date	06 November 2019

Results information

Result version number	v1 (current)
This version publication date	01 October 2020
First version publication date	01 October 2020

Trial information

Trial identification

Sponsor protocol code	MS201943_0029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03704467
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate a safe, tolerable recommended Phase 2 dose (RP2D) of carboplatin + M6620 in combination with avelumab in subjects with PARPi-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	3
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject signed informed consent: 04 Mar 2019, Last subject last visit: 08 Oct 2019.

Pre-assignment

Screening details:

This study was planned to be conducted in 2 parts: Part A was the safety run-in part and Part 2 was the randomized controlled part. However, after completing Part A and confirming the safe combination dose, the sponsor decided not to open Part B.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A: Carboplatin + M6620 + Avelumab

Arm description:

Subjects received intravenous infusion of Carboplatin area under the concentration-time curve 5 on Day 1 in combination with 90 milligrams per square meter (mg/m^2) of M6620 on Day 2 and avelumab at an established dose of 1600 mg over 60 minutes on Day 1 for every 3 weeks cycle for a maximum of 6 cycles. Thereafter, avelumab 800 mg intravenously on Day 1 of every two weeks as a maintenance mono-therapy until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or death.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was adminstered intravenoulsy on Day 1.

Investigational medicinal product name	M6620
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

M6620 was adminstered intravenoulsy on Day 2.

Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab was adminstered intravenoulsy on Day 1.

Number of subjects in period 1	Part A: Carboplatin + M6620 + Avelumab
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Carboplatin + M6620 + Avelumab

Reporting group description:

Subjects received intravenous infusion of Carboplatin area under the concentration-time curve 5 on Day 1 in combination with 90 milligrams per square meter (mg/m^2) of M6620 on Day 2 and avelumab at an established dose of 1600 mg over 60 minutes on Day 1 for every 3 weeks cycle for a maximum of 6 cycles. Thereafter, avelumab 800 mg intravenously on Day 1 of every two weeks as a maintenance mono-therapy until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or death.

Reporting group values	Part A: Carboplatin + M6620 + Avelumab	Total	
Number of subjects	3	3	
Age Categorical Units: years			
<=18 years	0	0	
Between 18 and 65 years	2	2	
>=65 years	1	1	
Sex: Female, Male Units: subjects			
Female	3	3	
Male	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	3	3	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	3	3	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Part A: Carboplatin + M6620 + Avelumab

Reporting group description:

Subjects received intravenous infusion of Carboplatin area under the concentration-time curve 5 on Day 1 in combination with 90 milligrams per square meter (mg/m^2) of M6620 on Day 2 and avelumab at an established dose of 1600 mg over 60 minutes on Day 1 for every 3 weeks cycle for a maximum of 6 cycles. Thereafter, avelumab 800 mg intravenously on Day 1 of every two weeks as a maintenance mono-therapy until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or death.

Primary: Part A: Number of Subjects with Dose Limiting Toxicities (DLTs)

End point title	Part A: Number of Subjects with Dose Limiting Toxicities (DLTs)[1]

End point description:

DLT any death not clearly due to underlying disease causes/Grade(Gr)>=3 nonhematologic/Gr>=4 hematologic toxicity that was probably related to any of study interventions, individually/combination that occurred during DLT observation period, except for any of following: Gr3 infusion-related reaction; Transient (<=6hr) Gr3 flu-like symptoms; Transient (<=72hr) Gr3 fatigue, local reactions, headache, nausea/emesis; Gr3 diarrhea, skin toxicity, liver function test increase; Single laboratory values out of normal range and controlled with medical management; Tumor flare phenomenon: local pain, irritation/rash, localized at sites of known/suspected tumor; Neutropenia (Gr3/4) for <7 days not associated with any infection; Gr3 thrombocytopenia for <7 days without clinically significant bleeding and not requiring platelet transfusion; Symptomatic thyroid dysfunction manageable with treatment. DLT analysis set all evaluable subjects who received at least 1 study intervention.

End point type	Primary

End point timeframe:

Up to 3 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this endpoint.

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs

End point title	Part A: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs

End point description:

An adverse event (AE) was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or

not considered related to the study drug. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs were defined as events that started or worsened after first dose of study intervention until 30 days after last dose. TEAEs included both serious and non-serious AEs. Treatment-related TEAE: 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. Safety analysis set included all subjects who received at least 1 dose of any study intervention.

End point type	Secondary

End point timeframe:

Time from first dose of study treatment up to 230 days

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: subjects				
TEAEs	3			
Treatment-Related TEAEs	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects with Confirmed Best Overall Response (BOR) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and Assessed by Investigator

End point title	Part A: Number of Subjects with Confirmed Best Overall Response (BOR) According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and Assessed by Investigator

End point description:

Confirmed BOR: best response of any of the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from the date of randomization until PD/recurrence (taking the smallest measurement recorded since the start of treatment as reference). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. Confirmed BOR was assessed by an Investigator. Number of subjects with best overall response in each category (CR, PR, SD, PD) were reported. Safety analysis set was used.

End point type	Secondary

End point timeframe:

Time from first dose of study treatment up to 230 days

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: subjects				
Complete Response	0			
Partial Response	0			
Stable Disease	1			
Progressive Disease	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Progression-Free Survival (PFS)

End point title	Part A: Progression-Free Survival (PFS)

End point description:

PFS time was defined as the time from date of randomization until date of the first observation of progressive disease (PD) or death due to any cause within 12 weeks of the last tumor assessment in the absence of documented PD, whichever occurs first. PD was defined as at least a 20% increase in the sum of longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. PFS was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as assessed by Investigator. Safety analysis set was used. No summary analysis was done as study was early discontinued as per Sponsor's decision and subject wise data was reported. Here, '"n" signifies specific subject evaluated in the arm.

End point type	Secondary

End point timeframe:

Time from first dose of study treatment up to 230 days

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
number (not applicable)				
Subject 1 (n = 1)	1.9			
Subject 2 (n = 1)	2.1			
Subject 3 (n = 1)	6.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Duration of Response (DoR)

End point title	Part A: Duration of Response (DoR)

End point description:

DoR according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and as assessed by an Investigator was defined as the time from first documentation of objective response (Complete Response [CR] or Partial Response [PR]) to the date of first documentation of objective progression of disease (PD) or death due to any cause whichever occurs first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. If a subject has not had an event (PD or death), DoR was censored at the date of last adequate tumor assessment. PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Time from first dose of study treatment up to 230 days

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[2] - Data could not be calculated as none of the subjects showed objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Time to Progression (TTP)

End point title	Part A: Time to Progression (TTP)

End point description:

TTP was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and by an Investigator. TTP was defined as the time from first dose of study intervention until progression disease (PD). PD was defined as at least a 20% increase in the sum of longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. Safety analysis set included all subjects who received at least 1 dose of any study intervention. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signifies specific subject evaluated in the arm.

End point type	Secondary

End point timeframe:

Time from first dose of study treatment up to 230 days

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
number (not applicable)				
Subject 1 (n = 1)	1.9			
Subject 2 (n = 1)	2.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Time to First Subsequent Therapy (TFST)

End point title	Part A: Time to First Subsequent Therapy (TFST)

End point description:

The TFST was defined as the time from the date of randomization to the start date of the first subsequent anti-cancer therapy or death.

End point type	Secondary

End point timeframe:

From date of randomization to the earliest date of first subsequent therapy or death, assessed up to 230 days

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: months				
median (full range (min-max))	(to)			

Notes:

[3] - Data could not be calculated since date of first subsequent treatment was not recorded in eCRF.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration-Time Curve From Time Zero to Last Quantifiable Concentration (AUC0-t) of M6620 and Avelumab

End point title	Part A: Area Under the Plasma Concentration-Time Curve From Time Zero to Last Quantifiable Concentration (AUC0-t) of M6620 and Avelumab

End point description:

Area under the plasma concentration vs time curve from time zero to the last sampling time t at which the concentration was at or above the lower limit of quantification (LLQ). AUC0-t was calculated according to the mixed log-linear trapezoidal rule.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: nanogram*hour per milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[4] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration-Time Curve From Time Zero Extrapolated to Infinity (AUC0-inf) of M6620 and Avelumab

End point title	Part A: Area Under the Plasma Concentration-Time Curve From Time Zero Extrapolated to Infinity (AUC0-inf) of M6620 and Avelumab

End point description:

AUC0-inf was calculated by combining AUC0-t and AUCextra. AUC extra represents an extrapolated value obtained by Clast/ Lambda z, where Clast was the calculated plasma concentration at the last sampling time point at which the measured plasma concentration was at or above the Lower Limit of quantification (LLQ) and Lambda z was the apparent terminal rate constant determined by log-linear regression analysis of the measured plasma concentrations of the terminal log-linear phase.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[5] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Concentration Time Curve During a Dosing Interval (AUCtau) of M6620 and Avelumab

End point title	Part A: Area Under the Concentration Time Curve During a Dosing Interval (AUCtau) of M6620 and Avelumab

End point description:

AUCtau was defined as area under the concentration-time curve (AUC) over the dosing interval from T1= 0 hour to T2 = tau hour. AUCtau was calculated using the mixed log linear trapezoidal rule.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[6] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Terminal Rate Constant (Lambda z) of M6620 and Avelumab

End point title	Part A: Terminal Rate Constant (Lambda z) of M6620 and Avelumab

End point description:

Lambda z was determined from the terminal slope of the log-transformed plasma concentration curve using linear regression method.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: per hour				
geometric mean (geometric coefficient of variation)	()			

Notes:

[7] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Maximum Observed Plasma Concentration (Cmax) of M6620 and Avelumab

End point title	Part A: Maximum Observed Plasma Concentration (Cmax) of M6620 and Avelumab

End point description:

Cmax was obtained directly from the concentration versus time curve.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: nangram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[8] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Minimum Observed Plasma Concentration (Cmin) of M6620 and Avelumab

End point title	Part A: Minimum Observed Plasma Concentration (Cmin) of M6620 and Avelumab

End point description:

Cmin was minimum observed plasma concentration obtained directly from the concentration versus time curve.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[9] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Time to Reach the Maximum Plasma Concentration (Tmax) of M6620 and Avelumab

End point title	Part A: Time to Reach the Maximum Plasma Concentration (Tmax) of M6620 and Avelumab

End point description:

Tmax was obtained directly from the concentration versus time curve.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: hour				
median (full range (min-max))	(to)			

Notes:

[10] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Apparent Terminal Half-life (t1/2) of M6620 and Avelumab

End point title	Part A: Apparent Terminal Half-life (t1/2) of M6620 and

	Avelumab

End point description:

t1/2 was the time measured for the concentration to decrease by one half. t1/2 was calculated by natural log 2 divided by Lambda z.

End point type	Secondary

End point timeframe:

Pre-dose, 0, 1, 2, 3 and 6 hours post-dose on Day 2 Cycle 1; post-dose 47 hours on Day 4 Cycle 1; pre-dose and at 0 hour on Day 2 Cycle 2 (each Cycle is 21 days)

End point values	Part A: Carboplatin + M6620 + Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: hour				
geometric mean (geometric coefficient of variation)	()			

Notes:

[11] - As per changes in planned analysis, endpoint related to pharmacokinetic parameters was not assessed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time from first dose of study treatment up to 230 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA Version 22.0
Dictionary version	22.0

Reporting groups	
Reporting group title	Part A: Carboplatin + M6620 + Avelumab

Reporting group description:

Subjects received intravenous infusion of Carboplatin area under the concentration-time curve 5 on Day 1 in combination with 90 milligrams per square meter (mg/m^2) of M6620 on Day 2 and avelumab at an established dose of 1600 mg over 60 minutes on Day 1 for every 3 weeks cycle for a maximum of 6 cycles. Thereafter, avelumab 800 mg intravenously on Day 1 of every two weeks as a maintenance mono-therapy until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or death.

Serious adverse events	Part A: Carboplatin + M6620 + Avelumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A: Carboplatin + M6620 + Avelumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Fatigue			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Investigations			
Blood urine present			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
White blood cell count decreased			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Tooth fracture			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Eye disorders			
Vision blurred			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Renal and urinary disorders			

Bladder pain subjects affected / exposed occurrences (all) Hydronephrosis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 1 / 3 (33.33%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Flank pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 2 / 3 (66.67%) 2 1 / 3 (33.33%) 1		
Infections and infestations Tooth infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2018	• Phase 1b Safety Run-in" was added to the study title • Added SoC option: carboplatin AUC 5 on Day 1 + pegylated liposomal doxorubicin (PLD) 30 mg/m2 every 4 weeks for up to 6 cycles with or without bevacizumab • Added that the recommended dosage for the SoC regimen may be adapted per Investigator discretion and in accordance to the local institutional guidelines • Reduced minimum time of prior PARPi treatment from at least 6 to 4 months • 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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported