Clinical trial results:
A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients

Summary

EudraCT number	2013-000684-85
Trial protocol	IS HU BE GB NL ES PT IT FR PL GR
Global end of trial date	26 October 2021

Results information

Result version number	v1 (current)
This version publication date	06 November 2022
First version publication date	06 November 2022

Trial information

Trial identification

Sponsor protocol code	213551

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	16 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare progression-free survival (PFS), as assessed by blinded central review, of participants with advanced/metastatic human epidermal growth factor receptor 2 (HER2)-negative gBRCAmutation breast cancer when treated with niraparib as compared to those treated with physician’s choice single agent chemotherapy standards (eribulin, vinorelbine, gemcitabine or capecitabine).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Iceland: 1
Country: Number of subjects enrolled	Poland: 1
Worldwide total number of subjects	216
EEA total number of subjects	120

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)	201
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Previously treated, human epidermal growth factor receptor 2 HER2 negative, germline Breast Cancer gene (gBRCA) mutation positive breast cancer participants were enrolled. The study was terminated due to futility.

Pre-assignment

Screening details:

Of the 216 participants enrolled, 1 participant was not randomized and 9 participants enrolled based on a local BRCA test results were later determined to be BRCA wild type by central testing. Therefore, only 206 of the 216 participants enrolled were included in the analysis & were considered in centrally confirmed intent-to-treat (ITT) Population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Physician's choice

Arm description:

Physician selection from 4 standard of care metastatic breast cancer chemotherapies (eribulin or vinorelbine or gemcitabine or capecitabine), until progression or unacceptable toxicity develops.

Arm type	Active comparator
Investigational medicinal product name	Eribulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin was administered intravenously as per Physician’s choice.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered orally as per Physician’s choice.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered intravenously as per Physician’s choice

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Vinorelbine was administered intravenously as per Physician’s choice

Arm title	Niraparib

Arm description:

Niraparib 300 milligram (mg) (3x100 mg) capsules once daily until progression or unacceptable toxicity develops.

Arm type	Experimental
Investigational medicinal product name	Niraparib 300mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Niraparib 300 mg (3 x 100 milligrams [mg] niraparib capsules) were administered orally once daily (QD).

Number of subjects in period 1[1]	Physician's choice	Niraparib
Started	71	135
Completed	0	0
Not completed	71	135
Sponsor's decision	1	1
Consent withdrawn by subject	10	2
Physician decision	-	2
Toxicity	1	16
Start of New anti-cancer treatment	1	-
Disease Progression	51	110
Not treated	7	3
Protocol deviation	-	1

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: Of the 216 participants enrolled, 1 participant was not randomized and 9 participants enrolled based on a local BRCA test results were later determined to be BRCA wild type by central testing. Therefore, only 206 of the 216 participants enrolled were included in the analysis, and were considered in centrally confirmed intent-to-treat (ITT) Population.

Baseline characteristics

Reporting groups	
Reporting group title	Physician's choice
Reporting group description:	
Physician selection from 4 standard of care metastatic breast cancer chemotherapies (eribulin or vinorelbine or gemcitabine or capecitabine), until progression or unacceptable toxicity develops.	
Reporting group title	Niraparib
Reporting group description:	
Niraparib 300 milligram (mg) (3x100 mg) capsules once daily until progression or unacceptable toxicity develops.	

Reporting group values	Physician's choice	Niraparib	Total
Number of subjects	71	135	206
Age Categorical			
The centrally-confirmed intent-to-treat population is defined as all randomized participants with a central confirmation of germline BRCA mutation.			
Units: Participants			
18-64 years	67	127	194
65-74 years	3	5	8
>=75 years	1	3	4
Sex: Female, Male			
The centrally-confirmed intent-to-treat population is defined as all randomized participants with a central confirmation of germline BRCA mutation.			
Units: Participants			
Female	68	135	203
Male	3	0	3
Ethnicity (NIH/OMB)			
The centrally-confirmed intent-to-treat population is defined as all randomized participants with a central confirmation of germline BRCA mutation.			
Units: Subjects			
Hispanic or Latino	6	6	12
Not Hispanic or Latino	50	110	160
Unknown or Not Reported	15	19	34
Race/Ethnicity, Customized			
The centrally-confirmed intent-to-treat population is defined as all randomized participants with a central confirmation of germline BRCA mutation.			
Units: Subjects			
Ashkenazi Jewish descendant	6	5	11
White or Caucasian	59	108	167
Black	3	6	9
Asian	0	2	2
Unknown	1	7	8
Missing	2	7	9

End points

End points reporting groups

Reporting group title	Physician's choice

Reporting group description:

Physician selection from 4 standard of care metastatic breast cancer chemotherapies (eribulin or vinorelbine or gemcitabine or capecitabine), until progression or unacceptable toxicity develops.

Reporting group title	Niraparib

Reporting group description:

Niraparib 300 milligram (mg) (3x100 mg) capsules once daily until progression or unacceptable toxicity develops.

Primary: Progression Free Survival (PFS) - Central Review Assessment

End point title	Progression Free Survival (PFS) - Central Review Assessment[1]

End point description:

The primary objective of this study is to compare PFS, as assessed by blinded central review, of participants with advanced/metastatic human epidermal growth factor receptor 2 (HER2)-negative gBRCA mutation breast cancer when treated with niraparib as compared to those treated with physician's choice single agent chemotherapy standards. PFS is defined as the date of randomization to the date of disease progression or death due to any cause, whichever occurs earlier as per Response evaluation criteria in solid tumors (RECIST) version (v)1.1 as determined by central review assessment. Progressive Disease is defined as at least a 20 percent (%) increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including Baseline) and an absolute increase of >= 5 millimeter (mm). Centrally Confirmed intent-to-treat (ITT)Population is defined as all randomized participants with a central confirmation of germline BRCA mutation.

End point type	Primary

End point timeframe:

From the date of randomization to the date of disease progression or death due to any cause, whichever occurs earlier, up to 4 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[2]	135[3]		
Units: Months				
median (confidence interval 95%)	3.1 (1.6 to 7.2)	4.1 (2.9 to 4.5)		

Notes:

[2] - Centrally Confirmed ITT Population

[3] - Centrally Confirmed ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall Survival (OS) was defined as the time from randomization to the date of death of any causes.

End point type	Secondary

End point timeframe:

From treatment randomization to date of death of any cause, up to 4 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[4]	135[5]		
Units: Months				
median (confidence interval 95%)	15.8 (12.1 to 18.4)	14.5 (11.7 to 17.2)		

Notes:

[4] - Centrally Confirmed ITT Population

[5] - Centrally Confirmed ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with central BRCA mutation status

End point title	Number of participants with central BRCA mutation status

End point description:

Blood samples were collected to evaluate central BRCA mutation status of participants. Baseline was defined as the most recent non-missing measurement prior to or on the first administration of study drug. Number of participants with central BRCA mutation status as BRCA1 positive only, BRCA2 positive only, Rearrangement only, BRCA1 and BRCA2 positive, BRCA1 positive and rearrangement, and BRCA2 positive and rearrangement were reported.

End point type	Secondary

End point timeframe:

At Baseline (Cycle 1 Day1) (Cycle duration was 21 days)

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[6]	135[7]		
Units: Participants				
BRCA1 positive only	38	66		
BRCA2 positive only	28	57		
Rearrangement only	3	7		
BRCA1 and BRCA2 positive	1	3		
BRCA1 positive and rearrangement	1	1		
BRCA2 positive and rearrangement	0	1		

Notes:

[6] - Centrally Confirmed ITT Population

[7] - Centrally Confirmed ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) - Investigator assessment

End point title	Progression Free Survival (PFS) - Investigator assessment

End point description:

PFS is defined as the date of randomization to the date of disease progression or death due to any cause, whichever occurs earlier as per RECIST version 1.1 as determined by Investigator assessment.Progressive Disease is defined as at least a 20 % increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including Baseline) and an absolute increase of >= 5 mm.

End point type	Secondary

End point timeframe:

Assessed up to 4 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[8]	135[9]		
Units: Months				
median (confidence interval 95%)	3.1 (2.7 to 5.1)	5.0 (4.2 to 5.5)		

Notes:

[8] - Centrally confirmed ITT Population

[9] - Centrally confirmed ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Serious Adverse Events (SAE) and Non-serious Adverse Events (Non-SAE)

End point title	Number of Participants With Serious Adverse Events (SAE) and Non-serious Adverse Events (Non-SAE)

End point description:

An AE is any untoward medical occurrence that occurs in a participant or clinical investigation participant administered a pharmaceutical product,and which does not necessarily have to have a causal relationship with this treatment. SAE is defined as any untoward medical occurrence or effect in participant, whether or not considered related to the protocol treatment,at any dose that results in death,is life-threatening,requires inpatient hospitalization or prolongation of existing participant hospitalization,results in persistent or significant disability or incapacity is a congenital anomaly or birth defect,is an medically important event or reaction as per medical and scientific judgment. AEs which were not serious adverse events were considered as non serious adverse events. Safety Population comprised of all participants who started their allocated treatment (received at least one dose of allocated drug)Only those participants with data available at specified time were analyzed.

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[10]	134[11]		
Units: Participants				
SAE	4	33		
Non-SAE	62	134		

Notes:

[10] - Safety Population

[11] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Time to treatment failure was defined from the date of randomization to progression or discontinuation of treatment for any reason, including but not restricted to disease progression, treatment toxicity and death.

End point type	Secondary

End point timeframe:

Date of randomization to discontinuation of treatment for any reason, up to 4 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[12]	135[13]		
Units: Months				
median (confidence interval 95%)	2.6 (1.6 to 3.2)	4.3 (4.0 to 5.5)		

Notes:

[12] - Centrally Confimed ITT Population

[13] - Centrally Confimed ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as the percentage of the participants who achieved a complete response (CR) or partial response (PR) to treatment evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Complete Response (CR)=disappearance of all target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm. Partial Response (PR)= at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the Baseline sum of diameters. Only those participants with confirmed response were analyzed. Percentage values are rounded off up to 1 decimal.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[14]	126[15]		
Units: Percentage of participants				
number (confidence interval 95%)	12.5 (5.6 to 23.2)	21.4 (14.6 to 29.6)		

Notes:

[14] - Centrally Confirmed ITT population

[15] - Centrally Confirmed ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response was defined as the time from first documentation of response (confirmed CR or PR) until the time of first documentation of disease progression by RECIST v1.1 or death by any cause. Only those participants with confirmed response were analyzed.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[16]	126[17]		
Units: Months				
median (inter-quartile range (Q1-Q3))	5.65 (5.65 to 14.78)	4.14 (2.79 to 6.90)		

Notes:

[16] - Centrally Confirmed ITT population

[17] - Centrally Confirmed ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with serious adverse events related to new malignancy

End point title	Number of Participants with serious adverse events related to new malignancy

End point description:

The number of participants with serious adverse events related to new malignancy were reported. Only those participants with data available at specified time were analyzed.

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[18]	134[19]		
Units: Participants	0	2		

Notes:

[18] - Safety Population

[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with subsequent anticancer therapies

End point title	Number of participants with subsequent anticancer therapies

End point description:

The number of participants with subsequent anticancer therapies was evaluated. Data has been reported as per following categories: any new anitumoral therapy, any chemotherapy, any radiotherapy, any surgery, any hormonal therapy, any targeted agents, and any other treatment. Participants may have received more than one subsequent therapies. Only those participants with data available at specified time were analyzed.

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	Physician's choice	Niraparib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[20]	134[21]		
Units: Participants				
Any new antitumoral therapy	55	108		
Any chemotherapy	48	96		
Any radiotherapy	22	48		
Any surgery	5	13		
Any hormonal therapy	13	27		
Any targeted agent therapy	19	22		
Any other treatment	8	17		

Notes:

[20] - Safety Population

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality, Serious adverse events (SAEs) and non-serious AEs (non-SAEs) were collected up to 7 years.

Adverse event reporting additional description:

Safety Population was used to assess SAEs and non-SAEs which comprised of all participants who started their allocated treatment (received at least one dose of allocated drug). Seven participants from Centrally Confirmed (ITT) Population (N=206) did not receive study treatment, hence was not included in Safety Population (N=199).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Physician's choice

Reporting group description:

Physician selection from 4 standard of care metastatic breast cancer chemotherapies (eribulin or vinorelbine or gemcitabine or capecitabine), until progression or unacceptable toxicity develops.

Reporting group title	Niraparib

Reporting group description:

Niraparib 300 milligram (mg) (3x100 mg) capsules once daily until progression or unacceptable toxicity develops.

Serious adverse events	Physician's choice	Niraparib	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 65 (6.15%)	33 / 134 (24.63%)	
number of deaths (all causes)	39	79	
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			

subjects affected / exposed	1 / 65 (1.54%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 65 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 65 (0.00%)	3 / 134 (2.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Language disorder			
subjects affected / exposed	1 / 65 (1.54%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 65 (0.00%)	9 / 134 (6.72%)	
occurrences causally related to treatment / all	0 / 0	17 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 65 (0.00%)	10 / 134 (7.46%)	
occurrences causally related to treatment / all	0 / 0	29 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 65 (0.00%)	5 / 134 (3.73%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 65 (1.54%)	3 / 134 (2.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 65 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 65 (1.54%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	1 / 65 (1.54%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 65 (0.00%)	4 / 134 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 65 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Physician's choice	Niraparib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 65 (95.38%)	134 / 134 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 65 (1.54%)	17 / 134 (12.69%)	
occurrences (all)	1	38	
Hot flush			
subjects affected / exposed	0 / 65 (0.00%)	7 / 134 (5.22%)	
occurrences (all)	0	8	
Lymphoedema			
subjects affected / exposed	4 / 65 (6.15%)	4 / 134 (2.99%)	
occurrences (all)	11	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 65 (44.62%)	66 / 134 (49.25%)	
occurrences (all)	49	121	
Asthenia			
subjects affected / exposed	9 / 65 (13.85%)	24 / 134 (17.91%)	
occurrences (all)	11	61	
Pyrexia			
subjects affected / exposed	4 / 65 (6.15%)	16 / 134 (11.94%)	
occurrences (all)	8	25	

Oedema peripheral			
subjects affected / exposed	6 / 65 (9.23%)	9 / 134 (6.72%)	
occurrences (all)	9	10	
Influenza like illness			
subjects affected / exposed	2 / 65 (3.08%)	8 / 134 (5.97%)	
occurrences (all)	5	9	
Ill-defined disorder			
subjects affected / exposed	4 / 65 (6.15%)	6 / 134 (4.48%)	
occurrences (all)	11	8	
Pain			
subjects affected / exposed	1 / 65 (1.54%)	7 / 134 (5.22%)	
occurrences (all)	1	7	
Mucosal inflammation			
subjects affected / exposed	4 / 65 (6.15%)	2 / 134 (1.49%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 65 (12.31%)	25 / 134 (18.66%)	
occurrences (all)	12	35	
Cough			
subjects affected / exposed	5 / 65 (7.69%)	15 / 134 (11.19%)	
occurrences (all)	5	17	
Epistaxis			
subjects affected / exposed	2 / 65 (3.08%)	10 / 134 (7.46%)	
occurrences (all)	2	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 65 (6.15%)	25 / 134 (18.66%)	
occurrences (all)	5	32	
Anxiety			
subjects affected / exposed	8 / 65 (12.31%)	18 / 134 (13.43%)	
occurrences (all)	9	24	
Depression			
subjects affected / exposed	0 / 65 (0.00%)	7 / 134 (5.22%)	
occurrences (all)	0	7	
Investigations			

Weight decreased			
subjects affected / exposed	10 / 65 (15.38%)	53 / 134 (39.55%)	
occurrences (all)	12	97	
Platelet count decreased			
subjects affected / exposed	3 / 65 (4.62%)	43 / 134 (32.09%)	
occurrences (all)	5	90	
White blood cell count decreased			
subjects affected / exposed	5 / 65 (7.69%)	32 / 134 (23.88%)	
occurrences (all)	12	83	
Neutrophil count decreased			
subjects affected / exposed	10 / 65 (15.38%)	26 / 134 (19.40%)	
occurrences (all)	15	66	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 65 (10.77%)	18 / 134 (13.43%)	
occurrences (all)	10	26	
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 65 (10.77%)	17 / 134 (12.69%)	
occurrences (all)	16	28	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 65 (7.69%)	15 / 134 (11.19%)	
occurrences (all)	8	25	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 65 (7.69%)	13 / 134 (9.70%)	
occurrences (all)	5	17	
Lymphocyte count decreased			
subjects affected / exposed	4 / 65 (6.15%)	9 / 134 (6.72%)	
occurrences (all)	6	31	
Weight increased			
subjects affected / exposed	7 / 65 (10.77%)	6 / 134 (4.48%)	
occurrences (all)	7	8	
Blood creatinine increased			
subjects affected / exposed	4 / 65 (6.15%)	6 / 134 (4.48%)	
occurrences (all)	5	7	
Cardiac disorders			

Tachycardia			
subjects affected / exposed	2 / 65 (3.08%)	11 / 134 (8.21%)	
occurrences (all)	3	11	
Sinus tachycardia			
subjects affected / exposed	2 / 65 (3.08%)	8 / 134 (5.97%)	
occurrences (all)	2	9	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 65 (15.38%)	44 / 134 (32.84%)	
occurrences (all)	11	75	
Dizziness			
subjects affected / exposed	6 / 65 (9.23%)	26 / 134 (19.40%)	
occurrences (all)	9	35	
Paraesthesia			
subjects affected / exposed	6 / 65 (9.23%)	5 / 134 (3.73%)	
occurrences (all)	6	5	
Lethargy			
subjects affected / exposed	4 / 65 (6.15%)	5 / 134 (3.73%)	
occurrences (all)	7	5	
Hypoaesthesia			
subjects affected / exposed	5 / 65 (7.69%)	4 / 134 (2.99%)	
occurrences (all)	5	7	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 65 (6.15%)	48 / 134 (35.82%)	
occurrences (all)	9	155	
Neutropenia			
subjects affected / exposed	19 / 65 (29.23%)	27 / 134 (20.15%)	
occurrences (all)	43	64	
Leukopenia			
subjects affected / exposed	9 / 65 (13.85%)	11 / 134 (8.21%)	
occurrences (all)	40	35	
Anaemia			
subjects affected / exposed	23 / 65 (35.38%)	91 / 134 (67.91%)	
occurrences (all)	63	396	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	24 / 65 (36.92%)	82 / 134 (61.19%)	
occurrences (all)	36	141	
Constipation			
subjects affected / exposed	11 / 65 (16.92%)	48 / 134 (35.82%)	
occurrences (all)	13	74	
Vomiting			
subjects affected / exposed	11 / 65 (16.92%)	51 / 134 (38.06%)	
occurrences (all)	16	77	
Diarrhoea			
subjects affected / exposed	22 / 65 (33.85%)	19 / 134 (14.18%)	
occurrences (all)	30	24	
Abdominal pain			
subjects affected / exposed	10 / 65 (15.38%)	14 / 134 (10.45%)	
occurrences (all)	12	21	
Abdominal pain upper			
subjects affected / exposed	3 / 65 (4.62%)	17 / 134 (12.69%)	
occurrences (all)	5	24	
Stomatitis			
subjects affected / exposed	6 / 65 (9.23%)	14 / 134 (10.45%)	
occurrences (all)	7	20	
Dry mouth			
subjects affected / exposed	5 / 65 (7.69%)	6 / 134 (4.48%)	
occurrences (all)	5	7	
Dyspepsia			
subjects affected / exposed	1 / 65 (1.54%)	9 / 134 (6.72%)	
occurrences (all)	1	10	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	12 / 65 (18.46%)	0 / 134 (0.00%)	
occurrences (all)	31	0	
Alopecia			
subjects affected / exposed	7 / 65 (10.77%)	3 / 134 (2.24%)	
occurrences (all)	8	3	
Pruritus			

subjects affected / exposed	1 / 65 (1.54%)	9 / 134 (6.72%)	
occurrences (all)	1	9	
Photosensitivity reaction			
subjects affected / exposed	0 / 65 (0.00%)	7 / 134 (5.22%)	
occurrences (all)	0	8	
Erythema			
subjects affected / exposed	5 / 65 (7.69%)	2 / 134 (1.49%)	
occurrences (all)	5	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 65 (10.77%)	29 / 134 (21.64%)	
occurrences (all)	9	42	
Pain in extremity			
subjects affected / exposed	4 / 65 (6.15%)	19 / 134 (14.18%)	
occurrences (all)	6	24	
Arthralgia			
subjects affected / exposed	9 / 65 (13.85%)	16 / 134 (11.94%)	
occurrences (all)	10	34	
Bone pain			
subjects affected / exposed	5 / 65 (7.69%)	9 / 134 (6.72%)	
occurrences (all)	7	11	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 65 (6.15%)	7 / 134 (5.22%)	
occurrences (all)	4	8	
Myalgia			
subjects affected / exposed	5 / 65 (7.69%)	5 / 134 (3.73%)	
occurrences (all)	5	5	
Neck pain			
subjects affected / exposed	3 / 65 (4.62%)	10 / 134 (7.46%)	
occurrences (all)	3	12	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 65 (6.15%)	9 / 134 (6.72%)	
occurrences (all)	4	9	
Urinary tract infection			

subjects affected / exposed	3 / 65 (4.62%)	7 / 134 (5.22%)	
occurrences (all)	3	9	
Nasopharyngitis			
subjects affected / exposed	3 / 65 (4.62%)	8 / 134 (5.97%)	
occurrences (all)	3	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 65 (10.77%)	41 / 134 (30.60%)	
occurrences (all)	10	56	
Hypokalaemia			
subjects affected / exposed	0 / 65 (0.00%)	7 / 134 (5.22%)	
occurrences (all)	0	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2013	The inclusion criteria were revised to include taxane and anthracycline as previous (neo-)adjuvant cytotoxic chemotherapy.
24 April 2014	Central testing of gBRCAmut was limited to Myriad only, & all participants were required to have blood samples taken for gBRCAmut testing to determine eligibility. Inclusion criteria were revised to clarify inclusion of participants who were previously treated with platinum; & direct bilirubin was no longer an inclusion criterion. Maximum period of 90 days was permitted from registration to randomization. Further, dose escalation was not allowed. "Treatment related" nonhematologic AEs was added as criteria for treatment interruption. Following dose interruption, time to restart of treatment was extended to 28 days. Thrombocytopenia was specified as one of the key parameters for monitoring hematologic toxicity. For the management of hematologic toxicities, guidelines based on platelet, neutrophil and hemoglobin counts were provided, administration of granulocyte colony-stimulating factor (GCSF) was allowed, and secondary prophylaxis was only allowed for participants in the physician's choice treatment arm. Guidelines for hematology testing during treatment cycles were provided, and time points for prothrombin time and serum chemistry testing were provided. For the measurement of tumors, chest X-ray was no longer used as a method for measuring tumor lesions. Further, cytology and positron emission tomography were not necessary methods for assessment of residual lesions and, therefore, were removed in Appendix H, the list of drugs known to inhibit or induce cytochrome P450 1A2 (CYP1A2) enzyme was updated.
04 May 2015	The study population was revised to allow participants with a deleterious or suspected deleterious germline BRCA1 or BRCA2 mutation to be enrolled into the study. Any participant that did not have a gBRCAmut per central laboratory results, was allowed to continue based on his/her physician discretion and preference. The ITT population was defined as all randomized participants with a central confirmation of gBRCAmut. Few changes were made to the inclusion criteria as follows: Palliative radiotherapy within 3 weeks prior to the start of study was added. The inclusion criterion related to the definition of participants with platinum resistance was revised. Exclusion of participant with platinum resistance was made. For participants with a prior history of ovarian cancer who had peritoneal disease and elevated serum CA-125, a biopsy of the peritoneal disease was required to be enrolled. Exclusion of participants with contraindication to all of the comparator treatments or who received a platelet transfusion within 4 weeks of the first dose of study treatment was added. Niraparib dose modification was revised to be interrupted and/or reduced at any time as considered intolerable by the participant. Missed doses of niraparib were not allowed to be taken at a later date. Information for prophylactic platelet transfusion per platelet count & anticoagulation or antiplatelet concomitant treatment was provided. The primary analysis population for efficacy was modified to constitute all randomized participant who have a gBRCAmut per central laboratory testing. Only 1 interim analysis for futility was revised and planned after 93 (40%) PFS events instead of 2 analyses (35 [15%] and 96 [40%] events).

04 November 2015	Two new secondary objectives were added (the first was for the relationship between cytogenetic abnormalities and safety parameters; the second was for descriptive summary statistics of post-treatment data). Inclusion criteria related to persistent Grade >=3 hematologic toxicity or fatigue from prior cancer therapy were provided. In addition, cytogenetic and mutational analysis for myeloid-related genes analysis at Screening and at the end of treatment was required. Exclusion criterion related to history of myelodysplastic syndrome (MDS) was provided. If treatment was resumed for participants with platelets or red blood cells transfusion or hematopoietic growth factor support, dose reduction was required. Involvement of a hematologist was required for participants who had more than 2 transfusions in the absence of non–treatment-related causes or if the treatment-related hematologic toxicities have not recovered to allow retreatment with niraparib after 4 weeks. In addition, if a diagnosis of MDS/ acute myeloid leukemia (AML) was confirmed by a hematologist, permanent discontinuation of niraparib treatment was required. In the physician's choice treatment arm, assessment of the tumors was revised. Assessment during follow-up visits was updated with collection of information related to new malignancy. In addition, mutational profile testing (mutations of selected myeloid-associated genes) for any highly clinically suspected MDS/AML cases during survival follow-up visits was added to the list of measurement. Evaluation of safety was updated for collection of SAEs/deaths (restricted to at least "likely related" SAEs and "related" death events) after 30 days of the last dose or the initiation of new anticancer therapy (whichever was earlier). Definition of SAEs was updated, and inclusion of any new malignancy at any time for the duration of the study was considered SAEs.
13 January 2017	The relationship between cytogenetic abnormalities and safety parameters was no longer one of the secondary objectives. The inclusion criterion related to definition of hormone receptor–positive participants who had hormone-resistant disease was provided; & serum creatinine was revised to >=50 mL/min. Mutational profile testing (for selected myeloid-related genes) was restricted for participants who developed MDS or AML during the study or the follow-up period. Detailed plans for niraparib-related dose modification based on hematologic and nonhematologic toxicity parameters were provided. In the physician's choice treatment arm, treatment interruption period was extended from 21 days to 28 days. Evaluation of response was revised, and restriction to participants with measurable disease at baseline was removed. In the statistical design, the original final progression-free survival (PFS) analysis of 232 PFS events was revised to occur at 137 PFS events or end of recruitment, whichever occurred later. The power was reduced to 80.0% (with a 1-sided alpha of 0.025) to detect a hazard ratio of 0.6 (equivalent to 3 to 5 months in median PFS [it was 3 to 6 months in the previous version]). A gatekeeping strategy was planned to test PFS and OS. The primary analysis of PFS & overall survival (OS) was determined to use stratified log-rank test, stratifying by the randomization strata. A non-stratified log-rank test was indicated to assess the robustness of the primary results. The PFS events for futility interim analysis was corrected to 68% (from 40%). A gamma family beta spending function with a nonbinding gamma (γ=-5) stopping boundary was indicated for the futility analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

IDMC interim analysis concluded that concerns with the quantity and quality of data in the control arm precluded meaningful comparative analyses and generation of a clinically useful endpoint, therefore enrollment was ended prematurely.

Notes: