Clinical trial results:
ATLAS: A Phase 2, Open-label Study of Rucaparib in Patients with Locally Advanced or Metastatic Urothelial Carcinoma

Summary

EudraCT number	2017-004166-10
Trial protocol	FR ES DE GB IT
Global end of trial date	15 January 2020

Results information

Result version number	v1 (current)
This version publication date	05 September 2020
First version publication date	05 September 2020

Trial information

Trial identification

Sponsor protocol code	CO-338-085

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03397394
WHO universal trial number (UTN)	-
Other trial identifiers	US IND: 129840

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 12233645500, lrolfe@clovisoncology.com
Scientific contact	Dr Lindsey Rolfe, Clovis Oncology UK Ltd, 44 12233645500, 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	Final
Date of interim/final analysis	22 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2019
Global end of trial reached?	Yes
Global end of trial date	15 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is:
• To evaluate objective response rate (ORR) in molecularly-defined homologous recombination deficiency (HRD)-positive and intent-to-treat (ITT) populations using a prospectively defined molecular signature.

Protection of trial subjects:

Safety was assessed by evaluating Eastern Cooperative Oncology Group performance status (ECOG PS), vital signs, hematology, serum chemistry, urinalysis, changes in physical examination, and by monitoring the incidence, severity, and relationship to rucaparib of adverse events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 58
Worldwide total number of subjects	97
EEA total number of subjects	39

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)	39
From 65 to 84 years	55
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

97 subjects were recruited from 40 sites across 5 countries.

Pre-assignment

Screening details:

This study enrolled patients with locally advanced unresectable or metastatic urothelial carcinoma who had received 1 or 2 prior treatment regimens and regardless of HRD status.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	HRD Unknown

Arm description:

Patients with HRD status unknown who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor genome-wide LOH was not tested or not determined were considered HRD unknown.

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:

All patients initiated treatment with oral rucaparib 600 mg BID and continued rucaparib in 28-day cycles. Patients took rucaparib with or without food.

Arm title	HRD Negative

Arm description:

Patients with HRD status negative who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH < 10% were considered HRD-negative.

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:

All patients initiated treatment with oral rucaparib 600 mg BID and continued rucaparib in 28-day cycles. Patients took rucaparib with or without food.

Arm title	HRD Positive

Arm description:

Patients with HRD status positive who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH ≥ 10% were considered HRD-

positive.

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:

All patients initiated treatment with oral rucaparib 600 mg BID and continued rucaparib in 28-day cycles. Patients took rucaparib with or without food.

Number of subjects in period 1	HRD Unknown	HRD Negative	HRD Positive
Started	47	30	20
Completed	47	30	20

Baseline characteristics

Reporting groups	
Reporting group title	HRD Unknown

Reporting group description:

Patients with HRD status unknown who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor genome-wide LOH was not tested or not determined were considered HRD unknown.

Reporting group title	HRD Negative

Reporting group description:

Patients with HRD status negative who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH < 10% were considered HRD-negative.

Reporting group title	HRD Positive

Reporting group description:

Patients with HRD status positive who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH ≥ 10% were considered HRD-positive.

Reporting group values	HRD Unknown	HRD Negative	HRD Positive
Number of subjects	47	30	20
Age categorical Units: Subjects			
Adults (18-64 years)	19	13	7
From 65-84 years	27	16	12
85 years and over	1	1	1
Age continuous Units: years			
median	66	66	71
full range (min-max)	50 to 85	47 to 85	39 to 87
Gender categorical Units: Subjects			
Female	9	3	9
Male	38	27	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	4	1
Not Hispanic or Latino	29	23	17
Unknown or Not Reported	11	3	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	0
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	1	2	0
White	32	24	18
More than one race	0	0	0
Unknown or Not Reported	12	3	2

Reporting group values	Total		
Number of subjects	97		
Age categorical Units: Subjects			
Adults (18-64 years)	39		
From 65-84 years	55		
85 years and over	3		
Age continuous Units: years median full range (min-max)	- -		
Gender categorical Units: Subjects			
Female	21		
Male	76		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	69		
Unknown or Not Reported	16		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	3		
White	74		
More than one race	0		
Unknown or Not Reported	17		

End points

End points reporting groups

Reporting group title	HRD Unknown

Reporting group description:

Patients with HRD status unknown who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor genome-wide LOH was not tested or not determined were considered HRD unknown.

Reporting group title	HRD Negative

Reporting group description:

Patients with HRD status negative who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH < 10% were considered HRD-negative.

Reporting group title	HRD Positive

Reporting group description:

Patients with HRD status positive who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH ≥ 10% were considered HRD-positive.

Subject analysis set title	All Patients
Subject analysis set type	Per protocol

Subject analysis set description:

Includes all patients evaluated for this endpoint.

Primary: Objective Response Rate (ORR) Per RECIST Version 1.1

End point title	Objective Response Rate (ORR) Per RECIST Version 1.1[1]

End point description:

ORR is defined as the proportion of patients with a confirmed response of complete response (CR) or partial response (PR) by RECIST v1.1 as assessed by the investigator. Complete Response (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. Partial Response (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.

End point type	Primary

End point timeframe:

Time from first dose to date of progression, up to approximately 19 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per EMA feedback, the statistical analyses section can not accommodate the end point results for this study. Therefore, all statistical analyses details are provided in the End point values sections.

End point values	HRD Unknown	HRD Negative	HRD Positive	All Patients
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	47	29	19	95
Units: Participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) According to RECIST v1.1, as Assessed by the Investigator

End point title	Progression-free Survival (PFS) According to RECIST v1.1, as Assessed by the Investigator

End point description:

PFS is calculated as 1+ the number of days from the first dose of study drug to disease progression by RECIST, as determined by the investigator or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 10 months

End point values	HRD Unknown	HRD Negative	HRD Positive	All Patients
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	47	30	20	97
Units: Months				
median (confidence interval 95%)	1.8 (1.6 to 2.0)	1.8 (1.5 to 2.0)	1.4 (1.2 to 3.6)	1.8 (1.6 to 1.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as time from the date of first dose of rucaparib to the date of death due to any cause. Patients without a known date of death were to be censored on the date the patient was last known to be alive. A Kaplan-Meier analysis of OS was planned, however, due to early study termination and limited duration of OS follow-up (median follow-up time = 2.7 months), a descriptive summary of deaths on study (from first dose of study drug to 28 days after the last dose of study drug) and deaths during long-term follow-up are presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to date of death, assessed up to 11 months

End point values	HRD Unknown	HRD Negative	HRD Positive	All Patients
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	47	30	20	97
Units: Participants				
Deaths on Study	9	8	7	24
Deaths During Long-Term Follow-Up	6	7	2	15

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - Trough (Cmin) Level Rucaparib Concentrations

End point title	Pharmacokinetics - Trough (Cmin) Level Rucaparib Concentrations

End point description:

Plasma were collected for trough level PK analysis of rucaparib 1 hour before the morning dose on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 4 Day 1.

End point type	Secondary

End point timeframe:

From Cycle 2 Day 1 to Cycle 4 Day 1, or approximately 2 months

End point values	HRD Unknown	HRD Negative	HRD Positive	All Patients
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	47[2]	30[3]	20[4]	97[5]
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 1	2354.03 (± 2173.055)	1927.77 (± 1352.707)	1853.84 (± 1533.622)	2129.70 (± 1831.099)
Cycle 3 Day 1	2037.90 (± 1253.715)	1331.17 (± 357.010)	643.00 (± 688.722)	1647.33 (± 1068.270)
Cycle 4 Day 1	2225.00 (± 763.348)	2058.00 (± 705.280)	1585.00 (± 487.904)	2032.73 (± 672.891)

Notes:

[2] - Cycle 2 = 24, Cycle 3 = 10, Cycle 4 = 4

[3] - Cycle 2 = 13, Cycle 3 = 6, Cycle 4 = 5

[4] - Cycle 2 = 10, Cycle 3 = 2, Cycle 4 = 2

[5] - Cycle 2 = 47, Cycle 3 = 18, Cycle 4 = 11

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 first dose until 28 days after last dose of study drug. Any Serious Adverse Events or Adverse Events of Special Interest were followed until resolution or stabilization, death, or until patient was lost to follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	HRD Unknown

Reporting group description:

Patients with HRD status unknown who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor genome-wide LOH was not tested or not determined were considered HRD unknown.

Reporting group title	HRD Negative

Reporting group description:

Patients with HRD status negative who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH < 10% were considered HRD-negative

Reporting group title	HRD Positive

Reporting group description:

Patients with HRD status positive who received continuous dosing with rucaparib 600 mg twice a day (BID) in 28-day cycles. Patients whose tumor had genome-wide LOH ≥ 10% were considered HRD-positive.

Reporting group title	Overall

Reporting group description: -

Serious adverse events	HRD Unknown	HRD Negative	HRD Positive
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 47 (42.55%)	14 / 30 (46.67%)	11 / 20 (55.00%)
number of deaths (all causes)	8	9	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	6 / 47 (12.77%)	9 / 30 (30.00%)	3 / 20 (15.00%)
occurrences causally related to treatment / all	0 / 6	0 / 9	0 / 3
deaths causally related to treatment / all	0 / 6	0 / 9	0 / 3
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
General physical health deterioration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Pyrexia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Hypoxia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Pleural effusion			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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

Pulmonary embolism			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Disorientation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Mental status changes			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 47 (2.13%)	1 / 30 (3.33%)	0 / 20 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 30 (3.33%)	3 / 20 (15.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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 disorders			
Constipation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Gastric ulcer perforation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Hepatobiliary disorders			

Hepatocellular injury			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Haematuria			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Hydronephrosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Urinary retention			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 47 (4.26%)	0 / 30 (0.00%)	0 / 20 (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
Pain in extremity			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Pubic pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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			
Lung infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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			
subjects affected / exposed	1 / 47 (2.13%)	1 / 30 (3.33%)	0 / 20 (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
Pyelonephritis			
subjects affected / exposed	2 / 47 (4.26%)	0 / 30 (0.00%)	0 / 20 (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
Respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Septic shock			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	0 / 20 (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
Urinary tract infection			
subjects affected / exposed	1 / 47 (2.13%)	1 / 30 (3.33%)	0 / 20 (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
Urosepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	0 / 20 (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
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 97 (46.39%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	18 / 97 (18.56%)		
occurrences causally related to treatment / all	0 / 18		
deaths causally related to treatment / all	0 / 18		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Mental status changes			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			

subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Intestinal obstruction				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatocellular injury				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				

subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pubic pain			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Sepsis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	HRD Unknown	HRD Negative	HRD Positive
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 47 (95.74%)	29 / 30 (96.67%)	19 / 20 (95.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 47 (6.38%)	0 / 30 (0.00%)	0 / 20 (0.00%)
occurrences (all)	4	0	0

Intermittent claudication			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lymphoedema			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 47 (25.53%)	4 / 30 (13.33%)	1 / 20 (5.00%)
occurrences (all)	16	5	1
Chest pain			
subjects affected / exposed	1 / 47 (2.13%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Chills			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	3	0	1
Fatigue			
subjects affected / exposed	21 / 47 (44.68%)	12 / 30 (40.00%)	7 / 20 (35.00%)
occurrences (all)	26	22	13
Localised oedema			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Mucosal inflammation			
subjects affected / exposed	1 / 47 (2.13%)	1 / 30 (3.33%)	2 / 20 (10.00%)
occurrences (all)	2	1	2
Nodule			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	3 / 47 (6.38%)	1 / 30 (3.33%)	4 / 20 (20.00%)
occurrences (all)	3	1	5
Pain			
subjects affected / exposed	4 / 47 (8.51%)	2 / 30 (6.67%)	1 / 20 (5.00%)
occurrences (all)	5	2	1
Peripheral swelling			

subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	4 / 47 (8.51%)	2 / 30 (6.67%)	3 / 20 (15.00%)
occurrences (all)	4	3	4
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 47 (0.00%)	2 / 30 (6.67%)	1 / 20 (5.00%)
occurrences (all)	0	3	1
Dyspnoea			
subjects affected / exposed	5 / 47 (10.64%)	6 / 30 (20.00%)	1 / 20 (5.00%)
occurrences (all)	5	8	1
Haemoptysis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 47 (14.89%)	2 / 30 (6.67%)	1 / 20 (5.00%)
occurrences (all)	7	2	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 47 (12.77%)	2 / 30 (6.67%)	3 / 20 (15.00%)
occurrences (all)	8	2	6
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 47 (10.64%)	5 / 30 (16.67%)	5 / 20 (25.00%)
occurrences (all)	6	5	9
Blood alkaline phosphatase increased			

subjects affected / exposed	3 / 47 (6.38%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	4	2	0
Blood bilirubin increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Blood creatinine increased			
subjects affected / exposed	6 / 47 (12.77%)	11 / 30 (36.67%)	4 / 20 (20.00%)
occurrences (all)	7	15	5
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Neutrophil count decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	4
Platelet count decreased			
subjects affected / exposed	2 / 47 (4.26%)	3 / 30 (10.00%)	3 / 20 (15.00%)
occurrences (all)	4	4	5
Transaminases increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	6 / 47 (12.77%)	7 / 30 (23.33%)	0 / 20 (0.00%)
occurrences (all)	7	9	0
White blood cell count decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Fall			

subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	3 / 20 (15.00%)
occurrences (all)	1	0	4
Head injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Toxicity to various agents			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 47 (10.64%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	5	0	1
Dysgeusia			
subjects affected / exposed	8 / 47 (17.02%)	7 / 30 (23.33%)	1 / 20 (5.00%)
occurrences (all)	8	8	1
Paraesthesia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	3 / 47 (6.38%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	3	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 47 (34.04%)	10 / 30 (33.33%)	8 / 20 (40.00%)
occurrences (all)	25	26	19
Leukocytosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Neutropenia			

subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Thrombocytopenia			
subjects affected / exposed	5 / 47 (10.64%)	6 / 30 (20.00%)	3 / 20 (15.00%)
occurrences (all)	10	9	3
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 47 (8.51%)	5 / 30 (16.67%)	2 / 20 (10.00%)
occurrences (all)	7	5	2
Abdominal pain upper			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	3 / 20 (15.00%)
occurrences (all)	0	1	3
Anorectal discomfort			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	10 / 47 (21.28%)	5 / 30 (16.67%)	5 / 20 (25.00%)
occurrences (all)	10	5	5
Diarrhoea			
subjects affected / exposed	6 / 47 (12.77%)	5 / 30 (16.67%)	1 / 20 (5.00%)
occurrences (all)	8	5	2
Dyspepsia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 30 (3.33%)	0 / 20 (0.00%)
occurrences (all)	3	1	0
Flatulence			
subjects affected / exposed	0 / 47 (0.00%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Dysphagia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	26 / 47 (55.32%)	9 / 30 (30.00%)	6 / 20 (30.00%)
occurrences (all)	35	11	8

Stomatitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	4
Swollen tongue			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	13 / 47 (27.66%)	6 / 30 (20.00%)	3 / 20 (15.00%)
occurrences (all)	19	8	4
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	1 / 47 (2.13%)	2 / 30 (6.67%)	1 / 20 (5.00%)
occurrences (all)	1	3	1
Rash			
subjects affected / exposed	2 / 47 (4.26%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	3
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 47 (4.26%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	4	0	1
Haematuria			
subjects affected / exposed	1 / 47 (2.13%)	4 / 30 (13.33%)	1 / 20 (5.00%)
occurrences (all)	1	4	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 47 (8.51%)	2 / 30 (6.67%)	1 / 20 (5.00%)
occurrences (all)	4	2	1
Back pain			
subjects affected / exposed	3 / 47 (6.38%)	3 / 30 (10.00%)	1 / 20 (5.00%)
occurrences (all)	3	3	1
Flank pain			
subjects affected / exposed	3 / 47 (6.38%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	3	3	0

Groin pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Muscle twitching			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	3
Musculoskeletal chest pain			
subjects affected / exposed	0 / 47 (0.00%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	1 / 47 (2.13%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Neck pain			
subjects affected / exposed	3 / 47 (6.38%)	0 / 30 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Pain in extremity			
subjects affected / exposed	0 / 47 (0.00%)	2 / 30 (6.67%)	0 / 20 (0.00%)
occurrences (all)	0	4	0
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Sialoadenitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Urinary tract infection			

subjects affected / exposed	4 / 47 (8.51%)	3 / 30 (10.00%)	3 / 20 (15.00%)
occurrences (all)	7	4	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 47 (29.79%)	7 / 30 (23.33%)	7 / 20 (35.00%)
occurrences (all)	20	9	9
Dehydration			
subjects affected / exposed	5 / 47 (10.64%)	4 / 30 (13.33%)	1 / 20 (5.00%)
occurrences (all)	5	5	1
Hyperglycaemia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 30 (3.33%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Hypokalaemia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 30 (3.33%)	2 / 20 (10.00%)
occurrences (all)	1	4	2
Hypomagnesaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 30 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Hyponatraemia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 30 (0.00%)	2 / 20 (10.00%)
occurrences (all)	4	0	2
Hypophosphataemia			
subjects affected / exposed	6 / 47 (12.77%)	3 / 30 (10.00%)	1 / 20 (5.00%)
occurrences (all)	7	5	2

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 97 (95.88%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant neoplasm progression			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	4		
Intermittent claudication			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 97 (17.53%)		
occurrences (all)	22		
Chest pain			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	40 / 97 (41.24%)		
occurrences (all)	61		
Localised oedema			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	5		
Nodule			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Oedema peripheral			

subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	8		
Peripheral swelling			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	9 / 97 (9.28%)		
occurrences (all)	11		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	14		
Haemoptysis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	10		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	16		

Aspartate aminotransferase increased			
subjects affected / exposed	15 / 97 (15.46%)		
occurrences (all)	20		
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	6		
Blood bilirubin increased			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	21 / 97 (21.65%)		
occurrences (all)	27		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	5		
Platelet count decreased			
subjects affected / exposed	8 / 97 (8.25%)		
occurrences (all)	13		
Transaminases increased			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	13 / 97 (13.40%)		
occurrences (all)	16		
White blood cell count decreased			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			

Back injury subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Fall subjects affected / exposed occurrences (all)	4 / 97 (4.12%) 5		
Head injury subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Joint injury subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Toxicity to various agents subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	6 / 97 (6.19%) 6		
Dysgeusia subjects affected / exposed occurrences (all)	16 / 97 (16.49%) 17		
Paraesthesia subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2		
Somnolence subjects affected / exposed occurrences (all)	4 / 97 (4.12%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	34 / 97 (35.05%) 70		
Leukocytosis			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	14 / 97 (14.43%)		
occurrences (all)	22		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 97 (11.34%)		
occurrences (all)	14		
Abdominal pain upper			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	4		
Anorectal discomfort			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	20 / 97 (20.62%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	12 / 97 (12.37%)		
occurrences (all)	15		
Dyspepsia			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	4		
Flatulence			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		

Nausea			
subjects affected / exposed	41 / 97 (42.27%)		
occurrences (all)	54		
Stomatitis			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	5		
Swollen tongue			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	22 / 97 (22.68%)		
occurrences (all)	31		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	5		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	5		
Haematuria			
subjects affected / exposed	6 / 97 (6.19%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	7		

Flank pain subjects affected / exposed occurrences (all)	5 / 97 (5.15%) 6		
Groin pain subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Muscle twitching subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Muscular weakness subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 5		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 3		
Neck pain subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 4		
Infections and infestations Bacterial vaginosis subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Lung infection subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1		
Sepsis subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 3		
Sialoadenitis			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	14		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 97 (28.87%)		
occurrences (all)	38		
Dehydration			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	11		
Hyperglycaemia			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	7		
Hypomagnesaemia			
subjects affected / exposed	2 / 97 (2.06%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	6		
Hypophosphataemia			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2018	Significant changes included: 1- Updates and clarifications to various inclusion/exclusion criteria. 2- The requirement for archival tumor tissue samples, which are tissue samples collected as part of the patient's standard of care in the past and are separate from the mandatory screening tumor tissue samples, were revised from being optional to being required, if available.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 April 2019	Enrollment was halted early on 09 April 2019 due to a lack of meaningful clinical benefit observed in an interim analysis as assessed by the DMC.	-

Notes:

Limitations and caveats

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

Data are available for 97 (of 200 planned) patients who received rucaparib 600 mg BID.

Notes: