



Clinical trial results:

A Phase 1/2 Trial of SRA737 (a Chk1 Inhibitor) Administered Orally in Subjects with Advanced Cancer

Summary

EudraCT number	2015-004486-86
Trial protocol	GB
Global end of trial date	28 October 2019

Results information

Result version number	v1 (current)
This version publication date	08 October 2021
First version publication date	08 October 2021
Summary attachment (see zip file)	SRA737-01 CSR Synopsis (SRA737-01 Final CSR synopsis (1).docx)

Trial information

Trial identification

Sponsor protocol code	SRA737-01
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02797964
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sierra Oncology, Inc.
Sponsor organisation address	1820 Gateway Drive, San Mateo, United States,
Public contact	Clinical Trial Information, Sierra Oncology, Inc., +1 604558-6575, pнадolny@sierraoncology.com
Scientific contact	Clinical Trial Information, Sierra Oncology, Inc., adye@sierraoncology.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	19 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2019
Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- 1) To establish the safety profile of SRA737.
- 2) To determine the maximum tolerated dose with 1 or more schedules of administrations of SRA737.
- 3) To propose a recommended Phase 2 dose and schedule of SRA737.
- 4) To evaluate the preliminary efficacy of SRA737 including efficacy in prospectively-selected genetically-defined subjects enrolled into indication-specific expansion cohorts.

Protection of trial subjects:

Ethics review and approval, informed consent, cohort review prior to enrolling new dose level cohort, dose modification in the event of toxicity, safety assessments including adverse events, clinical laboratory assessments, electrocardiograms, echocardiograms, vital signs, and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2016
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	United Kingdom: 107
Worldwide total number of subjects	107
EEA total number of subjects	0

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)	56
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening evaluations were carried out within 28 days before the first dose of SRA737, with the exception of pre-existing results for HPV status and tumor profiling from archival tumor tissue, which may have been carried out during pre-screening without time restriction.

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	Colorectal Cancer

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SRA737
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SRA737 was supplied as its citrate salt dispersed in a polyethylene glycol (PEG) semi solid formulation in capsules for oral administration, daily in 28 day cycles.

Arm title	High Grade Serous Ovarian Cancer
------------------	----------------------------------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SRA737
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SRA737 was supplied as its citrate salt dispersed in a polyethylene glycol (PEG) semi solid formulation in capsules for oral administration, daily in 28 day cycles.

Arm title	Non Small Cell Lung Cancer
------------------	----------------------------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	SRA737
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SRA737 was supplied as its citrate salt dispersed in a polyethylene glycol (PEG) semi solid formulation in

capsules for oral administration, daily in 28 day cycles.

Arm title	Metastatic Castration Resistant Prostate Cancer
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	SRA737
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SRA737 was supplied as its citrate salt dispersed in a polyethylene glycol (PEG) semi solid formulation in capsules for oral administration, daily in 28 day cycles.

Arm title	Head and Neck Squamous Cell Carcinoma
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	SRA737
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SRA737 was supplied as its citrate salt dispersed in a polyethylene glycol (PEG) semi solid formulation in capsules for oral administration, daily in 28 day cycles.

Arm title	Other Tumor Type
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	SRA737
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

SRA737 was supplied as its citrate salt dispersed in a polyethylene glycol (PEG) semi solid formulation in capsules for oral administration, daily in 28 day cycles.

Number of subjects in period 1	Colorectal Cancer	High Grade Serous Ovarian Cancer	Non Small Cell Lung Cancer
Started	32	37	10
Completed	32	37	10

Number of subjects in period 1	Metastatic Castration Resistant	Head and Neck Squamous Cell	Other Tumor Type
---------------------------------------	---------------------------------	-----------------------------	------------------

	Prostate Cancer	Carcinoma	
Started	16	4	8
Completed	16	4	8

Baseline characteristics

Reporting groups

Reporting group title	Colorectal Cancer
Reporting group description: -	
Reporting group title	High Grade Serous Ovarian Cancer
Reporting group description: -	
Reporting group title	Non Small Cell Lung Cancer
Reporting group description: -	
Reporting group title	Metastatic Castration Resistant Prostate Cancer
Reporting group description: -	
Reporting group title	Head and Neck Squamous Cell Carcinoma
Reporting group description: -	
Reporting group title	Other Tumor Type
Reporting group description: -	

Reporting group values	Colorectal Cancer	High Grade Serous Ovarian Cancer	Non Small Cell Lung Cancer
Number of subjects	32	37	10
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean standard deviation	61.3 ± 12.05	60.6 ± 9.81	64.4 ± 9.11
Gender categorical Units: Subjects			
Female	14	37	6
Male	18	0	4

Reporting group values	Metastatic Castration Resistant Prostate Cancer	Head and Neck Squamous Cell Carcinoma	Other Tumor Type
Number of subjects	16	4	8
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	68.3	63.0	58.4
standard deviation	± 6.76	± 6.06	± 6.46
Gender categorical Units: Subjects			
Female	0	0	4
Male	16	4	4

Reporting group values	Total		
Number of subjects	107		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	61		
Male	46		

Subject analysis sets

Subject analysis set title	Response Evaluable Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The Response Evaluable Population (REP) included all enrolled subjects who satisfy all of the following conditions:	
1. Measurable disease and assessment at baseline 2. Received at least 75% of 1 cycle of study medication, based on dosing information 3. At least one post baseline disease assessment OR discontinued treatment due to AE or disease progression or death	
Subject analysis set title	Safety Evaluable Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects received at least one dose of SRA737 are included in the Safety Evaluable Population.

Reporting group values	Response Evaluable Population	Safety Evaluable Population	
Number of subjects	81	107	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	62.8 ± 9.70	62.2 ± 10.04	
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Colorectal Cancer
Reporting group description: -	
Reporting group title	High Grade Serous Ovarian Cancer
Reporting group description: -	
Reporting group title	Non Small Cell Lung Cancer
Reporting group description: -	
Reporting group title	Metastatic Castration Resistant Prostate Cancer
Reporting group description: -	
Reporting group title	Head and Neck Squamous Cell Carcinoma
Reporting group description: -	
Reporting group title	Other Tumor Type
Reporting group description: -	
Subject analysis set title	Response Evaluable Population
Subject analysis set type	Per protocol

Subject analysis set description:

The Response Evaluable Population (REP) included all enrolled subjects who satisfy all of the following conditions:

1. Measurable disease and assessment at baseline
2. Received at least 75% of 1 cycle of study medication, based on dosing information
3. At least one post baseline disease assessment OR discontinued treatment due to AE or disease progression or death

Subject analysis set title	Safety Evaluable Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects received at least one dose of SRA737 are included in the Safety Evaluable Population.

Primary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR) ^{[1][2]}
End point description:	
The disease control rate (DCR) was defined as the number of subjects achieving complete response (CR) + partial response (PR) + stable disease (SD) per RECIST 1.1 criteria. Since no subjects achieved CR or PR in this study, the DCR represents the proportion of subjects in each group who achieved SD.	
End point type	Primary

End point timeframe:

Radiographic tumor assessments were performed every 2 cycles of therapy.

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: The DCR was calculated for each tumor-type subgroup.

[2] - 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: DCR was analyzed for each tumor-type subgroup.

End point values	Colorectal Cancer	High Grade Serous Ovarian Cancer	Non Small Cell Lung Cancer	Metastatic Castration Resistant Prostate Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	8	13
Units: Subjects	8	11	3	8

End point values	Head and Neck Squamous Cell Carcinoma	Response Evaluable Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	4	81		
Units: Subjects	3	34		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Progression (TTP)

End point title	Time to Progression (TTP) ^{[3][4]}
-----------------	---

End point description:

Time to progression (TTP) was defined as the time from Cycle 1 Day 1 to the earliest date of radiographic disease progression per RECIST 1.1, or if the subject did not experience disease progression, to the last imaging assessment. TTP was analyzed using the K-M method. The median value is reported without a measure of dispersion since the 95% CI could not be estimated due to insufficient number of participants with events.

End point type	Primary
----------------	---------

End point timeframe:

Radiographic tumor assessments were performed every 2 cycles of therapy. Follow-up assessments were made every 16 weeks for subjects who had not progressed and had not initiated new anticancer therapy.

Notes:

[3] - 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: TTP was analyzed using the Kaplan-Meier method. The output included count and percentage of subjects with death or censored outcome. Median OS and 95% CI based on log-log transformation were provided for tumor-type subgroups.

[4] - 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: TTP was analyzed for each tumor-type subgroup.

End point values	Colorectal Cancer	High Grade Serous Ovarian Cancer	Non Small Cell Lung Cancer	Metastatic Castration Resistant Prostate Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	26	8	13
Units: Months				
number (not applicable)	1.87	1.94	1.87	3.02

End point values	Head and Neck Squamous Cell Carcinoma	Response Evaluable Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	4	81		

Units: Months				
number (not applicable)	3.78	1.87		

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS) ^{[5][6]}
-----------------	---

End point description:

Progression free survival (PFS) was defined as time from Cycle 1 Day 1 to the earliest date of radiographic disease progression per RECIST 1.1 or death, whichever happened first. PFS was analyzed using the K-M method. The median value is reported without a measure of dispersion since the 95% CI could not be estimated due to insufficient number of participants with events.

End point type	Primary
----------------	---------

End point timeframe:

Radiographic tumor assessments were performed every 2 cycles of therapy. Follow-up assessments were made every 16 weeks for subjects who had not progressed and had not initiated new anticancer therapy.

Notes:

[5] - 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: PFS was analyzed using the Kaplan-Meier method. The output included count and percentage of subjects with death or censored outcome. Median OS and 95% CI based on log-log transformation were provided for tumor-type subgroups.

[6] - 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: PFS was analyzed for each tumor-type subgroup.

End point values	Colorectal Cancer	High Grade Serous Ovarian Cancer	Non Small Cell Lung Cancer	Metastatic Castration Resistant Prostate Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	26	8	13
Units: Months				
number (not applicable)	1.84	1.94	1.76	3.02

End point values	Head and Neck Squamous Cell Carcinoma	Response Evaluable Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	4	81		
Units: Months				
number (not applicable)	3.55	1.87		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS)

End point title	Overall Survival (OS) ^{[7][8]}
-----------------	---

End point description:

Overall survival (OS) was defined as time from Cycle 1 Day 1 to the date of death (or date last known to be alive). OS was analyzed using the K-M method. The median value is reported for 3 tumor type subgroups and without a measure of dispersion since the median survival and/or 95% CI could not be estimated in some cases due to insufficient number of participants with events.

End point type	Primary
----------------	---------

End point timeframe:

Follow-up assessments were made every 16 weeks for subjects who had not progressed and had not initiated new anticancer therapy.

Notes:

[7] - 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: OS was analyzed using the Kaplan-Meier method. The output included count and percentage of subjects with death or censored outcome. Median OS and 95% CI based on log-log transformation were provided for tumor-type subgroups.

[8] - 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: OS was analyzed for each tumor-type subgroup.

End point values	Colorectal Cancer	High Grade Serous Ovarian Cancer	Non Small Cell Lung Cancer	Response Evaluable Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	26	8	81
Units: Months				
number (not applicable)	5.72	6.93	6.08	6.93

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose (MTD)

End point title	Maximum Tolerated Dose (MTD) ^[9]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Cycle 1 (28 days) in the Dose Escalation Phase

Notes:

[9] - 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: The MTD of SRA737 was defined as the highest dose at which $\leq 33\%$ of subjects have a DLT in a cohort of up to 6 subjects during the dose escalation phase.

End point values	Safety Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	18 ^[10]			
Units: mg, QD				
number (not applicable)	1000			

Notes:

[10] - In the Dose Escalation Phase, a total of 18 subjects were enrolled into 8 daily dose levels

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase 2 Dose (RP2D)

End point title	Recommended Phase 2 Dose (RP2D) ^[11]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

Up to 30 days after last dose of SRA737

Notes:

[11] - 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: The RP2D of SRA737 was defined by the Cohort Review Committee at the end of the study and took all clinically relevant toxicity, PK and PDn data into account.

End point values	Safety Evaluable Population			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: mg QD				
number (not applicable)	800			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were reported until the safety Follow up (SFU) visit, 30 days after the last dose of SRA737 or prior to the initiation of a new anticancer treatment, whichever came first.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Safety Evaluable Population
-----------------------	-----------------------------

Reporting group description:

The Safety Evaluable Population includes all enrolled subjects who receive at least 1 dose of SRA737.

Serious adverse events	Safety Evaluable Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 107 (44.86%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	8		
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 107 (0.93%)		
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	10 / 107 (9.35%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 7		
Pyrexia			
subjects affected / exposed	4 / 107 (3.74%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stridor			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Biopsy liver			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Overdose			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Vomiting			

subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal discomfort			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	4 / 107 (3.74%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal sepsis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Intestinal sepsis				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lymphangitis				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal candidiasis				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 107 (0.93%)			
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	Safety Evaluable Population		
Total subjects affected by non-serious adverse events subjects affected / exposed	106 / 107 (99.07%)		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 7		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	54 / 107 (50.47%) 85 13 / 107 (12.15%) 13		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	19 / 107 (17.76%) 23		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 9		
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Blood creatinine increased	18 / 107 (16.82%) 22 14 / 107 (13.08%) 21 11 / 107 (10.28%) 19 10 / 107 (9.35%) 32		

subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	9		
Electrocardiogram QT prolonged			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	10		
White blood cell count decreased			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	24		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Platelet count decreased			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	14		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 107 (12.15%)		
occurrences (all)	13		
Lethargy			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	14		
Dysgeusia			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	25 / 107 (23.36%)		
occurrences (all)	48		
Neutropenia			

subjects affected / exposed	16 / 107 (14.95%)		
occurrences (all)	34		
Thrombocytopenia			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	16		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	74 / 107 (69.16%)		
occurrences (all)	131		
Nausea			
subjects affected / exposed	72 / 107 (67.29%)		
occurrences (all)	125		
Vomiting			
subjects affected / exposed	56 / 107 (52.34%)		
occurrences (all)	94		
Constipation			
subjects affected / exposed	19 / 107 (17.76%)		
occurrences (all)	26		
Abdominal pain			
subjects affected / exposed	17 / 107 (15.89%)		
occurrences (all)	23		
Abdominal distension			
subjects affected / exposed	11 / 107 (10.28%)		
occurrences (all)	17		
Dyspepsia			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	7		
Ascites			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	7		
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		

<p>Skin and subcutaneous tissue disorders</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash maculo-papular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 107 (10.28%)</p> <p>11</p> <p>11 / 107 (10.28%)</p> <p>18</p> <p>6 / 107 (5.61%)</p> <p>9</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 107 (6.54%)</p> <p>8</p>		
<p>Infections and infestations</p> <p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oral candidiasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cellulitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lower respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 107 (11.21%)</p> <p>15</p> <p>7 / 107 (6.54%)</p> <p>7</p> <p>6 / 107 (5.61%)</p> <p>8</p> <p>6 / 107 (5.61%)</p> <p>6</p> <p>6 / 107 (5.61%)</p> <p>8</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypokalaemia</p>	<p>26 / 107 (24.30%)</p> <p>36</p>		

subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	9		
Hypomagnesaemia			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	9		
Hyponatraemia			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2016	Addition of QTc exclusion criteria and amendments to contraceptive advice (prior to enrolment of subjects).
05 December 2016	The study was amended to assess preliminary efficacy in all subjects including 40 additional biomarker selected and indication specific subjects with tumors anticipated to be sensitive to inhibition of Chk1. Enrollment to Dose Escalation Phase and Cohort Expansion Phase was allowed to begin in parallel, prior to completion of the Dose Escalation Phase. Requirement was added for tumor tissue (archival or fresh biopsy) for tumor profiling.
10 February 2017	Clarification of the frequency of bone scans for subjects with prostate cancer. In addition, a clarification was provided for the microsatellite instability (MSI) testing criteria and ECG data collection.
18 May 2017	Removal of the maximum number of prior regimens criteria for subjects participating in the Cohort Expansion Phase and circulating tumor cells requirement for metastatic castration resistant prostate cancer (mCRPC) subjects.
14 September 2017	Increase the size of each indication specific cohort in the Cohort Expansion Phase from 8 to 20. The title of the study was changed from "Phase 1" to "Phase 1/2" to appropriately describe the current study design. The cohort enrolling subjects with squamous cell carcinoma of the head and neck (HNSCC) was amended to also include squamous cell carcinoma of the anus (SCCA). The schedule of assessments for PK sampling, central ECGs, and troponin were adjusted to improve coverage of relevant time points and reduce burden on subjects. Addition that the sponsor may choose to refine or select particular genomic profile requirements in expansion cohorts based on observations of tumor response and clinical benefit in the ongoing study and/or other emerging clinical and nonclinical data.
10 January 2018	Added a specific expansion cohort of approximately 20 subjects with high grade serous ovarian cancer (HGSOC) with CCNE1 gene amplification. This is in addition to the expansion cohort of subjects with HGSOC.
27 June 2018	The requirements for enrollment in the 2 expansion cohorts for subjects with HGSOC were revised. One cohort will enroll subjects with platinum resistant or refractory disease who are BRCA1 or BRCA2 mutant and the second will include subjects with platinum resistant or refractory disease who are BRCA1 and BRCA2 wild type. The size of both HGSOC cohorts was increased from the previous 20 subjects; the BRCA mutant cohort to 30 subjects and the BRCA wild type cohort to 35 subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported