Clinical trial results:
A Randomized, Phase II Study Evaluating MK-1775 in Combination with Paclitaxel and Carboplatin versus Paclitaxel and Carboplatin Alone in Adult Patients with Platinum Sensitive p53 Mutant Ovarian Cancer

Summary

EudraCT number	2011-002803-13
Trial protocol	DE SE HU GB
Global end of trial date	08 August 2016

Results information

Result version number	v1 (current)
This version publication date	06 August 2017
First version publication date	06 August 2017

Trial information

Trial identification

Sponsor protocol code	1775-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01357161
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	08 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a study of the safety and efficacy of MK-1775 in combination with paclitaxel plus carboplatin in the treatment of ovarian, fallopian tube, and primary peritoneal tumors with the P53 mutation. In Part 1, a small group of participants received MK-1775 along with paclitaxel plus carboplatin to establish the tolerability of MK-1775 with this combination. In Part 2, participants were randomly assigned to receive either MK-1775 plus paclitaxel and carboplatin OR placebo plus paclitaxel and carboplatin to assess efficacy of MK-1775 compared to placebo. The primary hypothesis of the study (Part 2) was that administration of MK-1775 in combination with paclitaxel plus carboplatin in participants with platinum sensitive p53 mutant ovarian cancer would result in improvement in progression free survival (PFS) per enhanced Response Evaluation Criteria In Solid Tumors version 1.1 (enhanced RECIST 1.1) compared to participants treated with paclitaxel plus carboplatin alone.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Russian Federation: 13
Worldwide total number of subjects	136
EEA total number of subjects	51

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)	94
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifteen participants were enrolled in the open label run-in (Part 1) and 121 participants were enrolled separately in the double-blind comparison (Part 2) for a total of 136 participants.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: MK-1775 225 mg + paclitaxel +carboplatin

Arm description:

During the open-label run-in, participants received 225 mg MK-1775 twice daily (BID) starting on Day 1 of Cycle 1 (cycle=21 days) for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (area under the curve [AUC] 5).

Arm type	Experimental
Investigational medicinal product name	MK-1775
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MK-1775 capsules, orally twice a day (BID) for a total of 5 doses starting on Day 1 of each 3-week cycle

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	Taxol
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

paclitaxel, intravenous (IV) infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	paraplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

carboplatin, IV infusion on Day 1 of each 3-week cycle

Arm title	Part 2: MK-1775 225 mg + paclitaxel +carboplatin

Arm description:

During Part 2, participants received 225 mg MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).

Arm type	Experimental

Investigational medicinal product name	MK-1775
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MK-1775 capsules, orally twice a day (BID) for a total of 5 doses starting on Day 1 of each 3-week cycle

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	Taxol
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

paclitaxel, intravenous (IV) infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	paraplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

carboplatin, IV infusion on Day 1 of each 3-week cycle

Arm title	Part 2: Placebo + paclitaxel +carboplatin

Arm description:

During Part 2, participants received matched placebo to MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received placebo in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

placebo capsule to MK-1775, orally BID for a total of 5 doses, starting on Day 1 of each 3-week cycle

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	Taxol
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

paclitaxel, intravenous (IV) infusion on Day 1 of each 3-week cycle

Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	paraplatin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

carboplatin, IV infusion on Day 1 of each 3-week cycle

Number of subjects in period 1	Part 1: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin
Started	15	59	62
Completed	0	0	0
Not completed	15	59	62
Adverse event, serious fatal	5	22	19
Physician decision	1	1	4
Consent withdrawn by subject	1	5	4
Study Terminated By Sponsor	5	29	26
Progressive Disease	-	1	3
Lost to follow-up	3	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: MK-1775 225 mg + paclitaxel +carboplatin
Reporting group description:	
During the open-label run-in, participants received 225 mg MK-1775 twice daily (BID) starting on Day 1 of Cycle 1 (cycle=21 days) for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (area under the curve [AUC] 5).	
Reporting group title	Part 2: MK-1775 225 mg + paclitaxel +carboplatin
Reporting group description:	
During Part 2, participants received 225 mg MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).	
Reporting group title	Part 2: Placebo + paclitaxel +carboplatin
Reporting group description:	
During Part 2, participants received matched placebo to MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received placebo in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).	

Reporting group values	Part 1: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin
Number of subjects	15	59	62
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	58.2	58.3	60.4
standard deviation	± 9.9	± 10.1	± 9.8
Gender, Male/Female			
Units: Subjects			
Female	15	59	62

Reporting group values	Total		
Number of subjects	136		
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	136		

End points

End points reporting groups

Reporting group title	Part 1: MK-1775 225 mg + paclitaxel +carboplatin
Reporting group description:	
During the open-label run-in, participants received 225 mg MK-1775 twice daily (BID) starting on Day 1 of Cycle 1 (cycle=21 days) for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (area under the curve [AUC] 5).	
Reporting group title	Part 2: MK-1775 225 mg + paclitaxel +carboplatin
Reporting group description:	
During Part 2, participants received 225 mg MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).	
Reporting group title	Part 2: Placebo + paclitaxel +carboplatin
Reporting group description:	
During Part 2, participants received matched placebo to MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received placebo in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).	

Primary: Part 2: Median Progression-free survival (PFS) in weeks based on Enhanced Response Evaluation Criteria In Solid Tumors version 1.1 (enhanced RECIST 1.1) by Independent Radiology Review

End point title	Part 2: Median Progression-free survival (PFS) in weeks based on Enhanced Response Evaluation Criteria In Solid Tumors version 1.1 (enhanced RECIST 1.1) by Independent Radiology Review[1]

End point description:

PFS was defined as the time from randomization to progressive disease (based on blinded independent central radiologic review) or death, whichever occurred earlier. Tumor response was evaluated every 6 weeks during treatment by diagnostic anatomic imaging and objective response assessments were performed based on enhanced RECIST 1.1 criteria. According to enhanced RECIST 1.1, progressive disease was the appearance of one or more new lesions, OR an unambiguous increase in the sum of target lesion volumes with both 1) >20% increase in the sum of volumes (SOV) of all target lesions (taking as reference the nadir) and 2) greater than two times the variability of the measurements estimated by the sponsor and/or its designees. PFS was analyzed for all randomized Part 2 participants (Intent to Treat [ITT] Population) using the Kaplan-Meier method and median PFS was reported in weeks. Per protocol, Part 1 participants were not included in this analysis.

End point type	Primary

End point timeframe:

Up to 57 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified by the protocol, this endpoint reported data for only the Part 2 arms.

End point values	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: weeks				
median (confidence interval 95%)	34.14 (29.86 to 43.14)	31.86 (24.43 to 35.57)		

Statistical analyses

Statistical analysis title	Part 2 PFS (enhanced RECIST): MK-1775 vs. Placebo

Statistical analysis description:

A stratified [number of prior platinum based regimens (1 vs. 2 and 3), time since last platinum based therapy (<12 months vs. ≥12 months)] Cox proportional hazards model, with Efron method of tie handling, was used to assess the magnitude of the treatment difference between the treatment arms. The p-value from the score test was used in the significance test and the hazard ratio (MK-1775 versus Placebo) and its 95% confidence interval (CI) from the same Cox model was reported.

Comparison groups	Part 2: Placebo + paclitaxel +carboplatin v Part 2: MK-1775 225 mg + paclitaxel +carboplatin
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.08
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.45
upper limit	0.89

Primary: Part 1: Number of participants with a dose limiting toxicity (DLT)

End point title	Part 1: Number of participants with a dose limiting toxicity (DLT)[2][3]

End point description:

DLTs assessed during first 21-day cycle of Part 1 and defined as toxicities that met pre-defined severity criteria, were possibly, probably, or definitely related to triplet therapy, and could possibly result in a change in the given dose. Hematologic DLTs included Grade (Gr) 3 or Gr 4 neutropenia with fever >38.5°C and/or infection requiring antibiotic or anti-fungal treatment, and any Gr 4-5 hematological toxicity EXCEPT Gr 4 anemia, leukopenia, lymphopenia, neutropenia lasting <7 days, and thrombocytopenia lasting <4 days, except if a platelet transfusion was required. Non-hematologic DLT defined as any Gr 3, 4, or 5 nonhematologic toxicity EXCEPT: Gr 3 nausea, vomiting, diarrhea, or dehydration judged by Investigator and SPONSOR to occur in setting of inadequate compliance with supportive care measures and last for less than 48 hours, alopecia of any grade, inadequately treated hypersensitivity reactions, or clinically non-significant, treatable or reversible lab abnormalities.

End point type	Primary

End point timeframe:

During Cycle 1 of Part 1 (first 21 days)

Notes:

[2] - 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: No between-group statistical analyses were planned for this endpoint.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified by the protocol, this endpoint reported data for only the Part 1 arm.

End point values	Part 1: MK-1775 225 mg + paclitaxel +carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	12[4]			
Units: participants				
Total	3			
Febrile neutropenia	1			
Neutropenia	1			
Thrombocytopenia	1			

Notes:

[4] - 3 participants excluded due to prohibited medication (1) and enrollment after interim analysis (2).

Statistical analyses

No statistical analyses for this end point

Primary: Parts 1 and 2: Percentage of participants that experienced an adverse event (AE)

End point title	Parts 1 and 2: Percentage of participants that experienced an adverse event (AE)

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's products, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product was also an AE.

The percentage of participants that experienced at least one AE was reported for each treatment arm. All participants who received at least one dose of study treatment during Parts 1 and 2 were analyzed.

End point type	Primary

End point timeframe:

Part 1: Day 1 through Post Study (286 days total). Part 2: Day 1 through Post Study (479 days total)

End point values	Part 1: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	59	60[5]	
Units: percentage of participants				
number (not applicable)	100	100	96.7	

Notes:

[5] - Two participants were randomized to the Part 2 placebo arm but were not treated.

Statistical analyses

Statistical analysis title	% with AEs: Part 2 MK-1775 vs. Placebo

Statistical analysis description:

P-values and 95% CIs were calculated using the Miettinen and Nurminen method for between-treatment differences (MK-1775 vs. placebo) in the percentage of participants with events.

Comparison groups	Part 2: MK-1775 225 mg + paclitaxel +carboplatin v Part 2: Placebo + paclitaxel +carboplatin
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentages
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	11.4

Primary: Parts 1 and 2: Percentage of participants that discontinued study treatment due to an AE

End point title	Parts 1 and 2: Percentage of participants that discontinued study treatment due to an AE

End point description:

An AE was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's products, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product was also an AE.

The percentage of participants that discontinued (DC) study treatment (paclitaxel, carboplatin, or MK-1775) due to an AE was reported for each treatment arm. All participants who received at least one dose of study treatment during Parts 1 and 2 were analyzed.

End point type	Primary

End point timeframe:

Part 1: Day 1 through Post Study (286 days total). Part 2: Day 1 through Post Study (479 days total)

End point values	Part 1: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	59	60[6]	
Units: percentage of participants				
number (not applicable)	20	20.3	21.7	

Notes:

[6] - Two participants were randomized to the Part 2 placebo arm but were not treated.

Statistical analyses

Statistical analysis title	% DC due to AEs: Part 2 MK-1775 vs. Placebo

Statistical analysis description:

P-values and 95% CIs were calculated using the Miettinen and Nurminen method for between-treatment differences (MK-1775 vs. placebo) in the percentage of participants with events.

Comparison groups	Part 2: MK-1775 225 mg + paclitaxel +carboplatin v Part 2: Placebo + paclitaxel +carboplatin

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Percentages
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	13.6

Secondary: Part 1: Objective response rate (ORR) per Gynecological Cancer Intergroup (GCIG) criteria based on both RECIST 1.1 and cancer antigen 125 (CA-125) level by Independent Radiology Review

End point title	Part 1: Objective response rate (ORR) per Gynecological Cancer Intergroup (GCIG) criteria based on both RECIST 1.1 and cancer antigen 125 (CA-125) level by Independent Radiology Review[7]

End point description:

ORR was defined as the percentage of participants whose best response was confirmed partial response (PR) or complete response (CR) based both on imaging per RECIST 1.1 and on serum marker CA-125 level according to GCIC criteria. CR was defined by RECIST 1.1 as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have had reduction in short axis to <10 mm. PR was defined by RECIST 1.1 as at least a 30% decrease in the sum of the diameters (SOD) of target lesions, taking as reference the baseline SOD. A response according to CA-125 had occurred if there was ≥50% reduction in CA-125 levels from a pretreatment sample. The response must have been confirmed and maintained for at least 28 days. Participants could be evaluated according to CA-125 only if they had a pretreatment sample that was ≥2 times the upper limit of normal and within 2 weeks prior to starting treatment. Only evaluable Part 1 participants were analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Up to 57 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified by the protocol, this endpoint reported data for only the Part 1 arm.

End point values	Part 1: MK-1775 225 mg + paclitaxel +carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	12[8]			
Units: percentage of participants				
number (confidence interval 95%)	75 (42.814 to 94.514)			

Notes:

[8] - 3 participants excluded due to prohibited medication (1) and enrollment after interim analysis (2).

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Median PFS in weeks based on RECIST 1.1 by Independent

Radiology Review

End point title	Part 2: Median PFS in weeks based on RECIST 1.1 by Independent Radiology Review[9]

End point description:

PFS was defined as the time from randomization to progressive disease (based on blinded independent central radiologic review) or death, whichever occurred earlier. Tumor response was evaluated every 6 weeks during treatment by diagnostic anatomic imaging and objective response assessments were performed based on RECIST 1.1 criteria. According to RECIST 1.1, progressive disease was the appearance of one or more new lesions, OR a ≥20% increase in the sum of target lesion diameters (SOD) taking as reference the nadir (smallest SOD recorded since treatment started). PFS was analyzed for all randomized participants in Part 2 using the Kaplan-Meier method and median PFS was reported in weeks. Per protocol, Part 1 participants were not included in this analysis.

End point type	Secondary

End point timeframe:

Up to 57 months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As pre-specified by the protocol, this endpoint reported data for only the Part 2 arms.

End point values	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: weeks				
median (confidence interval 95%)	42.86 (35 to 48.86)	34.86 (30.43 to 36.86)		

Statistical analyses

Statistical analysis title	Part 2 PFS (RECIST): MK-1775 vs. Placebo

Statistical analysis description:

A stratified [number of prior platinum based regimens (1 vs. 2 and 3), time since last platinum based therapy (<12 months vs. ≥12 months)] Cox proportional hazards model, with Efron method of tie handling, was used to assess the magnitude of the treatment difference between the treatment arms. The p-value from the score test was used in the significance test and the hazard ratio (MK-1775 versus Placebo) and its 95% CI from the same Cox model was reported.

Comparison groups	Part 2: MK-1775 225 mg + paclitaxel +carboplatin v Part 2: Placebo + paclitaxel +carboplatin
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.03
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.39
upper limit	0.79

Secondary: Part 2: ORR per GCIG criteria based on both Enhanced RECIST 1.1 and CA125 level by Independent Radiology Review

End point title	Part 2: ORR per GCIG criteria based on both Enhanced RECIST 1.1 and CA125 level by Independent Radiology Review[10]

End point description:

ORR defined as the percentage of participants with best response of confirmed PR or CR based both on imaging per enhanced RECIST 1.1 and on serum marker CA-125 level according to GCIC criteria. CR defined by enhanced RECIST 1.1 as disappearance of all target lesions. Any pathological lymph nodes (target or non-target) had reduction in short axis to <10 mm. PR defined by enhanced RECIST 1.1 as ≥30% decrease in SOV of target lesions, taking as reference baseline SOV. Response according to CA-125 had occurred if there was ≥50% reduction in CA-125 levels from pretreatment sample. Response must have been confirmed and maintained for ≥28 days. Participants could be evaluated according to CA-125 only if they had a pretreatment sample that was ≥2 times the upper limit of normal and within 2 weeks prior to starting treatment. All randomized participants in Part 2 were analyzed. Per protocol, Part 1 participants were not included in this analysis.

End point type	Secondary

End point timeframe:

Up to 57 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified by the protocol, this endpoint reported data for only the Part 2 arms.

End point values	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: percentage of participants				
number (confidence interval 95%)	74.58 (61.6 to 85)	69.35 (56.3 to 80.4)		

Statistical analyses

Statistical analysis title	Part 2 ORR (enhanced RECIST): MK-1775 vs. Placebo

Statistical analysis description:

Stratified Miettinen and Nurminen's method with a two-sided p-Value for testing was used for comparison of the ORRs between the treatment groups in Part 2 portion of the study. A 95% CI for the difference in response rates was provided.

Comparison groups	Part 2: MK-1775 225 mg + paclitaxel +carboplatin v Part 2: Placebo + paclitaxel +carboplatin
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5247
Method	Miettinen and Nurminen's Method
Parameter estimate	Difference in Response Rate
Point estimate	5.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	21.1

Secondary: Part 2: Median Overall survival (OS) in months

End point title	Part 2: Median Overall survival (OS) in months[11]

End point description:

OS was defined as the time from randomization to death due to any cause, reported in months. Participants without documented death at the time of analysis were censored at the date last known to be alive. For this endpoint, all randomized participants in Part 2 were analyzed. Per protocol, Part 1 participants were not evaluated for OS.

Median OS could not be calculated due to a small percentage of death events observed by the time of cut-off analysis date. A value of 9999 indicates that no data were calculated.

End point type	Secondary

End point timeframe:

Up to 57 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As pre-specified by the protocol, this endpoint reported data for only the Part 2 arms.

End point values	Part 2: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	62		
Units: months				
median (confidence interval 95%)	9999 (20.34 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Part 2 OS: MK-1775 vs. Placebo

Statistical analysis description:

A stratified [number of prior platinum based regimens (1 vs. 2 and 3), time since last platinum based therapy (<12 months vs. ≥12 months)] Cox proportional hazards model, with Efron method of tie handling, was used to assess the magnitude of the treatment difference between the treatment arms. The p-value from the score test was used in the significance test and the hazard ratio (MK-1775 versus Placebo) and its 95% CI from the same Cox model was reported.

Comparison groups	Part 2: MK-1775 225 mg + paclitaxel +carboplatin v Part 2: Placebo + paclitaxel +carboplatin

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.34

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1: Day 1 through Post Study (286 days total). Part 2: Day 1 through Post Study (479 days total)

Adverse event reporting additional description:

Part 1: All participants who received at least one dose of study treatment during the open-label period (n=15).

Part 2: All randomized participants who received at least one dose of study treatment (n=119). 2 participants were randomized to the Part 2 placebo arm but were not treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Part 1: MK-1775 225 mg + paclitaxel +carboplatin

Reporting group description:

During the open-label run-in, participants received 225 mg MK-1775 BID starting on Day 1 of Cycle 1 (cycle=21 days) for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).

Reporting group title	Part 2: Placebo + paclitaxel +carboplatin

Reporting group description:

During Part 2, participants received matched placebo to MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received placebo in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).

Reporting group title	Part 2: MK-1775 225 mg + paclitaxel +carboplatin

Reporting group description:

During Part 2, participants received 225 mg MK-1775 BID starting on Day 1 of each 21 day cycle for a total of 5 doses. Participants received MK-1775 in combination with paclitaxel (175 mg/m2) and carboplatin (AUC 5).

Serious adverse events	Part 1: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin	Part 2: MK-1775 225 mg + paclitaxel +carboplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 15 (60.00%)	12 / 60 (20.00%)	24 / 59 (40.68%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			

subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)	2 / 60 (3.33%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood magnesium decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical observation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			

subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	3 / 15 (20.00%)	2 / 60 (3.33%)	13 / 59 (22.03%)
occurrences causally related to treatment / all	3 / 3	2 / 2	16 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	3 / 15 (20.00%)	1 / 60 (1.67%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	3 / 3	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Thrombocytopenia			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	2 / 2	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			

subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1: MK-1775 225 mg + paclitaxel +carboplatin	Part 2: Placebo + paclitaxel +carboplatin	Part 2: MK-1775 225 mg + paclitaxel +carboplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	57 / 60 (95.00%)	59 / 59 (100.00%)
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	0	1	3
Flushing			
subjects affected / exposed	4 / 15 (26.67%)	4 / 60 (6.67%)	1 / 59 (1.69%)
occurrences (all)	5	7	3

Hypertension			
subjects affected / exposed	5 / 15 (33.33%)	3 / 60 (5.00%)	2 / 59 (3.39%)
occurrences (all)	7	8	2
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	1	1	1
Lymphoedema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	3 / 59 (5.08%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 15 (13.33%)	2 / 60 (3.33%)	9 / 59 (15.25%)
occurrences (all)	2	3	16
Chills			
subjects affected / exposed	3 / 15 (20.00%)	4 / 60 (6.67%)	3 / 59 (5.08%)
occurrences (all)	5	7	3
Face oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	13 / 15 (86.67%)	33 / 60 (55.00%)	32 / 59 (54.24%)
occurrences (all)	17	37	54
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	0	1	3
Injection site granuloma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	1	1	1
Malaise			
subjects affected / exposed	3 / 15 (20.00%)	4 / 60 (6.67%)	1 / 59 (1.69%)
occurrences (all)	4	5	1
Mucosal inflammation			

subjects affected / exposed	1 / 15 (6.67%)	3 / 60 (5.00%)	3 / 59 (5.08%)
occurrences (all)	1	3	3
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	3 / 60 (5.00%)	9 / 59 (15.25%)
occurrences (all)	3	3	12
Peripheral swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	3 / 59 (5.08%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	7 / 15 (46.67%)	6 / 60 (10.00%)	6 / 59 (10.17%)
occurrences (all)	8	6	7
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 15 (13.33%)	6 / 60 (10.00%)	6 / 59 (10.17%)
occurrences (all)	4	8	16
Hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)	4 / 60 (6.67%)	3 / 59 (5.08%)
occurrences (all)	1	5	4
Reproductive system and breast disorders			
Breast oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Breast pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	2	0	0
Pelvic pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences (all)	2	0	1
Vaginal discharge			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences (all)	1	1	0
Cough			

subjects affected / exposed	3 / 15 (20.00%)	6 / 60 (10.00%)	8 / 59 (13.56%)
occurrences (all)	4	10	10
Dysphonia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 60 (3.33%)	3 / 59 (5.08%)
occurrences (all)	0	2	3
Dyspnoea			
subjects affected / exposed	4 / 15 (26.67%)	8 / 60 (13.33%)	15 / 59 (25.42%)
occurrences (all)	6	10	23
Epistaxis			
subjects affected / exposed	0 / 15 (0.00%)	4 / 60 (6.67%)	4 / 59 (6.78%)
occurrences (all)	0	4	4
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	4 / 60 (6.67%)	4 / 59 (6.78%)
occurrences (all)	4	5	4
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 15 (6.67%)	2 / 60 (3.33%)	3 / 59 (5.08%)
occurrences (all)	1	2	3
Anxiety			
subjects affected / exposed	2 / 15 (13.33%)	3 / 60 (5.00%)	2 / 59 (3.39%)
occurrences (all)	2	4	3
Depression			
subjects affected / exposed	3 / 15 (20.00%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	3	1	1
Insomnia			
subjects affected / exposed	2 / 15 (13.33%)	8 / 60 (13.33%)	10 / 59 (16.95%)
occurrences (all)	3	8	13
Restlessness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	0	1	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 15 (20.00%)	3 / 60 (5.00%)	6 / 59 (10.17%)
occurrences (all)	3	3	6
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	4 / 59 (6.78%)
occurrences (all)	2	1	4
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	3 / 59 (5.08%)
occurrences (all)	0	0	3
Cardiac murmur			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 15 (13.33%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	2	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	1	2	3
Lymphocyte count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	3 / 59 (5.08%)
occurrences (all)	0	0	6
Neutrophil count decreased			
subjects affected / exposed	2 / 15 (13.33%)	9 / 60 (15.00%)	12 / 59 (20.34%)
occurrences (all)	8	34	30
Platelet count decreased			
subjects affected / exposed	5 / 15 (33.33%)	6 / 60 (10.00%)	8 / 59 (13.56%)
occurrences (all)	9	20	23
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	2 / 59 (3.39%)
occurrences (all)	1	1	2
White blood cell count decreased			
subjects affected / exposed	5 / 15 (33.33%)	6 / 60 (10.00%)	7 / 59 (11.86%)
occurrences (all)	9	15	17
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 15 (6.67%)	3 / 60 (5.00%)	2 / 59 (3.39%)
occurrences (all)	1	3	2
Fall			

subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences (all)	1	1	0
Spinal fracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 15 (6.67%)	3 / 60 (5.00%)	3 / 59 (5.08%)
occurrences (all)	1	3	4
Sinus tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 60 (3.33%)	3 / 59 (5.08%)
occurrences (all)	1	2	3
Tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 60 (3.33%)	5 / 59 (8.47%)
occurrences (all)	1	2	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 15 (26.67%)	7 / 60 (11.67%)	8 / 59 (13.56%)
occurrences (all)	4	11	15
Dysgeusia			
subjects affected / exposed	6 / 15 (40.00%)	7 / 60 (11.67%)	9 / 59 (15.25%)
occurrences (all)	9	15	11
Headache			
subjects affected / exposed	2 / 15 (13.33%)	8 / 60 (13.33%)	10 / 59 (16.95%)
occurrences (all)	3	11	11
Neuropathy peripheral			
subjects affected / exposed	2 / 15 (13.33%)	9 / 60 (15.00%)	8 / 59 (13.56%)
occurrences (all)	2	11	9
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	7 / 60 (11.67%)	3 / 59 (5.08%)
occurrences (all)	0	9	3
Peripheral sensory neuropathy			

subjects affected / exposed	5 / 15 (33.33%)	8 / 60 (13.33%)	12 / 59 (20.34%)
occurrences (all)	9	9	21
Polyneuropathy			
subjects affected / exposed	0 / 15 (0.00%)	4 / 60 (6.67%)	6 / 59 (10.17%)
occurrences (all)	0	5	10
Presyncope			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	0	1	4
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	4 / 59 (6.78%)
occurrences (all)	0	1	5
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	0	1	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 15 (40.00%)	19 / 60 (31.67%)	31 / 59 (52.54%)
occurrences (all)	12	36	68
Leukopenia			
subjects affected / exposed	2 / 15 (13.33%)	12 / 60 (20.00%)	9 / 59 (15.25%)
occurrences (all)	2	23	25
Lymph node pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	7 / 15 (46.67%)	24 / 60 (40.00%)	24 / 59 (40.68%)
occurrences (all)	16	58	52
Thrombocytopenia			
subjects affected / exposed	3 / 15 (20.00%)	16 / 60 (26.67%)	21 / 59 (35.59%)
occurrences (all)	3	31	64
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	5 / 59 (8.47%)
occurrences (all)	1	1	5
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)	2 / 60 (3.33%)	2 / 59 (3.39%)
occurrences (all)	1	2	5
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	2	0	0
Vision blurred			
subjects affected / exposed	0 / 15 (0.00%)	2 / 60 (3.33%)	4 / 59 (6.78%)
occurrences (all)	0	3	4
Visual acuity reduced			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 15 (20.00%)	14 / 60 (23.33%)	9 / 59 (15.25%)
occurrences (all)	3	15	11
Abdominal pain upper			
subjects affected / exposed	3 / 15 (20.00%)	2 / 60 (3.33%)	4 / 59 (6.78%)
occurrences (all)	3	4	9
Constipation			
subjects affected / exposed	5 / 15 (33.33%)	23 / 60 (38.33%)	17 / 59 (28.81%)
occurrences (all)	5	29	26
Diarrhoea			
subjects affected / exposed	13 / 15 (86.67%)	22 / 60 (36.67%)	44 / 59 (74.58%)
occurrences (all)	34	39	138
Dyspepsia			
subjects affected / exposed	3 / 15 (20.00%)	4 / 60 (6.67%)	6 / 59 (10.17%)
occurrences (all)	5	5	8
Dysphagia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	2	1	1
Flatulence			

subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences (all)	1	0	1
Gastric haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	3 / 15 (20.00%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	3	1	2
Nausea			
subjects affected / exposed	13 / 15 (86.67%)	36 / 60 (60.00%)	46 / 59 (77.97%)
occurrences (all)	27	67	103
Odynophagia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Oesophageal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Oral dysaesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	2	0	0
Proctalgia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 60 (3.33%)	0 / 59 (0.00%)
occurrences (all)	2	2	0
Rectal haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences (all)	2	0	2
Stomatitis			
subjects affected / exposed	1 / 15 (6.67%)	6 / 60 (10.00%)	8 / 59 (13.56%)
occurrences (all)	1	7	9
Vomiting			
subjects affected / exposed	13 / 15 (86.67%)	16 / 60 (26.67%)	37 / 59 (62.71%)
occurrences (all)	33	19	78
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	11 / 15 (73.33%)	40 / 60 (66.67%)	32 / 59 (54.24%)
occurrences (all)	11	40	33
Dermatitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences (all)	1	1	0
Dermatitis allergic			
subjects affected / exposed	2 / 15 (13.33%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	3	0	0
Hyperhidrosis			
subjects affected / exposed	2 / 15 (13.33%)	2 / 60 (3.33%)	1 / 59 (1.69%)
occurrences (all)	2	3	1
Pruritus			
subjects affected / exposed	3 / 15 (20.00%)	7 / 60 (11.67%)	6 / 59 (10.17%)
occurrences (all)	5	9	6
Rash			
subjects affected / exposed	1 / 15 (6.67%)	5 / 60 (8.33%)	2 / 59 (3.39%)
occurrences (all)	2	5	2
Rash maculo-papular			
subjects affected / exposed	3 / 15 (20.00%)	4 / 60 (6.67%)	4 / 59 (6.78%)
occurrences (all)	8	4	7
Skin lesion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	2 / 59 (3.39%)
occurrences (all)	3	1	4
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)	2 / 60 (3.33%)	0 / 59 (0.00%)
occurrences (all)	2	2	0
Pollakiuria			

subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	2 / 59 (3.39%)
occurrences (all)	2	1	2
Urinary incontinence			
subjects affected / exposed	1 / 15 (6.67%)	3 / 60 (5.00%)	0 / 59 (0.00%)
occurrences (all)	2	3	0
Urinary tract pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 60 (0.00%)	1 / 59 (1.69%)
occurrences (all)	3	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 15 (33.33%)	16 / 60 (26.67%)	15 / 59 (25.42%)
occurrences (all)	11	23	20
Back pain			
subjects affected / exposed	4 / 15 (26.67%)	2 / 60 (3.33%)	5 / 59 (8.47%)
occurrences (all)	5	2	5
Flank pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 60 (0.00%)	3 / 59 (5.08%)
occurrences (all)	0	0	3
Musculoskeletal pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	1 / 15 (6.67%)	11 / 60 (18.33%)	15 / 59 (25.42%)
occurrences (all)	1	17	20
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	5 / 60 (8.33%)	6 / 59 (10.17%)
occurrences (all)	2	8	8
Infections and infestations			
Fungal skin infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 15 (13.33%)	3 / 60 (5.00%)	0 / 59 (0.00%)
occurrences (all)	2	3	0
Oral herpes			

subjects affected / exposed	1 / 15 (6.67%)	1 / 60 (1.67%)	1 / 59 (1.69%)
occurrences (all)	1	1	1
Pyelonephritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	0	1	3
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	4 / 60 (6.67%)	3 / 59 (5.08%)
occurrences (all)	0	4	3
Urinary tract infection			
subjects affected / exposed	3 / 15 (20.00%)	5 / 60 (8.33%)	7 / 59 (11.86%)
occurrences (all)	6	7	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 15 (53.33%)	11 / 60 (18.33%)	11 / 59 (18.64%)
occurrences (all)	10	17	18
Dehydration			
subjects affected / exposed	5 / 15 (33.33%)	3 / 60 (5.00%)	4 / 59 (6.78%)
occurrences (all)	6	8	10
Glucose tolerance impaired			
subjects affected / exposed	5 / 15 (33.33%)	0 / 60 (0.00%)	0 / 59 (0.00%)
occurrences (all)	15	0	0
Hypocalcaemia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	0 / 59 (0.00%)
occurrences (all)	3	1	0
Hypokalaemia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 60 (0.00%)	8 / 59 (13.56%)
occurrences (all)	5	0	12
Hypomagnesaemia			
subjects affected / exposed	6 / 15 (40.00%)	9 / 60 (15.00%)	11 / 59 (18.64%)
occurrences (all)	11	9	16
Hyponatraemia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 60 (1.67%)	3 / 59 (5.08%)
occurrences (all)	2	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2012	Amendment 01 (AM1) was implemented primarily to update an inclusion criterion to include participants with primary peritoneal and fallopian tube cancers.
10 June 2013	AM5 was implemented primarily to clarify the requirement of CA-125 during the follow up period.
02 October 2013	AM8 was implemented primarily to re-calculate sample size to expand from 80 to 120 participants for Part 2 of the study and re-estimate the power accordingly. The recruitment timelines were extended 6 more months and 15 sites were added as a result of the change. The change was made without unblinding the trial data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported