Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Summary

EudraCT number	2013-000518-39
Trial protocol	GB BE DE IT ES FR
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	20 May 2021
First version publication date	20 May 2021

Trial information

Trial identification

Sponsor protocol code	CO-338-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01968213
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clovis Oncology UK Ltd
Sponsor organisation address	Granta Centre, Granta Park, Great Abington, Cambridge, United Kingdom, CB21 6GP
Public contact	Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 1223 645500, lrolfe@clovisoncology.com
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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	15 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST), as assessed by the investigator, in molecularly-defined homologous recombination deficiency (HRD) subgroups

Protection of trial subjects:

The following safety assessments were performed: adverse events, physical examination, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis [screening only]), vital signs, and 12-lead ECG (baseline and End of Study only). Patients were assessed for disease status per RECIST v1.1 every 12 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	07 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
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	Australia: 53
Country: Number of subjects enrolled	Canada: 74
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	United States: 128
Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	United Kingdom: 67
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 59
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 73
Worldwide total number of subjects	564
EEA total number of subjects	277

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)	354
From 65 to 84 years	209
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

564 subjects were recruited from 87 sites across 11 countries and randomized (2:1) to treatment with rucaparib or placebo

Pre-assignment

Screening details:

Eligible patients, as determined based on screening assessments, were randomly assigned 2:1 to treatment with rucaparib or placebo. Patients were stratified at randomization into one of 3 HRD subgroups (tBRCA [tumor tissue alteration in BRCA1 or BRCA2, includes germline BRCA and somatic BRCA], non-BRCA HRD [nbHRD], and biomarker negative).

Period 1

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

Blinding implementation details:

Active and placebo tablets were identical in appearance and supplied in identical containers. The medication labeling ensured that no staff member or patient was able to identify whether the tablets were placebo or contained active medication. Patients took the equivalent number of active or placebo tablets according to the treatment assignment and scheduled dose. In the event of a medical emergency, an individual patient's treatment assignment was unblinded using IVRS/IWRS.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rucaparib 600 mg Tablets

Arm description:

Rucaparib tablets taken orally twice daily (continuous 28 day treatment 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:

The starting dose was 600 mg rucaparib BID. Each dose was to be taken with at least 8 oz (240 mL) of room temperature water. Tablets were to be swallowed whole.

Arm title	Placebo Tablets

Arm description:

Placebo tablets taken orally twice daily (continuous 28 day treatment cycles)

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

Dosage and administration details:

Matched placebo taken BID

Number of subjects in period 1	Rucaparib 600 mg Tablets	Placebo Tablets
Started	375	189
Completed	285	180
Not completed	90	9
Ongoing	90	9

Baseline characteristics

Reporting groups	
Reporting group title	Rucaparib 600 mg Tablets
Reporting group description:	
Rucaparib tablets taken orally twice daily (continuous 28 day treatment cycles)	
Reporting group title	Placebo Tablets
Reporting group description:	
Placebo tablets taken orally twice daily (continuous 28 day treatment cycles)	

Reporting group values	Rucaparib 600 mg Tablets	Placebo Tablets	Total
Number of subjects	375	189	564
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	61	62	
full range (min-max)	39 to 84	36 to 85	-
Gender categorical Units: Subjects			
Female	375	189	564
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	1	4
Asian	14	7	21
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	2	8
White	302	149	451
More than one race	3	3	6
Unknown or Not Reported	47	27	74
Best Response from Previous Platinum Therapy			
Measure Description: Complete and partial responses at baseline must have been reported according to RECIST v1.1, as assessed by CT/MRI, and GCIG CA-125 response criteria, and defined as: Complete Response (CR) i.e. absence of any detectable disease and CA-125<ULN; Partial Response (PR), ≥30% decrease in sum of the longest diameter of measurable lesions or if non-measurable disease at baseline, a GCIG CA-125 response (least a 50% reduction in CA-125 levels from a pretreatment sample (which must have initially been 2xULN) and confirmed after ≥21 days). CA-125 must have been <ULN for all PRs.			
Units: Subjects			
RECIST CR	126	64	190
RECIST / CA-125 PR	249	125	374
Penultimate Progression-free (PF) Interval			
Measure Description: Progressive disease is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of measurable lesions, an unequivocal increase in existing nonmeasurable lesion(s), or the appearance of unequivocal new lesion			

(s).			
Units: Subjects			
6-12 Months	151	76	227
>12 Months	224	113	337
Bulky Lesions (lesion >20 mm) at Baseline Units: Subjects			
Yes	71	29	100
No	304	160	464

End points

End points reporting groups

Reporting group title	Rucaparib 600 mg Tablets
Reporting group description:	
Rucaparib tablets taken orally twice daily (continuous 28 day treatment cycles)	
Reporting group title	Placebo Tablets
Reporting group description:	
Placebo tablets taken orally twice daily (continuous 28 day treatment cycles)	

Primary: Disease Progression According to RECIST Version 1.1, as Assessed by the Investigator, or Death From Any Cause (Investigator Progression Free Survival as Per invPFS)

End point title	Disease Progression According to RECIST Version 1.1, as Assessed by the Investigator, or Death From Any Cause (Investigator Progression Free Survival as Per invPFS)
End point description:	
Progression-free survival by Investigator (invPFS) is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by the investigator, or death due to any cause, whichever occurs first. Progressive disease is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of measurable lesions, an unequivocal increase in existing non-measurable lesion(s), or the appearance of unequivocal new lesion(s).	
End point type	Primary
End point timeframe:	
Every 12 calendar weeks (within 7 days prior is permitted) after start of treatment until treatment discontinuation due to disease progression. Study data collection expected to last for ~3 years.	

End point values	Rucaparib 600 mg Tablets	Placebo Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	189		
Units: Months				
median (confidence interval 95%)	10.8 (8.3 to 11.4)	5.4 (5.3 to 5.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib 600 mg Tablets v Placebo Tablets

Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.365
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.295
upper limit	0.451

Secondary: Disease Progression According to RECIST v1.1, as Assessed by Independent Radiology Review (IRR) or Death From Any Cause (invPFS)

End point title	Disease Progression According to RECIST v1.1, as Assessed by Independent Radiology Review (IRR) or Death From Any Cause (invPFS)

End point description:

To evaluate PFS by RECIST, as assessed by independent radiology review (IRR)

End point type	Secondary

End point timeframe:

Every 12 calendar weeks (within 7 days prior is permitted) after start of treatment until treatment discontinuation due to disease progression. Study data collection expected to last for ~3 years.

End point values	Rucaparib 600 mg Tablets	Placebo Tablets		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	189		
Units: Months				
median (confidence interval 95%)	13.7 (11.0 to 19.1)	5.4 (5.1 to 5.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rucaparib 600 mg Tablets v Placebo Tablets
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.354

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.278
upper limit	0.45

Secondary: Individual Model Parameter Estimates of Rucaparib and Covariates Identification

End point title	Individual Model Parameter Estimates of Rucaparib and Covariates Identification[1]

End point description:

Concentration summary statistics

End point type	Secondary

End point timeframe:

Study data collection expected to last for ~7 months.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint includes rucaparib patients only

End point values	Rucaparib 600 mg Tablets			
Subject group type	Reporting group			
Number of subjects analysed	295			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	1128 (± 95.42)			
Cycle 4 Day 1	1136 (± 86.19)			
Cycle 7 Day 1	1165 (± 78.53)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of first dose of study drug and until 28 days after last dose of study drug.

Adverse event reporting additional description:

Three patients were randomized to the rucaparib arm and discontinued prior to receiving study drug. Reason for discontinuation were due to withdrawal of consent, physician decision, and laboratory value (did not meet eligibility criteria).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Rucaparib 600 mg Tablets

Reporting group description:

Rucaparib tablets taken orally twice daily (continuous 28 day treatment cycles)

Reporting group title	Placebo Tablets

Reporting group description:

Placebo tablets taken orally twice daily (continuous 28 day treatment cycles)

Serious adverse events	Rucaparib 600 mg Tablets	Placebo Tablets	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 372 (20.97%)	20 / 189 (10.58%)	
number of deaths (all causes)	7	2	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
B-cell unclassifiable lymphoma high grade			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			

subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelodysplastic syndrome			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 372 (1.61%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis allergic			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 372 (0.54%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	4 / 372 (1.08%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma output			

increased			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 372 (0.27%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seroma			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoaesthesia			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 372 (0.81%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 372 (4.30%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	22 / 22	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 372 (1.34%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haemotophagic			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	5 / 372 (1.34%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	5 / 372 (1.34%)	2 / 189 (1.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			

subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 372 (0.81%)	2 / 189 (1.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 372 (0.54%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	4 / 372 (1.08%)	3 / 189 (1.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 372 (1.88%)	2 / 189 (1.06%)	
occurrences causally related to treatment / all	3 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 372 (1.08%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (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	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (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			
Arthritis infective			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 372 (0.54%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
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 / 372 (0.00%)	1 / 189 (0.53%)	
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	2 / 372 (0.54%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 372 (0.27%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	3 / 372 (0.81%)	0 / 189 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 372 (0.00%)	1 / 189 (0.53%)	
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	Rucaparib 600 mg Tablets	Placebo Tablets	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	372 / 372 (100.00%)	182 / 189 (96.30%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	126 / 372 (33.87%)	6 / 189 (3.17%)	
occurrences (all)	312	6	
Aspartate aminotransferase increased			
subjects affected / exposed	97 / 372 (26.08%)	5 / 189 (2.65%)	
occurrences (all)	230	7	
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 372 (5.11%)	1 / 189 (0.53%)	
occurrences (all)	26	1	
Blood creatinine increased			
subjects affected / exposed	61 / 372 (16.40%)	3 / 189 (1.59%)	
occurrences (all)	154	3	
Neutrophil count decreased			
subjects affected / exposed	27 / 372 (7.26%)	6 / 189 (3.17%)	
occurrences (all)	77	12	
Platelet count decreased			
subjects affected / exposed	51 / 372 (13.71%)	3 / 189 (1.59%)	
occurrences (all)	108	3	
Weight decreased			

subjects affected / exposed	25 / 372 (6.72%)	2 / 189 (1.06%)	
occurrences (all)	47	2	
White blood cell count decreased			
subjects affected / exposed	22 / 372 (5.91%)	8 / 189 (4.23%)	
occurrences (all)	56	10	
Vascular disorders			
Hot flush			
subjects affected / exposed	22 / 372 (5.91%)	8 / 189 (4.23%)	
occurrences (all)	26	9	
Hypertension			
subjects affected / exposed	36 / 372 (9.68%)	16 / 189 (8.47%)	
occurrences (all)	71	26	
Nervous system disorders			
Dizziness			
subjects affected / exposed	57 / 372 (15.32%)	15 / 189 (7.94%)	
occurrences (all)	76	19	
Dysgeusia			
subjects affected / exposed	148 / 372 (39.78%)	13 / 189 (6.88%)	
occurrences (all)	195	13	
Headache			
subjects affected / exposed	71 / 372 (19.09%)	31 / 189 (16.40%)	
occurrences (all)	108	47	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	135 / 372 (36.29%)	10 / 189 (5.29%)	
occurrences (all)	477	19	
Neutropenia			
subjects affected / exposed	47 / 372 (12.63%)	3 / 189 (1.59%)	
occurrences (all)	83	8	
Thrombocytopenia			
subjects affected / exposed	64 / 372 (17.20%)	2 / 189 (1.06%)	
occurrences (all)	158	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	86 / 372 (23.12%)	20 / 189 (10.58%)	
occurrences (all)	171	29	

Fatigue			
subjects affected / exposed	189 / 372 (50.81%)	65 / 189 (34.39%)	
occurrences (all)	383	92	
Mucosal inflammation			
subjects affected / exposed	33 / 372 (8.87%)	9 / 189 (4.76%)	
occurrences (all)	62	11	
Oedema peripheral			
subjects affected / exposed	41 / 372 (11.02%)	14 / 189 (7.41%)	
occurrences (all)	56	17	
Pyrexia			
subjects affected / exposed	45 / 372 (12.10%)	9 / 189 (4.76%)	
occurrences (all)	59	10	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	42 / 372 (11.29%)	24 / 189 (12.70%)	
occurrences (all)	47	24	
Abdominal pain			
subjects affected / exposed	112 / 372 (30.11%)	49 / 189 (25.93%)	
occurrences (all)	179	69	
Abdominal pain upper			
subjects affected / exposed	54 / 372 (14.52%)	11 / 189 (5.82%)	
occurrences (all)	82	11	
Constipation			
subjects affected / exposed	141 / 372 (37.90%)	46 / 189 (24.34%)	
occurrences (all)	231	55	
Diarrhoea			
subjects affected / exposed	121 / 372 (32.53%)	41 / 189 (21.69%)	
occurrences (all)	206	55	
Dry mouth			
subjects affected / exposed	29 / 372 (7.80%)	9 / 189 (4.76%)	
occurrences (all)	32	9	
Dyspepsia			
subjects affected / exposed	54 / 372 (14.52%)	9 / 189 (4.76%)	
occurrences (all)	73	11	
Nausea			

subjects affected / exposed	282 / 372 (75.81%)	69 / 189 (36.51%)	
occurrences (all)	583	104	
Stomatitis			
subjects affected / exposed	35 / 372 (9.41%)	5 / 189 (2.65%)	
occurrences (all)	43	5	
Vomiting			
subjects affected / exposed	138 / 372 (37.10%)	29 / 189 (15.34%)	
occurrences (all)	262	40	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	55 / 372 (14.78%)	25 / 189 (13.23%)	
occurrences (all)	75	35	
Dyspnoea			
subjects affected / exposed	53 / 372 (14.25%)	14 / 189 (7.41%)	
occurrences (all)	68	22	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	32 / 372 (8.60%)	14 / 189 (7.41%)	
occurrences (all)	33	14	
Dry skin			
subjects affected / exposed	34 / 372 (9.14%)	17 / 189 (8.99%)	
occurrences (all)	39	17	
Erythema			
subjects affected / exposed	33 / 372 (8.87%)	5 / 189 (2.65%)	
occurrences (all)	44	5	
Photosensitivity reaction			
subjects affected / exposed	68 / 372 (18.28%)	1 / 189 (0.53%)	
occurrences (all)	102	1	
Pruritis			
subjects affected / exposed	51 / 372 (13.71%)	20 / 189 (10.58%)	
occurrences (all)	71	24	
Rash			
subjects affected / exposed	50 / 372 (13.44%)	17 / 189 (8.99%)	
occurrences (all)	65	18	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	28 / 372 (7.53%)	14 / 189 (7.41%)	
occurrences (all)	36	14	
Depression			
subjects affected / exposed	33 / 372 (8.87%)	6 / 189 (3.17%)	
occurrences (all)	45	6	
Insomnia			
subjects affected / exposed	54 / 372 (14.52%)	15 / 189 (7.94%)	
occurrences (all)	65	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	59 / 372 (15.86%)	24 / 189 (12.70%)	
occurrences (all)	82	35	
Back pain			
subjects affected / exposed	50 / 372 (13.44%)	28 / 189 (14.81%)	
occurrences (all)	64	42	
Muscle spasms			
subjects affected / exposed	12 / 372 (3.23%)	16 / 189 (8.47%)	
occurrences (all)	13	20	
Myalgia			
subjects affected / exposed	21 / 372 (5.65%)	7 / 189 (3.70%)	
occurrences (all)	27	11	
Neck pain			
subjects affected / exposed	19 / 372 (5.11%)	4 / 189 (2.12%)	
occurrences (all)	20	4	
Pain in extremity			
subjects affected / exposed	18 / 372 (4.84%)	15 / 189 (7.94%)	
occurrences (all)	20	17	
Infections and infestations			
Influenza			
subjects affected / exposed	25 / 372 (6.72%)	4 / 189 (2.12%)	
occurrences (all)	29	4	
Nasopharyngitis			
subjects affected / exposed	33 / 372 (8.87%)	12 / 189 (6.35%)	
occurrences (all)	42	17	
Sinusitis			

subjects affected / exposed	19 / 372 (5.11%)	3 / 189 (1.59%)	
occurrences (all)	23	6	
Upper respiratory tract infection			
subjects affected / exposed	44 / 372 (11.83%)	6 / 189 (3.17%)	
occurrences (all)	61	10	
Urinary tract infection			
subjects affected / exposed	34 / 372 (9.14%)	9 / 189 (4.76%)	
occurrences (all)	65	14	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	88 / 372 (23.66%)	26 / 189 (13.76%)	
occurrences (all)	127	32	
Hypercholesterolaemia			
subjects affected / exposed	27 / 372 (7.26%)	4 / 189 (2.12%)	
occurrences (all)	42	4	
Hypomagnesaemia			
subjects affected / exposed	43 / 372 (11.56%)	11 / 189 (5.82%)	
occurrences (all)	77	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2014	Significant changes included: 1) Changes to nonclinical and clinical summaries; 2) Changes to objectives and endpoints: Independent radiology review (IRR) was removed from secondary objectives and endpoints and was now indicated as a supportive analysis; 3) Changes to study design; 4) Changes to inclusion and exclusion criteria; 5) Changes to description of study treatments and dose modifications, 6) Changes to prior and concomitant therapies; 7) Changes to study procedures; 8) Changes to safety management; 9) Changes to statistical analyses; 10) GCIG CA-125 response criteria in Appendix C was revised
09 March 2015	Significant changes included: 1) Changes to study endpoints and statistical analyses a) Progression-free survival by independent radiology review (irrPFS) was incorporated as a secondary endpoint. This had previously been a supportive analysis in Amendment 1 of the protocol. b) Exploratory endpoints of ORR and DOR were to be assessed by both the investigator and independent radiology review; 2) Clarifications to study procedures a) AEs related to screening procedures should have been recorded. b) Prior/concomitant medications/procedures should have been recorded at the 28-day follow-up assessment post-treatment discontinuation. c) CA-125 was not required to be collected during the follow-up period. This was corrected in all sections of the protocol.
07 July 2016	Significant changes included in Amendment 3 were to align the protocol with the recent update to the rucaparib IB (Version 7). Changes included: 1) Changes to pregnancy/ birth control language; 2) Updated CYP inhibition, induction, and down regulation data; 3) Additional guidance was included regarding management of study drug with treatment-emergent ALT/AST Elevations; 4) Included adverse events of special interest (AESIs) based on the current list of AESIs for rucaparib found in Version 7 of the IB and included brief description of these AESIs (acute myeloid leukemia [AML] and myelodysplastic syndrome [MDS]). Also, incorporated appropriate general updates to the safety reporting section to coincide with the current Pharmacovigilance department text and study practice.; 5) Clarified the parameters that define the end of the study, including description of IDMC involvement and clarification that survival follow-up continued after PFS was analyzed to assess the OS endpoint.; 6) Clarification on the use of rucaparib with digoxin or certain statins.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported