Clinical trial results:
A Phase 1/2 Trial of Oral SRA737 (a Chk1 Inhibitor) Given in Combination with Gemcitabine plus Cisplatin or Gemcitabine Alone in Subjects with Advanced Cancer

Summary

EudraCT number	2015-004467-36
Trial protocol	GB ES
Global end of trial date	08 April 2020

Results information

Result version number	v1 (current)
This version publication date	25 November 2021
First version publication date	25 November 2021
Summary attachment (see zip file)	SRA737-02 CSR synopsis (2021_11_09 SRA737-02 CSR Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	SRA737-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02797977
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sierra Oncology, Inc.
Sponsor organisation address	1820 Gateway Drive Suite 110 , San Mateo, CA , United States, 94404
Public contact	Clinical Trial Information, Sierra Oncology, Inc., +1 604558-6575, sarbour@sierraoncology.com
Scientific contact	Clinical Trial Information, Sierra Oncology, Inc., +1 604558-6575, sarbour@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	14 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2020
Global end of trial reached?	Yes
Global end of trial date	08 April 2020
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 administered in combination with gemcitabine +/- cisplatin.

2) To determine the maximum tolerated dose (MTD) of SRA737 administered in combination with gemcitabine

3) To define a recommended Phase 2 dose (RP2D) of SRA737 in combination with gemcitabine

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	27 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	Spain: 36
Country: Number of subjects enrolled	United Kingdom: 117
Worldwide total number of subjects	153
EEA total number of subjects	36

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)	96
From 65 to 84 years	57
85 years and over	0

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?	No
Arm title	Stage 1 Dose Escalation

Arm description:

Stage 1 Dose Escalation included subjects with solid tumors who were treated in 3 different dose level cohorts of SRA737 (mg) plus gemcitabine (mg/m2) plus cisplatin (mg/m2): 20|600|80 (3 subjects), 20|875|80 (5 subjects) and 20|1250|80 (2 subjects).

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.
in Stage 1, SRA737 was taken PO approximately 24 and 48 hours after the end of the Day 1 and Day 8 gemcitabine infusions (ie, on Days 2, 3, 9, and 10).
In Stage 2, SRA737 was taken PO approximately 24 and 48 hours after the end of the Day 1, 8, and 15 gemcitabine infusions (ie, on Days 2, 3, 9, 10, 16, and 17).

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

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

Dosage and administration details:

Cisplatin was administered IV over 2 hours following gemcitabine on Day 1 of each 21-day cycle

Arm title	Stage 2 Dose Escalation

Arm description:

Stage 2 included subjects with solid tumors who were treated in 14 different dose level cohorts of SRA737 plus gemcitabine with SRA737 doses ranging from 20 to 600 mg and gemcitabine doses ranging from 50 to 300 mg/m2. Two subjects who were concurrently enrolled in both Stage 2 Dose Escalation and Stage 2 Cohort Expansion groups.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 Anogenital Cancer

Arm description:

This subset of Cohort Expansion patients with anogenital cancer also includes 1 Dose Escalation subject with anogenital cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 Cervical Cancer

Arm description:

This subset of Cohort Expansion patients with cervical cancer includes 1 concurrently-enrolled Dose Escalation/Expansion subject with cervical cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 HGSOC

Arm description:

This is a subset of Cohort Expansion patients with high-grade serous ovarian cancer (HGSOC). The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 Rectal Cancer

Arm description:

This is a subset of Dose Escalation patients with rectal cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 SCLC

Arm description:

This is a subset of Cohort Expansion patients with small cell lung cancer (SCLC). The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 STS

Arm description:

This subset of Cohort Expansion patients with soft tissue sarcoma (STS) includes 1 concurrently-enrolled Dose Escalation/Expansion subject with STS. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Stage 2 Urothelial Cancer

Arm description:

This is a subset of Cohort Expansion patients with urothelial cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

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.

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

Arm title	Overall Stage 1 and Stage 2

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.
in Stage 1, SRA737 was taken PO approximately 24 and 48 hours after the end of the Day 1 and Day 8 gemcitabine infusions (ie, on Days 2, 3, 9, and 10).
In Stage 2, SRA737 was taken PO approximately 24 and 48 hours after the end of the Day 1, 8, and 15 gemcitabine infusions (ie, on Days 2, 3, 9, 10, 16, and 17).

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

Dosage and administration details:

In Stage 1, gemcitabine was administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle.
In Stage 2, gemcitabine was administered IV over 30 minutes on Days 1, 8 and 15.

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

Dosage and administration details:

Cisplatin was administered IV over 2 hours following gemcitabine on Day 1 of each 21-day cycle

Number of subjects in period 1	Stage 1 Dose Escalation	Stage 2 Dose Escalation	Stage 2 Anogenital Cancer
Started	10	58	15
Completed	10	58	15

Number of subjects in period 1	Stage 2 Cervical Cancer	Stage 2 HGSOC	Stage 2 Rectal Cancer
Started	12	24	15
Completed	12	24	15

Number of subjects in period 1	Stage 2 SCLC	Stage 2 STS	Stage 2 Urothelial Cancer
Started	22	11	4
Completed	22	11	4

Number of subjects in period 1	Overall Stage 1 and Stage 2
Started	153
Completed	153

Baseline characteristics

Reporting groups

Reporting group title	Stage 1 Dose Escalation

Reporting group description:

Stage 1 Dose Escalation included subjects with solid tumors who were treated in 3 different dose level cohorts of SRA737 (mg) plus gemcitabine (mg/m2) plus cisplatin (mg/m2): 20|600|80 (3 subjects), 20|875|80 (5 subjects) and 20|1250|80 (2 subjects).

Reporting group title	Stage 2 Dose Escalation

Reporting group description:

Stage 2 included subjects with solid tumors who were treated in 14 different dose level cohorts of SRA737 plus gemcitabine with SRA737 doses ranging from 20 to 600 mg and gemcitabine doses ranging from 50 to 300 mg/m2. Two subjects who were concurrently enrolled in both Stage 2 Dose Escalation and Stage 2 Cohort Expansion groups.

Reporting group title	Stage 2 Anogenital Cancer

Reporting group description:

This subset of Cohort Expansion patients with anogenital cancer also includes 1 Dose Escalation subject with anogenital cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 Cervical Cancer

Reporting group description:

This subset of Cohort Expansion patients with cervical cancer includes 1 concurrently-enrolled Dose Escalation/Expansion subject with cervical cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 HGSOC

Reporting group description:

This is a subset of Cohort Expansion patients with high-grade serous ovarian cancer (HGSOC). The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 Rectal Cancer

Reporting group description:

This is a subset of Dose Escalation patients with rectal cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 SCLC

Reporting group description:

This is a subset of Cohort Expansion patients with small cell lung cancer (SCLC). The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 STS

Reporting group description:

This subset of Cohort Expansion patients with soft tissue sarcoma (STS) includes 1 concurrently-enrolled Dose Escalation/Expansion subject with STS. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 Urothelial Cancer

Reporting group description:

This is a subset of Cohort Expansion patients with urothelial cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Overall Stage 1 and Stage 2

Reporting group description: -

Reporting group values	Stage 1 Dose Escalation	Stage 2 Dose Escalation	Stage 2 Anogenital Cancer
Number of subjects	10	58	15
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.9	61.0	61.3
standard deviation	± 12.63	± 12.35	± 8.60
Gender categorical Units: Subjects			
Female	4	32	11
Male	6	26	4

Reporting group values	Stage 2 Cervical Cancer	Stage 2 HGSOC	Stage 2 Rectal Cancer
Number of subjects	12	24	15
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.4	61.6	61.8
standard deviation	± 13.47	± 8.76	± 11.38
Gender categorical Units: Subjects			
Female	12	24	4
Male	0	0	11

Reporting group values	Stage 2 SCLC	Stage 2 STS	Stage 2 Urothelial Cancer
Number of subjects	22	11	4
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.5	57.5	61.5
standard deviation	± 8.91	± 15.58	± 7.85
Gender categorical Units: Subjects			
Female	8	7	1
Male	14	4	3

Reporting group values	Overall Stage 1 and Stage 2	Total	
Number of subjects	153	153	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	 59.9 ± 11.49	 -	
Gender categorical Units: Subjects			
Female Male	91 62	91 62	

Subject analysis sets

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

Subject analysis set description:

The Safety Evaluable Population includes all enrolled subjects who receive at least 1 dose of SRA737, gemcitabine, or cisplatin. Subjects who received the single dose for PK evaluation but never received study treatment during the treatment phase are also included in this population.

Subject analysis set title	Response Evaluable Population
Subject analysis set type	Per protocol

Subject analysis set description:

The Response Evaluable Population (REP) is the primary population used for efficacy analyses. The REP includes all enrolled subjects who satisfy all of the following conditions:
1. Have measurable disease assessment at baseline (for inclusion in Expansion Cohorts, subjects also need to meet the appropriate protocol criteria for genetically defined tumor)
2. Received at least 75% (Stage 1) or 83% (Stage 2) of SRA737 in Cycle 1
3. Have at least one post baseline disease assessment OR discontinued treatment due to AE or disease progression or death

Reporting group values	Safety Evaluable Population	Response Evaluable Population	
Number of subjects	153	105	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	 59.9 ± 11.49	 ±	
Gender categorical Units: Subjects			
Female Male	91 62		

End points

End points reporting groups

Reporting group title	Stage 1 Dose Escalation

Reporting group description:

Stage 1 Dose Escalation included subjects with solid tumors who were treated in 3 different dose level cohorts of SRA737 (mg) plus gemcitabine (mg/m2) plus cisplatin (mg/m2): 20|600|80 (3 subjects), 20|875|80 (5 subjects) and 20|1250|80 (2 subjects).

Reporting group title	Stage 2 Dose Escalation

Reporting group description:

Stage 2 included subjects with solid tumors who were treated in 14 different dose level cohorts of SRA737 plus gemcitabine with SRA737 doses ranging from 20 to 600 mg and gemcitabine doses ranging from 50 to 300 mg/m2. Two subjects who were concurrently enrolled in both Stage 2 Dose Escalation and Stage 2 Cohort Expansion groups.

Reporting group title	Stage 2 Anogenital Cancer

Reporting group description:

This subset of Cohort Expansion patients with anogenital cancer also includes 1 Dose Escalation subject with anogenital cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 Cervical Cancer

Reporting group description:

This subset of Cohort Expansion patients with cervical cancer includes 1 concurrently-enrolled Dose Escalation/Expansion subject with cervical cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 HGSOC

Reporting group description:

This is a subset of Cohort Expansion patients with high-grade serous ovarian cancer (HGSOC). The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 Rectal Cancer

Reporting group description:

This is a subset of Dose Escalation patients with rectal cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 SCLC

Reporting group description:

This is a subset of Cohort Expansion patients with small cell lung cancer (SCLC). The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 STS

Reporting group description:

This subset of Cohort Expansion patients with soft tissue sarcoma (STS) includes 1 concurrently-enrolled Dose Escalation/Expansion subject with STS. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Stage 2 Urothelial Cancer

Reporting group description:

This is a subset of Cohort Expansion patients with urothelial cancer. The majority of subjects in Stage 2 received doses of at least 500 mg SRA737 + 250 mg/m2 gemcitabine, which was ultimately determined to be the RP2D.

Reporting group title	Overall Stage 1 and Stage 2

Reporting group description: -

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

Subject analysis set description:

The Safety Evaluable Population includes all enrolled subjects who receive at least 1 dose of SRA737, gemcitabine, or cisplatin. Subjects who received the single dose for PK evaluation but never received study treatment during the treatment phase are also included in this population.

Subject analysis set title	Response Evaluable Population
Subject analysis set type	Per protocol

Subject analysis set description:

The Response Evaluable Population (REP) is the primary population used for efficacy analyses. The REP includes all enrolled subjects who satisfy all of the following conditions:
1. Have measurable disease assessment at baseline (for inclusion in Expansion Cohorts, subjects also need to meet the appropriate protocol criteria for genetically defined tumor)
2. Received at least 75% (Stage 1) or 83% (Stage 2) of SRA737 in Cycle 1
3. Have at least one post baseline disease assessment OR discontinued treatment due to AE or disease progression or death

Primary: Stage 2 Recommended Phase 2 Dose (RP2D)

End point title	Stage 2 Recommended Phase 2 Dose (RP2D)[1][2]

End point description:

The recommended phase 2 dose (RP2D) of SRA737 combined with 250 mg/m2 gemcitabine.

End point type	Primary

End point timeframe:

Stage 2 Dose Escalation Phase

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 RP2D of SRA737 + LDG 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.
[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: The RP2D of SRA737 + LDG 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	Stage 2 Dose Escalation			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: mg				
number (not applicable)	500			

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2 Objective Response Rate (ORR)

End point title	Stage 2 Objective Response Rate (ORR)[3]

End point description:

The objective response rate (ORR) was defined as the number of subjects achieving CR + PR, including unconfirmed responses. Since no subjects achieved CR in this study, the ORR represents the proportion of subjects in each group who achieved PR.

End point type	Secondary

End point timeframe:

Radiographic tumor assessments were performed every 2 cycles of therapy.

Notes:

[3] - 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: ORR was analyzed for each tumor-type subgroup.

End point values	Stage 2 Anogenital Cancer	Stage 2 Cervical Cancer	Stage 2 HGSOC	Stage 2 Rectal Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	15	10
Units: Patients	3	1	1	1

End point values	Stage 2 SCLC	Stage 2 STS	Stage 2 Urothelial Cancer	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	4	
Units: Patients	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2 Disease Control rate (DCR)

End point title	Stage 2 Disease Control rate (DCR)[4]

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 in this study, the DCR represents the proportion of subjects in each group who achieved SD or PR.

End point type	Secondary

End point timeframe:

Radiographic tumor assessments were performed every 2 cycles of therapy.

Notes:

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

End point values	Stage 2 Anogenital Cancer	Stage 2 Cervical Cancer	Stage 2 HGSOC	Stage 2 Rectal Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	15	10
Units: Patients	6	4	10	6

End point values	Stage 2 SCLC	Stage 2 STS	Stage 2 Urothelial Cancer	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	4	
Units: Patients	5	5	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2 Time to Progression (TTP)

End point title	Stage 2 Time to Progression (TTP)[5]

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	Secondary

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] - 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	Stage 2 Anogenital Cancer	Stage 2 Cervical Cancer	Stage 2 HGSOC	Stage 2 Rectal Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	15	10
Units: Months				
number (not applicable)	3.6	3.06	3.48	2.83

End point values	Stage 2 SCLC	Stage 2 STS	Stage 2 Urothelial Cancer	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	4	
Units: Months				
number (not applicable)	2.99	3.15	6.51	

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2 Progression Free Survival (PFS)

End point title	Stage 2 Progression Free Survival (PFS)[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 for 6 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	Secondary

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:

[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	Stage 2 Anogenital Cancer	Stage 2 Cervical Cancer	Stage 2 HGSOC	Stage 2 Rectal Cancer
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	15	10
Units: Months				
number (not applicable)	3.6	3.06	3.48	2.83

End point values	Stage 2 SCLC	Stage 2 STS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Months				
number (not applicable)	1.97	3.15		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2 Overall Survival (OS)

End point title	Stage 2 Overall Survival (OS)[7]

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 1 tumor type subgroup and without a measure of dispersion since the median survival and/or 95% CI could not be estimated in other groups due to insufficient number of participants with events.

End point type	Secondary

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] - 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	Stage 2 SCLC			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Months				
number (not applicable)	3.81			

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 Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 153 (31.37%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	2 / 153 (1.31%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	2 / 153 (1.31%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 153 (1.31%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Incisional hernia repair			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureteral stent insertion			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 153 (11.11%)		
occurrences causally related to treatment / all	8 / 19		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 6		
Oedema peripheral			
subjects affected / exposed	3 / 153 (1.96%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Non-cardiac chest pain			
subjects affected / exposed	2 / 153 (1.31%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 153 (0.65%)		
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	6 / 153 (3.92%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	4 / 153 (2.61%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 153 (1.96%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stoma output decreased				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Troponin I increased				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Overdose				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Drug administration error				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				

subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiation pneumonitis				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pericardial effusion				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dysaesthesia				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sensory disturbance				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				

Febrile neutropenia				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Small intestinal obstruction				
subjects affected / exposed	4 / 153 (2.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Ascites				
subjects affected / exposed	3 / 153 (1.96%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 153 (1.96%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				

subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lip swelling				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 153 (0.65%)			
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 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Swelling face				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urticaria				

subjects affected / exposed	1 / 153 (0.65%)		
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	2 / 153 (1.31%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	2 / 153 (1.31%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive uropathy			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	5 / 153 (3.27%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		

Lung infection				
subjects affected / exposed	5 / 153 (3.27%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Bronchitis				
subjects affected / exposed	3 / 153 (1.96%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	3 / 153 (1.96%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 153 (1.96%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	3 / 153 (1.96%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal infection				

subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter infection				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gingivitis				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious colitis				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 153 (69.28%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	41 / 153 (26.80%)		
occurrences (all)	92		
Aspartate aminotransferase increased			
subjects affected / exposed	36 / 153 (23.53%)		
occurrences (all)	81		
Platelet count decreased			
subjects affected / exposed	17 / 153 (11.11%)		
occurrences (all)	59		
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 153 (9.80%)		
occurrences (all)	24		
Weight decreased			
subjects affected / exposed	14 / 153 (9.15%)		
occurrences (all)	16		
White blood cell count decreased			
subjects affected / exposed	11 / 153 (7.19%)		
occurrences (all)	23		
Blood creatinine increased			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	14		
Neutrophil count decreased			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	31		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 153 (13.73%)		
occurrences (all)	34		
Lethargy			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	17		
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	80 / 153 (52.29%)		
occurrences (all)	156		
Pyrexia			
subjects affected / exposed	44 / 153 (28.76%)		
occurrences (all)	94		
Influenza like illness			
subjects affected / exposed	23 / 153 (15.03%)		
occurrences (all)	36		
Asthenia			
subjects affected / exposed	16 / 153 (10.46%)		
occurrences (all)	39		
Oedema peripheral			
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	17		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	69 / 153 (45.10%)		
occurrences (all)	168		
Neutropenia			
subjects affected / exposed	52 / 153 (33.99%)		
occurrences (all)	170		
Thrombocytopenia			
subjects affected / exposed	41 / 153 (26.80%)		
occurrences (all)	100		
Lymphopenia			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	18		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	95 / 153 (62.09%)		
occurrences (all)	213		
Vomiting			
subjects affected / exposed	84 / 153 (54.90%)		
occurrences (all)	193		
Diarrhoea			

subjects affected / exposed	73 / 153 (47.71%)		
occurrences (all)	134		
Constipation			
subjects affected / exposed	41 / 153 (26.80%)		
occurrences (all)	52		
Abdominal pain			
subjects affected / exposed	21 / 153 (13.73%)		
occurrences (all)	33		
Dyspepsia			
subjects affected / exposed	14 / 153 (9.15%)		
occurrences (all)	16		
Abdominal distension			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	10		
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 153 (14.38%)		
occurrences (all)	25		
Dyspnoea			
subjects affected / exposed	22 / 153 (14.38%)		
occurrences (all)	34		
Oropharyngeal pain			
subjects affected / exposed	9 / 153 (5.88%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	16 / 153 (10.46%)		
occurrences (all)	25		
Rash maculo-papular			
subjects affected / exposed	13 / 153 (8.50%)		
occurrences (all)	23		
Pruritus			

subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	14		
Dry skin			
subjects affected / exposed	9 / 153 (5.88%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	26 / 153 (16.99%)		
occurrences (all)	36		
Arthralgia			
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	15		
Myalgia			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	12		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	21 / 153 (13.73%)		
occurrences (all)	32		
Lower respiratory tract infection			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	11		
Oral candidiasis			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	11		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 153 (30.07%)		
occurrences (all)	75		
Hypokalaemia			
subjects affected / exposed	13 / 153 (8.50%)		
occurrences (all)	20		
Hypomagnesaemia			
subjects affected / exposed	13 / 153 (8.50%)		
occurrences (all)	39		
Hyponatraemia			

subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	19		
Hypoalbuminaemia			
subjects affected / exposed	9 / 153 (5.88%)		
occurrences (all)	16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2016	Addition of hearing impairment and history of allergy to cisplatin or gemcitabine exclusion criteria and amendments to contraceptive advice (made at the request of the MHRA prior to approval)
11 October 2016	Sponsor change – All sponsor-specific details were updated to reflect the new sponsor Sierra Oncology, Inc. (formerly known as ProNAi Therapeutics, Inc.), including sponsor name, responsibilities, address, emergency contact details, and the protocol title and number.
05 December 2016	Protocol Amendment v4.0 included changes to the name of the sponsor and investigational product. In addition, the study was amended to focus on assessment of safety and preliminary efficacy in subjects with tumors anticipated to be sensitive to inhibition of Chk1 mainly in the SRA737+gemcitabine combination. Procedures were revised to ensure appropriate subject selection, in accordance with the new and retained study objectives. Protocol Amendment v4.0 removed the Stage 2 expansion cohort of 8 subjects with solid tumors of any type, but retained the Stage 2 expansion cohort of 6 subject with bladder or pancreatic cancer as defined in previous protocol versions.
17 February 2017	Protocol Amendment v5.0 updated the frequency of bone scans. In addition, clarifications were provided for IMP dosing, tumor biopsies, and laboratory assessments. Protocol Amendment Version 5.0 ended enrollment in Stage 1 of the protocol and initiated Stage 2.
05 October 2017	Protocol Amendment v6.0 changed the indications in the Stage 2 Cohort Expansion Phase (adding small cell lung cancer, cervical/anogenital cancer, and soft tissue sarcoma; retaining bladder/urothelial cancer; and removing pancreatic cancer) and increased the size of each cohort from 6-8 subjects to approximately 20 subjects. The genetic selection strategy was modified so that the sponsor could choose to refine or select particular genetic 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported