TITLE PAGE

Title:

A Phase I/II Trial of Oral SRA737 (a Chk1 Inhibitor) Given in Combination with Low-Dose Gemcitabine in Patients with Advanced Cancer

Running title: SRA737 plus low-dose gemcitabine in solid tumors

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Preliminary data from this study were presented at the Annual Meeting of the American Society of Clinical Oncology (31 May to 4 June 2019, Chicago, Illinois) in abstract 3095 entitled: 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.

Translational Relevance

Chk1 is a key component of the response to replication stress (RS) within DNA and a regulator of the G2/M cell cycle checkpoint. This manuscript describes the clinical study of the Chk1 inhibitor SRA737 delivered orally 24 and 48 hours after low dose gemcitabine (LDG). LDG has low myelotoxicity and causes RS in tumors, allowing unrepaired DNA within S phase cancer cells past the G2/M check point leading to cell death. In the expansion phase, patients with genetic alterations related to tumor suppression, DNA damage repair, or oncogenic drivers were enrolled, all of which would cause endogenous RS potentially enhancing response. Of 65 evaluable patients 7 partial tumor responses were observed, including 3 patients with anogenital cancer harboring alterations in FANC/BRCA/PIK3CA, intermediate to high tumor mutational burden, and possibly increased RS from HPV infection. These partial responses provide proof-of-concept of the efficacy of LDG plus SRA737 which warrants further evaluation.

ABSTRACT

Purpose: This was a phase I/II trial of the novel checkpoint kinase 1 (Chk1) inhibitor SRA737 given in combination with gemcitabine. Its objectives were to establish the safety profile, recommended phase 2 dose (RP2D), pharmacokinetics profile, and clinical activity of SRA737.

Patients and Methods: Patients with advanced solid tumors were enrolled into dose-escalation cohorts and treated in 28-day cycles with oral SRA737 on days 2, 3, 9, 10, 16 and 17, and intravenous gemcitabine on days 1, 8 and 15. Treatment was continued until progression. Each expansion cohort included up to 20 patients with specific genetically defined tumors.

Results: The RP2D was determined to be 500 mg SRA737 combined with low-dose (250 mg/m^2) gemcitabine. Of 143 enrolled patients, 77 were treated at doses of at least 500 mg SRA737 combined with 250 mg/m^2 gemcitabine. Common toxicities of nausea, vomiting, fatigue and diarrhea were primarily mild to moderate, and rarely led to treatment discontinuation. Anemia, neutropenia and thrombocytopenia were grade ≥3 in 8.3% to 11.7% of patients treated at the RP2D. The objective response rate (ORR) was 10.8% overall and notably the ORR in anogenital cancer was 25%. Partial tumor responses were observed in anogenital cancer, cervical cancer, high-grade serous ovarian cancer, rectal cancer, and small cell lung cancer.

Conclusions: SRA737 in combination with low-dose gemcitabine was well tolerated with lower myelotoxicity than has been seen at standard doses of gemcitabine or with other combinations of Chk1 inhibitors with gemcitabine. Tumor responses were observed in anogenital and other solid tumors.

Trial Registration: Clinicaltrials.gov ID: NCT02797977.

Introduction

DNA damage in cancer cells occurs as a result of multiple endogenous and exogenous factors. Endogenous factors include rapid proliferation caused by oncogenic signalling and inability to repair DNA damage due to defective repair or cell cycle checkpoints; exogenous factors may include chemotherapy or radiotherapy used in cancer treatment (1). Checkpoint kinase 1 (Chk1) is a key component of the ATR-Chk1-Wee1 pathway; it is activated in response to replication stress and double-strand DNA breaks and is associated with stability of the cell-cycle S-phase. Cancer cells can have a loss of fidelity of the G1/S checkpoint and oncogenic signalling, which leads to replication stress. In this context, the role of Chk1 in cell survival is critical (2). The current study investigated the combination of the novel Chk1 inhibitor SRA737 (Sierra Oncology, Inc., San Mateo, California) and low doses of the chemotherapeutic agent gemcitabine. Gemcitabine, a pyrimidine analogue, undergoes a series of phosphorylation steps to be converted to its active form, gemcitabine triphosphate, which is then incorporated into DNA and RNA where it causes DNA damage and replication stress (3, 4). Additionally, gemcitabine is an irreversible inhibitor of ribonucleotide reductase, a critical enzyme responsible for the production of the deoxynucleoside triphosphates (dNTP), which are important building blocks of DNA replication. Importantly, preclinical work has shown that low, non-cytotoxic concentrations of gemcitabine in combination with Chk1 inhibition can result in tumor growth inhibition, thought to be a consequence of dNTP depletion, resulting in stalled replication forks, replication stress and activation of Chk1 (5-7). SRA737 is a novel, orally bioavailable, selective Chk1 inhibitor that has shown activity as a single agent and in combination with gemcitabine in preclinical models (8-10). The combination of SRA737 and a low dose of gemcitabine is hypothesized

147 to have synergistic antitumor activity while circumventing some of the expected
148 toxicities of DNA damage response inhibitors in combination with gemcitabine (11-
149 17).

Patients and methods

Study design

The objectives of this first-in-human, phase I/II, open-label, dose-escalation study were to establish the safety profile, recommended phase 2 dose (RP2D), pharmacokinetics (PK) profile and clinical activity (including objective response rate [ORR] and duration of response [DOR]) of SRA737 in combination with low-dose gemcitabine. The trial (ClinicalTrials.gov identifier NCT02797977, EudraCT Number: 2015-004467-36) was conducted at 21 centers in the UK and Spain between 3 August 2016 and 8 April 2020. Research ethics committees approved the study protocol before initiation of patient enrolment, and the study was carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable local regulations. The study was approved in the UK by the Research Ethics Committees (REC) London Centre and in Spain by the Research Ethics Committee (REC) at 12 de Octubre Hospital in Madrid. All patients provided written informed consent prior to taking part.

Participants

The dose-escalation phase included patients with solid tumors after prior standard-of-care chemotherapy, World Health Organization performance status 0–1 and organ function within limits of standard phase I studies (Supplementary Methods). Tumor type-specific expansion cohorts were planned to recruit up to approximately 20 prospectively identified genetically defined patients in each cohort. Enrolment of expansion cohorts was initiated prior to the completion of dose escalation with subjects enrolled at the highest dose level determined to be safe and tolerable at the

time of their enrolment. Subjects were able to undergo intra-patient dose escalation to receive higher doses of SRA737 and/or gemcitabine if a higher dose level had been deemed safe and tolerable.

The prevalence of genetic alterations related to increased RS hypothesized to enhance response to Chk1 inhibition varies depending on the tumor type. In order to select for patients with higher levels of endogenous RS, and therefore potentially greater benefit from SRA737 + LDG in the expansion phase, patients were selected with tumor types known to harbor high levels of genomic instability: high-grade serous ovarian cancer (HGSOC), small cell lung cancer (SCLC), soft tissue sarcoma (STS), anogenital cancer or cervical cancer. In addition, patients with HGSOC or STS were required to have the presence of specific genetic alterations related to tumor suppression, DNA damage repair, replicative stress or oncogenic drivers. Tumor-specific eligibility criteria for expansion cohorts are summarized in **Table 1**. Based on the eligibility criteria of an earlier version of the protocol, patients with urothelial and rectal cancers were also enrolled in the expansion phase.

This analysis focuses on patients treated with the doublet combination of SRA737 and low-dose gemcitabine.

Treatment and dose escalation

A single dose of SRA737 was given at one visit on day –7 to day –4 (prior to the start of cycle 1) for PK assessments. Study treatment was given in 28-day cycles: SRA737 was administered orally on days 2, 3, 9, 10, 16 and 17; and gemcitabine was given intravenously on days 1, 8 and 15 of each cycle. This dosing regimen was based on in vitro and in vivo preclinical modelling of SRA737 and gemcitabine which

demonstrated maximum efficacy when SRA737 was administered 16-24 hours following gemcitabine (10).

Dose escalation of SRA737 in combination with varying doses of gemcitabine was conducted in cohorts of three to six patients according to a rolling-six design wherein once the first subject completed the 7-day observation period following the first dose of gemcitabine, subsequent subjects in that cohort started treatment. Patients were assessed for dose-limiting toxicity from the first SRA737 dose (day –7 to day –4) until the end of cycle 1 (up to 35 days). Safety and other supporting data were reviewed by the cohort review committee consisting of the lead investigator, study investigators representing the site(s) currently enrolling patients, and representatives of the study sponsor prior to dose escalation of SRA737 and/or gemcitabine. A minimum of 3 subjects with no DLT, or 6 subjects with up to 1 DLT were required prior to escalation to the next SRA737 plus gemcitabine dose level. Dose escalation of SRA737 was started at 40 mg per day and increased in up to 100% increments until the C_{min} of SRA737at 24 hours reached 100nM. Thereafter, the dose of SRA737 was increased in less than 100% increments (typically 25-75%). Gemcitabine dose was started at 300 mg/m^2 and could escalate to a maximum of 600 mg/m^2.

Expansion cohorts of up to 20 patients with specified tumor profiles were treated with SRA737 and gemcitabine doses selected by the cohort review committee based on all available safety and PK data; expansion doses were at, or lower than, the maximum tolerated doses from the dose-escalation phase. Patients could continue treatment until disease progression or discontinuation from the study due to unacceptable toxicity, investigator/sponsor decision or withdrawal of consent.

Assessments

Safety assessments, including adverse events, laboratory parameters, electrocardiograms and echocardiograms, were conducted throughout treatment and until 30 days after the last study treatment or initiation of new anticancer treatment. Toxicity was recorded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Serial sampling of blood for PK assessment was conducted before and after dosing with single-agent SRA737 (10 time points over 48 hours) and on cycle 1 day 10 following administration of SRA73 and gemcitabine. Plasma SRA737 was quantified using liquid chromatography-mass spectrometry (18).

Radiologic tumor assessments were performed every two cycles, and tumors were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (19). The ORR was defined as percentage of patients with a best response of complete response (CR) or partial response (PR) to treatment according to RECIST criteria. Clinical response data were summarized in cohorts defined by tumor type, including indication-specific expansion cohorts (anogenital, cervical, HGSOC, SCLC and STS), a grouping of patients with rectal cancer who were enrolled in the dose-escalation phase, and four patients with urothelial cancer enrolled under previous protocol versions.

Statistical analysis

The safety-evaluable population included all patients who received at least one dose of either investigational medicinal product (SRA737 or gemcitabine). The response-evaluable population included patients who had measurable disease at baseline, received at least 83% of planned SRA737 doses in cycle 1, and had at least one

postbaseline disease assessment or discontinued treatment due to disease progression, adverse event or death.

Data availability statement

The trial sponsor, Sierra Oncology, commits to share clinical study data with qualified researchers to enable enhancement of public health. As such, Sierra will share anonymized patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Sierra pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the United States and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approvals. Such requests are assessed at Sierra's discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. If Sierra agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release, to ensure that the patient data are de-identified. In case of any risk of re-identification on anonymized data despite measures to protect patient confidentiality, the data will not be shared. The patients' informed consent will always be respected. If the anonymization process will provide futile data, Sierra will have the right to refuse the request. Sierra will provide access to patient-level clinical trial analysis datasets in a secured environment upon execution of the data sharing agreement. Sierra will also provide the protocol, statistical analysis plan, and the clinical study report synopsis if needed. For additional information or requests for access to Sierra clinical trial data for research purposes, please contact us at: Medinfo@sierraoncology.com.

Figure Legends

Figure 1: Enrolment by SRA737 and low-dose gemcitabine dose level.

Description: This figure represents the number of patients enrolled at each SRA737 plus low-dose gemcitabine dose level. In addition, the number of patients who received their allocated treatment in each cohort and the number who were evaluable for dose limiting toxicity in the dose escalation phase are shown. The SRA737 dose is listed first, followed by gemcitabine dose. Abbreviations: AE, adverse event; C1, cycle 1; C1D1, cycle 1 day 1; DLT, dose-limiting toxicity; G1, grade 1; GI, gastrointestinal.

Figure 2: SRA737 and low-dose gemcitabine: best tumor response by tumor type.

Description: This figure displays the best tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria in the per-protocol response-evaluable population (REP). Prior lines of therapy, starting doses of study treatment, duration on study, and Grade 3 or higher AEs related to SRA737 for each patient are also shown. Three patients (1 with HGSOC, 2 with SCLC) included in the REP discontinued prior to completing a post-treatment tumor assessment and therefore best response could not be determined for these patients. Abbreviations: HGSOC, high-grade serous ovarian cancer; SCLC, small cell lung cancer; STS, soft tissue sarcoma

Figure 3: SRA737 and low-dose gemcitabine: duration on treatment and best response.

Description: This figure displays the duration on therapy (cycles) for each patient in the per-protocol response-evaluable population, and their categorical best tumor

response per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.

Abbreviations: HGSOC, high-grade serous ovarian cancer; SCLC, small cell lung cancer; STS, soft tissue sarcoma.

Results

Patient demographics

A total of 143 patients were enrolled in the SRA737 and low-dose gemcitabine treatment cohorts. They included 58 patients across 13 dose-escalation cohorts and 85 patients in the expansion cohorts (**Fig. 1**). In the analysis of tumor response, groups of patients identified by tumor-type were defined (15 with anogenital cancer, 15 with rectal cancer, 12 with cervical cancer, 24 with HGSOC, 22 with SCLC, 11 with STS, and 4 with urothelial cancer). In these groups, a total of 18 patients who participated in dose escalation are included (15 with rectal cancer, 1 with anogenital cancer, 1 with cervical cancer, and 1 with STS). The RP2D was determined to be 500 mg SRA737 combined with low-dose (250 mg/m^2) gemcitabine. Including patients with intra-patient dose escalation, the majority (77 of 143) received SRA737 at doses of at least 500 mg in combination with gemcitabine 250 mg/m^2.

The median age of patients was 62 years (range 54–68 years), the male/female ratio was 39.2%/60.8%, and World Health Organization performance status 0/1 ratio was 44.1%/55.9% (Supplementary Table 1). HGSOC (*n* = 24), SCLC (*n* = 22), anogenital cancer (*n* = 15) and rectal cancer (*n* = 15) were the most common tumor types. The median number of prior lines of therapy was two (range one to nine lines).

Safety profile

The most common treatment-emergent adverse events irrespective of relationship to SRA737 or gemcitabine included nausea (61.5%), vomiting (54.5%), fatigue (51.0%), diarrhea (49.0%) and anemia (45.5%). The incidence of grade ≥3 toxicities was low (**Table 2**).

In a previous study of SRA737 monotherapy in patients with advanced cancer, daily dose levels from 20 mg to 1300 mg were evaluated. The MTD was determined to be 1000 mg QD with DLTs observed at daily doses of 1000 mg to 1300 mg including gastrointestinal events, neutropenia, and thrombocytopenia. The RP2D of SRA737 monotherapy was 800 mg QD. At the monotherapy RP2D, common toxicities with SRA737 included diarrhoea, nausea, and vomiting which were generally mild to moderate.

The starting dose of SRA737 (40 mg QD) in combination with gemcitabine was chosen to be conservative due to the potential overlapping toxicity with gemcitabine and consideration that with the allowed 100% dose escalation increments, the 150 mg dose modelled to exceed the minimal effective dose in humans could be reached in a timely manner by the third escalation cohort. The starting dose of 300 mg/m^2 gemcitabine is approximately one-third of a typical clinical dose and is based on preclinical models where synergistic antitumor effect of SRA737 plus gemcitabine was observed at gemcitabine doses approximately one-third of the typical dose in that model.

Following the enrolment of 13 dose escalation cohorts (**Fig. 1**), no protocol-defined dose-limiting toxicities had occurred and the cohort review committee determined the MTD was not reached. As described later in this report, the RP2D was declared based on an overall assessment of tolerability in patients alongside preclinical data.

In 60 patients treated with the RP2D, the predominant toxicities were gastrointestinal, with nausea, diarrhea and vomiting reported by 63.3%, 55.0% and 56.7% of patients, respectively. Although prophylactic antiemetics or antidiarrheals were not mandated in the study, their use was left to the clinical judgement of the

Investigators where clinically indicated. The rates of grade ≥3 events for these toxicities were 3.3%, 3.3% and 6.7%, respectively, and gastrointestinal adverse events led to treatment discontinuation in one patient due to nausea, two patients due to vomiting and one patient due to diarrhea. The relatively low rate of treatment discontinuation due to GI toxicities in comparison with the overall frequency of GI events reported suggests that these do not substantially affect the tolerability of SRA737 in combination with gemcitabine and, no special precautions are required. However, appropriate management of GI effects, including prophylaxis such as an anti-emetic regimen, would be advised with the SRA737 plus gemcitabine combination where clinically indicated.

Other toxicities of note were fatigue (58.3%), anemia (56.7%), neutropenia (46.7%) and thrombocytopenia (41.7%), with grade ≥3 events occurring in 3.3%, 11.7%, 16.7% and 10.0%, respectively (**Table 3**).

Adverse events leading to treatment discontinuation were reported for 29 (20.3%) patients. The most common event leading to treatment discontinuation was disease progression (3 patients), followed by fatigue, lung infection, metastases to CNS, intestinal obstruction, thrombocytopenia, and vomiting (2 patients each); all other reasons for discontinuation applied to only 1 patient each. Events leading to discontinuation which were assessed as causally related to SRA737 occurred in only 4.9% of subjects, and only two of these related AEs were reported in more than a single subject; fatigue and vomiting occurred in two subjects each. Fatal adverse events were reported for 10 patients (6 were progression of disease, 1 cardiac arrest, 1 lung infection, 1 respiratory failure, and 1 small bowel obstruction); none of

these were attributed to SRA737, however, one fatal event of cardiac arrest was considered possibly related to gemcitabine.

Adverse events related to cardiac failure have been recorded in previous phase I trials (13); cardiac parameters were therefore analyzed in the current study. Of the 143 patients treated with SRA737 and low-dose gemcitabine, 80 had baseline and postbaseline (cycle 2 day 1) echocardiograms. Five patients had a ≥10 percentage point absolute reduction in ejection fraction, and of these, four had ejection fraction values of >50% at all time points. One patient's ejection fraction dropped from 60% to 43% but this patient did not exhibit symptoms of cardiac failure. Grade 3 QTcF prolongation (QTcF values of >500 msec and/or increase in QTcF by >60 msec) was seen in seven patients; four of these patients had a maximum QTcF of <500 msec, and none of the QTcF elevations was associated with cardiac signs or symptoms. One patient had cardiac arrest during the study, which was a grade 5 event.

Pharmacokinetic profile

The maximum plasma concentration (C_{max}) of SRA737, area under the concentration-time curve from 0 to 12 hours ($AUC_{0–12}$), half-life and clearance were measured at SRA737 doses of 40 mg to 600 mg (**Table 4**). The systemic exposure to SRA737 ($AUC_{0–12}$ and C_{max}) was approximately dose-proportional, particularly at doses within the 150 mg to 300 mg range (**Supplementary Fig. 1**).

In preclinical models, synergistic antitumor effect of SRA737 plus low-dose gemcitabine has been observed at gemcitabine doses approximately one-third of the typical dose in preclinical studies. SRA737 at dose levels of 150 mg or higher result in plasma concentrations modelled from preclinical work to exceed the minimal effective dose in humans. Based on this model, the plasma concentrations of

SRA737 observed in patients who received SRA737 at dose levels of 150 mg or higher, in combination with low-dose gemcitabine, are predicted to produce an antitumor effect, consistent with the efficacy signal observed in this clinical study.

Determination of the recommended phase 2 dose

SRA737 at 500 mg administered 24 and 48 hours following gemcitabine infusion, in combination with gemcitabine at 250 mg/m^2 given on days 1, 8 and 15 of a 28-day cycle, was determined to be the RP2D. This decision was based on overall tolerability, particularly in terms of gastrointestinal and hematological toxicity, which may be associated with SRA737 and gemcitabine (**Table 2**), and a pharmacokinetic profile showing plasma concentrations of SRA737 reaching the minimal effective concentration of SRA737 extrapolated from preclinical models (**Supplementary Fig. 2**).

Tumor response

Sixty-five patients were treated with SRA737 and low-dose gemcitabine and included in the per-protocol response-evaluable population for tumor types of anogenital cancer, cervical cancer, HGSOC, rectal cancer, SCLC, STS, and urothelial cancer. The ORR was 10.8% (7/65) across all cohorts. No CRs were observed, and 7 patients had a best response of PR. PRs were seen in anogenital cancer, 3/12 (25%); cervical cancer, 1/6 (16.7%); HGSOC, 1/15 (6.7%); rectal cancer, 1/10 (10%); and SCLC, 1/9 (11.1%) (**Fig. 2**). The duration on therapy in patients in the expansion cohort is shown in **Fig. 3**.

Discussion

This is the first clinical report of a Chk1 inhibitor with a novel, low-dose (250 mg/m^2) gemcitabine combination designed to provide exogenous replicative stress while minimizing gemcitabine-associated myelotoxicity and maximizing Chk1 inhibition. It is also the first clinical report of SRA737 used in combination.

Several Chk1 inhibitors have been evaluated in trials with gemcitabine chemotherapy (13, 15-18). However, the lowest dose of gemcitabine recommended for phase II evaluation was 500 mg/m^2 and the majority of clinical trials proposed that the 1000 mg/m^2 dose should be used for further study. However, at this standard dose of 1000 mg/m^2, gemcitabine is known to have significant myelotoxicity. The pharmacological basis of previous single-agent, low-dose gemcitabine explored in a clinical setting stems from the knowledge that the rate-limiting enzyme for the activation of gemcitabine, deoxycytidine kinase, is saturated at concentrations of gemcitabine in circulation after infusion at 250 mg/m^2 (17). DNA repair studies now suggest that gemcitabine is a potent inducer of DNA replication fork stress via inhibition of ribonucleotide reductase, activating ATR and Chk1 to allow for DNA repair prior to mitosis (11, 20, 21). The current study exploits this hypothesis to evaluate low-dose gemcitabine (at levels of 50-300 mg/m^2), with the RP2D of gemcitabine in combination with SRA737 being 250 mg/m^2, which is significantly lower than that used in routine clinical practice. The RP2D of SRA737 in the combination was 500 mg for 2 days beginning 24 hours after gemcitabine administration. The plasma SRA737 concentrations achieved at these dose levels were in excess of 40-500 ng/mL, the range corresponding to the minimal effective dose extrapolated from preclinical models. Although the study protocol did include a

provision for non-mandatory tumor biopsy analysis to study pharmacodynamic effects, none were obtained and this is shortcoming of the current study.

The adverse-effect profile in the current study differs significantly from other gemcitabine and Chk1 inhibitor combinations (11-17). Interestingly, the Grade ≥3 neutropenia and thrombocytopenia rates in the current study were 11.7% and 8.3%, respectively, at the RP2D. These rates are lower than those described at maximally tolerated doses of Chk1 inhibitor and gemcitabine combinations: AZD7762 (57% and 0% at the MTD; thrombocytopenia at 33-83% at lower doses; ref 11); GDC-0425 (38% and 12%; ref 15); and GDC-0575 (79% and 14%; ref 16). At the RP2D, gastrointestinal side effects of nausea and vomiting occurred in 63.3% and 56.7% of patients, respectively; these were Grade ≥3 in 3.3% and 6.7% of patients, respectively. Similar upper gastrointestinal toxicities were seen in other oral Chk1 plus gemcitabine combinations, such as GDC-0425 and GDC-0575, but were less frequent with the intravenous Chk1 inhibitor AZD7762.

There were seven patients with partial responses in the current study – three with anogenital cancer and one each with rectal cancer, HGSOC, SCLC and cervical cancer. These occurred at gemcitabine dose levels of 250 mg/m^2 or lower. Clinical responses in Chk1 inhibitor and gemcitabine combinations have been seen in patients across a variety of tumor types in Chk1 inhibitor plus gemcitabine combinations: AZD7762 (non-small cell lung cancer [NSCLC]; ref 11), GDC-0425 (15) (triple-negative breast cancer [TNBC], melanoma), and GDC-0575 (TNBC, sarcoma, NSCLC; ref 16). Of note, the doses of gemcitabine at which these responses were seen were 1000 mg/m^2 (AZD7762), 750–1000 mg/m^2 (GDC-0425) and 500 mg/m^2 (GDC-0575) however, it is difficult to analyze the contribution of

gemcitabine alone, versus the combination of gemcitabine and Chk1 inhibitors, to these reported responses. There have been no phase II trials of single agent full dose gemcitabine in anal cancers and response rates for full dose gemcitabine in cervical cancer range from 0-11% (22). Given the modest numbers of patients with anogenital cancer (response rate 25%) treated in this study it is difficult to extrapolate if full dose gemcitabine would have had equal activity to the combination of SRA737 + LDG. Equally, given the low response rate of full dose gemcitabine, it is unlikely that treatment with gemcitabine alone at the low 250 mg/m^2 dose would have resulted in responses; it is more likely that the combination was effective.

Several of the robust responses observed in this study were associated with genomic alterations in the FA/ BRCA network and related factors involved in replication fork repair. The response in anogenital cancers is noteworthy. Where genetic profiles were available for two of the three responding anogenital tumors, they showed alterations in FANC/BRCA genes or CDK12/ARID1A, and intermediate to high tumor mutational burden. Although it was not possible to confirm HPV infection in all samples, it is conceivable that an HPV infection could cause a functional abrogation of the G1/S checkpoint, as has been established in preclinical models (21).

The interaction of Chk1 inhibition with immune response has been documented in preclinical models (23, 24) and early clinical trials (25). The combination of SRA737 with low-dose gemcitabine plus an immune checkpoint inhibitor has been shown to be effective in SCLC models (26). As it is unlikely there would be overlapping toxicities with combinations of SRA737 and low-dose gemcitabine doublets with anti-programmed death-1 antibodies, the addition of anti-programmed death-1 antibodies

could increase response rates in tumor types with an unmet need.. Given the preclinical data and observations in the expansion cohorts, anogenital tumors and small cell lung cancer are cancers with a significant unmet need for where SRA737 + low dose gemcitabine doublet or a further combination with a immune checkpoint inhibitor as a triplet therapy are of particular interest for further evaluation of SRA737.

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Authors' Contributions

Jones, Plummer, Moreno, Carter, Roda, Garralda, Kristeleit, Sarker, Arkenau, Roxburgh, Walter, Castellano, Blagden, Anthoney, and **Banerji**: Investigation and review.

Klencke: review and editing

Banerji and **Kowalski**: Conceptualization, writing, review and editing.

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Table 1: Tumor-specific eligibility requirements for expansion cohorts

Expansion Cohort	Tumor-type specific eligibility requirement
HGSOC	Known germline BRCA mutations or alterations in genes related to tumor suppression, DNA damage repair, replicative stress or oncogenic drivers (Supplementary Methods)
STS	Alterations in genes related to tumor suppression, DNA damage repair, replicative stress or oncogenic drivers (Supplementary Methods)
SCLC	Not required to have genetic testing due to the known high incidence of TP53 mutations
Anogenital or cervical cancer	Not required to have genetic testing due to the known high incidence of human papillomavirus (HPV)

Table 2.

Title: Treatment-emergent adverse events reported by ≥10% of the overall patient population.

	SRA737 dose <500 mg (*N* = 30)	SRA737 dose ≥500 mg (*N* = 113)	Overall (*N* = 143)
Preferred term			
Any treatment-emergent adverse event	29 (96.7)	113 (100)	142 (99.3)
Nausea	13 (43.3)	75 (66.4)	88 (61.5)
Vomiting	17 (56.7)	61 (54.0)	78 (54.5)
Fatigue	9 (30.0)	64 (56.6)	73 (51.0)
Diarrhea	11 (36.7)	59 (52.2)	70 (49.0)
Anemia	14 (46.7)	51 (45.1)	65 (45.5)
Pyrexia	7 (23.3)	41 (36.3)	48 (33.6)
Thrombocytopenia	8 (26.7)	39 (34.5)	47 (32.9)
Neutropenia	5 (16.7)	44 (38.9)	49 (34.3)
Decreased appetite	4 (13.3)	40 (35.4)	44 (30.8)
ALT increased	7 (23.3)	33 (29.2)	40 (28.0)
AST increased	7 (23.3)	30 (26.5)	37 (25.9)
Constipation	5 (16.7)	30 (26.5)	35 (24.5)
Back pain	8 (26.7)	17 (15.0)	25 (17.5)
Influenza-like illness	5 (16.7)	18 (15.9)	23 (16.1)
Urinary tract infection	4 (13.3)	18 (15.9)	22 (15.4)
Cough	2 (6.7)	19 (16.8)	21 (14.7)
Dyspnea	6 (20.0)	15 (13.3)	21 (14.7)
Abdominal pain	4 (13.3)	16 (14.2)	20 (14.0)
Headache	7 (23.3)	12 (10.6)	19 (13.3)
Asthenia	2 (6.7)	14 (12.4)	16 (11.2)

Data are *n* (%) of patients.

Note: the terms “thrombocytopenia” and “neutropenia” are inclusive of the terms “platelet count decreased” and “neutrophil count decreased”. Patients with multiple adverse events within the same preferred term were only counted once within the respective category.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3.

Title: Treatment-emergent adverse events reported by ≥10% of patients treated at the recommended phase 2 dose.

	Patients treated at the recommended phase 2 dose of 500 mg SRA737 + 250 mg/m^2 gemcitabine (*N* = 60)		
Preferred term	**Grade 1–2**	**Grade 3–4**	**All grades**
Nausea	36 (60.0)	2 (3.3)	38 (63.3)
Fatigue	33 (55.0)	2 (3.3)	35 (58.3)
Diarrhea	31 (51.7)	2 (3.3)	33 (55.0)
Vomiting	30 (50.0)	4 (6.7)	34 (56.7))
Anemia	27 (45.0)	7 (11.7)	34 (56.7)
Neutropenia	18 (30.0)	10 (16.7)	28 (46.7)
Thrombocytopenia	19 (31.7)	6 (10.0)	25 (41.7)
Pyrexia	23 (38.3)	1 (1.7)	24 (40.0)
Decreased appetite	22 (36.7)	1 (1.7)	23 (38.3)
AST increased	13 (21.7)	3 (5.0)	16 (26.7)
ALT increased	12 (20.0)	3 (5.0)	15 (25.0)
Cough	12 (20.0)	0	12 (20.0)
Urinary tract infection	12 (20.0)	0	12(20.0)
Constipation	11 (18.3)	2 (3.3)	13 (21.7)
Asthenia	10 (16.7)	0	10 (16.7)
Back pain	9 (15.0)	0	9 (15.0)
Dyspnoea	9 (15.0)	1 (1.7)	10 (16.7)
Rash	9 (15.0)	0	9 (15.0)
Abdominal pain	8 (13.3)	2 (3.3)	10 (16.7)
Hypomagnesemia	6 (10.0)	1 (1.7)	7 (11.7)
Influenza-like illness	6 (10.0)	0	6 (10.0)
Rash maculopapular	6 (10.0)	0	6 (10.0)
Edema peripheral	5 (8.3)	1 (1.7)	6 (10.0)
Lower respiratory tract infection	2 (3.3)	4 (6.7)	6 (10.0)

Data are *n* (%) of patients.

Note: the terms “thrombocytopenia” and “neutropenia” are inclusive of the terms “platelet count decreased” and “neutrophil count decreased”. Patients with multiple adverse events within the same

preferred term were only counted once within the respective category.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

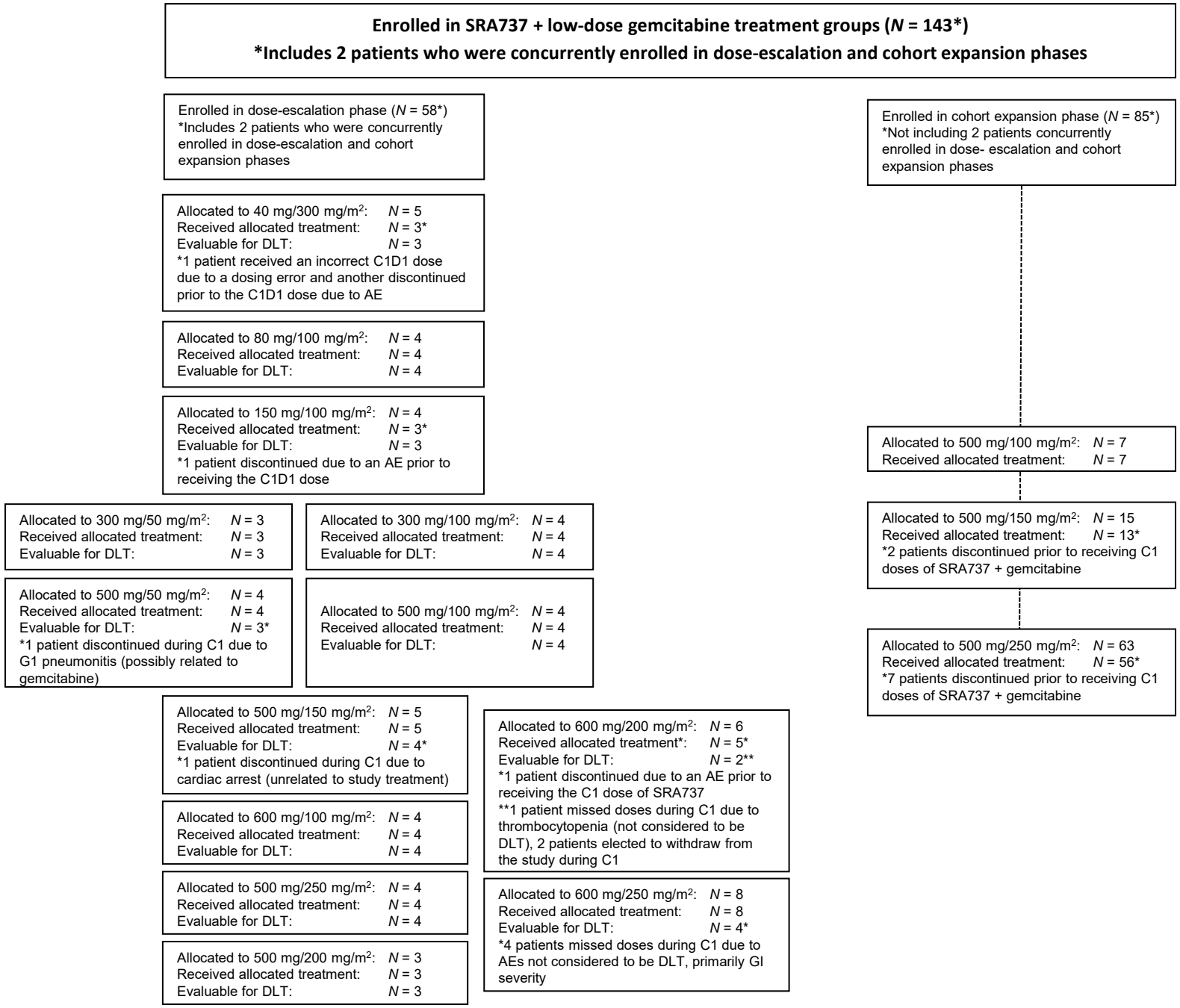
Table 4.

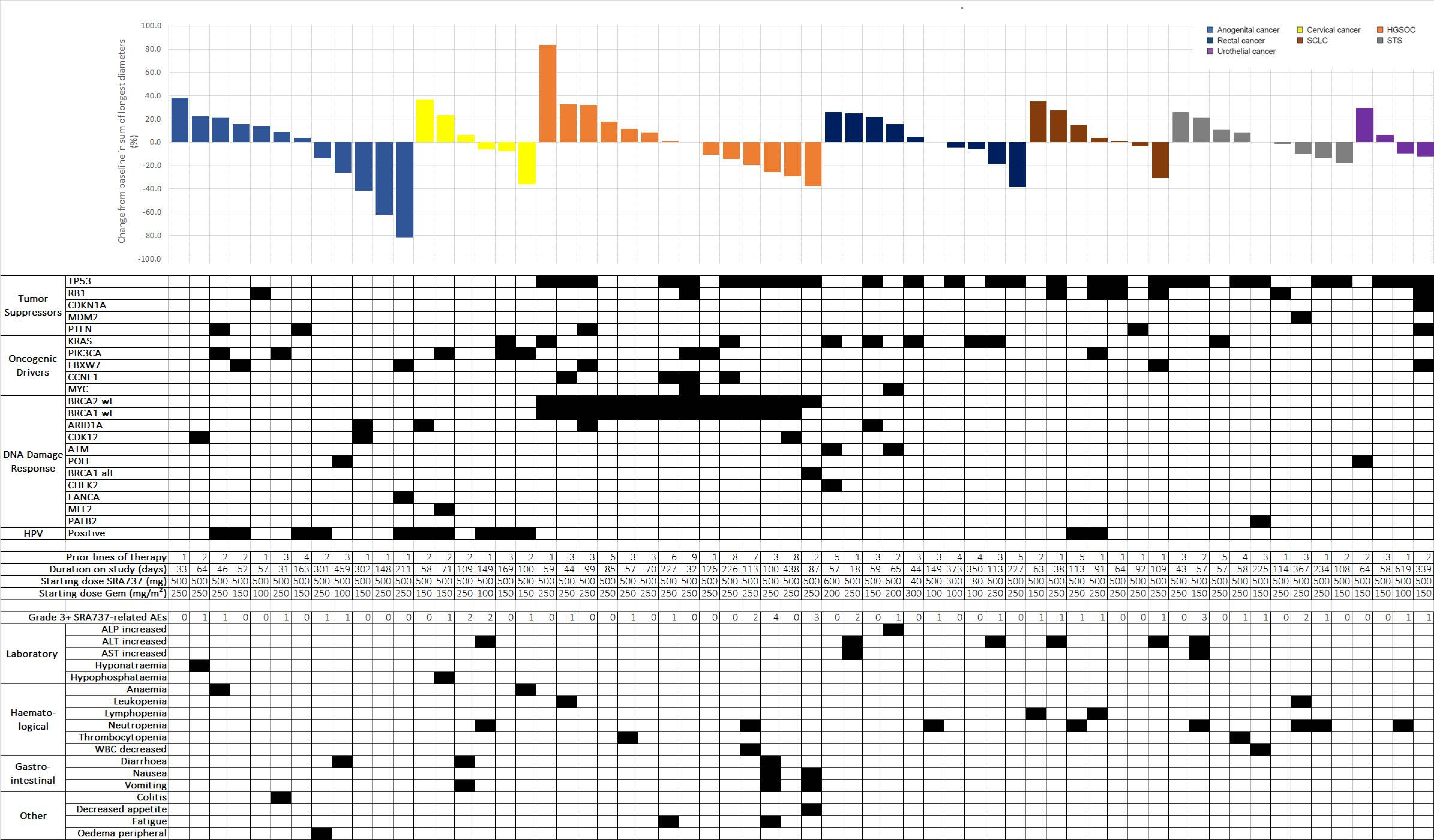
Title: Pharmacokinetic parameters for plasma SRA737.

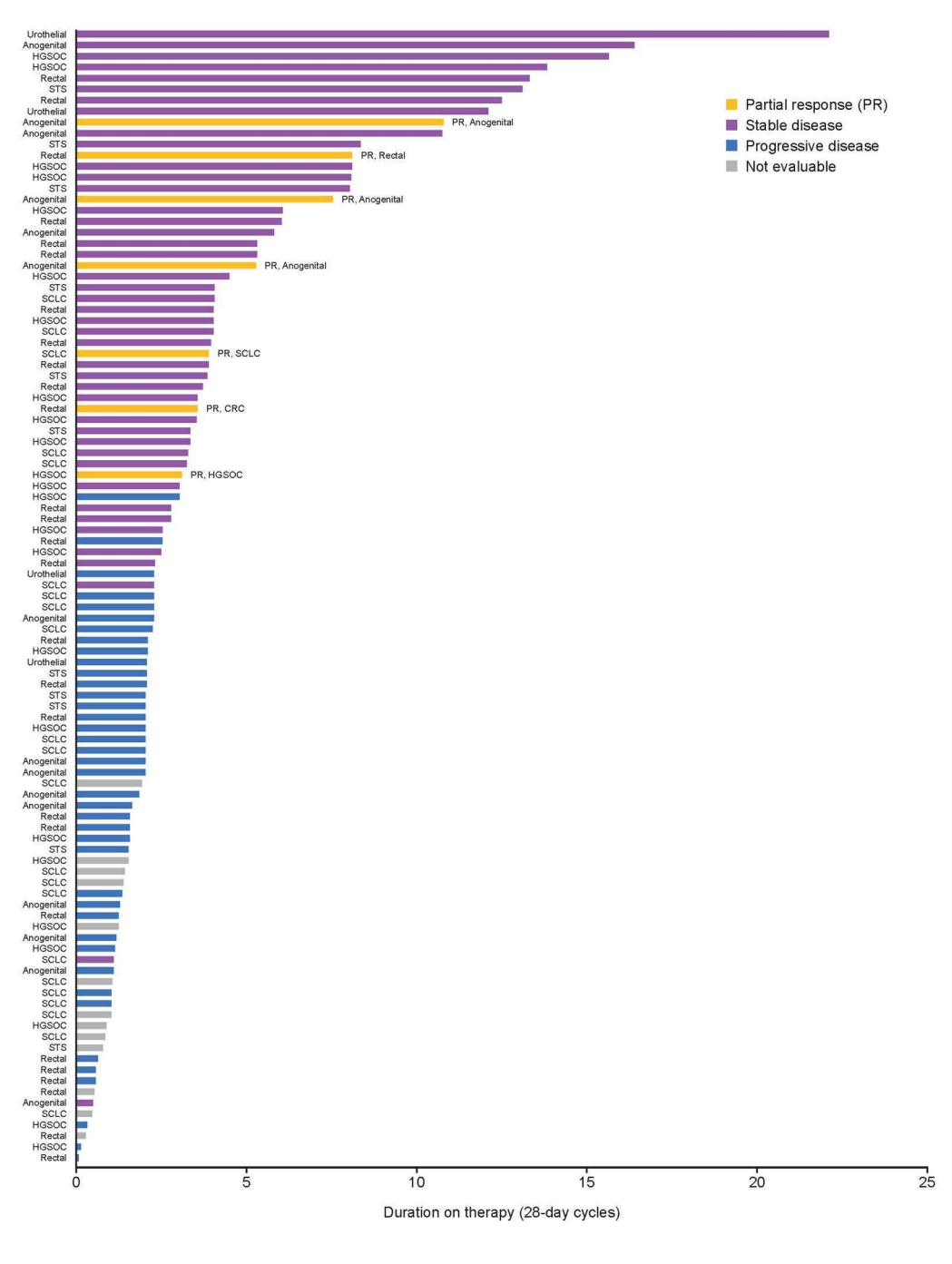
Day	Dose (mg)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-12} (ng•h/mL)	$t_{½}$ (h)	CL (L/h)	V_d (L)
–7 to –4	40	1.8–2.3	61.4–155	-	10.3–17.4	40–75	-
	80	2.0–2.1	11–173	-	10.8–11.9	69–104	-
	150	2 (1–2)	548 ± 63.9	2630 ± 944	12.7 ± 1.13	38.0 ± 15.9	717 ± 357
	300	2 (1–6)	995 ± 449	4530 ± 1590	11.7 ± 1.07	46.0 ± 16.5	764 ± 241
	500	2 (1–8)	1470 ± 605	8330 ± 3390	11.6 ± 2.22	42.3 ± 22.1	695 ± 342
	600	2 (1–4)	1720 ± 556	10200 ± 2970	10.7 ± 2.11	39.1 ± 11.4	597 ± 199
C1D10	40	1.1–2.2	83.3–152	-	-	-	-
	80	1.9–2.2	89.3–142	-	-	-	-
	150	2 (2–2)	478 ± ID	2390 ± ID	-	-	-
	300	1 (1–4)	1080 ± 563	5140 ± 1610	-	-	-
	500	2 (1–12)	1580 ± 645	9410 ± 4270	-	-	-
C1D10/C1D17	600	2 (1–6)	1740 ± 509	9990 ± 2920	-	-	-

Note: data for 40 mg and 80 mg doses displayed as minimum–maximum; data for 150 mg to 600 mg doses displayed as median (minimum–maximum) for t_{max} and as median ± SD for other parameters. "-" indicates values that were not calculated. At C1D10 the $T_{1/2}$, CL, and V_d were not assessed due to the shortened PK sampling schedule at this timepoint.

Abbreviations: AUC_{0-12}, area under the concentration-time curve from 0 to 12 hours; C1, cycle 1; CL, total clearance rate of the drug from plasma; C_{max}, maximum plasma concentration; D10, day 10 (of cycle); D17, day 17 (of cycle); h, hour; ; $t_{½}$, elimination half-life; t_{max}, time of maximum plasma concentration; V_d, apparent volume of distribution.


Enrolled in SRA737 + low-dose gemcitabine treatment groups (N = 143*)
*Includes 2 patients who were concurrently enrolled in dose-escalation and cohort expansion phases
Enrolled in dose-escalation phase (N = 58*)
*Includes 2 patients who were concurrently enrolled in dose-escalation and cohort expansion phases
Allocated to 40 mg/300 mg/m2: N = 5
Received allocated treatment: N = 3*
Evaluable for DLT: N = 3
*1 patient received an incorrect C1D1 dose due to a dosing error and another discontinued prior to the C1D1 dose due to AE
Allocated to 80 mg/100 mg/m2: N = 4
Received allocated treatment: N = 4
Evaluable for DLT: N = 4
Allocated to 150 mg/100 mg/m2: N = 4
Received allocated treatment: N = 3*
Evaluable for DLT: N = 3
*1 patient discontinued due to an AE prior to receiving the C1D1 dose
Allocated to 300 mg/50 mg/m2: N = 3
Received allocated treatment: N = 3
Evaluable for DLT: N = 3
Allocated to 300 mg/100 mg/m2: N = 4
Received allocated treatment: N = 4
Evaluable for DLT: N = 4
Allocated to 500 mg/50 mg/m2: N = 4
Received allocated treatment: N = 4
Evaluable for DLT: N = 3*
*1 patient discontinued during C1 due to G1 pneumonitis (possibly related to gemcitabine)
Allocated to 500 mg/100 mg/m2: N = 4
Received allocated treatment: N = 4
Evaluable for DLT: N = 4
Allocated to 500 mg/150 mg/m2: N = 5
Received allocated treatment: N = 5
Evaluable for DLT: N = 4*
*1 patient discontinued during C1 due to cardiac arrest (unrelated to study treatment)
Allocated to 600 mg/100 mg/m2: N = 4
Received allocated treatment: N = 4
Evaluable for DLT: N = 4
Allocated to 500 mg/250 mg/m2: N = 4
Received allocated treatment: N = 4
Evaluable for DLT: N = 4
Allocated to 500 mg/200 mg/m2: N = 3
Received allocated treatment: N = 3
Evaluable for DLT: N = 3
Allocated to 600 mg/200 mg/m2: N = 6
Received allocated treatment*: N = 5*
Evaluable for DLT: N = 2**
*1 patient discontinued due to an AE prior to receiving the C1 dose of SRA737
**1 patient missed doses during C1 due to thrombocytopenia (not considered to be DLT), 2 patients elected to withdraw from the study during C1
Allocated to 600 mg/250 mg/m2: N = 8
Received allocated treatment: N = 8
Evaluable for DLT: N = 4*
*4 patients missed doses during C1 due to AEs not considered to be DLT, primarily GI severity
Enrolled in cohort expansion phase (N = 85*)
*Not including 2 patients concurrently enrolled in dose- escalation and cohort expansion phases
Allocated to 500 mg/100 mg/m2: N = 7
Received allocated treatment: N = 7
Allocated to 500 mg/150 mg/m2: N = 15
Received allocated treatment: N = 13*
*2 patients discontinued prior to receiving C1 doses of SRA737 + gemcitabine
Allocated to 500 mg/250 mg/m2: N = 63
Received allocated treatment: N = 56*
*7 patients discontinued prior to receiving C1 doses of SRA737 + gemcitabine


Anogenital cancer
Cervical cancer
HGSOC
Rectal cancer
SCLC
STS
Urothelial cancer
Change from baseline in sum of longest diameters (%)
100.0
80.0
60.0
40.0
20.0
0.0
-20.0
-40.0
-60.0
-80.0
-100.0
Tumor Suppressors
TP53
RB1
CDKN1A
MDM2
PTEN
Oncogenic Drivers
KRAS
PIK3CA
FBXW7
CCNE1
MYC
DNA Damage Response
BRCA2 wt
BRCA1 wt
ARID1A
CDK12
ATM
POLE
BRCA1 alt
CHEK2
FANCA
MLL2
PALB2
HPV
Positive
Prior lines of therapy 1 2 2 2 1 3 4 2 3 1 1 1 2 2 2 1 3 2 1 3 3 6 3 3 6 9 1 8 7 3 8 2 5 1 3 2 3 3 4 4 3 5 2 1 5 1 1 1 1 3 2 5 4 3 1 3 1 2 2 3 1 2
Duration on study (days) 33 64 46 52 57 31 163 301 459 302 148 211 58 71 109 149 169 100 59 44 99 85 57 70 227 32 126 226 113 100 438 87 57 18 59 65 44 149 373 350 113 227 63 38 113 91 64 92 109 43 57 57 58 225 114 367 234 108 64 58 619 339
Starting dose SRA737 (mg) 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 600 600 500 600 40 500 300 80 600 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500 500
Starting dose Gem (mg/m²) 250 250 250 150 100 250 150 250 100 150 250 250 150 150 250 100 150 150 250 250 250 250 250 250 250 250 250 250 250 250 250 250 200 250 150 200 300 100 100 100 250 250 150 250 250 250 250 250 250 250 150 250 250 150 250 250 250 150 150 150 100 150
Grade 3+ SRA737-related AEs 0 1 1 0 0 1 0 1 1 0 0 0 0 1 2 2 0 1 0 1 0 0 1 0 1 0 0 0 2 4 0 3 0 2 0 1 0 1 0 0 1 0 1 1 1 1 0 0 1 0 3 0 1 1 0 2 1 0 0 0 1 1
Laboratory
ALP increased
ALT increased
AST increased
Hyponatraemia
Hypophosphataemia
Haemato-logical
Anaemia
Leukopenia
Lymphopenia
Neutropenia
Thrombocytopenia
WBC decreased
Gastro-intestinal
Diarrhoea
Nausea
Vomiting
Other
Colitis
Decreased appetite
Fatigue
Oedema peripheral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HGSOC
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HGSOC
Rectal
PR, Anogenital
PR, Rectal
PR, Anogenital
PR, Anogenital
PR, SCLC
PR, CRC
PR, HGSOC
Partial response (PR)
Stable disease
Progressive disease
Not evaluable
0
5
10
15
20
25
Duration on therapy (28-day cycles)

Supplementary Table 1. Demographic and Disease Characteristics

	All dose escalation (*N* = 58)	Anogenital cancer (*N* = 15)	Cervical cancer (*N* = 12)	HGSOC (*N* = 24)	Rectal cancer (*N* = 15)	SCLC (*N* = 22)	STS (*N* = 11)	Urothelial cancer (*N* = 4)	Overall (*N* = 143)
Age, years									
Median (Q1, Q3)	63.5 (54.0, 71.0)	59.0 (55.0, 69.0)	48.0 (37.0, 58.5)	63.0 (55.5, 68.0)	63.0 (52.0, 72.0)	61.5 (56.0, 65.0)	60.0 (50.0, 68.0)	60.5 (56.5, 66.5)	62.0 (54.0, 68.0)
Range	18, 81	49, 75	34, 75	44, 79	40, 81	32, 74	28, 77	53, 72	18, 81
Sex, *n* (%)									
Male	32 (55.2)	4 (26.7)	0	0	11 (73.3)	14 (63.6)	4 (36.4)	3 (75.0)	56 (39.2)
Female	26 (44.8)	11 (73.3)	12 (100)	24 (100)	4 (26.7)	8 (36.4)	7 (63.6)	1 (25.0)	87 (60.8)
WHO PS at baseline, *n* (%)									
0	31 (53.4)	5 (33.3)	6 (50.0)	13 (54.2)	12 (80.0)	4 (18.2)	5 (45.5)	1 (25.0)	63 (44.1)
1	27 (46.6)	10 (66.7)	6 (50.0)	11 (45.8)	3 (20.0)	18 (81.8)	6 (54.5)	3 (75.0)	80 (55.9)
Line of therapy[a], *n* (%)									
1	14 (24.1)	6 (40.0)	4 (33.3)	2 (8.3)	1 (6.7)	8 (36.4)	2 (18.2)	1 (25.0)	35 (24.5)
2	11 (19.0)	5 (33.3)	6 (50.0)	5 (20.8)	1 (6.7)	7 (31.8)	3 (27.3)	2 (50.0)	38 (26.6)
3	18 (31.0)	2 (13.3)	2 (16.7)	6 (25.0)	7 (46.7)	5 (22.7)	4 (36.4)	1 (25.0)	38 (26.6)
4	10 (17.2)	1 (6.7)	0	2 (8.3)	4 (26.7)	1 (4.5)	1 (9.1)	0	15 (10.5)
5+	4 (6.9)	1 (6.7)	0	9 (37.5)	2 (13.3)	1 (4.5)	1 (9.1)	0	16 (11.2)

Note: patients are displayed in cohorts defined by tumor type, including indication-specific expansion cohorts (anogenital, cervical, HGSOC, SCLC and STS), a grouping of patients with rectal cancer who were enrolled under dose escalation, and four patients with urothelial cancer enrolled under previous protocol versions. A total of 18 patients were "double counted" in that they appear under both "All dose escalation" and in their specific tumor-type cohorts. These 18 patients consisted of 15 dose-escalation patients with rectal cancer, one dose-escalation patient with anogenital cancer, one concurrently enrolled dose-escalation/expansion patient with cervical cancer, and one concurrently enrolled dose-escalation/expansion patient with STS.

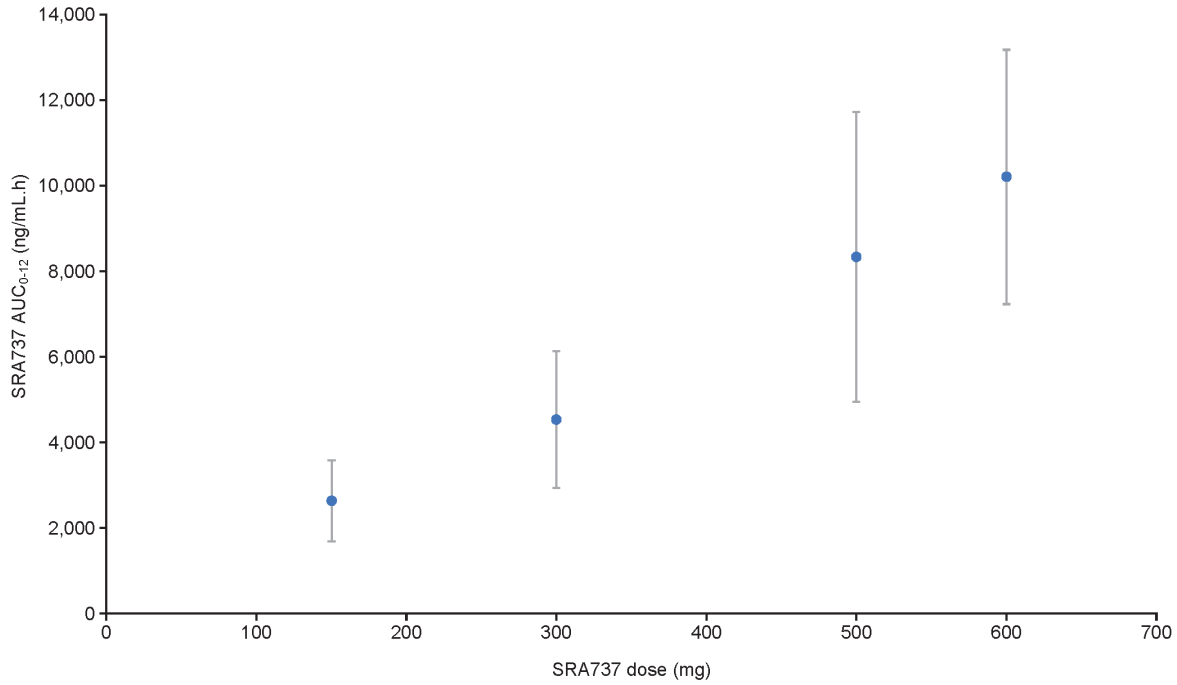
[a]Based on the last anticancer therapy before enrolment. One patient in the dose-escalation group did not have prior lines of therapy reported.

Abbreviations: HGSOC, high-grade serous ovarian cancer; SCLC, small cell lung cancer; STS, soft tissue sarcoma; SD, standard deviation; WHO PS, World Health Organization performance status.

Supplementary Figure 1.

Title: Mean exposure ($AUC_{0–12}$) by dose level following a single oral dose of SRA737.

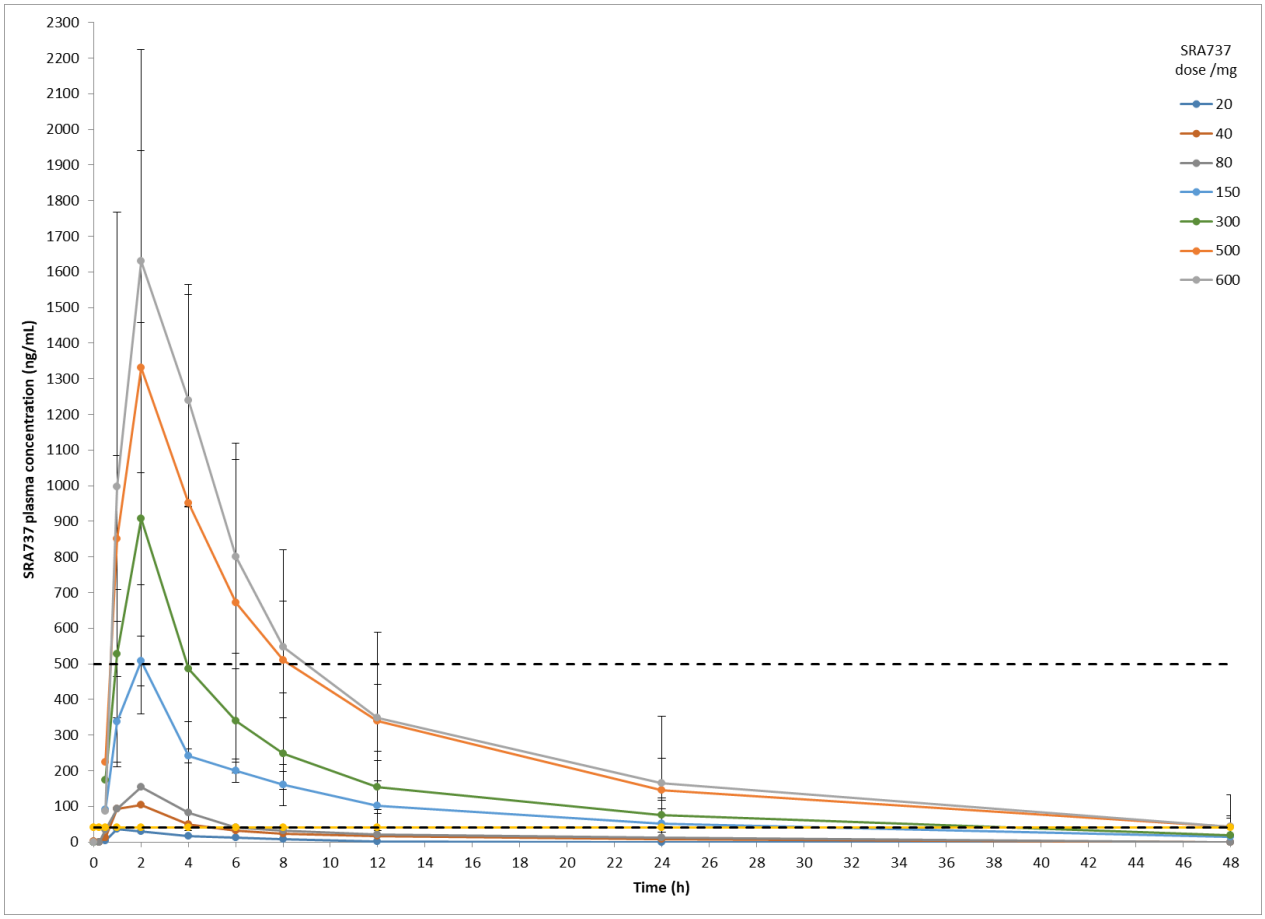
Description: This figure displays the mean area under the SRA737 plasma concentration-time curve from 0 to 12 hours ($AUC_{0–12}$) following a single oral dose of SRA737 at doses of 150, 300, 500 and 600 mg. Error bars represent standard deviation.



Supplementary Figure 2.

Title: Mean plasma SRA737 concentration over time by dose level following a single oral dose of SRA737.

Description: This figure displays the mean SRA737 plasma concentration at each assessment timepoint by dose level. The dotted lines indicates a plasma concentration of 40-500 ng/mL, the range corresponding to the minimal effective dose extrapolated from preclinical models. Error bars represent standard deviation.



Supplementary Data

Methods

Inclusion criteria

Dose-escalation and cohort expansion patients:

Written (signed and dated) informed consent and be capable of co-operating with treatment and follow up.

In the dose-escalation phase, patients 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 patient.

Life expectancy of at least 12 weeks.

World Health Organization (WHO) performance status of 0–1.

Haematological and biochemical indices within the ranges shown below measured within 1 week prior to the patient receiving the first dose of study treatment.

- Haemoglobin ≥90 g/L
- Absolute neutrophil count ≥1.5 × 10^9/L
- Platelet count ≥100 × 10^9/L
- Bilirubin ≤1.5 × upper limit of normal (ULN) unless due to Gilbert's syndrome in which case up to 3 × ULN is permissible
- Alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase ≤2.5 × ULN unless raised due to tumor in which case up to 5 × ULN is permissible
- Serum creatinine ≤1.5 × ULN
- Electrolytes: magnesium, potassium and calcium. If electrolyte levels are low, it must be demonstrated that they can be normalized and maintained using supplements prior to the patient beginning study treatment

Supplement use should continue while on study as appropriate

Patients must be 18 years or older at the time consent is given.

Patients 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:

Patients 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 patient.

Have measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) criteria.

Patients must have predicted sensitivity to Chk1 inhibition based on factors including genetic profiling of tumor tissue or circulating tumor DNA, HPV status, and germline BRCA1 and BRCA2 gene status. All patients will have genetic profiling from tumor tissue or circulating tumor DNA; profiling to be performed prospectively if required to evaluate Chk1 sensitivity or otherwise performed retrospectively.

For patients with high-grade serous ovarian cancer (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.
Patients with small cell lung cancer (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 (e.g., TP53 and RB1) in this population.
For patients with soft tissue sarcoma (STS), and any others for whom genetic profiling is performed prospectively, eligibility was determined by the sponsor’s review of genetic abnormalities detected in genes in the following categories, as detailed in 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.

For patients 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. Patients 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.

Patients must meet one of the following criteria:

HGSOC, defined by the following:
Histologically confirmed high-grade serous ovarian, fallopian tube, or primary peritoneal cancer
Platinum-resistant or refractory disease (defined per protocol), or the patient is intolerant to platinum therapy.
Small cell lung cancer

i. Must have received at least one but no more than three prior regimens for advanced disease, unless otherwise approved by sponsor.

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 one but no more than three prior regimens for advanced disease, unless otherwise approved by sponsor.

Cervical/anogenital cancer

Including all cervical carcinoma and advanced/metastatic squamous cell carcinoma of the anus, penis, vagina, and vulva
Must have received at least one but no more than three prior regimens for advanced disease, unless otherwise approved by sponsor.

Exclusion criteria

Have received prior or current anticancer therapy within the noted time periods prior to receiving SRA737 and have recovered from toxicity consistent with exclusion criterion 5:

Radiotherapy (except for symptom control and where the lesions will not be used as measurable disease), chemotherapy, PARP inhibitors, other targeted therapies, or other investigational medicinal products within 2 weeks
Nitrosoureas or mitomycin C within 6 weeks
Any prior treatment with a Chk1 inhibitor, or prior treatment with an ATR inhibitor within 6 months.

No more than three 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.

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%.

If, in the opinion of the investigator, the patient is highly likely to experience clinically significant myelosuppression, based on previous experience with chemotherapy.

Ongoing toxic manifestations of previous treatments greater than 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 patient.

History of allergy to gemcitabine.

New or progressing brain metastases. Patients 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.

Women of childbearing potential (WOCBP) or women who are already pregnant or lactating. However, those patients who have a negative serum or urine pregnancy test before enrolment and agree to use two forms of contraception or agree to sexual abstinence, effective from the first administration of SRA737, throughout the trial and for 6 months afterwards are considered eligible.

Male patients with partners of childbearing potential, unless they agree to take measures not to father children by using a barrier method of contraception, effective from the first administration of SRA737, through 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 (e.g., condom plus spermicidal gel) to prevent exposure of a fetus or neonate.

Major surgery from which the patient has not yet recovered.

At high medical risk because of nonmalignant systemic disease including active uncontrolled infection.

Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus.

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 ischaemia within the past 6 months, or prior history of cardiac arrhythmia requiring treatment, unless approved by the sponsor.

Prior bone marrow transplant or have had extensive radiotherapy to greater than 25% of bone marrow within the previous 8 weeks.

Peanut allergy unless this restriction is removed by the sponsor (refer to Section 6.1 for additional details).

QTcF >450 msec in adult males and >470 msec in adult females.

Impairment of GI function or GI disease that may significantly alter the absorption of SRA737 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea or malabsorption syndrome).

Not able to swallow capsules without chewing or crushing.

Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this phase I/II study of SRA737. Participation in an observational trial or interventional clinical trial that does not involve administration of an IMP and which would not place an unacceptable burden on the patient in the opinion of the investigator and sponsor would be acceptable.

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

Genetic profiling of tumor types

Patients must have predicted sensitivity to Chk1 inhibition for enrolment into the cohort expansion phase. Factors including genetic profiling of tumor tissue or ctDNA, HPV status (including very high prevalence of HPV positivity in some tumor types), and BRCA1 and BRCA2 gene status may considered for evaluation of Chk1 sensitivity. Evaluation of genetic profiles will identify gene mutations documented or predicted to enhance sensitivity to Chk1 inhibition/loss. These genes of interest are grouped into four main classes, consistent with the Hallmarks of Cancer (Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74). Note, this list is not exhaustive as scientific discoveries and technology continue to evolve.

Tumor Suppressor
CDKN1A
CDKN1B
CDKN2A
CDKN2B
CDKN2C
PTEN
RB1
STK11
TP53
MDM2[1]
Other

DNA Damage Repair			
ARID1A	FANCE	PALB2	RAD54L
ATM	FANCF	PMS2	RPA1
BLM	FANCG	POLD1	SETD2
BRCA1	FANCI	POLE	SMARCA4
BRCA2	FANCL	RAD50	TP53BP1
CDK12	FANCM	RAD51	XRCC2
CHEK2	MLH1	RAD51B	XRCC3
FANCA	MRE11A	RAD51C	Other
FANCC	MSH2	RAD51D	
FANCD2	MSH6	RAD52	

Replicative Stress
ATR
CHEK1
Other

Oncogenic Driver
CCNE1
FBXW7[2]
HRAS
KRAS
NRAS
MYC
MYCN
PARK2
PIK3CA
Other

1. Amplification or gain of function mutations are desired for this gene
2. Loss of function mutations are desired for this gene

Other genetic predictors that can be added to this list include mutations meeting any of the following criteria:

A new gene/mutation that has been identified and published in at least one peer reviewed article documenting its relationship or sensitivity to genetic alterations with a Chk1 or ATR mutation.

Data from patient-derived xenograft studies performed by the sponsor or its collaborator demonstrating evidence of genetic sensitivity.

Data of similar quality that have been reviewed by the sponsor but are not yet published or conducted by the sponsor or their collaborator.

Detection of microsatellite instability in a tumor sample may increase the probability of detecting a germline mutation in a DNA mismatch repair gene. Five mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27) are used to determine microsatellite instability status. Genetic predictors may also be removed from this list as new information on the relationship or sensitivity of genetic alterations in genes included in the list becomes available or the technology employed in genomic profiling evolves. The Laboratory Manual will be updated if/when genes are added to, or removed from, this list.