



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/m²) 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 administered intravenously 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 administered intravenously 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 administered intravenously 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/m²) 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 $\text{Clast} / \text{Lambda } z$, 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: nanogram 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 |
|-----------------|---|

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/m²) 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 | | |

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

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) Tooth fracture subjects affected / exposed occurrences (all) | 2 / 3 (66.67%) 2 1 / 3 (33.33%) 1 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 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) | 1 / 3 (33.33%) 1 | | |
| Hydronephrosis subjects affected / exposed occurrences (all) | 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) | 1 / 3 (33.33%) 1 | | |
| Flank pain subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 2 / 3 (66.67%) 2 | | |
| Myalgia subjects affected / exposed occurrences (all) | 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 | <ul style="list-style-type: none">• 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