Clinical trial results:
ARIEL4 (Assessment of Rucaparib In Ovarian CancEr TriaL): A Phase 3 Multicenter, Randomized Study of Rucaparib versus Chemotherapy in Patients with Relapsed, BRCA-Mutant, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Summary

EudraCT number	2016-000816-14
Trial protocol	GB HU CZ ES PL IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	CO-338-043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02855944
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 106289

Notes:

Sponsors

Sponsor organisation name	Clovis Oncology, Inc.
Sponsor organisation address	5500 Flatiron Parkway, Suite 100, Boulder, CO, United States, 80301
Public contact	Dr Lindsey Rolfe, Clovis Oncology, Inc., +44 12233 645500, lrolfe@clovisoncology.com
Scientific contact	Dr Lindsey Rolfe, Clovis Oncology, Inc., +44 12233 645500, lrolfe@clovisoncology.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	Interim
Date of interim/final analysis	30 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine investigator-assessed progression-free survival (invPFS) by RECIST Version 1.1 for rucaparib versus chemotherapy.

Protection of trial subjects:

The following safety assessments were performed: adverse events, physical examinations, clinical laboratory evaluations (hematology, serum chemistry), vital signs, 12-lead ECGs, ECOG performance status. Patients were assessed for disease status per RECIST v1.1 every 8 calendar weeks following initiation of study treatment on Day 1 of Cycle 1. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, were discontinued from treatment and entered follow-up.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 43
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Russian Federation: 113
Country: Number of subjects enrolled	Ukraine: 41
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Czechia: 25
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 44
Worldwide total number of subjects	349
EEA total number of subjects	102

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)	277
From 65 to 84 years	71
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 349 patients from 64 sites across 12 countries were enrolled in the initial Treatment Part of the study and randomized to receive rucaparib or chemotherapy. Patients randomized to chemotherapy had the option to cross over to receive rucaparib in the Crossover Part of the study upon progression of disease.

Pre-assignment

Screening details:

The study enrolled patients with a deleterious BRCA1/2 mutation and who had received at least 2 prior chemotherapy regimens, with at least 1 regimen including a platinum. Patients with confirmation of all other eligibility criteria in the screening phase were randomized 2:1 to receive rucaparib or chemotherapy.

Period 1

Period 1 title	Period 1 - Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rucaparib

Arm description:

Patients randomized to the rucaparib arm received oral rucaparib 600 mg twice a day (BID) in continuous 28- day cycles.

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

Dosage and administration details:

Patients randomized to the rucaparib arm received oral rucaparib 600 mg BID in continuous 28-day cycles. Patients were to take rucaparib with or without food.

Arm title	Chemotherapy

Arm description:

Patients randomized to the chemotherapy arm received either weekly intravenous (IV) paclitaxel or IV platinum-based chemotherapy per investigator choice and per standard of care. Patients with platinum-resistant or partially platinum-sensitive disease received weekly paclitaxel. The starting dose of weekly paclitaxel was 60 to 80 mg/m2 administered via IV infusion (ie, on Days 1, 8, and 15) in each 28-day cycle (with a week break from dosing on Day 22 in each cycle). The dosage and administration of single-agent cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion followed institutional guidelines for each agent. Upon progression of disease, patients had the option to cross over to rucaparib and receive oral rucaparib 600 mg BID in continuous 28-day cycles.

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

Dosage and administration details:

The starting dose of weekly paclitaxel was 60 to 80 mg/m2 administered via IV infusion (ie, on Days 1,

8, and 15) in each 28-day cycle (with a week break from dosing on Day 22 in each cycle).

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosage, dosing schedule, and administration of single-agent cisplatin or carboplatin, or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion followed institutional guidelines for each agent. No more than 8 cycles of platinum monotherapy or doublet therapy were to be administered in this study. Patients received the same chemotherapy in 21-day or 28-day cycles, as appropriate, throughout the study.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosage, dosing schedule, and administration of single-agent cisplatin or carboplatin, or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion followed institutional guidelines for each agent. No more than 8 cycles of platinum monotherapy or doublet therapy were to be administered in this study. Patients received the same chemotherapy in 21-day or 28-day cycles, as appropriate, throughout the study.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

The dosage, dosing schedule, and administration of single-agent cisplatin or carboplatin, or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion followed institutional guidelines for each agent. No more than 8 cycles of platinum monotherapy or doublet therapy were to be administered in this study. Patients received the same chemotherapy in 21-day or 28-day cycles, as appropriate, throughout the study.

Number of subjects in period 1	Rucaparib	Chemotherapy
Started	233	116
Completed	188	108
Not completed	45	8
Ongoing	44	5
Discontinued prior to starting study drug	1	3

Period 2

Period 2 title	Period 2 - Crossover to Rucaparib
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Rucaparib

Arm description:

Upon progression of disease, patients initially randomized to the chemotherapy arm had the option to cross over to rucaparib and receive oral rucaparib 600 mg BID in continuous 28-day cycles.

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

Dosage and administration details:

Patients who crossed over to rucaparib received oral rucaparib 600 mg BID in continuous 28-day cycles. Patients were to take rucaparib with or without food.

Number of subjects in period 2[1]	Rucaparib
Started	74
Completed	47
Not completed	27
Ongoing	27

Notes:

[1] - 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: Upon progression of disease in Period 1, patients had the option to cross over to rucaparib.

Baseline characteristics

Reporting groups	
Reporting group title	Rucaparib
Reporting group description:	
Patients randomized to the rucaparib arm received oral rucaparib 600 mg twice a day (BID) in continuous 28- day cycles.	
Reporting group title	Chemotherapy
Reporting group description:	
Patients randomized to the chemotherapy arm received either weekly intravenous (IV) paclitaxel or IV platinum-based chemotherapy per investigator choice and per standard of care. Patients with platinum-resistant or partially platinum-sensitive disease received weekly paclitaxel. The starting dose of weekly paclitaxel was 60 to 80 mg/m2 administered via IV infusion (ie, on Days 1, 8, and 15) in each 28-day cycle (with a week break from dosing on Day 22 in each cycle). The dosage and administration of single-agent cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion followed institutional guidelines for each agent. Upon progression of disease, patients had the option to cross over to rucaparib and receive oral rucaparib 600 mg BID in continuous 28-day cycles.	

Reporting group values	Rucaparib	Chemotherapy	Total
Number of subjects	233	116	349
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	58.0	58.5	
full range (min-max)	38 to 81	38 to 85	-
Gender categorical Units: Subjects			
Female	233	116	349
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	2	6
White	219	113	332
More than one race	1	0	1
Unknown or Not Reported	5	1	6
ECOG at Baseline			
Measure Description: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. ECOG 0 = Fully active, able to carry on all pre-disease performance without restriction. ECOG 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or office work).			
Units: Subjects			
ECOG 0	125	72	197
ECOG 1	108	44	152

Number of Prior Chemotherapy Regimens Units: Subjects			
=2	134	68	202
=3	58	28	86
=4	23	11	34
=5	7	5	12
>5	11	4	15
Number of Prior Platinum Regimens Units: Subjects			
=1	12	6	18
=2	156	74	230
=3	48	28	76
=4	11	7	18
=5	2	1	3
>5	4	0	4
Randomization Stratification: Platinum Status			
Platinum resistant: patients who progressed ≥ 1 to < 6 months after the last dose of platinum-based chemotherapy; Partially platinum sensitive: patients who progressed ≥ 6 to < 12 months after last dose of platinum-based chemotherapy; Platinum sensitive: patients who progressed ≥ 12 months after last dose of platinum-based chemotherapy			
Units: Subjects			
Platinum resistant	120	59	179
Partially platinum sensitive	65	31	96
Platinum sensitive	48	26	74
Combined Local and Central Lab BRCA Mutation Results			
BRCA1: patients with a deleterious breast cancer susceptibility gene 1 (BRCA1) mutation in their tumor; BRCA2: patients with a deleterious breast cancer susceptibility gene 2 (BRCA2) mutation in their tumor; Non-BRCA: patients without a BRCA mutation in their tumor			
Units: Subjects			
BRCA1	181	79	260
BRCA2	52	36	88
Non-BRCA	0	1	1
Mutation Type Units: Subjects			
Germline	198	95	293
Somatic	35	19	54
Not Available	0	2	2
Patients with a BRCA Reversion Mutation Units: Subjects			
With reversion	13	10	23
Without reversion	220	106	326

End points

End points reporting groups

Reporting group title	Rucaparib

Reporting group description:

Patients randomized to the rucaparib arm received oral rucaparib 600 mg twice a day (BID) in continuous 28- day cycles.

Reporting group title	Chemotherapy

Reporting group description:

Patients randomized to the chemotherapy arm received either weekly intravenous (IV) paclitaxel or IV platinum-based chemotherapy per investigator choice and per standard of care. Patients with platinum-resistant or partially platinum-sensitive disease received weekly paclitaxel. The starting dose of weekly paclitaxel was 60 to 80 mg/m2 administered via IV infusion (ie, on Days 1, 8, and 15) in each 28-day cycle (with a week break from dosing on Day 22 in each cycle). The dosage and administration of single-agent cisplatin or carboplatin or doublet carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine IV infusion followed institutional guidelines for each agent. Upon progression of disease, patients had the option to cross over to rucaparib and receive oral rucaparib 600 mg BID in continuous 28-day cycles.

Reporting group title	Rucaparib

Reporting group description:

Upon progression of disease, patients initially randomized to the chemotherapy arm had the option to cross over to rucaparib and receive oral rucaparib 600 mg BID in continuous 28-day cycles.

Primary: Investigator Assessed Progression-Free Survival (invPFS) by RECIST Version 1.1 for Rucaparib Versus Chemotherapy (Efficacy Population)

End point title	Investigator Assessed Progression-Free Survival (invPFS) by RECIST Version 1.1 for Rucaparib Versus Chemotherapy (Efficacy Population)

End point description:

The primary efficacy endpoint is invPFS for the Treatment Part of the study. The time to invPFS is calculated in months as the time from randomization to disease progression +1 day, as determined by RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) criteria or death due to any cause, whichever occurs first. Progression is defined using RECIST v1.1, as at least a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. Efficacy Population - All randomized patients in the treatment part of study with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation.

End point type	Primary

End point timeframe:

Assessments every 8 weeks from Cycle 1 Day 1 (C1D1) until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	105		
Units: Months				
median (confidence interval 95%)	7.4 (7.3 to 9.1)	5.7 (5.5 to 7.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib v Chemotherapy
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.639
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.489
upper limit	0.835

Primary: Investigator Assessed Progression-Free Survival (invPFS) by RECIST Version 1.1 for Rucaparib Versus Chemotherapy (ITT Population)

End point title	Investigator Assessed Progression-Free Survival (invPFS) by RECIST Version 1.1 for Rucaparib Versus Chemotherapy (ITT Population)

End point description:

The primary efficacy endpoint is invPFS for the Treatment Part of the study. The time to invPFS is calculated in months as the time from randomization to disease progression +1 day, as determined by RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) criteria or death due to any cause, whichever occurs first. Progression is defined using RECIST v1.1, as at least a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. Intent-to-treat (ITT) Population - All randomized patients in the treatment part of study.

End point type	Primary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	116		
Units: Months				
median (confidence interval 95%)	7.4 (6.7 to 7.9)	5.7 (5.5 to 6.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib v Chemotherapy

Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.665
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.516
upper limit	0.858

Secondary: Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 (Efficacy Population)

End point title	Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 (Efficacy Population)

End point description:

A secondary endpoint is the ORR for the Treatment Part of the study. ORR is defined as the percentage of patients with a confirmed CR (complete response) or PR (partial response) by RECIST v1.1. The confirmed response is defined as a CR or PR on subsequent tumor assessment at least 28 days after first response documentation. CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Efficacy population with measurable disease at baseline. Efficacy population defined as all randomized patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation.

End point type	Secondary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	96		
Units: Percentage of patients				
number (confidence interval 95%)	40.3 (33.6 to 47.2)	32.3 (23.1 to 42.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The stratified Cochran-Mantzel-Haenszel (CMH) test was used to test the difference in proportions between treatment adjusting for the randomization strata for the PFI after most recent platinum-containing therapy (ie, platinum resistant, partially platinum-sensitive, or platinum sensitive).

Comparison groups	Rucaparib v Chemotherapy

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1287
Method	Cochran-Mantel-Haenszel

Secondary: Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 (ITT Population)

End point title	Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 (ITT Population)

End point description:

A secondary endpoint is the ORR for the Treatment Part of the study. ORR is defined as the percentage of patients with a confirmed CR (complete response) or PR (partial response) by RECIST v1.1. The confirmed response is defined as a CR or PR on subsequent tumor assessment at least 28 days after first response documentation. CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Intent-to-treat (ITT) population with measurable disease at baseline. ITT population defined as all randomized patients.

End point type	Secondary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	106		
Units: Percentage of patients				
number (confidence interval 95%)	37.9 (31.6 to 44.7)	30.2 (21.7 to 39.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The stratified CMH test was used to test the difference in proportions between treatment adjusting for the randomization strata for the progression-free interval after most recent platinum-containing therapy (ie, platinum resistant, partially platinum-sensitive, or platinum sensitive).

Comparison groups	Rucaparib v Chemotherapy
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125
Method	Cochran-Mantel-Haenszel

Secondary: Investigator Assessed Duration of Response (DOR) by RECIST v1.1 (Efficacy Population)

End point title	Investigator Assessed Duration of Response (DOR) by RECIST v1.1 (Efficacy Population)

End point description:

A secondary endpoint is the DOR for the Treatment Part of the study. The DOR as assessed by investigator is analyzed in the subgroup of patients who had a confirmed response by RECIST v1.1. DOR for any confirmed RECIST CR or PR will be measured from the date of the first response until the first date that progressive disease (PD) is documented. DOR is calculated in months as the time from the first date of the scan showing a response to the first scan with disease progression +1 day. Any patients with an ongoing response are censored at the date of the last post-baseline scan. Only tumor scans up to and within 6 weeks of start of any subsequent anti-cancer treatment are included. Progressive disease (PD) is defined using RECIST v1.1, as at least a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a nontarget lesion, or the appearance of new lesions. Efficacy population with measurable disease at baseline and a confirmed response.

End point type	Secondary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	31		
Units: Months				
median (confidence interval 95%)	9.4 (7.5 to 11.1)	7.2 (4.0 to 11.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib v Chemotherapy
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0401
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.589
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.356
upper limit	0.976

Secondary: Investigator Assessed Duration of Response (DOR) by RECIST v1.1 (ITT Population)

End point title	Investigator Assessed Duration of Response (DOR) by RECIST v1.1 (ITT Population)

End point description:

A secondary endpoint is the DOR for the Treatment Part of the study. The DOR as assessed by investigator is analyzed in the subgroup of patients who had a confirmed response by RECIST v1.1. DOR for any confirmed RECIST CR or PR will be measured from the date of the first response until the first date that progressive disease (PD) is documented. DOR is calculated in months as the time from the first date of the scan showing a response to the first scan with disease progression +1 day. Any patients with an ongoing response are censored at the date of the last post-baseline scan. Only tumor scans up to and within 6 weeks of start of any subsequent anti-cancer treatment are included. Progressive disease (PD) is defined using RECIST v1.1, as at least a 20% increase in the sum of the longest diameter of target lesions, or measurable increase in a nontarget lesion, or the appearance of new lesions. Intent-to-treat (ITT) population with measurable disease at baseline and confirmed response.

End point type	Secondary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	32		
Units: Months				
median (confidence interval 95%)	9.4 (7.5 to 11.1)	7.2 (3.9 to 9.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib v Chemotherapy
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.564
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.343
upper limit	0.927

Secondary: Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 and/or CA-125 Response (Efficacy Population)

End point title	Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 and/or CA-125 Response (Efficacy Population)

End point description:

A secondary endpoint is ORR for the Treatment Part of the study defined as the percentage of patients with best response of CR or PR using RECIST v1.1 or response per Gynecologic Cancer InterGroup Cancer Antigen 125 (GCIG CA-125) criteria. CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Response to CA-125 has occurred if there is at least a 50% decrease from baseline: 1. in a sample collected after initiation of study treatment AND 2. that is confirmed in a subsequent sample collected ≥21 days after the prior sample. The absolute value of this confirmatory sample must be ≤110% of the prior sample. The date when the first sample with a 50% decrease from baseline is observed is the date of the CA-125 response.

End point type	Secondary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	101		
Units: Percentage of patients				
number (confidence interval 95%)	50.7 (43.8 to 57.5)	43.6 (33.7 to 53.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 and/or CA-125 Response (ITT Population)

End point title	Investigator Assessed Overall Response Rate (ORR) by RECIST v1.1 and/or CA-125 Response (ITT Population)

End point description:

A secondary endpoint is ORR for the Treatment Part of the study defined as the percentage of patients with best response of CR or PR using RECIST v1.1 or response per Gynecologic Cancer InterGroup Cancer Antigen 125 (GCIG CA-125) criteria. CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Response to CA-125 has occurred if there is at least a 50% decrease from baseline: 1. in a sample collected after initiation of study treatment AND 2. that is confirmed in a subsequent sample collected ≥21 days after the prior sample. The absolute value of this confirmatory sample must be ≤110% of the prior sample. The date when the first sample with a 50% decrease from baseline is observed is the date of the CA-125 response.

End point type	Secondary

End point timeframe:

Assessments every 8 weeks from C1D1 until disease progression, death, or initiation of subsequent treatment. After 18 months on study, assessments every 16 weeks. Total follow-up was up to approximately 3.5 years.

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	111		
Units: Percentage of patients				
number (confidence interval 95%)	47.8 (41.2 to 54.5)	40.5 (31.3 to 50.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Least Squares Mean Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status Score for the First 6 Cycles (Efficacy Population)

End point title	Least Squares Mean Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status Score for the First 6 Cycles (Efficacy Population)

End point description:

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer patients. The first 28 questions use a 4-point scale (1=not at all to 4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, and pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor to 7=excellent) to evaluate overall health and quality of life. Global scores are converted to a score of 0 to 100, with a higher score indicating improved health status. Mean changes from baseline global score over the first 6 cycles in the Treatment Part of the study were analyzed. Efficacy population - All randomized patients with a deleterious BRCA mutation, excluding those identified to have a BRCA reversion mutation, and with a baseline value and at least one post-baseline value for the EORTC QLQ-C30 Global Health Status score during the first 6 cycles.

End point type	Secondary

End point timeframe:

Baseline to the end of Cycle 6, or up to approximately 6 months

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	91		
Units: Score on a scale				
least squares mean (standard error)	0.5 (± 0.55)	0.3 (± 0.86)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Chemotherapy v Rucaparib
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8528
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2.2

Secondary: Least Squares Mean Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status Score for the First 6 Cycles (ITT Population)

End point title	Least Squares Mean Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status Score for the First 6 Cycles (ITT Population)

End point description:

EORTC QLQ-C30 is a questionnaire that rates the overall quality of life in cancer patients. The first 28 questions use a 4-point scale (1=not at all to 4=very much) for evaluating function (physical, role, social, cognitive, emotional), symptoms (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea/vomiting, constipation, and pain) and financial difficulties. The last 2 questions use a 7-point scale (1=very poor to 7=excellent) to evaluate overall health and quality of life. Global scores are converted to a score of 0 to 100, with a higher score indicating improved health status. Mean changes from baseline global score over the first 6 cycles in the Treatment Part of the study were analyzed. Intent-to-treat (ITT) population - All randomized patients with a baseline value and at least one post-baseline value for the EORTC QLQ-C30 Global Health Status score during the first 6 cycles.

End point type	Secondary

End point timeframe:

Baseline to the end of Cycle 6, or up to approximately 6 months

End point values	Rucaparib	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	101		
Units: Score on a scale				
least squares mean (standard error)	0.6 (± 0.54)	0.4 (± 0.82)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib v Chemotherapy
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7742
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from date of first dose of study drug until 28 days after last dose of study drug, approximately 3.5 years.

Adverse event reporting additional description:

Adverse events are reported for the Safety Population, defined as patients who received at least one dose of protocol-specified treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Rucaparib (Treatment Part)

Reporting group description:

Patients randomized to the rucaparib arm in the Treatment Part of the study.

Reporting group title	Chemotherapy (Treatment Part)

Reporting group description:

Patients randomized to the chemotherapy arm in the Treatment Part of the study.

Reporting group title	Rucaparib (Crossover Part)

Reporting group description:

Patients randomized to chemotherapy who then crossed over upon disease progression and were treated with rucaparib.

Serious adverse events	Rucaparib (Treatment Part)	Chemotherapy (Treatment Part)	Rucaparib (Crossover Part)
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 232 (26.72%)	13 / 113 (11.50%)	17 / 74 (22.97%)
number of deaths (all causes)	15	3	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	5 / 232 (2.16%)	2 / 113 (1.77%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 5	0 / 2	0 / 1
Myelodysplastic syndrome			

subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 232 (1.29%)	1 / 113 (0.88%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 232 (1.29%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 232 (0.86%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated hernia			
subjects affected / exposed	0 / 232 (0.00%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Reproductive system and breast disorders			
Fibrocystic breast disease			

subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural effusion			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Pulmonary embolism			
subjects affected / exposed	1 / 232 (0.43%)	1 / 113 (0.88%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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

Blood creatinine increased			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Platelet count decreased			
subjects affected / exposed	2 / 232 (0.86%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 232 (0.00%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Post procedural fever			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Radius fracture			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Seroma			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Tibia fracture			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Pericardial effusion			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Ischaemic stroke			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Sciatica			
subjects affected / exposed	0 / 232 (0.00%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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			
Anemia			
subjects affected / exposed	19 / 232 (8.19%)	2 / 113 (1.77%)	4 / 74 (5.41%)
occurrences causally related to treatment / all	0 / 29	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Leukopenia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Neutropenia			
subjects affected / exposed	4 / 232 (1.72%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 232 (0.00%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	5 / 232 (2.16%)	1 / 113 (0.88%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Abdominal pain			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
subjects affected / exposed	2 / 232 (0.86%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Diarrhoea			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Dolichocolon acquired			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Haematemesis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Ileus			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Intestinal obstruction			
subjects affected / exposed	5 / 232 (2.16%)	0 / 113 (0.00%)	4 / 74 (5.41%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			

subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Large intestine perforation			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Megacolon			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Nausea			
subjects affected / exposed	0 / 232 (0.00%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Peritoneal adhesions			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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	1 / 232 (0.43%)	1 / 113 (0.88%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	3 / 232 (1.29%)	1 / 113 (0.88%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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 failure			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Cellulitis			
subjects affected / exposed	0 / 232 (0.00%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Cytomegalovirus colitis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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

Device related infection			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Osteomyelitis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Pneumonia			
subjects affected / exposed	4 / 232 (1.72%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Urinary tract infection			
subjects affected / exposed	2 / 232 (0.86%)	1 / 113 (0.88%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Cachexia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (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
Dehydration			
subjects affected / exposed	2 / 232 (0.86%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 232 (0.00%)	1 / 113 (0.88%)	0 / 74 (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
Hypomagnesaemia			
subjects affected / exposed	1 / 232 (0.43%)	0 / 113 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 232 (0.43%)	1 / 113 (0.88%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	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	Rucaparib (Treatment Part)	Chemotherapy (Treatment Part)	Rucaparib (Crossover Part)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 232 (94.83%)	105 / 113 (92.92%)	63 / 74 (85.14%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 232 (3.45%)	7 / 113 (6.19%)	4 / 74 (5.41%)
occurrences (all)	8	9	8
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	64 / 232 (27.59%)	24 / 113 (21.24%)	12 / 74 (16.22%)
occurrences (all)	116	48	29

Fatigue			
subjects affected / exposed	55 / 232 (23.71%)	28 / 113 (24.78%)	15 / 74 (20.27%)
occurrences (all)	91	65	38
Oedema peripheral			
subjects affected / exposed	12 / 232 (5.17%)	8 / 113 (7.08%)	0 / 74 (0.00%)
occurrences (all)	14	15	0
Pyrexia			
subjects affected / exposed	23 / 232 (9.91%)	7 / 113 (6.19%)	2 / 74 (2.70%)
occurrences (all)	26	9	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 232 (8.19%)	9 / 113 (7.96%)	7 / 74 (9.46%)
occurrences (all)	24	10	11
Dyspnoea			
subjects affected / exposed	25 / 232 (10.78%)	9 / 113 (7.96%)	6 / 74 (8.11%)
occurrences (all)	29	16	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 232 (8.19%)	7 / 113 (6.19%)	3 / 74 (4.05%)
occurrences (all)	21	11	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	74 / 232 (31.90%)	12 / 113 (10.62%)	29 / 74 (39.19%)
occurrences (all)	185	21	99
Aspartate aminotransferase increased			
subjects affected / exposed	72 / 232 (31.03%)	8 / 113 (7.08%)	26 / 74 (35.14%)
occurrences (all)	139	11	80
Blood alkaline phosphatase increased			
subjects affected / exposed	16 / 232 (6.90%)	3 / 113 (2.65%)	9 / 74 (12.16%)
occurrences (all)	24	3	13
Blood bilirubin increased			
subjects affected / exposed	20 / 232 (8.62%)	0 / 113 (0.00%)	6 / 74 (8.11%)
occurrences (all)	35	0	15
Blood cholesterol increased			
subjects affected / exposed	6 / 232 (2.59%)	6 / 113 (5.31%)	6 / 74 (8.11%)
occurrences (all)	12	15	9

Blood creatinine increased			
subjects affected / exposed	33 / 232 (14.22%)	9 / 113 (7.96%)	15 / 74 (20.27%)
occurrences (all)	76	20	27
Blood urea increased			
subjects affected / exposed	9 / 232 (3.88%)	4 / 113 (3.54%)	5 / 74 (6.76%)
occurrences (all)	25	8	6
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 232 (2.16%)	6 / 113 (5.31%)	4 / 74 (5.41%)
occurrences (all)	14	21	12
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	3 / 232 (1.29%)	4 / 113 (3.54%)	4 / 74 (5.41%)
occurrences (all)	6	6	5
Neutrophil count decreased			
subjects affected / exposed	5 / 232 (2.16%)	7 / 113 (6.19%)	2 / 74 (2.70%)
occurrences (all)	8	17	2
Weight decreased			
subjects affected / exposed	25 / 232 (10.78%)	3 / 113 (2.65%)	6 / 74 (8.11%)
occurrences (all)	36	3	6
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	7 / 232 (3.02%)	6 / 113 (5.31%)	3 / 74 (4.05%)
occurrences (all)	12	19	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 232 (5.17%)	9 / 113 (7.96%)	2 / 74 (2.70%)
occurrences (all)	15	12	2
Dysgeusia			
subjects affected / exposed	39 / 232 (16.81%)	8 / 113 (7.08%)	10 / 74 (13.51%)
occurrences (all)	44	8	11
Headache			
subjects affected / exposed	17 / 232 (7.33%)	6 / 113 (5.31%)	2 / 74 (2.70%)
occurrences (all)	26	6	3
Neuropathy peripheral			
subjects affected / exposed	2 / 232 (0.86%)	16 / 113 (14.16%)	2 / 74 (2.70%)
occurrences (all)	2	19	2
Neurotoxicity			

subjects affected / exposed	1 / 232 (0.43%)	7 / 113 (6.19%)	2 / 74 (2.70%)
occurrences (all)	1	11	7
Paraesthesia			
subjects affected / exposed	4 / 232 (1.72%)	11 / 113 (9.73%)	1 / 74 (1.35%)
occurrences (all)	5	26	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	123 / 232 (53.02%)	35 / 113 (30.97%)	30 / 74 (40.54%)
occurrences (all)	359	103	122
Leukopenia			
subjects affected / exposed	21 / 232 (9.05%)	18 / 113 (15.93%)	30 / 74 (40.54%)
occurrences (all)	48	65	122
Lymphopenia			
subjects affected / exposed	7 / 232 (3.02%)	7 / 113 (6.19%)	3 / 74 (4.05%)
occurrences (all)	20	18	8
Neutropenia			
subjects affected / exposed	47 / 232 (20.26%)	28 / 113 (24.78%)	7 / 74 (9.46%)
occurrences (all)	112	129	24
Thrombocytopenia			
subjects affected / exposed	46 / 232 (19.83%)	13 / 113 (11.50%)	10 / 74 (13.51%)
occurrences (all)	116	30	27
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	14 / 232 (6.03%)	4 / 113 (3.54%)	4 / 74 (5.41%)
occurrences (all)	17	4	4
Abdominal pain			
subjects affected / exposed	54 / 232 (23.28%)	18 / 113 (15.93%)	13 / 74 (17.57%)
occurrences (all)	95	24	26
Abdominal pain lower			
subjects affected / exposed	12 / 232 (5.17%)	2 / 113 (1.77%)	3 / 74 (4.05%)
occurrences (all)	17	2	4
Abdominal pain upper			
subjects affected / exposed	20 / 232 (8.62%)	5 / 113 (4.42%)	8 / 74 (10.81%)
occurrences (all)	23	7	10
Ascites			

subjects affected / exposed	13 / 232 (5.60%)	2 / 113 (1.77%)	2 / 74 (2.70%)
occurrences (all)	27	4	2
Constipation			
subjects affected / exposed	37 / 232 (15.95%)	19 / 113 (16.81%)	14 / 74 (18.92%)
occurrences (all)	58	28	20
Diarrhoea			
subjects affected / exposed	47 / 232 (20.26%)	24 / 113 (21.24%)	12 / 74 (16.22%)
occurrences (all)	66	35	19
Dyspepsia			
subjects affected / exposed	19 / 232 (8.19%)	7 / 113 (6.19%)	2 / 74 (2.70%)
occurrences (all)	24	10	3
Intestinal obstruction			
subjects affected / exposed	10 / 232 (4.31%)	0 / 113 (0.00%)	6 / 74 (8.11%)
occurrences (all)	12	0	8
Nausea			
subjects affected / exposed	124 / 232 (53.45%)	36 / 113 (31.86%)	31 / 74 (41.89%)
occurrences (all)	240	95	72
Stomatitis			
subjects affected / exposed	11 / 232 (4.74%)	7 / 113 (6.19%)	3 / 74 (4.05%)
occurrences (all)	11	13	4
Vomiting			
subjects affected / exposed	79 / 232 (34.05%)	19 / 113 (16.81%)	17 / 74 (22.97%)
occurrences (all)	159	33	37
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 232 (5.17%)	38 / 113 (33.63%)	2 / 74 (2.70%)
occurrences (all)	12	49	2
Erythema			
subjects affected / exposed	5 / 232 (2.16%)	2 / 113 (1.77%)	7 / 74 (9.46%)
occurrences (all)	6	4	9
Photosensitivity reaction			
subjects affected / exposed	10 / 232 (4.31%)	0 / 113 (0.00%)	5 / 74 (6.76%)
occurrences (all)	12	0	6
Pruritus			
subjects affected / exposed	9 / 232 (3.88%)	3 / 113 (2.65%)	7 / 74 (9.46%)
occurrences (all)	11	4	10

Rash			
subjects affected / exposed	12 / 232 (5.17%)	4 / 113 (3.54%)	4 / 74 (5.41%)
occurrences (all)	13	6	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 232 (6.03%)	9 / 113 (7.96%)	5 / 74 (6.76%)
occurrences (all)	16	13	6
Back pain			
subjects affected / exposed	12 / 232 (5.17%)	5 / 113 (4.42%)	9 / 74 (12.16%)
occurrences (all)	13	5	14
Pain in extremity			
subjects affected / exposed	8 / 232 (3.45%)	5 / 113 (4.42%)	4 / 74 (5.41%)
occurrences (all)	8	9	8
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	8 / 232 (3.45%)	3 / 113 (2.65%)	5 / 74 (6.76%)
occurrences (all)	8	3	8
Urinary tract infection			
subjects affected / exposed	16 / 232 (6.90%)	5 / 113 (4.42%)	5 / 74 (6.76%)
occurrences (all)	20	6	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	44 / 232 (18.97%)	20 / 113 (17.70%)	19 / 74 (25.68%)
occurrences (all)	65	39	31
Hypercholesterolaemia			
subjects affected / exposed	9 / 232 (3.88%)	5 / 113 (4.42%)	5 / 74 (6.76%)
occurrences (all)	18	7	6
Hyperglycaemia			
subjects affected / exposed	16 / 232 (6.90%)	15 / 113 (13.27%)	4 / 74 (5.41%)
occurrences (all)	32	40	4
Hypertriglyceridaemia			
subjects affected / exposed	8 / 232 (3.45%)	7 / 113 (6.19%)	5 / 74 (6.76%)
occurrences (all)	23	11	12
Hypomagnesaemia			
subjects affected / exposed	14 / 232 (6.03%)	2 / 113 (1.77%)	2 / 74 (2.70%)
occurrences (all)	28	6	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2018	Significant changes included in this amendment are summarized as follows: • Updated and consolidated the rucaparib background and safety information based on analyses of other Clovis Oncology studies in patients with ovarian cancer, including information on photosensitivity. • Updated the in vitro and in vivo rucaparib PK and drug-drug interaction (DDI) data based on results from rucaparib clinical studies. • Updated the rucaparib dose modification criteria to include additional guidance specific to suspected cases of drug-induced liver injury (DILI).
23 October 2020	Significant changes included in this amendment are summarized as follows: • Updated the AESIs to include pneumonitis and similar events, including management guidance and Clovis Oncology Pharmacovigilance (PV) reporting and follow-up requirements to align with the rucaparib IB. • Included guidance for management of anemia for consistency with the rucaparib IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported