Clinical trial results:
Niraparib versus niraparib-bevacizumab combination in Women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

Part 1: AVANOVA1 - A phase I study to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the Recommended Phase 2 Dose (RP2D) in women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

Part 2: AVANOVA2 - A two-arm, open-label, phase II randomized study to evaluate the efficacy of niraparib versus niraparib-bevacizumab combination in women with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

Summary

EudraCT number	2014-004269-26
Trial protocol	DK SE NO FI
Global end of trial date	01 February 2022

Results information

Result version number	v1 (current)
This version publication date	30 December 2023
First version publication date	30 December 2023

Trial information

Trial identification

Sponsor protocol code	ENGOT-ov24-NSGO/AVANOVA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02354131
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU)
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Medical Director, Mansoor Raza Mirza, Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU), +45 35453311, mansoor.raza.mirza@regionh.dk
Scientific contact	Medical Director, Mansoor Raza Mirza, Nordic Society of Gynaecological Oncology - Clinical Trial Unit (NSGO-CTU), +45 35453311, mansoor.raza.mirza@regionh.dk

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	17 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2020
Global end of trial reached?	Yes
Global end of trial date	01 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1 (Phase 1): To evaluate the safety and tolerability of bevacizumab-niraparib combination therapy. Furthermore to determine the Recommended Phase 2 Dose (RP2D) of bevacizumab-niraparib combination for platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

Part 2 (Phase 2): The primary objective is to obtain preliminary evidence of efficacy of bevacizumab-niraparib combination or niraparib single agent treatment for patients with platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.
Progression-Free Survival (PFS) between bevacizumab-niraparib combination or niraparib single agent for the patient cohorts will be determined, incl. the secondary endpoints Overall Respose Rate (ORR) and Disease Control Rate (DCR).

Protection of trial subjects:

The IDSMC was established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study.
For phase 1 a go/no go decision was made by IDMC after all subjects in the corresponding cohort had passed cycle one without a DLT. The composition of the IDMC consisted of 3 independent individuals, who made recommendation to Sponsor, based on their review of safety information to continue or stop the trial.
The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the ICH-GCP guidelines.
Local principal investigators were responsible for ensuring study conductance according to the protocol, the ethical principles of the Declaration of Helsinki, current ICH guidelines on Good Clinical practice (GCP) and applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Sweden: 22
Country: Number of subjects enrolled	Denmark: 60
Country: Number of subjects enrolled	Finland: 21
Worldwide total number of subjects	109
EEA total number of subjects	105

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)	49
From 65 to 84 years	59
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Potential candidates for the trial may be identified by a member of the treatment team or by referrals from other departments/hospitals/GP.
Enrollment will occur only after the patient has given written informed consent, all screening assessments have been completed and the patient meets all eligibility criteria.

Pre-assignment

Screening details:

Written ICF, In-Exclusion Criteria, Demographics, BRCA testing, Medical history, Physical examination, ECOG PS , Gyn examination,, height + weight, Blood Pressure, Pulse + Temperature, O2 Saturation, ECG, Serum pregnancy test, Urinanalysis, TSH, Coagulation parameters, CA 125, CT scan, concomitant medication and baseline symptoms

Period 1

Period 1 title	Phase 2 (Part 2)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 2 (Arm 1)

Arm description:

Patients receive niraparib 300mg daily until progression

Arm type	Active comparator
Investigational medicinal product name	Niraparib
Investigational medicinal product code	MK-4827
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients receive niraparib 300mg daily until progression

Arm title	Phase 2 (Arm 2)

Arm description:

Patients receive bevacizumab 15 mg/kg iv q 3 weeks + niraparib 300mg daily until progression

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	MK-4827
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients receive niraparib 300mg daily until progression

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive bevacizumab 15 mg/kg iv q 3 weeks

Number of subjects in period 1[1]	Phase 2 (Arm 1)	Phase 2 (Arm 2)
Started	49	48
Completed	5	15
Not completed	44	33
Consent withdrawn by subject	-	1
Disease progression	36	21
Performance status deteriorated	-	1
Serious compliance issues	1	-
Unknown	-	1
Adverse event	5	9
Investigator decision	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: This trial consists of a Phase 1 (Part 1) and a Phase 2 (Part 2). In Part 1, 12 subjects were included; in Part 2, 97 subjects were included. Part 2 is reported as the baseline period, and therefore the number of subjects in the baseline period (97 subjects) is not the same as the worldwide number of enrolled subjects (109).

Period 2

Period 2 title	Phase 1 (Part 1)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Phase 1 (Arm 1)

Arm description:

Arm to determine safety and Recommended Phase 2 Dose (RP2D) for the phase 2 trial

Arm type	Dose-escalation
Investigational medicinal product name	Niraparib
Investigational medicinal product code	MK-4827
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients receive bevacizumab 15 mg/kg iv q 3 weeks (fixed dose) + niraparib 100mg to 300mg daily (depending on dose-escalation step) until progression

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive bevacizumab 15 mg/kg iv q 3 weeks (fixed dose) + niraparib 100mg to 300mg daily (depending on dose-escalation step) until progression

Number of subjects in period 2[2]	Phase 1 (Arm 1)
Started	12
Completed	1
Not completed	11
Disease progression	9
Adverse event, non-fatal	1
Pancreatitis (unrelated to study)	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: This trial consists of a Phase 1 (Part 1) and a Phase 2 (Part 2). In Part 1, 12 subjects were included; in Part 2, 97 subjects were included. Part 1 is reported as Period 2, and therefore the number of subjects in Period 2 (12 subjects) is not the same as the numer of subjects completing the preceding period (Period 1).

Baseline characteristics

Reporting groups	
Reporting group title	Phase 2 (Arm 1)
Reporting group description:	
Patients receive niraparib 300mg daily until progression	
Reporting group title	Phase 2 (Arm 2)
Reporting group description:	
Patients receive bevacizumab 15 mg/kg iv q 3 weeks + niraparib 300mg daily until progression	

Reporting group values	Phase 2 (Arm 1)	Phase 2 (Arm 2)	Total
Number of subjects	49	48	97
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	23	42
From 65-84 years	30	24	54
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	49	48	97
Primary tumour site Units: Subjects			
Ovary	33	38	71
Fallopian tube	9	5	14
Peritoneum	7	5	12
FIGO stage at diagnosis Units: Subjects			
I or II	5	3	8
IIIA or IIIB	2	2	4
IIIC	26	29	55
IV	15	14	29
Unknown	1	0	1
Chemotherapy-free interval Units: Subjects			
6-12 months	17	20	37
>12 months	32	28	60
HRD status			
*Two patients in Part 2 Arm 1 (niraparib) and one in Part 2 Arm 2 (niraparib plus bevacizumab) had BRCA-mutated tumours but were considered as HRD negative or unknown for stratification in error.			
Units: Subjects			
Positive*	30	28	58

Negative or unknown	19	20	39
BRCA mutation status			
** Subjects with BRCA mutations could have either somatic BRCA mutation, germline BRCA mutation or both somatic and germline BRCA mutations.			
Units: Subjects			
BRCA mutated **	18	15	33
Non-BRCA mutated	31	33	64
Number of previous lines of therapy Units: Subjects			
One	27	21	48
Two	19	24	43
≥ Three	3	3	6
Previous bevacizumab Units: Subjects			
Yes	13	10	23
No	36	38	74
Previous non-ovarian cancer Units: Subjects			
Yes	6	5	11
No	43	43	86
Pre-existing diabetes Units: Subjects			
Yes	2	0	2
No	47	48	95
Pre-existing hypertension Units: Subjects			
Yes	17	20	37
No	32	28	60
Histology Units: Subjects			
High grade	49	48	97
Low grade	0	0	0
Unknown	0	0	0

Subject analysis sets

Subject analysis set title	Phase 1 (Arm 1)
Subject analysis set type	Safety analysis

Subject analysis set description:

Phase 1 Arm 1 of the trial to determine safety and Recommended Phase 2 Dose (RP2D) for Phase 2 of the trial.

Reporting group values	Phase 1 (Arm 1)		
Number of subjects	12		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	7		
From 65-84 years	5		
85 years and over	0		
Gender categorical Units: Subjects			
Female	12		
Primary tumour site Units: Subjects			
Ovary	12		
Fallopian tube	0		
Peritoneum	0		
FIGO stage at diagnosis Units: Subjects			
I or II	2		
IIIA or IIIB	1		
IIIC	5		
IV	4		
Unknown	0		
Chemotherapy-free interval Units: Subjects			
6-12 months	3		
>12 months	9		
HRD status			
*Two patients in Part 2 Arm 1 (niraparib) and one in Part 2 Arm 2 (niraparib plus bevacizumab) had BRCA-mutated tumours but were considered as HRD negative or unknown for stratification in error.			
Units: Subjects			
Positive*	4		
Negative or unknown	8		
BRCA mutation status			
** Subjects with BRCA mutations could have either somatic BRCA mutation, germline BRCA mutation or both somatic and germline BRCA mutations.			
Units: Subjects			
BRCA mutated **	3		
Non-BRCA mutated	9		
Number of previous lines of therapy Units: Subjects			
One	7		
Two	3		
≥ Three	2		
Previous bevacizumab Units: Subjects			
Yes	1		
No	11		
Previous non-ovarian cancer Units: Subjects			
Yes	2		
No	10		
Pre-existing diabetes Units: Subjects			

Yes	0		
No	12		
Pre-existing hypertension Units: Subjects			
Yes	7		
No	5		
Histology Units: Subjects			
High grade	8		
Low grade	1		
Unknown	3		

End points

End points reporting groups

Reporting group title	Phase 2 (Arm 1)
Reporting group description:	
Patients receive niraparib 300mg daily until progression	
Reporting group title	Phase 2 (Arm 2)
Reporting group description:	
Patients receive bevacizumab 15 mg/kg iv q 3 weeks + niraparib 300mg daily until progression	
Reporting group title	Phase 1 (Arm 1)
Reporting group description:	
Arm to determine safety and Recommended Phase 2 Dose (RP2D) for the phase 2 trial	
Subject analysis set title	Phase 1 (Arm 1)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Phase 1 Arm 1 of the trial to determine safety and Recommended Phase 2 Dose (RP2D) for Phase 2 of the trial.	

Primary: Part 2: Progression-Free Survival (PFS) (ITT)

End point title	Part 2: Progression-Free Survival (PFS) (ITT)
End point description:	
Progression-Free Survival (PFS) of patients treated with Niraparib-bevacizumab combination against niraparib alone. The progression events are defined by well-documented and verifiable imaging data. PFS will be censored if the patient is lost to follow-up or refuses to continue in the study (i.e. withdraws consent). For patients alive and without progression at the time of analysis, PFS will be censored. In any case of censoring, the date of censoring will be the last time point documenting survival status.	
End point type	Primary
End point timeframe:	
PFS is defined as the duration of time from date of randomization/enrolment to date of progression or death, whichever occurs first.	

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: months				
median (confidence interval 95%)	5.5 (3.8 to 6.3)	11.9 (8.5 to 16.7)		

Statistical analyses

Statistical analysis title	Comparison of PFS between arms
Statistical analysis description:	
The two treatment arms are compared using the log-rank test	
Comparison groups	Phase 2 (Arm 1) v Phase 2 (Arm 2)

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.094

Secondary: Part 1: Best overall response by RECIST 1.1

End point title	Part 1: Best overall response by RECIST 1.1

End point description:

Anti-tumor activity will be described in terms of best overall response by disease that is measurable according to RECIST. All patients who have been on study treatment for at least 1 (one) dose will be evaluable for response.

End point type	Secondary

End point timeframe:

from start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)	Phase 1 (Arm 1)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	48	12	
Units: patients				
CR	5	7	1	
PR	8	22	5	
SD	21	16	5	
PD	15	3	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Progression free survival (PFS)

End point title	Part 1: Progression free survival (PFS)

End point description:

Anti-tumor activity will be described in terms of progression free survival (PFS). All patients who have been on study treatment for at least 1 (one) doses will be evaluable for response.

End point type	Secondary

End point timeframe:

From start of treatment until end of follow-up

End point values	Phase 1 (Arm 1)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: months				
median (confidence interval 95%)	11.6 (8.4 to 20.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Objective Response Rate (ORR)

End point title	Part 2: Objective Response Rate (ORR)

End point description:

Objective Response Rate (ORR) is determined as the rate of patients with an observed tumor response. ORR will be evaluated for three types of responders:
• Patients who have a response as defined per RECIST and as defined using the 50% response criteria for CA-125 (“responders”)
• Patients who have a response as defined per RECIST but no response as defined using the 50% response criteria for CA-125 (“RECIST responders”)
• Patients who do not have a response as defined per RECIST but who do have a response as defined using the 50% response criteria for CA-125 (“CA-125 responders”)

End point type	Secondary

End point timeframe:

From start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: patients				
CR	5	7		
PR	8	22		
SD	21	16		
PD	15	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Disease control rate (DCR) (CR+PR+SD)

End point title	Part 2: Disease control rate (DCR) (CR+PR+SD)

End point description:

The analysis of disease control rate will be performed for each treatment arm by calculating the point estimate of the percentage of patients in the treatment arm who have complete response or partial response or stable disease for at least 12 weeks, assessed according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

from start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: patients				
Yes	14	30		
No	35	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Patient reported outcomes (PROs)

End point title	Part 2: Patient reported outcomes (PROs)

End point description:

Quality of Life scores, assessed by EORTC's general EORTC-QLQ-C30 questionnaire, will be calculated using EORTC's Scoring Manual.

End point type	Secondary

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	47		
Units: score				
arithmetic mean (standard deviation)				
Time=1	67.7 (± 23.7)	65.6 (± 25.4)		
Time=2	67.0 (± 23.4)	59.1 (± 21.0)		
Time=3	67.1 (± 18.3)	62.4 (± 20.6)		
Time=4	66.7 (± 19.3)	64.0 (± 28.4)		
Time=5	64.4 (± 23.9)	68.6 (± 19.1)		
Time=6	74.5 (± 24.4)	66.7 (± 22.1)		
Time=7	75.8 (± 25.1)	58.3 (± 28.5)		
Time=8	66.7 (± 27.6)	65.4 (± 20.9)		

Time=9	50 (± 23.6)	64.3 (± 15.0)		
Time=10	50 (± 23.6)	75.0 (± 35.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Progression-free survival 2 (PFS2)

End point title	Part 2: Progression-free survival 2 (PFS2)

End point description:

Progression Free Survival 2 (PFS2) is defined as the time from enrolment/randomization until second investigator assessed disease progression or death. PFS2 will be censored if the patient is lost to follow-up or refuses to continue in the study (i.e. withdraws consent). For patients alive and without progression at the time of analysis, PFS2 will be censored. In any case of censoring, the date of censoring will be the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time from randomization to second objective disease evaluation.

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: months				
median (confidence interval 95%)	15.7 (13.7 to 17.3)	20.5 (18.1 to 22.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to first subsequent therapy (TFST)

End point title	Part 2: Time to first subsequent therapy (TFST)

End point description:

Time to first subsequent therapy (TFST) is defined as the time from enrolment/randomization until initiation of second-line anti-cancer treatment or death. TFST will be censored if the patient is lost to follow-up or refuses to continue in the study (i.e. withdraws consent). For patients alive and without initiation of second-line treatment at the time of analysis, TFST will be censored. In any case of censoring, the date of censoring will be the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time from randomization to first subsequent therapy or death.

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: months				
median (confidence interval 95%)	7.2 (5.2 to 8.8)	14.3 (10.3 to 17.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to second subsequent therapy (TSST)

End point title	Part 2: Time to second subsequent therapy (TSST)

End point description:

Time to second subsequent therapy (TSST) is defined as the time from enrolment/randomization until initiation of third-line anti-cancer treatment or death. TSST will be censored if the patient is lost to follow-up or refuses to continue in the study (i.e. withdraws consent). For patients alive and without initiation of third-line treatment at the time of analysis, TSST will be censored. In any case of censoring, the date of censoring will be the last time point documenting survival status.

End point type	Secondary

End point timeframe:

Time from randomization to second subsequent therapy or death.

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: months				
median (confidence interval 95%)	17.3 (14.2 to 20.2)	21.8 (18.7 to 27.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (HRDpos)

End point title	Part 2: Expl. Sub-group analyses; PFS (HRDpos)

End point description:

Progression-free survival in the subgroup of HRD positive patients

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	28		
Units: months				
median (confidence interval 95%)	6.1 (3.9 to 9.0)	11.9 (8.5 to 22.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (HRDneg)

End point title	Part 2: Expl. Sub-group analyses; PFS (HRDneg)
End point description: Progression-free survival in the subgroup of HRD negative patients	
End point type	Other pre-specified
End point timeframe: start of treatment until end of follow-up	

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: months				
median (confidence interval 95%)	4.2 (2.1 to 5.9)	11.3 (5.3 to 16.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (BRCA-mutated)

End point title	Part 2: Expl. Sub-group analyses; PFS (BRCA-mutated)
End point description: Progression-free survival in patients with BRCA mutation	
End point type	Other pre-specified
End point timeframe: start of treatment until end of follow-up	

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: months				
median (confidence interval 95%)	8.9 (3.9 to 13.0)	14.4 (6.2 to 20.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (non-BRCA-mutated)

End point title	Part 2: Expl. Sub-group analyses; PFS (non-BRCA-mutated)
End point description:	
Progression-free survival in patients with BRCA wild type	
End point type	Other pre-specified
End point timeframe:	
start of treatment until end of follow-up	

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: months				
median (confidence interval 95%)	4.1 (2.2 to 5.9)	12.5 (6.0 to 16.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (chemo-free interval 6-12 months)

End point title	Part 2: Expl. Sub-group analyses; PFS (chemo-free interval 6-12 months)
End point description:	
Progression-free survival in patients with a chemo free interval between 6 and 12 months	
End point type	Other pre-specified
End point timeframe:	
start of treatment until end of follow-up	

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: months				
median (confidence interval 95%)	2.2 (1.8 to 6.0)	11.3 (4.2 to 16.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (chemo-free interval over 12 months)

End point title	Part 2: Expl. Sub-group analyses; PFS (chemo-free interval over 12 months)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[1]	28[2]		
Units: months				
number (not applicable)	6.1	13.1		

Notes:

[1] - The median in months is indicated as 'number' (95% CI 4.1-9.3).

[2] - The median in months is indicated as 'number' (95% CI 8.5-NE).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; OS (HRDpos)

End point title	Part 2: Expl. Sub-group analyses; OS (HRDpos)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[3]	28[4]		
Units: month				
number (not applicable)	28.1	34.9		

Notes:

[3] - The median in months is indicated as 'number' (95% CI 19.9-NE).

[4] - The median in months is indicated as 'number' (95% CI 25.8-NE).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; OS (HRDneg)

End point title	Part 2: Expl. Sub-group analyses; OS (HRDneg)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[5]	20[6]		
Units: months				
number (not applicable)	25.7	24.8		

Notes:

[5] - The median in months is indicated as 'number' (95% CI 17.6-34.9).

[6] - The median in months is indicated as 'number' (95% CI 17.6-NE).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; OS (chemo-free interval 6-12 months)

End point title	Part 2: Expl. Sub-group analyses; OS (chemo-free interval 6-12 months)

End point description:

Overall survival survival in patients with a chemo-free interval of 6-12 months

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[7]	20[8]		
Units: months				
number (not applicable)	26.5	27.7		

Notes:

[7] - The median in months is indicated as 'number' (95% CI 7.2-NE).

[8] - The median in months is indicated as 'number' (95% CI 16.1-NE).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses OS (chemo-free interval over 12 months)

End point title	Part 2: Expl. Sub-group analyses OS (chemo-free interval over 12 months)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[9]	28[10]		
Units: months				
number (not applicable)	27.8	31.8		

Notes:

[9] - The median in months is indicated as 'number' (95% CI 19.5-NE).

[10] - The median in months is indicated as 'number' (95% CI 24.6-NE).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; OS (non-BRCA-mutated)

End point title	Part 2: Expl. Sub-group analyses; OS (non-BRCA-mutated)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[11]	33[12]		
Units: months				
number (not applicable)	22.6	29.0		

Notes:

[11] - The median in months is indicated as 'number' (95% CI 18.2-28.1).

[12] - The median in months is indicated as 'number' (95% CI 23.5-NE).

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (Bevacizumab naive)

End point title	Part 2: Expl. Sub-group analyses; PFS (Bevacizumab naive)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: months				
median (confidence interval 95%)	6.0 (4.1 to 8.9)	14.4 (10.4 to 19.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; PFS (Prior Bevacizumab)

End point title	Part 2: Expl. Sub-group analyses; PFS (Prior Bevacizumab)

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: months				
median (confidence interval 95%)	3.1 (1.8 to 5.1)	5.9 (3.5 to 11.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part 2: Expl. Sub-group analyses; Confirmed complete response

End point title	Part 2: Expl. Sub-group analyses; Confirmed complete response

End point description:

End point type	Other pre-specified

End point timeframe:

start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	48		
Units: responders				
CR	5	7		
PR or less	44	41		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Part 2: Expl. Sub-group analyses; PFS (non-BRCA-mutated & HRD)

End point title	Part 2: Expl. Sub-group analyses; PFS (non-BRCA-mutated & HRD)

End point description:

Progression-free survival in the subgroup of HRD positive patients with BRCA wild type

End point type	Post-hoc

End point timeframe:

From start of treatment until end of follow-up

End point values	Phase 2 (Arm 1)	Phase 2 (Arm 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[13]	13[14]		
Units: month				
number (not applicable)	15.7	21.6		

Notes:

[13] - The median in months is indicated as 'number' (95% CI 7.2-20.2).

[14] - The median in months is indicated as 'number' (95% CI 13.3-NE).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs will be collected and recorded for each patient from the day of first dose until treatment discontinuation visit. Serious adverse events will be collected as of 14 days prior to randomization until 30 days after last dose/study discontinuation.

Adverse event reporting additional description:

For SAE's reported as 'Occurrences causally related to treatment number', the following were included: SAE unlikely related, SAE likely related, SAE related

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	2014AB

Reporting groups

Reporting group title	Phase 2 (Arm 1)
Reporting group description: -	
Reporting group title	Phase 2 (Arm 2)
Reporting group description: -	
Reporting group title	Phase 1 (Arm 1)
Reporting group description: -	

Serious adverse events	Phase 2 (Arm 1)	Phase 2 (Arm 2)	Phase 1 (Arm 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 49 (34.69%)	23 / 48 (47.92%)	6 / 12 (50.00%)
number of deaths (all causes)	29	25	8
number of deaths resulting from adverse events	1	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Laryngeal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Intracranial haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dizziness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
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 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy	Additional description: metabolic encephalopathy secondary to narcotics		
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 49 (4.08%)	1 / 48 (2.08%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 49 (2.04%)	5 / 48 (10.42%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased	Additional description: Increased GGT		
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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 disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Fatigue			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Febrile neutropenia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Fever			
subjects affected / exposed	0 / 49 (0.00%)	2 / 48 (4.17%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)	4 / 48 (8.33%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Constipation			
subjects affected / exposed	1 / 49 (2.04%)	1 / 48 (2.08%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Ileus			
subjects affected / exposed	1 / 49 (2.04%)	1 / 48 (2.08%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Subileus			
subjects affected / exposed	0 / 49 (0.00%)	2 / 48 (4.17%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 49 (4.08%)	2 / 48 (4.17%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	1 / 49 (2.04%)	1 / 48 (2.08%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Lung embolia	Additional description: Blood clot in lung		
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Cholecystitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Hepatobiliary disease	Additional description: Shock liver		
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Renal and urinary disorders			
Proteinuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Pain in extremity			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Fracture in distal radius	Additional description: Fracture in distal radius, left side		
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 48 (2.08%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 49 (4.08%)	1 / 48 (2.08%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 48 (2.08%)	0 / 12 (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
Infection	Additional description: Infections, Infection - focus unknown, infection of unknown origin		

subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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
Oedema peripheral	Additional description: Oedema limbs		
subjects affected / exposed	1 / 49 (2.04%)	0 / 48 (0.00%)	0 / 12 (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

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

Non-serious adverse events	Phase 2 (Arm 1)	Phase 2 (Arm 2)	Phase 1 (Arm 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)	48 / 48 (100.00%)	12 / 12 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 49 (22.45%)	28 / 48 (58.33%)	12 / 12 (100.00%)
occurrences (all)	12	58	42
Haemorrhage			
subjects affected / exposed	2 / 49 (4.08%)	2 / 48 (4.17%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Haemorrhoids			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 49 (42.86%)	24 / 48 (50.00%)	10 / 12 (83.33%)
occurrences (all)	33	65	21
Mucosal inflammation			
subjects affected / exposed	5 / 49 (10.20%)	7 / 48 (14.58%)	0 / 12 (0.00%)
occurrences (all)	5	11	0

Discomfort			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Pain	Additional description: General pain		
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	6 / 12 (50.00%)
occurrences (all)	0	0	13
Hot flush			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fever			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 49 (8.16%)	10 / 48 (20.83%)	2 / 12 (16.67%)
occurrences (all)	5	12	2
Dysphonia			
subjects affected / exposed	2 / 49 (4.08%)	4 / 48 (8.33%)	0 / 12 (0.00%)
occurrences (all)	3	4	0
Dyspnoea			
subjects affected / exposed	10 / 49 (20.41%)	8 / 48 (16.67%)	1 / 12 (8.33%)
occurrences (all)	11	11	1
Epistaxis			
subjects affected / exposed	3 / 49 (6.12%)	5 / 48 (10.42%)	1 / 12 (8.33%)
occurrences (all)	3	6	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 49 (12.24%)	6 / 48 (12.50%)	1 / 12 (8.33%)
occurrences (all)	9	16	1
Investigations			

Blood creatinine increased			
subjects affected / exposed	4 / 49 (8.16%)	7 / 48 (14.58%)	4 / 12 (33.33%)
occurrences (all)	12	9	18
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Lactate dehydrogenase increased			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	3 / 49 (6.12%)	3 / 48 (6.25%)	0 / 12 (0.00%)
occurrences (all)	4	4	0
Palpitations			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 49 (10.20%)	10 / 48 (20.83%)	5 / 12 (41.67%)
occurrences (all)	5	17	8
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 49 (16.33%)	11 / 48 (22.92%)	1 / 12 (8.33%)
occurrences (all)	10	13	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 49 (42.86%)	22 / 48 (45.83%)	3 / 12 (25.00%)
occurrences (all)	46	51	11
Leukopenia			
subjects affected / exposed	2 / 49 (4.08%)	3 / 48 (6.25%)	1 / 12 (8.33%)
occurrences (all)	2	10	1
Neutropenia			
subjects affected / exposed	5 / 49 (10.20%)	6 / 48 (12.50%)	0 / 12 (0.00%)
occurrences (all)	6	11	0
Thrombocytopenia			
alternative assessment type: Non-systematic			

subjects affected / exposed	12 / 49 (24.49%)	9 / 48 (18.75%)	2 / 12 (16.67%)
occurrences (all)	26	22	5
Eye disorders			
Corneal abrasion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 49 (18.37%)	11 / 48 (22.92%)	3 / 12 (25.00%)
occurrences (all)	15	15	9
Ascites			
subjects affected / exposed	3 / 49 (6.12%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	4	0	1
Constipation			
subjects affected / exposed	22 / 49 (44.90%)	20 / 48 (41.67%)	4 / 12 (33.33%)
occurrences (all)	32	39	12
Diarrhoea			
subjects affected / exposed	9 / 49 (18.37%)	10 / 48 (20.83%)	3 / 12 (25.00%)
occurrences (all)	11	25	3
Dysgeusia			
subjects affected / exposed	1 / 49 (2.04%)	4 / 48 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Gastrointestinal disorder			
subjects affected / exposed	4 / 49 (8.16%)	4 / 48 (8.33%)	0 / 12 (0.00%)
occurrences (all)	4	5	0
Nausea			
subjects affected / exposed	29 / 49 (59.18%)	31 / 48 (64.58%)	6 / 12 (50.00%)
occurrences (all)	50	61	15
Vomiting			
subjects affected / exposed	8 / 49 (16.33%)	18 / 48 (37.50%)	1 / 12 (8.33%)
occurrences (all)	12	37	5
Stomatitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mucosal dryness			

subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 49 (12.24%)	6 / 48 (12.50%)	1 / 12 (8.33%)
occurrences (all)	11	7	2
Dry skin			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Pain of skin			
subjects affected / exposed	0 / 49 (0.00%)	3 / 48 (6.25%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Rash			
subjects affected / exposed	4 / 49 (8.16%)	8 / 48 (16.67%)	0 / 12 (0.00%)
occurrences (all)	5	15	0
Nail disorder			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin discolouration			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 49 (2.04%)	10 / 48 (20.83%)	5 / 12 (41.67%)
occurrences (all)	1	32	14
Renal disorder	Additional description: Renal function decreased		
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	5 / 12 (41.67%)
occurrences (all)	0	0	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 49 (6.12%)	6 / 48 (12.50%)	0 / 12 (0.00%)
occurrences (all)	4	11	0
Muscular weakness			

subjects affected / exposed	0 / 49 (0.00%)	4 / 48 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Myalgia			
subjects affected / exposed	1 / 49 (2.04%)	5 / 48 (10.42%)	0 / 12 (0.00%)
occurrences (all)	1	10	0
Pain in extremity			
subjects affected / exposed	4 / 49 (8.16%)	2 / 48 (4.17%)	1 / 12 (8.33%)
occurrences (all)	4	3	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 49 (10.20%)	7 / 48 (14.58%)	4 / 12 (33.33%)
occurrences (all)	15	18	7
Respiratory tract infection			
subjects affected / exposed	3 / 49 (6.12%)	9 / 48 (18.75%)	0 / 12 (0.00%)
occurrences (all)	3	15	0
Infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	6 / 12 (50.00%)
occurrences (all)	0	0	6
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	6 / 49 (12.24%)	15 / 48 (31.25%)	5 / 12 (41.67%)
occurrences (all)	7	39	8
Hypomagnesaemia			
subjects affected / exposed	2 / 49 (4.08%)	3 / 48 (6.25%)	1 / 12 (8.33%)
occurrences (all)	2	4	2
Oedema peripheral			
subjects affected / exposed	4 / 49 (8.16%)	2 / 48 (4.17%)	0 / 12 (0.00%)
occurrences (all)	4	3	0
Decreased appetite			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 48 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Hyperkalaemia			

subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	0 / 48 (0.00%) 0	4 / 12 (33.33%) 8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2017	The study design in Phase 2 (part 2) was changed from 3 arms to 2 arms, and the study was expanded to the whole platinum-sensitive population regardless of gBRCA and HRD status. The study title, secondary objectives, planned patient number, study rationale, risk-benefit-assessment, study design of part 2, stratification factors, study arms, dosing and duration of treatment, inclusion and exclusion criteriae and study statistics were adapted. Sponsor name was changed. The protocol version number was updated from 2.0 to 3.1. The protocol v.3.0 also included changes previously approved locally in Swedish local amendment 02 (18.4.2016) in order to harmonize the study protocol for all participating countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31375879

http://www.ncbi.nlm.nih.gov/pubmed/31474354