SRA737-02 CLINICAL STUDY REPORT SYNOPSIS

Study Title:	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
Study Number:	SRA737-02
Study Phase:	Phase 1/2
Compound:	SRA737
Indication:	Solid tumors
Brief Description:	Multicenter, first-in-human, Phase 1/2, open-label, dose-escalation trial of SRA737 given in combination with gemcitabine + cisplatin or gemcitabine alone in subjects with advanced solid tumors, with expansion to indication-specific Expansion Cohorts
Study Sponsor:	Sierra Oncology, Inc. 46701 Commerce Center Drive Plymouth, MI 48170 Tel: 734-233-3966
Study Initiation Date:	03 August 2016 (first dose of SRA737)
Study Completion Date:	08 April 2020 (last subject visit) The analyses presented in this report are based on a database lock date of 14 May 2020
Regulatory Agency Identifier Number:	EudraCT Number: 2015-004467-36 NCT Number: NCT02797977
Report Date:	Final CSR 09 Nov 2021
This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline, including the archiving of essential documents.	

SYNOPSIS

Number of Study Center(s) and Countries: This study was conducted at 21 centers: 15 centers in the UK and 6 centers in Spain.

Publications:

U Banerji, ER Plummer, V Moreno, et al. A phase I/II first-in-human trial of oral SRA737 (a Chk1 inhibitor) given in combination with low-dose gemcitabine in subjects with advanced cancer. American Society of Clinical Oncology. 2019; Abstract 3095.

Rationale: SRA737 is a highly selective, orally bioavailable small molecule inhibitor of Chk1, a central regulator of the DNA damage response (DDR) network. In cancer cells, replication stress (RS) induced by oncogenes (eg, MYC and RAS oncogenes) combined with loss of function in tumor suppressors (eg, TP53) or DDR genes (eg, BRCA1) results in persistent DNA damage, genomic instability, and increased reliance on the functional DDR network. Additional RS can be generated by treatment with exogenous inducers of RS, ie, cytotoxic chemotherapy. Combination of SRA737 with exogenous inducers of RS is hypothesized to synergize with active doses of SRA737 leading to greater antitumor effect.

In Stage 1 of the of this study, SRA737 was combined with cisplatin which causes DNA cross-linking, and gemcitabine which is a potent inducer of RS and DNA damage via multiple mechanisms, including induction of DNA double strand breaks and stalled replication forks. In Stage 2 of the Cohort Expansion Phase, SRA737 was combined with only gemcitabine.

Gemcitabine is a potent and irreversible inhibitor of ribonucleotide reductase (RNR), the rate-limiting enzyme responsible for generating the deoxyribonucleotide (dNTP) supply needed for DNA replication. Very low, non-cytotoxic concentrations of gemcitabine can result in dNTP depletion, stalled replication forks, and activation of Chk1. Once activated, Chk1 manages RS by pausing cell cycle progression and limiting further replication origin firing. In addition, activated Chk1 triggers increased RNR expression to recover the diminished dNTP pool. As such, simultaneous inhibition of Chk1 by SRA737 results in synergy with low-dose gemcitabine (LDG), leading to catastrophic RS and tumor cell death.

In summary, preclinical and clinical data support the hypothesis that low-dose gemcitabine may strongly synergize with active doses of SRA737. To test this hypothesis, low-dose gemcitabine in combination with SRA737 was explored in Stage 2 of this study.

Specific Expansion Cohort indications were selected with prospectively-selected genetically-defined subjects in tumor types that are known to have a high prevalence of genomic aberrations hypothesized to sensitize the tumor to Chk1 inhibition. Prospective selection of patients most likely to derive benefit from SRA737 in combination with gemcitabine was implemented to provide data to support the selection of specific indications and inform refinement of patient selection strategies in further clinical development. The indications for the Expansion Cohorts were selected both on the scientific hypothesis of greater likelihood for benefit as well as the high unmet medical need in these populations where alternative therapies are required.

Objectives, Endpoints, Estimands, and Statistical Methods: Study SRA737-02 study objectives and endpoints are described in the table below.

SRA737-02 Study Objectives

Primary Objectives	**Endpoints**
To establish the safety profile of SRA737 administered in combination with gemcitabine ± cisplatin.	Safety parameters (referencing National Cancer Institute – Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.03) including: incidence, seriousness, severity and causality of each adverse event (AE) to SRA737, cisplatin, and/or gemcitabine, timing of AE onset, AE duration, and AEs leading to interruption, modification, or discontinuation of study treatment, and primary reason for discontinuation of study treatment if other than disease progression [PD], laboratory (eg, clinical chemistry, hematology, urinalysis) and vital sign data.
To determine the maximum tolerated dose (MTD) of SRA737 administered in combination with gemcitabine.	The highest dose at which ≤ 33% of subjects have a dose limiting toxicity (DLT) in a cohort of up to 6 subjects.
To define a recommended Phase 2 dose (RP2D) of SRA737 administered in combination with gemcitabine.	A safe and well tolerated dose and schedule that provides high exposure, based on all available PK, PDn, and safety parameter data from all cycles of therapy.
Secondary Objectives	**Endpoints**
To characterize the pharmacokinetic profile of SRA737	Plasma concentration-time profiles of SRA737 based on PK parameters including but not limited to: AUC_{inf}, AUC_{tau}, Cmin, C_{max}, t_{max}, and $t_{1/2}$
To assess clinical activity of SRA737 in combination with gemcitabine. Activity of SRA737 in combination with gemcitabine + cisplatin will also be explored as feasible based on the number of subjects enrolled.	• Objective response rate (ORR) as measured by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) • Duration of response (DOR) • Disease control rate (DCR) • Time to response (TTR) • Progression-free survival (PFS) • Time to progression (TTP) • Overall survival (OS)

SRA737-02 Study Objectives (Continued)

Primary Objectives	**Endpoints**
Exploratory Objectives	**Endpoints**
To assess the relationship between response and the presence of selected genetic alterations detected in tumor tissue or circulating tumor deoxyribonucleic acid (ctDNA)	Objective response rate as measured by RECIST v1.1 and gene alterations in tumor tissue or ctDNA at baseline as measured by next generation sequencing (NGS).

To explore possible clinical predictors of outcomes.	Characteristics such as performance status, prior therapy, indication and other known or potential prognostic or predictive factors.
To investigate the PDn of SRA737 in combination with gemcitabine in tumor tissue.	Proof of target engagement and changes in mechanism of action biomarkers between baseline and on treatment with SRA737, including, but not limited to: pSer296 Chk1, pS317 Chk1, and total Chk1.
To investigate the PDn of SRA737 in combination with gemcitabine in surrogate tissues such as blood or peripheral blood mononuclear cell (PBMCs).	Proof of target engagement and changes in mechanism of action biomarkers between baseline and on treatment with SRA737, including but not limited to: Comet assay, pS296 Chk1, pS317 Chk1, pS345 Chk1, total Chk1, gammaH2AX and RAD51.

Statistical Methods:

Sample Size: The study was planned to enroll up to 140 subjects in total. Planned subjects included 10 subjects in Stage 1, 30 to 40 subjects in Stage 2 Dose Escalation, and 90 subjects in the Stage 2 expansion cohorts (up to 8 subjects from the original protocol-defined expansion cohort plus 20 prospectively-selected genetically-defined subjects in each of 4 indication-specific expansion cohorts added with Protocol Amendment v6.0). The sample size for the Dose Escalation phase was based on assumptions of the likely MTD based on allometric scaling and was dependent on the number of dose levels required to establish the MTD and RP2D. A planned sample size of 20 subjects enrolled in each indication specific Dose Expansion cohort was chosen such that 0 responses of 20 subjects observed excludes an observed objective response rate (ORR) of 16% in the 95% confidence interval.

Analysis Populations: The Safety Evaluable Population includes all enrolled subjects who receive at least 1 dose of any IMP (SRA737, gemcitabine, or cisplatin).

The definition of DLT evaluable used for the Stage 1 triplet combination was as follows (per Protocol Version 2.0): “All subjects receiving at least 75% of planned doses of SRA737 within Cycle 1 and those subjects receiving less than these planned dose of SRA737 due to DLT will be evaluable for dose review decisions.” Subsequently (Protocol Version 4.0 onward), the following definition of DLT evaluable was used for the Stage 2 doublet combination: “All subjects receiving at least 5 out of the 6 (83%) planned doses of SRA737 and all doses of gemcitabine (or the equivalent if the sponsor elects to evaluate an alternative dosing schedule) within Cycle 1 and those subjects receiving less than these planned doses of SRA737 due to IMP-related toxicity will be included in the DLT evaluable population.”

The Response Evaluable Population (REP), which is the primary population used for efficacy analyses, and the alternative Response Evaluable Population (aREP) includes all enrolled subjects who satisfy all of the following conditions:

1. Have measurable disease and assessment at baseline (for inclusion in Expansion Cohorts, subjects also need to meet the appropriate protocol criteria for genetically-defined tumor)
2. Meet REP criteria (a) or aREP alternative criteria (b), based on the dosing information:

a. Received at least 75% (Stage 1) or 83% (Stage 2) of SRA737 in Cycle 1
b. Alternative definition used for some exploratory efficacy analyses: Received at least 75% (Stage 1) or 83% (Stage 2) of SRA737 in Cycle 1 with initial dose ≥ 150 mg and initial gemcitabine dose ≥ 100 mg/m^2, or still on study treatment in Cycle 3.

3. Have at least one post-baseline disease assessment OR discontinued treatment due to AE or disease progression or death

The PK Evaluable Population included all subjects who received at least 1 dose of SRA737 and provided at least 1 evaluable PK concentration. The PDn Evaluable Population included all enrolled subjects who received at least 1 dose of SRA737 and for whom adequate data were available.

Efficacy Analysis: The analysis of all efficacy endpoints was performed on the REP and in addition, subjects meeting the criteria for the aREP were identified. Efficacy endpoints were based on the investigator's determination of Overall Response at each disease assessment time point. Response was assessed by the investigator using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria (Eisenhauer, 2009). Partial or complete responses were to be confirmed by repeat tumor imaging assessments not less than 4 weeks from the date the response was first documented. In addition, the best overall response without checking the confirmation (Unconfirmed + Confirmed) was also presented alongside the confirmed responses.

The best overall response was summarized for the following endpoints with count and percentage: CR (complete response); PR (partial response); SD (stable disease); PD (progressive disease); NE (not evaluable), and ORR (CR + PR) with 95% confidence interval (Exact [Clopper-Pearson] method (Clopper, 1934).

Descriptive analyses were prepared of the distribution of ORR, DCR, TTR, DOR, PFS, and TTP. In addition to TTP by RECIST 1.1 criteria based only on radiographic assessments, a second definition of TTP which incorporates clinical progression was used.

Duration of stable disease was defined as time from Cycle 1 Day 1 to the date of disease progression or death. Change in target tumor size was based on each time point of imaging assessment, at which the sum of the longest diameter of each target lesions was derived. The change and percentage change in tumor size from baseline to the post baseline nadir was summarized. A waterfall plot of best percent change from baseline (from baseline to nadir) by tumor type cohorts was created. 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 Kaplan–Meier method.

Rigorous evaluation of associations between tumor response and genetic alterations was not possible due to paucity of necessary data; however a preliminary survey of the genetic profiles was performed for subjects who achieved PR or achieved SD for at least 4 cycles.

Extent of Exposure and Compliance: Cycle 1 SRA737 compliance was used as part of the definition of the Response Evaluable Population and was summarized as follows:

- Stage 1: Number of SRA737 doses received on Day 2, 3, 9, and 10 divided by 4 * 100%
- Stage 2: Number of SRA737 doses received on Day 2,3, 9, 10, 16, and 17 divided by 6 * 100%

Treatment duration and dose intensity for SRA737, gemcitabine, and cisplatin were summarized numerically.

Safety Analysis: Adverse event data were collected from the date of written informed consent. Safety variables were summarized by descriptive statistics. Treatment-emergent AEs were reported for each dose level and coded using MedDRA version 19.1, presented as tables of incidence of AEs by body system and by worst severity grade observed. Treatment-related AEs were defined as AEs for which the investigator classified the relationship to that IMP (SRA737, gemcitabine, or cisplatin) as "highly probable", "probable", or "possible, whereas those marked "unlikely" or "not related" were considered unrelated to that IMP.

Laboratory variables were described using the NCI CTCAE v4.03. All continuous laboratory parameters in biochemistry and hematology were summarized descriptively by actual value at each scheduled visit and the corresponding changes from baseline. The maximum post baseline and minimum post baseline (including both scheduled and unscheduled results) was also provided. Shift tables from baseline to visit were provided for hematology and chemistry parameters to display low, normal, high, and missing values by treatment group in a 3-by-3 contingency table.

Local ECG parameters, ECHO parameters, and vital signs were presented using actual values and change from baseline for scheduled visits.

Pharmacokinetics Analysis: Plasma concentrations of SRA737 were determined using a validated bioanalytical method and summarized using descriptive statistics. Pharmacokinetic parameters including but not limited to C_{min}, C_{max}, t_{max}, AUC, $t_{½}$, total body clearance, and apparent volume of distribution were determined using non-compartmental methods.

Methodology: This was a multicenter, first-in-human, Phase 1/2, open-label, dose escalation trial in subjects with advanced solid tumors.

The trial consisted of 2 stages:

- Stage 1: SRA737 + gemcitabine + cisplatin Dose Escalation Phase

  Subjects were recruited to Stage 1 and Stage 2 Dose Escalation cohorts according to a rolling 6 design. Ten subjects with solid tumors in cohorts of 3 to 6 subjects were enrolled in Stage 1 of the study. Upon implementation of Protocol Amendment v5.0, dose escalation in Stage 1 was halted.

- Stage 2: SRA737 + low-dose gemcitabine (LDG) Dose Escalation and Cohort Expansion Phases

  In the Stage 2 Dose Escalation Phase, approximately 30-40 subjects with solid tumors in cohorts of 3 to 6 subjects were to receive escalating doses of SRA737 in combination with varying doses of gemcitabine in 28-day cycles to establish the MTD. Upon reaching the MTD for SRA737, or earlier (eg, when minimum efficacious dose range had been achieved or evidence of anti-tumor activity was observed), gemcitabine could have been escalated to a maximum dose of 600 mg/m^2 (with corresponding decreases in the SRA737 dose, as necessary for safety).

  In the Stage 2 Cohort Expansion Phase, approximately 20 prospectively-selected genetically-defined subjects were to be enrolled in each of 4 indication-specific cohorts: HGSOC, SCLC, STS, or cervical/anogenital cancer. In addition, 6 to 8 subjects with biomarker-selected bladder cancer or pancreatic cancer were enrolled into the Stage 2 Cohort Expansion Phase under prior versions of the protocol. Cohort Expansion subjects were to be treated at the MTD or a lower dose selected by the sponsor.

Overview of Treatment and Assessments:

Study treatment regimens**:**

- Stage 1 (SRA737 + gemcitabine + cisplatin): A single dose of SRA737 was given at one visit on Day -7 to Day -4 for PK assessments. Study treatment was given in 21-day cycles as follows: SRA737 administered orally on Days 2, 3, 9 and 10; gemcitabine given IV on cycle Day 1 and Day 8; and cisplatin given IV on cycle Day 1.
- Stage 2 (SRA737 + LDG): A single dose of SRA737 was given at one visit on Day -7 to Day -4 for PK assessments. Study treatment was given in 28-day cycles as follows: SRA737 administered orally on Days 2, 3, 9, 10, 16 and 17; and gemcitabine given IV on cycle Days 1, 8, and 15.

Subjects could continue study treatment until disease progression or discontinuation for other protocol-specified reasons.

As part of pre-screening, blood and available suitable archival or fresh tissue were collected for genetic tumor profiling for Cohort Expansion subjects, or confirmed as available for collection at baseline for Dose Escalation subjects. Optional triplet tumor biopsies were collected within 28 days prior to receiving the first SRA737 dose.

Safety assessments included adverse events, concomitant medications, laboratory assessments (hematology, biochemistry, troponin I or T, and urinalysis), physical examinations, World Health Organization (WHO) performance status, vital signs, echocardiograms (ECHO), and electrocardiograms (ECG).

Disease assessments were conducted throughout the study to evaluate preliminary efficacy of SRA737. Assessments included radiological tumor assessments performed within 4 weeks from the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK was omitted), repeated every 6 weeks in Stage 1 or every 8 weeks in Stage 2, and then in long-term follow-up every 6 weeks in Stage 1 and every 16 weeks in Stage 2. Response was assessed using RECIST 1.1.

A Safety Follow-up (SFU) visit was conducted 30 days after the last dose of SRA737 or prior to the initiation of a new anticancer treatment, whichever came first. Long-term Follow-up (LTFU) visits were conducted every 16 weeks for subjects who had not progressed and had not initiated new anticancer therapy.

Additional contact could be made as requested by the sponsor or the investigator to obtain disease and survival updates on an as-needed basis until the subject discontinued from the study.

Number of Subjects (planned and analyzed): A total of approximately 140 subjects were planned, and 153 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The Stage 1 Dose Escalation Phase and the Stage 2 Dose Escalation Phase were conducted in subjects with advanced solid tumors. The Cohort Expansion Phase was conducted in prospectively-selected genetically-defined subjects with HGSOC, SCLC, STS, or cervical/anogenital cancer, as defined below.

Inclusion Criteria:

Dose Escalation and Cohort Expansion:

1. Written (signed and dated) informed consent and capable of co-operating with treatment and follow up.
2. In the Dose Escalation Phase, subjects with a locally advanced or metastatic, histologically or cytologically proven solid tumor, relapsed after or progressing despite conventional treatment for which no conventional therapy is considered appropriate by the investigator or is declined by the subject.
3. Life expectancy of at least 12 weeks.
4. World Health Organization (WHO) performance status of 0-1.
5. Hematological and biochemical indices as specified in the protocol.
6. Subjects must be 18 years or older at the time consent is given.
7. Subjects must have archival tumor tissue available for genetic tumor profiling OR accessible tumor and willingness to consent to a biopsy for the collection of tumor tissue.

Cohort Expansion:

8. Subjects in the indication-specific cohort expansion must have histologically or cytologically proven advanced malignancy of the types specified in Inclusion Criterion 11, for which no conventional therapy is considered appropriate by the investigator or is declined by the subject.
9. Have measurable disease according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) criteria.
10. Subjects must have predicted sensitivity to Chk1 inhibition based on factors including genetic profiling of tumor tissue or ctDNA, HPV status, and germline BRCA1 and BRCA2 gene status. All subjects will have genetic profiling from tumor tissue or ctDNA; profiling were performed prospectively if required to evaluate Chk1 sensitivity or otherwise performed retrospectively.
    a. For subjects with HGSOC, documented somatic or germline BRCA1 and BRCA2 wild-type status will confer eligibility without requirement for prospective genetic profiling. If documented BRCA status is not available, genetic profiling may be performed prospectively to determine eligibility.
    b. Subjects with SCLC are eligible without requirement for prospective genetic profiling on the basis of very high prevalence of cancer related alterations in the tumor suppressor genes (eg, TP53 and RB1) in this population.
    c. For subjects with STS, and any others for whom genetic profiling is performed prospectively, eligibility were determined by the sponsor's review of genetic abnormalities detected in genes in the following categories, as detailed in Appendix 6 of the protocol:
        – Key tumor suppressor genes regulating G1 cell cycle progression/arrest such as RB1, TP53, etc. For relevant cancers, positive human papilloma virus (HPV) status is also considered for eligibility.
        – The DNA damage response pathway including ATM, BRCA1, BRCA2, mismatch repair genetic alterations and/or high microsatellite instability.
        – Genetic indicators of replicative stress such as gain of function/amplification of Chk1 or ATR or other related gene.
        – Oncogenic drivers such as MYC, CCNE1, etc.
    d. For subjects with anogenital cancer, known HPV positive status will confer eligibility without requirement for prospective genetic profiling. If HPV status is not known or not positive, genetic profiling (or HPV testing where appropriate) may be performed prospectively to determine eligibility. Subjects with cervical cancer or squamous cell carcinoma of the anus are eligible without requirement for prospective genetic profiling based on the very high prevalence of HPV positivity in these populations.

11. Subjects must meet one of the following criteria:
    a. HGSOC, defined by the following:
        i. Histologically confirmed high-grade serous ovarian, fallopian tube, or primary peritoneal cancer.
        ii. Platinum-resistant or refractory disease (defined as in Section 2.2.1), or if the subject is intolerant to platinum therapy.
    b. Small Cell Lung Cancer
        i. Must have received at least 1 but no more than 3 prior regimens for advanced disease, unless otherwise approved by sponsor
    c. Soft Tissue Sarcoma
        i. Including undifferentiated pleiomorphic sarcoma / malignant fibrous histiocytoma (MFH) (including high-grade spindle cell sarcoma / pleomorphic liposarcomas), leiomyosarcoma, and dedifferentiated liposarcomas. Other types of STS may be eligible with sponsor's approval.
        ii. Must have received at least 1 but no more than 3 prior regimens for advanced disease, unless otherwise approved by sponsor
    d. Cervical/Anogenital Cancer
        i. Including all cervical carcinoma and advanced/metastatic squamous cell carcinoma of the anus, penis, vagina, and vulva.
        ii. Must have received at least 1 but no more than 3 prior regimens for advanced disease, unless otherwise approved by sponsor

<u>Exclusion Criteria</u>:

1. Have received prior or current anticancer therapy within the noted time periods prior to receiving SRA737 or have not recovered from toxicity consistent with Exclusion Criterion 5:
    a. Radiotherapy (except for symptom control and where the lesions will not be used as measurable disease), chemotherapy, therapy with poly ADP ribose polymerase (PARP) inhibitors, other targeted therapies, or other IMPs within 2 weeks
    b. Nitrosoureas or Mitomycin C within 6 weeks
    c. Any prior treatment with a Chk1 inhibitor, or prior treatment with an ATR inhibitor within 6 months
2. No more than 3 previous treatment regimens for advanced disease (not applicable to HGSOC expansion cohort), unless otherwise approved by sponsor. Prior gemcitabine therapy is permitted as previous therapy.
3. Other malignancies within the past 2 years with the exception of adequately treated tumors that are associated with an expected 5 year disease-free survival of ≥ 95%.
4. If, in the opinion of the investigator, the subject is highly likely to experience clinically significant myelosuppression, based on previous experience with chemotherapy.
5. Ongoing toxic manifestations of previous treatments greater than National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 1.

Exceptions to this are alopecia or certain toxicities, which in the opinion of the investigator and the sponsor's Medical Monitor should not exclude the subject.

6. History of allergy to gemcitabine.
7. New or progressing brain metastases. Subjects with brain metastases that have been asymptomatic and radiologically stable over an 8-week period and have not been treated with steroids during that time may be included with approval from the sponsor.
8. Women of childbearing potential (WOCBP) or women who are already pregnant or lactating. However, those subjects who have a negative serum or urine pregnancy test before enrollment and agree to use 2 forms of contraception as per Protocol Appendix 4 or agree to sexual abstinence, effective from the first administration of SRA737, throughout the trial, and for 6 months afterwards, are considered eligible.
9. Male subjects with partners of childbearing potential, unless they agree to take measures not to father children by using a barrier method of contraception defined per Protocol Appendix 4, effective from the first administration of SRA737 throughout the trial, and for 6 months after their final SRA737 dose. Men with pregnant or lactating partners must be advised to use barrier method contraception (eg, condom plus spermicidal gel) to prevent exposure of the fetus or neonate.
10. Major surgery from which the subject has not yet recovered.
11. At high medical risk because of nonmalignant systemic disease including active uncontrolled infection.
12. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus.
13. Serious cardiac condition, such as concurrent congestive heart failure, prior history of class III/IV cardiac disease (New York Heart Association [NYHA), left ventricular ejection fraction < 45% at baseline, history of cardiac ischemia within the past 6 months, or prior history of cardiac arrhythmia requiring treatment, unless approved by the sponsor.
14. Prior bone marrow transplant or have had extensive radiotherapy to greater than 25% of bone marrow within the previous 8 weeks.
15. Peanut allergy unless this restriction was removed by the sponsor.
16. QTcF > 450 msec in adult males and > 470 msec in adult females.
17. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of SRA737 (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
18. Not able to swallow capsules without chewing or crushing.
19. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase 1/2 study of SRA737. Participation in an observational trial or interventional clinical trial which does not involve administration of an IMP and which would not place an unacceptable burden on the subject in the opinion of the investigator and sponsor would be acceptable.

20. Any other condition which in the investigator's opinion would not make the subject a good candidate for the clinical trial.

Study Interventions, Dose, Mode of Administration, and Batch Number(s): SRA737 was supplied in capsules containing 20, 25, 50, or 100 mg of drug. Gemcitabine and cisplatin were supplied by each study site. SRA737 capsules were administered orally. Gemcitabine and cisplatin were administered IV.

SRA737-02 Dosing Regimens

	Cycle Duration	SRA737 Dosing	Gemcitabine Dosing	Cisplatin Dosing
Stage 1 SRA737 + gemcitabine + cisplatin	21 days	Days 2, 3, 9 and 10	Days 1 and 8	Day 1
Stage 2 SRA737 + LDG	28 days	Days 2, 3, 9, 10, 16 and 17	Days 1, 8, and 15	Not applicable

LDG = low-dose gemcitabine

The starting dosages in the Stage 1 Dose Escalation Phase were 20 mg SRA737, 1250 mg/m^2 gemcitabine, and 80 mg/m^2 cisplatin. The starting dosages in the Stage 2 Dose Escalation Phase were 40 mg SRA737 and 3000 mg/m^2 gemcitabine. Doses were escalated in subsequent cohorts as described in the Clinical Study Report (CSR).

Duration of Study Intervention: Subjects could continue treatment with SRA737 until disease progression or discontinuation for other protocol-specified reasons.

Summary of Results and Conclusions:

Demographic and Other Baseline Characteristics: A total of 153 subjects were enrolled and received at least one dose of IMP (SRA737, gemcitabine, and/or cisplatin), and thus were included in the Safety Evaluable Population. Stage 1 Dose Escalation included a total of 10 subjects with solid tumors who were treated in 3 different dose level cohorts of SRA737 + gemcitabine + cisplatin, respectively: 20 mg + 600 mg/m^2 + 80 mg/m^2, 20 mg + 875 mg/m^2 + 80 mg/m^2, and 20 mg + 1250 mg/m^2 + 80 mg/m^2. Stage 2 included an overall total of 143 subjects who were enrolled in 13 different dose level cohorts of SRA737 and low dose gemcitabine (LDG), with SRA737 doses ranging from 40 mg to 600 mg and LDG doses ranging from 50 mg to 300 mg/m^2. A total of 58 subjects participated in Stage 2 Dose Escalation, including 2 subjects who were concurrently enrolled in both Stage 2 Dose Escalation and Stage 2 Cohort Expansion groups.

The majority of subjects in Stage 1 were under 65 years of age (70.0%) and male (60.0%). In Stage 2, the majority of subjects were under 65 years of age (62.7%), a minority were male (40.5%), and nearly all were white (90.8% of Stage 2 overall).

The median time since the initial cancer diagnosis was 31.70 months for the Stage 1 population and 28.81 months for Stage 2. In the Stage 2 population overall, 87% had 1 to 3 prior lines of therapy and 54.2% had prior radiotherapy. Most Stage 2 subjects (57.5%) had discontinued prior therapy due to disease progression.

Exposure: The median duration of SRA737 treatment in Stage 1 (SRA737 + gemcitabine + cisplatin) was 72.5 weeks, with a range of 38 days to 186 days. In Stage 2 overall (SRA737 + LDG), the median SRA737 treatment duration was 52 days, with a range of 1 day to 599 days. Median treatment duration was slightly longer in the lower SRA737 dose group (< 500 mg) than in the higher dose group (≥ 500 mg), at 17.5 days vs. 12.0 days, respectively. The majority of subjects in Stage 2 (77 of 143 subjects) received doses of at least 500 mg SRA737 + 250 mg/m^2 LDG, which was ultimately determined to be the RP2D.

Efficacy Results: One subject in Stage 1 (SRA737 + gemcitabine + cisplatin) achieved a PR during the study; however, since dose escalation and enrollment in Stage 1 were halted due to concern over events of neutropenia, the analysis of efficacy focuses on Stage 2 and examining the antitumor effect of SRA737 + LDG.

In Stage 2 Dose Escalation, the RP2D was defined as 500 mg SRA737 + 250 mg/m^2 (low-dose) gemcitabine based on overall tolerability, particularly in terms of GI and hematologic toxicity which may be associated with SRA737 and gemcitabine. The majority of subjects in Stage 2 (77 of 143 subjects) received doses of at least 500 mg SRA737 + 250 mg/m^2 gemcitabine.

A total of 7 subjects in Stage 2 (SRA737 + LDG) achieved a PR. Notably, 3 of the 7 PRs in Stage 2 occurred in subjects with anogenital cancer, giving an ORR of 25% for anogenital tumors. Additional evidence of efficacy included DCRs of at least 50% in all tumor type cohorts, and a total of 30 subjects who maintained SD for at least 4 cycles of therapy. Of these subjects, 21 (70%) achieved a reduction in tumor measurement from baseline.

These observations of PRs and prolonged SD with reductions in target tumors in Stage 2 suggest that SRA737 + LDG possess antitumor activity.

A preliminary survey of genetic alterations in the subjects who achieved PR or prolonged SD supports several potential genetic biomarkers to be explored in future clinical studies.

Safety Results: In Stage 1, a total of 10 subjects were enrolled into 3 dose level cohorts of SRA737 + gemcitabine + cisplatin. Stage 1 Dose Escalation was halted due to concern over events of neutropenia, both DLT and non-DLT. Grade 3 or higher neutropenia or neutropenic sepsis was reported by 8 of the 10 Stage 1 subjects. No MTD was defined.

In Stage 2 Dose Escalation, a total of 58 subjects were enrolled into 13 dose cohorts of SRA737 + LDG. No DLTs were reported in Stage 2. The RP2D was defined as 500 mg SRA737 + 250 mg/m^2 gemcitabine based on overall tolerability, particularly in terms of GI and hematologic toxicity which may be associated with SRA737 and gemcitabine.

Virtually all subjects (100% in Stage 1, 99.3% in Stage 2) reported at least TEAE, most of whom experienced at least one TEAE considered to be related to study treatment (SRA737, gemcitabine, and/or cisplatin).

SRA737-02 Overall Summary of Subjects with Treatment-Emergent Adverse Events by SRA737 Dose Group

	Stage 1 (N = 10)	Stage 2 < 500mg (N = 30)	Stage 2 ≥ 500mg (N = 113)	Stage 2 Overall (N = 143)
	n (%)	n (%)	n (%)	n (%)
Any Treatment-Emergent Adverse Event (TEAE)	10 (100)	29 (96.7)	113 (100)	142 (99.3)
Any SRA737-Related TEAE	10 (100)	25 (83.3)	111 (98.2)	136 (95.1)
Any Gemcitabine-Related TEAE	10 (100)	21 (70.0)	110 (97.3)	131 (91.6)
Any Cisplatin-Related TEAE	10 (100)	0	0	0
Any Treatment-Related TEAE	10 (100)	25 (83.3)	112 (99.1)	137 (95.8)
Any Grade ≥ 3 TEAE	10 (100)	16 (53.3)	78 (69.0)	94 (65.7)
Any Grade ≥ 3 SRA737-Related TEAE	8 (80.0)	2 (6.7)	47 (41.6)	49 (34.3)
Any Grade ≥ 3 Gemcitabine-Related TEAE	9 (90.0)	3 (10.0)	52 (46.0)	55 (38.5)
Any Grade ≥ 3 Cisplatin-Related TEAE	10 (100)	0	0	0
Any Grade ≥ 3 Study Treatment-Related TEAE	10 (100)	3 (10.0)	53 (46.9)	56 (39.2)
Any Serious TEAE	8 (80.0)	20 (66.7)	64 (56.6)	84 (58.7)
Any Serious SRA737-Related TEAE	4 (40.0)	3 (10.0)	19 (16.8)	22 (15.4)
Any Serious Gemcitabine-Related TEAE	6 (60.0)	1 (3.3)	24 (21.2)	25 (17.5)
Any Serious Cisplatin-Related TEAE	7 (70.0)	0	0	0
Any Serious Study Treatment-Related TEAE	7 (70.0)	3 (10.0)	24 (21.2)	27 (18.9)
Any Serious AE Occurred Prior to First Dose	1 (10.0)	0	6 (5.3)	6 (4.2)
Any TEAE Leading to Treatment Withdrawn	4 (40.0)	8 (26.7)	21 (18.6)	29 (20.3)
Any SRA737-Related TEAE Leading to Treatment Withdrawn	3 (30.0)	1 (3.3)	6 (5.3)	7 (4.9)
Any Gemcitabine-Related TEAE Leading to Treatment Withdrawn	3 (30.0)	0	8 (7.1)	8 (5.6)
Any Cisplatin-Related TEAE Leading to Treatment Withdrawn	4 (40.0)	0	0	0
Any Study Treatment-Related TEAE Leading to Treatment Withdrawn	4 (40.0)	1 (3.3)	8 (7.1)	9 (6.3)

Source: Table 14.3.2.1.1
AE = adverse event; TEAE = treatment-emergent adverse event

The most common TEAEs in the study were nausea, vomiting, fatigue, and diarrhea. These events were reported by Stage 1 subjects and Stage 2 subjects overall as follows: nausea, 90.0% and 61.5%; vomiting, 60.0% and 54.5%; fatigue, 70.0% and 51.0%; and diarrhea, 30.0% and 49.0%, respectively. The majority of these 4 common TEAEs were attributed to study treatment. In general, these TEAEs were reported less frequently in lower SRA737 dose groups compared with higher dose groups. At the RP2D dose level of 500 mg SRA737 + 250 mg/m^2 gemcitabine, nausea, vomiting, fatigue, diarrhea, and anemia were each reported by at least 50% of the 60 subjects treated at the RP2D, primarily Grade 1 or 2.

GI TEAEs of nausea, vomiting, and diarrhea were primarily mild to moderate; in Stage 2, these GI TEAEs were reported at Grade 3 or higher by 2 subjects for nausea, 4 subjects for vomiting, and 3 subjects for diarrhea. GI TEAEs led to treatment discontinuation in 1 subject for nausea, 2 subjects for vomiting, and 1 subject for diarrhea. The relatively low rate of treatment discontinuation due to GI TEAEs in comparison with the overall frequency of GI TEAEs suggests that GI events are clinically manageable and do not seriously affect the tolerability of SRA737 in combination with gemcitabine and cisplatin.

Fatal SAEs were reported for 11 subjects; none were attributed to SRA737. Treatment-emergent SAEs were reported by 8 subjects (80.0%) in Stage 1 and 84 subjects (58.7%) in Stage 2 overall. Pyrexia was the most common treatment-related SAE, attributed to SRA737 in 8 subjects (5.6%) and to gemcitabine in 12 subjects (8.4%). Most of the SAEs reported were for PTs that can be expected to occur in subjects with advanced cancer.

Adverse events leading to treatment discontinuation were reported by 4 subjects (40.0%) in Stage 1 and 29 subjects (20.3%) in Stage 2 overall.

Serious cardiac AEs were observed in 2 subjects in Stage 2 of the study; however, based on an assessment of the details of these events and the overall safety observations in the study, a definitive association of cardiac adverse effects with SRA737 + LDG is not considered to be likely.

Pharmacokinetics Results: Pharmacokinetic analyses were generated from SRA737 individual concentrations in plasma from the Day -7 to -4 visit (single dose) and after repeated daily doses on C1D10 or C1D17.

Following single dose oral administration of SRA737 (Day -7 to Day -4), t_{max} generally occurred at 1 or 2 hours, but ranged between 1 and 8 hours. When estimable, the individual apparent $t_{½}$ ranged from 6.49 to 18.6 hours, individual CL/F ranged from 10 to 170 L/hour, and individual V_d ranged from 171 to 2340 L. Systemic exposure (mean C_{max}, AUC_{0-12}) generally increased with increasing doses in a close to dose-proportional manner between 150 mg and 300 mg. Within the observed inter-subject variability, there was no consistent pattern for dose-proportionality from 300 mg to 600 mg.

After repeated doses, t_{max} generally occurred at 1 or 2 hours, but ranged between 1 and 12 hours. When estimable, individual $t_{½}$ ranged from 2.74 to 5.9 hours, individual CL ranged from 29.3 to 119 L/hour, and individual Vd ranged from 199 to 770 L. Systemic exposure (mean C_{max}, AUC_{0-12}) generally increased with increasing doses in a close to dose-proportional manner

between 150 mg and 300 mg. Within the observed inter-subject variability, there was no consistent pattern for dose-proportionality from 300 mg to 600 mg.

Upon repeated dosing at 150 mg, 300 mg, 500 mg and 600 mg, systemic exposure generally remained similar on C1D10 compared to the first single dosing, with individual accumulation ratio (R_{AUC}) values ranging from 0.586 to 1.86. The exception, at the 500 mg dose level, was for Subjects 031-063, 039-016, 244-004, 404-006, and 404-021 that had decreased or increased exposure with R_{AUC} values of 2.18, 2.70, 0.468, 2.24, and 0.321, respectively

Conclusions:

- Stage 1 of the study investigated SRA737 + gemcitabine + cisplatin. Stage 1 Dose Escalation was halted due to concern over events of neutropenia or neutropenic sepsis reported for 8 of the 10 subjects treated. No MTD was defined in Stage 1.
- Stage 2 investigated SRA737 + low-dose gemcitabine (LDG). During Stage 2 Dose Escalation, a total of 58 subjects were enrolled into 13 dose level cohorts. No DLTs were reported.
- The RP2D was defined at 500 mg SRA737 + 250 mg/m^2 gemcitabine based on overall tolerability and the minimum effective concentration of SRA737 extrapolated from preclinical models. Gemcitabine at 250 mg/m^2 is hypothesized to enhance sensitivity to Chk1 inhibition by acting as an exogenous inducer of RS, as supported by preclinical models where the biological effects of increased RS were observed at 15-30% of the typical dose used to elicit an antiproliferative effect in tumors in mice.
- Stage 2 expansion cohorts were initiated in 7 tumor types associated with higher levels of RS hypothesized to be more sensitive to Chk1 inhibition, particularly in combination with LDG.
- A total of 143 subjects were evaluable for safety in Stage 2. The combination of SRA737 + gemcitabine was well tolerated. Gastrointestinal disorders (nausea, vomiting) and fatigue were reported by over 50% of subjects, but most cases were mild to moderate and did not require treatment discontinuation.
- A total of 65 subjects with anogenital, cervical, HGSOC, rectal, SCLC, STS, or urothelial tumors were evaluable for tumor response. The second largest group of evaluable subjects (N=12) enrolled in expansion was the anogenital cancer cohort, in which the second longest median TTP (3.6 months), the highest ORR (25% ie, 3/12 evaluable subjects), and a DCR of 50% were observed. These data support further clinical development of SRA737 + LDG in anogenital cancer.
- A preliminary survey of the genetic profiles of subjects who achieved PR or prolonged SD suggests responses occurred in tumors harboring cancer-related mutations expected to produce higher levels of RS. In addition, multiple replication fork-associated mutations including variants of unknown significance may exacerbate replication stress and/or be a consequence thereof.
- Based on the non-clinical and clinical data currently available, the balance between potential efficacy/benefits and the safety risks for SRA737 + LDG remains favorable and

supports further clinical development of this combination, or other therapy combinations including these elements.

References:

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