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

Sponsor Protocol Number: SRA737-02

EudraCT Number: 2015-004467-36

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Compliance Statement: This study will be conducted in accordance with Protocol SRA737-02, the International Conference on Harmonization (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

VERSION HISTORY

Version No.	Date of Issue	Reason for Update
1.0	25-January-2016	Initial version submitted for MHRA/REC approval
2.0	03-March-2016	Addition of hearing impairment and history of allergy to cisplatin or gemcitabine exclusion criteria and amendments to contraceptive advice (made at the request of the MHRA prior to approval)
		Note: Superseding version 2.0 was withdrawn prior to review in order to retain the current Investigational Medicinal Product name (CCT245737).
Superseding 3.0	11-October-2016	Sponsor change – All sponsor specific details have been updated to reflect the new sponsor Sierra Oncology, Inc. (formerly known as ProNAi Therapeutics, Inc.), including sponsor name, responsibilities, address, emergency contact details, and the protocol title and number.
4.0	05-December-2016	Protocol Amendment Version 4.0 of the protocol includes changes to the name of the sponsor and investigational product. In addition, the study is being amended to focus on assessment safety and preliminary efficacy in subjects with tumors anticipated to be sensitive to inhibition of Chk1 mainly in the SRA737+gemcitabine combination. Procedures are being revised to ensure appropriate subject selection, in accordance with the new and retained study objectives.
5.0	17-February-2017	Protocol Amendment Version 5.0 updates the frequency of bone scans. In addition, clarifications have been provided for IMP dosing, tumor biopsies, and laboratory assessments.
6.0	05-October-2017	Protocol Amendment Version 6.0 changes the indications in the Cohort Expansion Phase (adding small cell lung cancer, cervical/anogenital cancer, and soft tissue sarcoma, and removing pancreatic cancer) and increases the size of each cohort from 6-8 to approximately 20 subjects. The genetic selection strategy is modified so that the sponsor may choose to refine or select particular genomic profile requirements in expansion cohorts based on observations of tumor response and clinical benefit in the ongoing study and/or other emerging clinical and nonclinical data. In addition, clarifications and corrections were made.

ES-6.1	27-April-2018	Protocol Version ES-6.1 is specific to Spain and contains the changes submitted in response to questions from the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) dated 23-March-2018. An Introduction was added to clarify the trial design, stage of participation, and the number of patients enrolled to date. Exclusion criterion 2 was revised to clarify that prior gemcitabine therapy is permitted. Section 2.3.1.1 Dose Justification for Stage 2 Expansion Phase was added to provide justification from previous studies of the dose in the expansion phase. Sections 2.4.1.1 and 2.4.1.2 were added to provide safety summaries of the two ongoing clinical trials of SRA737.
7.0	03-Aug-2018	This amendment superseded versions 6.0 and 6.1-ES and includes the following changes: Removal of urothelial carcinoma cohort and replacement with a cohort of 20 subjects with platinum resistant or refractory high-grade serous ovarian cancer (HGSOC). The inclusion criterion describing predictors of sensitivity to Chk1 inhibition (#10) was updated to include eligibility according to factors including: genetic profiling of tumor tissue or ctDNA, HPV status, and germline *BRCA1* and *BRCA2* gene status. Washout periods for prior therapy were updated (exclusion #1). Guidance was included on treatment in the event of rash (Section 5.5.1.8). The requirement for triplet biopsies was amended such that biopsies will be taken when subjects have accessible tumor and consent to a biopsy in up to 1 subject, if available, per dose level in Dose Escalation, and subjects with accessible tumor and who consent to a biopsy in Cohort Expansion. The Trial Status (Section 2) and Clinical Experience (Sections 2.4.1.1 and 2.4.1.2) were updated with more current information. The background section was updated to include background on ovarian cancer. Clarification of the term "first dose" was made to specify whether this applies to SRA737 or gemcitabine in each instance.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ADMET	adsorption, distribution, metabolism, excretion, and toxicity
	AE	adverse event
	AUC	area under the curve
	AUC_{0-t}	area under the curve from time zero to last measured concentration
	AUC_{inf}	area under the curve from time zero to infinity
	AUC_{tau}	area under the curve from time zero to tau (tau = dosing interval)
B	BP	blood pressure
	BSA	body surface area
C	95% CI	95% confidence interval
	C1D1	Cycle 1 Day 1
	CBC	Complete blood count (full blood count)
	Chk1 or 2	Checkpoint kinase 1 or 2
	CI	Chief Investigator
	C_{max}	maximum observed plasma concentration
	C_{min}	minimum observed plasma concentration
	CR	complete response
	CRA	Clinical Research Associate
	CRUK	Cancer Research UK (previous sponsor of this trial with investigational medicinal product CCT245737 now known as SRA737)
	CT	computerized tomography
	CTCAE	Common Terminology Criteria for Adverse Events
	ctDNA	circulating tumor deoxyribonucleic acid
	CYP	Cytochrome P450
D	Day	calendar day
	DCR	disease control rate
	DDR	DNA damage response
	DLT	dose-limiting toxicity
	DNA	deoxyribonucleic acid
	DOR	duration of response
E	EC	Ethics Committee
	EC_{50}	half maximal efficacious concentration
	ECG	Electrocardiogram
	ECHO	Echocardiogram
	eCRF	electronic case report form
	EDC	electronic data capture
	ESMO	European Society for Medical Oncology
F	FDG	Fluorodeoxyglucose
	FIH	First-in-human
	FOLFIRINOX	leucovorin, fluorouracil, irinotecan, oxaliplatin
G	G or G-alone	gemcitabine alone
	GC	gemcitabine + cisplatin
	GCP	Good Clinical Practice
	GI	Gastrointestinal
	GLP	Good Laboratory Practice
H	h	Hour
	HGSOC	High-grade serous ovarian cancer
	HPV	human papilloma virus
I	IC_{50}	half maximal inhibitory concentration

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	ICD	informed consent document
	ICH	International Conference on Harmonisation
	ICR	Institute for Cancer Research
	IMP	investigational medicinal product
	IRB	Institutional Review Board
	ITF	Investigator Trial File
	IV	Intravenously
L	LTFU	Long term follow-up
M	MEC	minimum effective concentration
	min	minute(s)
	MHRA	Medicines and Healthcare products Regulations Agency
	MRI	magnetic resonance imaging
	MTD	maximum tolerated dose
	MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
N	NCCN	National Comprehensive Cancer Network
	NCI	National Cancer Institute
	NE	not evaluable
	NGS	next generation sequencing
	NOAEL	No observed adverse effect level
	NSCLC	Non-small cell lung cancer
	NYHA	New York Heart Association
O	OD	oncogenic driver
	ORR	overall response rate
	OS	overall survival
P	PARP	poly ADP ribose polymerase
	PBMC	peripheral blood mononuclear cell
	PD	progressive disease or disease progression
	PDn	pharmacodynamics
	PET	positron emission tomography
	PFS	progression-free survival
	PI	Principal Investigator
	PK	pharmacokinetics
	PO	oral (orally)
	PPI	proton pump inhibitors
	PR	partial response
Q	QT, QTc	QT interval, corrected QT interval
	QTcF	QTc interval corrected for heart rate using Fridericia's formula
R	RBC	Red blood cell
	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumors
	RNAi	ribonucleic acid interface
	RP2D	recommended Phase II dose
	RS	replication stress
S	SAE	serious adverse event
	SCLC	small cell lung cancer
	SD	stable disease
	SFU	Safety follow-up
	Sierra Oncology	Sierra Oncology, Inc.
	SmPC	Summary of Product Characteristics

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	SRA737 (investigational medicinal product)	Previously known as CCT245737
	STS	soft tissue sarcoma
T	$t_{1/2}$	terminal elimination half-life
	TEAE	treatment-emergent adverse event
	TK	toxicokinetics
	TS	tumor suppressor
	T_{max}	time to reach C_{max}
	TTP	Time to progression
	TTR	Time to response
U	ULN	upper limit of normal
	USM	urgent safety measure
W	WBC	white blood cell
	WHO	World Health Organisation
	WOCBP	women of child bearing potential

PROTOCOL ACCEPTANCE PAGE

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
Protocol Number	SRA737-02
Version (Date)	7.0 (03-Aug-2018)

Investigator Signature:

I have reviewed the protocol and agree to conduct the study as outlined herein and in compliance with Good Clinical Practices and all applicable regulatory requirements. I understand that neither I nor any member of my staff may modify this protocol without obtaining written concurrence of Sierra Oncology, Inc. (Sierra Oncology), and that Sierra Oncology and the institutional review board/independent ethics committee must approve any substantive changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after termination of the study, any confidential information acquired regarding the investigational product and Sierra Oncology processes or methods. All data pertaining to this study will be provided to Sierra Oncology. I understand that any presentation or publication of study data must be reviewed by Sierra Oncology, before release, as specified in the protocol.

I certify that neither I nor any member of my staff have been disqualified or debarred by the US Food and Drug Administration or any European regulatory body for clinical investigations or any other purpose.

Investigator's Name: _____

Name of site: _____

Signature: _____

Date: _____

1 PROTOCOL SYNOPSIS

Name of sponsor/company:	Sierra Oncology, Inc.
Name of product:	SRA737
Full title of study and protocol number and phase:	SRA737-02: 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.
Short Title of Study:	SRA737-02: A Phase 1/2 trial of SRA737 in combination with gemcitabine plus cisplatin or gemcitabine alone in subjects with advanced cancer.
Study objective(s):	**Primary Objectives:** • To establish the safety profile of SRA737 administered in combination with gemcitabine ± cisplatin • To determine the maximum tolerated dose (MTD) of SRA737 administered in combination with gemcitabine • To define a recommended Phase 2 dose (RP2D) of SRA737 in combination with gemcitabine **Secondary Objectives**: • To characterize the pharmacokinetic (PK) profile of SRA737 administered in combination with gemcitabine ± cisplatin • 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. **Exploratory Objectives**: • To assess the relationship between tumor response and the presence of selected genetic alterations as detected in tumor tissue or circulating tumor deoxyribonucleic acid (ctDNA) • To explore possible clinical predictors of outcomes • To investigate the pharmacodynamics (PDn) of SRA737 in combination with gemcitabine in tumor tissue • To investigate the PDn of SRA737 in combination with gemcitabine in surrogate tissues such as blood or peripheral blood mononuclear cell (PBMCs)
Study design:	This is a multicenter, first-in-human, Phase 1/2, open-label, dose escalation trial, in subjects with advanced solid tumors. The trial will consist of 2 stages: • Stage 1: A SRA737 and gemcitabine + cisplatin Dose Escalation Phase. Upon implementation of Protocol Amendment Version 5.0 (hereafter referred to as Amendment v5.0), further dose-escalation in this stage was halted and Stage 2 began. Ten subjects with solid tumors were enrolled in the SRA737 + gemcitabine + cisplatin Dose Escalation Phase (Stage 1) of the study. • Stage 2: A SRA737 and gemcitabine Dose Escalation Phase to establish the MTD, and a Cohort Expansion Phase In the Stage 2 Dose Escalation Phase, approximately 30 to 40 subjects with solid tumors in cohorts of 3 to 6 subjects will 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 has been achieved or evidence of anti-tumor activity observed), gemcitabine may be escalated to a maximum dose of 600 mg/m^2 (with corresponding decreases in the SRA737 dose, as necessary for safety). In the Cohort Expansion Phase, approximately 20 prospectively-selected genetically-defined subjects will be enrolled in each of 4 indication-specific cohorts: high-grade serous ovarian cancer (HGSOC), small cell lung cancer (SCLC), soft tissue sarcoma (STS), and cervical/anogenital cancer. These subjects will be treated at the MTD or at a lower dose as selected by the sponsor. Subjects may continue treatment as long as none of the treatment discontinuation criteria are met (see Section 5.6). Subjects who are not evaluable for dose-limiting toxicity (DLT) assessments may be replaced.
Number of investigational sites:	This is a multicenter study.
Planned number of subjects:	It is estimated that approximately 140 subjects will be required to complete this trial. The final number of subjects enrolled in this trial will depend on the number of dose levels explored.
Sample size justification:	The sample size for this study is based on assumptions of allometric scaling and the estimated number of dose levels required to establish the MTD and the optimal number of subjects needed to further evaluate the safety profile of the MTD/RP2D and schedule in this Phase 1/2 study. For the Cohort Expansion Phase, the sample size of 20 subjects enrolled in each indication-specific expansion cohort was chosen such that 0 of 20 responses observed excludes an objective response rate (ORR) of 16% in the 95% confidence interval (CI).
Study population:	Dose Escalation Phase: Subjects with advanced solid tumors. Cohort Expansion Phase: Prospectively-selected genetically-defined subjects with HGSOC, SCLC, STS, or cervical/anogenital cancer.
Test product, dose, and mode of administration:	SRA737 is a highly potent and selective orally administered checkpoint kinase 1 (Chk1) inhibitor. In this first-in-human trial, the starting dose of SRA737 in Stage 1 was 20 mg/day on Day 2, 3, 9 & 10 of each 21-day cycle. The starting dose of SRA737 for Cohort 1 of Stage 2 Dose Escalation Phase was 40 mg/day.
Treatment regimen(s):	All subjects will receive a single dose of SRA737 between Day -7 and Day -4 for the purposes of PK evaluation. The sponsor reserves the

option to remove this requirement once sufficient intensive single-dose PK data has been obtained, if applicable.

Stage 1:

- Gemcitabine: Administered intravenously (IV) over 30 minutes on Days 1 and 8 of each 21-day cycle. The starting dose of gemcitabine for Cohort 1 was 1250 mg/m^2.
- Cisplatin: Administered IV over 2 hours following gemcitabine on Day 1 of each cycle with pre- and post-infusion hydration. The starting dose of cisplatin for Cohort 1 was 80 mg/m^2.
- SRA737: Taken PO daily on Days 2, 3, 9 and 10 of each 21-day cycle. The starting dose for Cohort 1 was 20 mg.

Stage 2:

- Gemcitabine: Administered IV over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. The starting dose and schedule for the first cohort 1 of Stage 2 was 300 mg/m^2. The dose and schedule may be adjusted based on accumulating data.
- SRA737: Taken PO daily on Days 2, 3, 9, 10, 16, and 17 of each 28-day cycle. The starting dose of SRA737 for the first cohort of Stage 2 was 40 mg. The dose and schedule may be adjusted based on accumulating data.

Inclusion criteria:

Dose Escalation and Cohort Expansion:

1. Written (signed and dated) informed consent and be 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 (Appendix 1).
5. Hematological and biochemical indices within the ranges shown below measured within 1 week prior to the subject receiving their first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted).

Laboratory Test	Value Required
Hemoglobin	≥ 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 and 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 subject beginning study treatment. Supplement use should continue while on study as appropriate.

6. Subjects who are 18 years or older at the time consent is given.
7. Subjects must have archival tumor tissue available for tumor profiling OR accessible tumor and willingness to consent to a biopsy for the collection of tumor tissue. Refer to Section 7.1.1 for more information.

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 will be 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 will be determined by the sponsor's review of genetic abnormalities detected in genes in the following categories, as detailed in Appendix 6:
        - 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. iii. Must have received at least 1 but no more than 3 prior regimens for advanced disease, unless otherwise approved by sponsor
Exclusion criteria:	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 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 child bearing potential, unless they agree to take measures not to father children by using a barrier method of contraception defined per Appendix 4, 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 (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] - refer to Appendix 3), 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 is removed by the sponsor (refer to Section 6.1 for additional details). 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.
Overview of assessments:	As part of Pre-Screening the following will be performed: written informed consent; blood and available suitable archival or fresh tissue will be collected for tumor profiling for cohort expansion subjects, or confirmed as available for collection at baseline for dose escalation subjects. Up to 28 days prior to the first scheduled dose, the following will be performed/obtained: demographic information, medical history, and concomitant medications will be recorded. Serious adverse events (SAEs) will be collected starting on the date of informed consent. Radiological assessment will be performed within 4 weeks from the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted) and repeated every 6 weeks in Stage 1. In Stage 2, assessments will be performed every 8 weeks and then in long-term follow-up every 16 weeks. Assessments may be performed more frequently, when clinically indicated. Cardiac assessments (echocardiogram [ECHO] and electrocardiogram [ECG]) will also be conducted. Optional triplet tumor biopsies may be collected within 28 days prior to receiving the first SRA737 dose. Within 7 days of the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), the following assessments will be completed: complete physical examination, clinical disease assessment, SAE and concomitant medication, WHO performance status and local laboratory assessment of blood (for hematology, biochemistry, and pregnancy testing), At the single-dose PK run-in on Day -7 to Day -4 visit, concomitant medication, vital signs (including temperature, blood pressure, and pulse), height, weight, body surface area (BSA), and WHO performance status will be collected. Blood samples will be obtained predose for hematology, biochemistry, pregnancy testing, troponin I or T, as well as for tumor markers and tumor profiling. Adverse events (AEs) will be collected starting at the administration of SRA737. Archival tissue will be submitted for tumor profiling. PK samples will be collected at up to 10 time points over a 48-hour time period on Day - 7 to - 4 (first dose of SRA737 for PK). The sponsor may reduce the requirement for PK sampling, including modification or elimination of the Day -7 to Day -4

	visit once sufficient data to evaluate the single-dose PK of SRA737 have been collected and analyzed. Dosing will begin on Day 1 with the following procedures occurring at regular intervals. • Adverse event and concomitant medication: On an ongoing basis • Symptom-directed physical exam (if medically indicated): Day 1 of each cycle • Radiological disease assessment: Every 6 weeks after Day 1 for Stage 1 and every 8 weeks after Day 1 for Stage 2 • Clinical disease assessment: Every 6 weeks after Day 1 for Stage 1 and every 4 weeks after Day 1 for Stage 2 • Tumor markers (serum or urine) (if applicable): every 6 weeks from Cycle 1 Day 1 for Stage 1 and every 4 weeks from Cycle 1 Day 1 for Stage 2 • WHO Performance Status and weight/BSA: Day 1 of each cycle • Vital signs: Days 1 and 8 for Stage 1 and Days 1, 8, and 15 for Stage 2 • Local laboratory assessment of blood (for hematology, biochemistry, troponin I or T) and urine (urinalysis) – see Section 7.2.2 for detailed schedule • ECHO: Cycle 2 Day 1 • ECG: Day 1 of Cycles 1 and 2, and then predose Day 1 at each third subsequent cycle, and Day 1 of any cycle with intra-subject dose escalation • Pharmacokinetics Samples for PK will be taken at the following timepoints in Cycle 1: pre-dose on Day 1, pre-dose on Day 10, up to 6 time points post-dose on Day 10. For Stage 2 only, additional samples will be taken pre-dose on Day 8 and pre-dose on Day 15. Compliance review of subject diary card Subjects who discontinue treatment will complete the Safety Follow-up (SFU) visit 30 days (± 7 days) after the last dose. Assessments required at the SFU visit include AEs and concomitant medication collection, symptom-directed physical exam, vital signs, weight, WHO performance status, ECG, ECHO, laboratory assessment of blood (for pregnancy testing, hematology, biochemistry, Troponin T or I, tumor markers if applicable]), urinalysis, radiological and clinical disease assessment (if applicable), and subject diary card review. Subjects without disease progression (PD) at the time of SRA737 discontinuation will continue in Long-Term Follow-Up and undergo disease evaluations every 16 ± 2 weeks in Stage 2 (or 6 weeks for Stage 1) and have the following assessments: radiological and clinical disease evaluation, SAEs determined as related to SRA737 by the investigator, first subsequent anticancer therapy, and tumor markers (if applicable) until disease progression or initiation of subsequent cancer therapy. Additional contact may be made as requested by the sponsor or the investigator to obtain disease and survival updates on an as needed basis until the subject discontinues from the study.
Criteria for evaluation:	
Dose-Escalation:	An enrolled subject will be evaluable for dose escalation review if within Cycle 1, the subject received at least 3 of the 4 (75%) planned doses in Stage 1 or 5 of the 6 (83%) planned doses in Stage 2 of SRA737 and all

	doses of gemcitabine or the subject received less than these planned IMP doses due to drug-related toxicity (unless not applicable due to the sponsor having elected to evaluate an alternative schedule).
Efficacy:	All enrolled subjects who have measurable disease, receive at least 75% (Stage 1) or 83% (Stage 2) of SRA737 in 1 cycle (or the equivalent if the sponsor elects to evaluate an alternative dosing schedule), and have a baseline assessment of disease plus at least 1 postbaseline disease assessment will be evaluable for response. All subjects who enroll into the Cohort Expansion Phase will be evaluable for response if they have measurable disease, receive at least 1 cycle of study medication as defined above, have a baseline assessment of disease plus at least 1 postbaseline disease assessment and are confirmed as having met the genetic selection requirements. In addition, subjects who have measurable disease and received at least 83% of SRA737 (if the sponsor elects to evaluate an alternative dosing schedule) in 1 cycle but developed PD, intolerable toxicity, or death prior to the postbaseline assessment will also be considered evaluable and will be classified as non-responders.
Safety:	All enrolled subjects who receive at least 1 dose of SRA737 will be evaluable for safety.
Other:	Pharmacokinetics: All enrolled subjects who receive at least 1 dose of SRA737 and provide at least 1 evaluable PK concentration will be evaluable for PK. Pharmacodynamics: All enrolled subjects who receive at least 1 dose of SRA737 and have evaluable data for each specific PDn assessment will be evaluable for PDn.
Statistical methods and analyses:	Data will be presented in a descriptive fashion. Variables will be analyzed to determine whether the criteria for the trial conduct are met. Baseline characteristics will be summarized for all enrolled subjects. Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described. The analysis of all efficacy endpoints will be based on the Response Evaluable Population and will be evaluated using RECIST v1.1 criteria. An estimate of the ORR (defined as the proportion of subjects who achieved best response of complete response [CR] or partial response [PR]) and its 1-sided 95% exact binomial confidence interval (95% CI) for the recommended dose group(s) will be determined. Additionally, the ORR and disease control rate along with the associated 2-sided 95% CI will be determined for each dose cohort (within each of the following variables: category of genomic alteration and number of categories of genomic alterations, schedule, expansion versus dose escalation subjects, Stage 1 or Stage 2). Additional subgroups of interest may also be identified, and the ORR will be estimated, as described in the Statistical Analysis Plan. Duration of response (DOR) is defined the interval from the first evidence of objective response (of PR or CR) to the earlier of the first documentation of PD or death from any cause. Duration of response will be right-censored for subjects who at least achieve a PR based on the censoring conventions defined for progression-free survival (see Section 11.2). Analysis of DOR will be performed using the Kaplan-Meier

	method. Medians and other quartiles for DOR will be estimated in addition to the corresponding 2-sided 95% CI. Pharmacokinetic parameters will be determined using non-compartmental method(s). Pharmacokinetic parameters such as AUC_{tau}, C_{min}, C_{max}, T_{max}, $t_{½}$, will be estimated and reported, as appropriate. Pharmacodynamic parameters utilizing tumor and surrogate tissue to analyze biomarkers to identify possible predictors of clinical outcome will be further defined in the statistical analysis plan.

2 INTRODUCTION

TRIAL STATUS

The study was designed with two stages (Stage 1 and Stage 2); each stage has a dose escalation phase and an expansion phase (refer to protocol Section 3.2). Stage 1 explored a combination of SRA737 + gemcitabine + cisplatin and Stage 1 was permanently discontinued at the dose escalation phase upon initiation of Protocol Amendment version 5.0 (hereafter referred to as Amendment v5.0) which allowed Stage 2 to supersede further exploration of the Stage 1 triplet regimen. Thus, Stage 1 was discontinued after 10 subjects across 3 gemcitabine dose levels (with constant SRA737 and cisplatin doses) had received the triplet combination in the dose escalation phase (refer to protocol Section 2.4.2 for a clinical summary).

Stage 2 of the study explores the combination of SRA737 + gemcitabine. The dose escalation phase of Stage 2 consists of cohorts of 3 to 6 subjects in a rolling 6 design (refer to protocol Section 3.3).

As of 06 Jul 2018, 35 subjects have been treated in the UK in Stage 2 dose escalation with no dose-limiting toxicities (DLTs) reported with SRA737 dose levels shown below, each given in combination with low-dose gemcitabine (refer to protocol Section 2.4.2).

SRA737-02 Stage 2 Dose Escalation (n=35 as of 06 Jul 2018)			
Cohort	**Dose Level SRA737 (mg) / gemcitabine (mg/m^2)**	**Number of Subjects**	**Cumulative Number of Subjects**
1	40 / 300	5	5
2	80 / 100	4	9
3	150 / 100	4	13
4	300 / 100	4	17
5	300 / 50	3	20
6	500/100	4	24
7	500/50	4	28
8	500/150	4 (enrollment ongoing)	32
9	600/100	3 (enrollment ongoing)	35

The 500 mg SRA737 + 100 mg/m^2 gemcitabine and 500 mg SRA737 + 50 mg/m^2 gemcitabine dose levels were completed in May 2018 without a DLT and the dose escalation proceeded to open a 600 mg SRA737 + 100 mg/m^2 cohort and 500 mg SRA737 + 150 mg/m^2 cohort (refer to protocol Section 2.4.2 for details). Subsequent escalation cohorts may receive higher doses of SRA737 and/or gemcitabine, and alternative treatment schedules may also be explored if deemed appropriate (refer to protocol Section 3.3).

Based on the preclinical efficacy studies and preliminary PK data, an efficacious concentration of SRA737 has been achieved and expansion cohorts will be initiated in parallel with the escalation cohorts at a dose level of 500 mg SRA737 + 100 mg/m^2 gemcitabine (ie, the current highest dose level completed without DLT in the escalation phase) or a higher dose level based on emerging clinical data from the ongoing escalation phase (refer to Section 2.3.1.1). Four expansion cohorts of approximately 20 subjects each are planned in high-grade serous ovarian cancer (HGSOC), small cell lung cancer (SCLC), soft tissue sarcoma (STS), and cervical/anogenital cancer. These subjects may be enrolled at sites in countries including the UK and Spain. Subjects entering the expansion phase will be treated at the highest dose level determined to be safe and tolerable in the concurrent escalation phase. Any subject may, at the discretion of the investigator and with the agreement of the sponsor, be offered treatment at the higher dose of SRA737 and/or gemcitabine once that higher dose level has been shown to be safe and approved by the Cohort Review Committee.

2.1 BACKGROUND

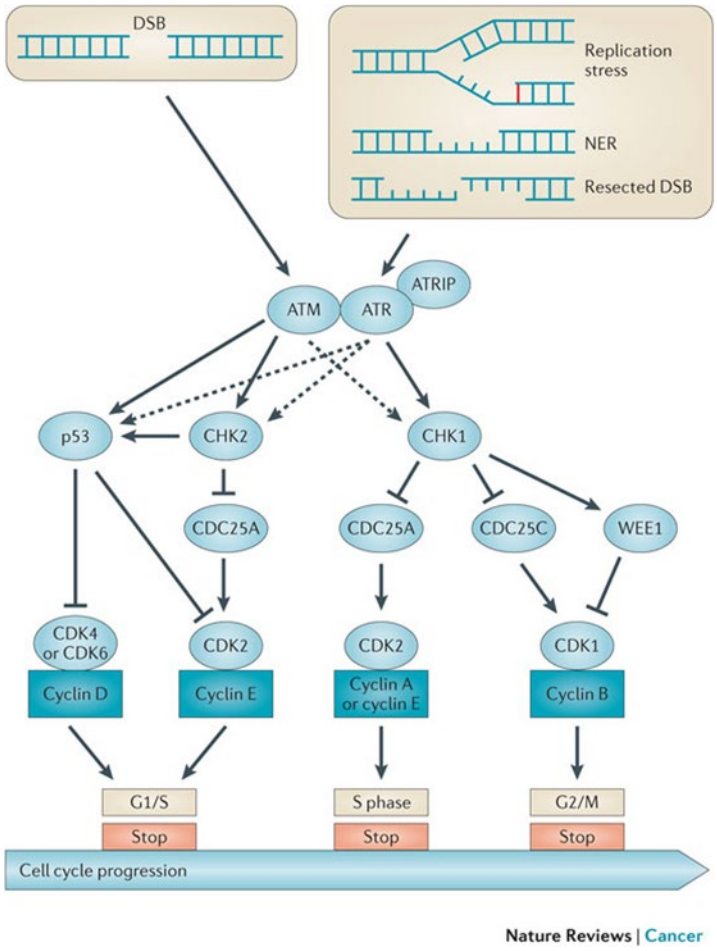
2.1.1 DNA DAMAGE/CHK1 BIOLOGY

The maintenance of genomic integrity is critical for cell survival and proliferation (Negrini 2010). Genomic integrity is compromised by deoxyribonucleic acid (DNA) damage arising from either intrinsic processes (such as oxidative stress or genomic instability) or exogenous sources such as environmental mutagens and chemotherapy. Consequently, organisms have developed a myriad of intra- and inter-cellular mechanisms to address this genomic damage – collectively known as the DNA damage response (DDR). Cells respond to DNA damage by activating a number of cell-cycle checkpoints as part of the DDR to facilitate cell cycle arrest, DNA repair or apoptosis (Kaufmann 2007, Meek 2009). Genotoxic antitumor drugs causing DNA damage also cause activation of G1/S, S and G2/M cell-cycle checkpoints and the DDR. This cancer cell response can potentially limit the efficacy of chemotherapeutic agents (Dai 2010, Garrett 2011, Zhou 2000).

The DDR to double strand breaks is predominately mediated through the PI3K-related kinase family member, ATM kinase, and that to single strand breaks, stalled replication forks and cross links mediated though ATR kinase (Weber 2015). In general, activation of ATR leads to downstream phosphorylation and activation of checkpoint kinase-1 (Chk1). One of the functions of Chk1 is to prevent cells harboring DNA damage from continuing through the cell-cycle, until DNA repair is completed (Weber 2015).

Chk1 has been shown to activate the S and G2/M checkpoints by modulating the expression and function of CDC25 A and C, respectively, and as such acts as a critical effector of two out of three cell cycle checkpoints (Dai 2010, Xiao 2003, Sorensen 2012). In addition, Chk1 has an additional important role in the S phase checkpoint where it stabilizes and preserves replication fork complexes following replication stress, preventing catastrophic replication fork collapse (Dai 2010, Feijoo 2001, Curtin 2012, Figure 1). Chk1 is also involved in homologous recombination repair of DNA through activation of Rad51 (Sorensen 2005) and in regulation of mitosis through direct phosphorylation of Aurora B (Peddibhotla 2009).

Figure 1. Schematic of key roles of Chk1 in the DNA damage response



Source: Curtin 2012.

Preclinical studies using Chk1 ribonucleic acid interface (RNAi) and selective Chk1 inhibitors provide evidence that certain chemotherapeutic agents such as topoisomerase 1 inhibitors and anti-metabolites (Garrett 2011, Walton 2012, Lowenberg 2011) show enhanced activity in combination with Chk1 inhibitors. Chk1 inhibitors are expected to prevent cells entering cell cycle arrest thereby enhancing the activity of genotoxic agents by preventing the cell from pausing the cell cycle to allow for repair of DNA damage. Both gemcitabine and etoposide have been shown to cause cell cycle arrest in human colon cancer cell lines at 24 and 48 hours post administration, and this arrest could be overcome by Chk1 inhibition (Walton 2012).

As noted above, Chk1 has an important role in stabilizing replication fork complexes following replication stress, preventing catastrophic replication fork collapse (Dai 2010, Feijoo 2001, Curtin 2012, Figure 1). Replication stress (RS) involves dysregulated origin firing and the stalling of DNA replication forks that can lead to DNA damage and genomic instability along with

an increased frequency of transcription replication collisions, elevated oxidative stress, and depletion of the nucleotide supply.

Chk1 is an essential effector of the cellular response to RS. Highly proliferating cancer cells experience elevated intrinsic RS, thus, tumor cells become highly reliant on Chk1 to manage RS and its downstream consequences in order to maintain proliferation and survival. Chk1 activation stabilizes replication forks, abrogates origin firing, arrests the cell cycle and mediates DNA repair. Therefore, inhibition of Chk1 is expected to be synthetically lethal in tumor cells with increased RS.

Chk1 inhibitors (along with inhibitors of the upstream kinase ATR) are now in early phase trials both as monotherapies and in combination (see Section 2.5).

2.1.2 IDENTIFYING CORRELATES OF CHK1 SENSITIVITY (REPLICATION STRESS)

Tumor cells frequently harbor genomic alterations that result in increased intrinsic RS including mutations in genes involved in proliferation, cell cycle control, DNA replication and repair. Loss of function mutations in tumor suppressors (TS), such as TP53 and RB1 as well as DNA damage repair (DDR) genes such as ATM or BRCA1, contribute to genetic instability and RS. Similarly, gain of function alterations in oncogenic drivers (OD) like MYC, CCNE1 or KRAS also generate genomic instability and RS through cell cycle and replication origin dysregulation. Finally, viral infection such as human papillomavirus (HPV) can also elevate RS through inactivation of TS genes and enhancement of cell cycle and DNA repair machinery.

Genetics have proven to be powerful predictors of clinical response to a variety of agents and genetic alterations are currently being used in a variety of trials for prospective patient recruitment. Preclinical and preliminary clinical data has shown genetic alterations in TS, DDR or OD genes are associated with greater efficacy of Chk1 inhibition. Detailed examples of alterations in TS, DDR or OD genes enhancing Chk1i sensitivity are detailed below. A complete list of genes shown to influence Chk1i sensitivity and RS levels can be found in Appendix 6.

- Oncogenic drivers such as MYC and RAS are frequently amplified and/or hyperactivated in a range of tumors and have been strongly implicated in contributing to RS and potently enhancing sensitivity to Chk1 inhibitors (Gaillard 2015). Moreover, SRA737 and its analogues demonstrate robust single agent activity in tumor models with MYC or MYCN overexpression (Cole 2011; Derenzini 2015).

- TS alterations result in defective G1/S cell cycle checkpoints, arising through inactivation of the p53 and Rb pathways, and can result in synthetic lethality in the context of Chk1 inhibition given Chk1's role in controlling the S and G2M checkpoints. Rb and p53 pathway deficiencies can arise through direct inactivating mutation or deletion of genes encoding RB1 and TP53, or through mutation/deletion of other genes in the pathway, including CDKN1A, CDKN2A, or hyperactivation of MDM2 (Negrini 2010). HPV infection also results in G1/S loss due to inactivation of p53 and Rb1.

- Multiple DDR mutations contribute to genomic instability (Negrini 2010) and RS. Interestingly, similar to what is observed with poly ADP ribose polymerase (PARP) inhibitors, Chk1 phosphorylates BRCA2 and Chk1 inhibitors are synthetically lethal in cell lines deficient in BRCA2 (Chen and Sanchez 2004; Chen 2009). Beyond the BRCA genes, studies have demonstrated that loss of several Fanconi anemia genes involved in homologous recombination repair and inter-strand crosslink repair result in enhanced sensitivity to Chk1 inhibition (Chen 2009). Loss of function in other genes in these and related DNA repair processes, such as RPA1 and POLD1 generate synthetic lethal backgrounds for Chk1 inactivation (Chen 2009; Hocke 2016).

2.1.3 EXOGENOUS SOURCES OF REPLICATION STRESS AND GEMCITABINE SYNERGY

Exogenous sources of RS, such as chemotherapeutic agents can be utilized to heighten RS and increase the efficacy of Chk1 inhibition. The critical role of Chk1 in mediating cellular responses to RS affords the opportunity to combine SRA737 with sub-therapeutic concentrations the RS-inducing agent, gemcitabine.

Extensive preclinical data, as well as clinical data, supports the synergistic interaction between Chk1 inhibition and gemcitabine. Gemcitabine, a nucleotide analogue and inhibitor of ribonucleotide reductase, targets proliferating cells by inducing RS through induction of stalled replication forks and double-strand breaks. Low concentrations of gemcitabine cause a prolonged S-phase and induce hallmarks of RS without inducing overt cytotoxicity. Preclinical experiments have shown that clinically relevant doses as well as very low, subtherapeutic doses of gemcitabine when combined with Chk1i, result in significant tumor growth inhibition. The clinical activity noted at subcytotoxic doses is thought to be a consequence of depletion of deoxyribonucleoside triphosphate pools, particularly deoxyadenosine triphosphate (dATP) (Heinemann et al. 1990; Shewatch et al 1994; Caffo et al 2016). The combination of

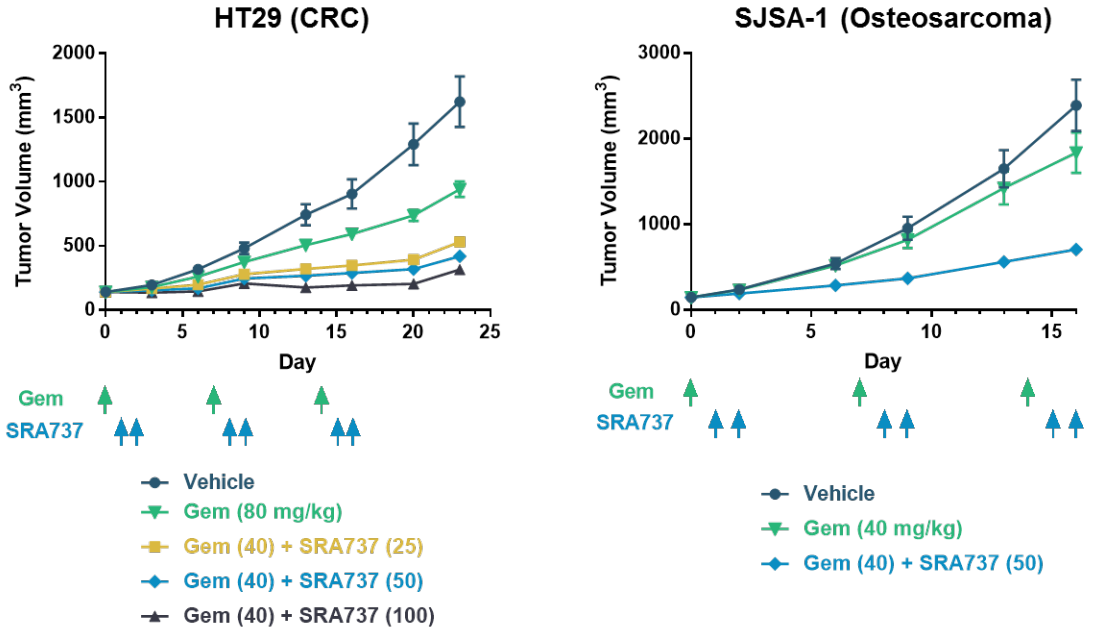
gemcitabine with Chk1 inhibition results in cell death independent of an abrogated G2-M checkpoint or premature mitotic entry, suggesting synergistic induction of replication catastrophe (Koh et al 2015; Montano et al. 2017).

Extensive preclinical data, as well as clinical data, supports the synergistic interaction between Chk1 inhibition and gemcitabine. A reverse genetic siRNA screen of 1006 genes identified CHEK1 (encodes Chk1 kinase) and ATR (Chk1 pathway kinase) as targets whose loss of function is most synergistic with gemcitabine in tumor cells (Smith 2014). Consistent with this observation, numerous small molecule inhibitors of Chk1 have been demonstrated to potentiate gemcitabine in vitro and in vivo (reviewed in Manic 2015). SRA737 has been previously shown to increase the cytotoxic potential of gemcitabine in several tumor cell lines and in an HT29 colorectal xenograft (Walton 2016).

We have extended these findings in extensive pair-wise combination studies demonstrating profound cytotoxic potentiation of low concentrations of gemcitabine and SRA737 in a panel of 15 cancer cell lines (data on file). Importantly, the cytotoxic effects of the combination are sustained at low nanomolar concentrations of gemcitabine, and synergy/efficacy is observed over a broad concentration range.

In vivo tumor growth inhibitory synergy was observed combining SRA737 with low-dose gemcitabine (40 mg/kg) in colorectal HT29 and osteosarcoma SJSA-1 xenograft models (Figure 2) and pharmacodynamics (PDn) effects were demonstrated in HT29 tumor xenograft tumors isolated from mice treated with a single IV dose of gemcitabine (40 mg/kg) followed 24 hr later with a single PO dose of SRA737 or vehicle (Figure 2; unpublished data). Low-dose gemcitabine induced Chk1 activity as evident by the increase of autophosphorylation of Chk1 at S296, while SRA737 inhibited this increase in a dose-dependent manner resulting in a reduction of S296 levels. At the same time, SRA737 increased markers of replication fork stalling and collapse such as pS33 RPA32 and γH2AX, as well as ATR-mediated phosphorylation of Chk1 at S317 and S345. In addition, these increased cell toxic effects are reflected in pancreas tumor xenografts, wherein gemcitabine induced γH2AX (a marker of DNA damage and apoptosis) levels were potentiated and reached equivalent levels over a gemcitabine dose range of 40 mg/kg to 240 mg/kg when dosed in combination with a Chk1 inhibitor (Montano et al., 2017).

Figure 2. SRA737 potentiates the efficacy of low-dose gemcitabine in HT29 and SJSA-1 xenografts in mice in a dose dependent manner.



Mice bearing subcutaneous colorectal HT29 (left) or osteosarcoma SJSA-1 (right) tumors were treated with vehicle or gemcitabine (IV; green arrows) plus or minus vehicle or SRA737 (PO; blue arrows) at indicated doses when initial tumor volumes were approximately 100 mm^3. Note: In both HT29 and SJSA-1 tumor models, monotherapy SRA737 lacks tumor inhibitory growth effects using the indicated dosing schedule (data not shown).

2.1.4 LOW-DOSE GEMCITABINE

Gemcitabine is a nucleoside analogue and is used extensively for the treatment of a wide variety of cancers. It is typically administered IV over 30 minutes and is classified as mildly emetogenic and requires antiemetic medication. Gemcitabine's dose and administration schedule varies based on indication and its therapeutic use. When used as a radio-potentiator for muscle invasive bladder cancer with intent to cure, for example, the gemcitabine dose can be more than 20-fold or even 30-fold lower than a standard dose of gemcitabine given as a single agent for its direct cytotoxic effect. One Phase 1 study identified a maximum tolerated dose (MTD) of gemcitabine of 27 mg/m^2 when administered twice-weekly with concurrent radiotherapy (Kent et al, 2004). This regimen achieved a very high rate of bladder preservation and is currently being tested in a multi-center randomized Phase 2 study (NCT00777491). A more recent pooled analysis of individual data from eight Phase I–II trials of concurrent

gemcitabine and radiotherapy for the treatment of muscle-invasive bladder cancer demonstrated outcomes that appear to be at least as good as with cystectomy alone while historically, neither radiation therapy alone nor chemotherapy alone could match the survival results achieved with surgical resection (cystectomy) (Caffo et al, 2016). Although the regimens tested across these 8 studies varied, 81% of the patients received an intended weekly dose of gemcitabine of 100 mg/m^2 (32.1%) or less (48.9%). Similar approaches have been pursued in lung and pancreatic cancer and other settings (van Putten et al, 2003).

The parallel between low-dose gemcitabine when used as a radiosensitizer or a sensitizer to Chk1 inhibition, based on the preclinical evidence and proposed mechanism of action suggest that there may be parallels in the clinic with regard to the dose of gemcitabine required to achieve a safe and active regimen when given in combination with SRA737. This hypothesis is further supported by the clinical study evaluating the Chk1 inhibitor GDC-0575 combined with low-dose gemcitabine (500 mg/m^2 weekly) which demonstrated evidence of significant tumor responses in patients with STS, triple negative breast cancer and non-small cell lung cancer (Italiano 2017).

In summary, preclinical and clinical data supports the hypothesis that sub-therapeutic doses of gemcitabine strongly synergize with active doses of SRA737 which should lead to clinical efficacy. To test this hypothesis, low-dose gemcitabine in combination with SRA737 is being explored in stage 2 of this study.

2.2 BACKGROUND ON COHORT EXPANSION INDICATIONS

Collectively, the available data suggests that tumors with high levels of intrinsic RS are likely to be sensitive to Chk1 inhibition and that this sensitivity should be further enhanced by the addition of gemcitabine, an exogenous inducer of RS. Moreover, the heightened intrinsic RS in cancer cells is hypothesized to increase sensitivity to RS-inducing chemotherapy in combination with Chk1 inhibition thereby increasing the therapeutic window.

Genetics have proven to be a powerful predictor of clinical response to a variety of agents and genetic alterations are currently being used in a variety of trials for prospective patient recruitment. Patients whose tumors contain genetic alterations in TS, DDR or OD genes may be the most likely to benefit from Chk1 inhibition. The prevalence of genetic alterations varies depending on the tumor type but collectively, the data described above supports the likelihood that patients with tumors such as HGSOC, SCLC, certain subtypes of STS and the

cervical/anogenital (HPV) tumors, all of which harbor high levels of genomic instability, may be uniquely sensitive and therefore will be included in the expansion phase of this clinical trial.

2.2.1 OVARIAN CANCER

Ovarian cancer is the eighth most common cancer worldwide, with 239,000 new cases diagnosed in 2012 and 152,000 deaths worldwide (Ferlay 2013). About 75% of women with ovarian cancer are diagnosed with Stage 3 or Stage 4 disease and 75% of women with advanced stage disease suffer relapse or die from their disease despite treatment (Jemal 2011).

Nearly all ovarian cancers originate in the surface epithelium of the ovaries or fallopian tubes, with the papillary serous histology subtype accounting for approximately 75% of those, and of which a significant majority (90%) are high grade (Cannistra 2004).

Initial therapy typically consists of cytoreductive surgery and 6–8 cycles of platinum and taxane based chemotherapy. PARP inhibitors have shown substantial benefit as maintenance therapy when administered to patients who have completed their initial chemotherapy regimen.

The choice of subsequent therapy for patients who relapse is based on the treatment-free period and chemotherapy agents already utilized. Patients are further categorized as having platinum sensitive, resistant or refractory disease. Primary refractory is defined as disease progression during therapy or within 1 month of the last dose of the first line of platinum-based chemotherapy. Platinum resistant is defined as those who are not primary refractory but have disease progression within 6 months of the last dose of platinum-based chemotherapy.

Patients with platinum-resistant disease have a poor prognosis with a short expected median overall survival (OS) of less than 12 months. Four different agents, weekly or 3-weekly paclitaxel, topotecan, pegylated liposomal doxorubicin and gemcitabine, have been shown to have some activity in Phase 3 trials, with overall response rates of less than 15% and a median progression-free survival (PFS) of 3 to 4 months. Occasionally, platinum drugs continue to be used in the platinum-resistant population with, for example, a dose-dense regimen. However, as no agent has proven to be superior to another, the selection of therapy is mostly based on toxicity, clinical situation of the patient and convenience of administration. Randomized trials of combination chemotherapy have shown no advantage in this population and have shown compound toxicity. Accordingly, sequential single-agent therapy is currently the recommended

management for this group of patients, as per European Society for Medical Oncology (ESMO) guidelines for newly diagnosed and relapsed epithelial ovarian carcinoma (Ledermann 2013).

New approaches which leverage the underlying biology, especially if adverse effects can be minimized without the addition of cytotoxic chemotherapy are warranted. The underlying biology of HGSOC includes high levels of genomic instability mainly due to defects in homologous recombination (e.g. mutation in *BRCA* genes) as well as high rates of *TP53* mutations suggesting a defective G1/S checkpoint (Landen 2008; Kurman 2011).

The Cancer Genome Atlas profiled over 400 HGSOC patient samples and reported TP53 mutations in 96% of samples. Additionally, key oncogenes such as *MYC*, *KRAS* and *CCNE1* were altered in at least 40% of patient samples. *BRCA1* and *BRCA2* were found to be altered in roughly 12% of samples (TCGA 2011). The progression of genomic instability in HGSOC, could make this cancer type highly susceptible to Chk1 inhibition.

Of particular interest, approximately 20% of patients with HGSOC have *CCNE1* amplification which is associated with resistance to platinum-based therapy and insensitivity to PARP inhibitors (Kanska 2016). It is hypothesized that *CCNE1* amplification may sensitize tumor cells to Chk1 inhibition via increased replication stress due to increased S-phase entry, increased DNA replication and increased transcriptional activity (Zeman 2014). Supporting this hypothesis are preliminary pre-clinical data suggesting *CCNE1* amplified, *BRCA* wild-type, HGSOC patient-derived xenograft (PDX) tumor models resistant to platinum-based therapy and PARP inhibition are responsive to SRA737 monotherapy (data not shown).

Additional support is provided by preliminary clinical data with the Chk1 inhibitor LY2606368 in patients with HGSOC, squamous cell carcinoma of the head and neck and squamous cell carcinoma of the anus; demonstrating that treatment benefit is correlated with tumor genomic profiles indicative of high cyclin E expression (Lee 2016; Martinez 2017).

The BRCA wild-type population has been shown to be enriched for *CCNE1* overexpression through *CCNE1* gene amplification and/or mRNA upregulation and/or cyclin E protein overexpression (Lee 2018). In order to evaluate SRA737 in this population an expansion cohort of subjects with *BRCA* wild-type, platinum-resistant or refractory HGSOC will be enrolled in this study.

2.2.2 SMALL CELL LUNG CANCER

Lung cancer is the most common cancer worldwide, with 1,825,000 new cases diagnosed in 2012 and 1,590,000 deaths worldwide (Ferlay 2013). Small cell lung cancer accounts for about 10% to 15% of all lung cancers, with non-small cell lung cancer (NSCLC) accounting for 70 to 80%. SCLC, which originates from neuroendocrine-cell precursors, is distinguished from NSCLC by its rapid doubling time and the early development of widespread metastases.

As per guidelines of the European Society for Medical Oncology (ESMO) (Früh 2013) treatment of stage IV SCLC is palliative, with combination chemotherapy being the main treatment option. Overall response rates (ORRs) with combination chemotherapy are close to 70%, however, median progression-free survival (PFS) is only 5.5 months and a median OS less than 10 months. Response rates to second-line treatment are typically around 10% in resistant disease and 20% in sensitive disease; dependent on the treatment-free interval. The clinical benefit of further systemic therapy in the case of patients with resistant disease and early relapse (<6 weeks) is not clear as outcomes are poor. Participation in a clinical trial or supportive care is recommended for patients with relapsed or progressive disease.

Despite recent advances, mainly in the use of radiation therapy, the median survival time of 8-10 months for patients with extensive state SCLC has remained approximately the same over the last 30 years and exploring novel treatments for these patients remains an area of unmet medical need. Several novel agents have recently been evaluated in patients with SCLC. Immune checkpoint inhibition, for example via pembrolizumab was explored in a Phase Ib trial for 135 patients who had progressed on platinum-based chemotherapy and were screened for PD-L1 expression, with 27% testing positive (Ott et al, 2015). Ultimately, 17 patients were enrolled with 25% achieving a partial response. Other examples include aurora A kinase inhibitors, such as alisertib, which was tested in a Phase I/II trial of 60 patients with relapsed or refractory SCLC, of whom 21% had a partial response on therapy (Melichar et al, 2015). Another novel agent is rovalpituzumab tesirine, an antibody-drug conjugate designed to bind to the delta-like protein 3 (DLL3), has recently been investigated in a Phase Ia/Ib trial in SCLC. In 29 DLL3-positive patients with SCLC who had progressed after first- or second-line therapy, 34% of patients had a partial response and 31% achieved disease stability (Pietanza et al, 2015).

Genetically, 85-90% of all SCLC tumors have genetic alterations in the sponsor's defined tumor suppressor genes (George 2015). In general, the sponsor-defined DDR genes are individually

altered in less than 5% of tumors; however, due to their non-overlapping occurrences about 37% of SCLC tumors harbor a DDR defect (POLE and SMARCA4 are two exceptions with alterations in 12.5% and 9.5% of tumors respectively) (Zehir 2017). The above described genetic alterations in SCLC make this indication an ideal therapeutic target for a Chk1 inhibitor, such as SRA737 in combination with gemcitabine. Due to the presence of cancer related alterations in the tumor suppressor genes (eg, *TP53* and *RB1*) in the majority (approximately 90%) of patients with SCLC, enrollment in the SCLC cohort of the study is not dependent on prospective genetic testing.

2.2.3 SOFT TISUE SARCOMA

Sarcomas are a group of rare malignant tumors of connective tissues, capable of differentiation into many different cell types such as connective tissues (lipocytes, fibrous supporting structures, muscle, etc.), visceral tissues, and bone. These tumors can occur in almost any anatomic site, although they are reported to be more frequent in the extremities and are typically classified by origin in soft tissue or bone.

Soft tissue sarcomas are reported to account for <1% of all adult malignancies and bone sarcomas for <1% of all adult malignancies respectively (Ducimetière 2013). It is estimated that adult STS and visceral sarcomas occur with an estimated age-standardized incidence ranging from 3-5/100,000/year in Europe (Stiller 2013).

Soft tissue sarcoma is a biologically heterogeneous malignancy with over 100 histological subtypes (Fletcher 2013). Generally, STSs can be classified into two broad categories: those driven by complex karyotypes and those by specific translocations. The genotype of the former category is generally more sporadic; however, alterations in the p53 pathway are common for multiple histological subtypes such as leiomyosarcomas and undifferentiated pleomorphic sarcomas. Unlike STS of complex karyotypes, STS driven by translocations are transcriptionally dysregulated and have very few genetic alterations making it difficult to prospectively select patients genetically.

Historically, there have been few systemic treatment options for this relatively rare disease. ESMO guidelines (2014) specify surgery as the standard treatment of all patients with an adult type, localized STS. Some lesions may also be treated with surgery followed by radiation therapy.

For patients whose disease is not fully resectable or whose disease has recurred, traditional cytotoxic agents, such as anthracyclines, alkylating agents, and taxanes are employed although they have limited clinical benefit beyond the first-line setting. Across all STS subtypes, median overall survival remains approximately 12–18 months for those with locally advanced or metastatic disease. The development of targeted therapies has led to recent approval of four new treatments for advanced STS in the EU and US. Among these, olaratumab is most notable for its improvement in overall survival for patients with anthracycline-naïve disease. The other three novel agents, trabectedin, pazopanib and eribulin, have been approved for the treatment of specific histologic subtypes of STS in the second-line setting after progression on anthracyclines (In 2017).

Recently, encouraging preliminary results were reported for a clinical study evaluating the oral Chk1 inhibitor GDC-0575 combined with low-dose gemcitabine (500 mg/m^2 every 2 weeks) with evidence of significant tumor responses in STS (PR lasting 52 weeks in leiomyosarcoma and CR lasting 24 weeks in undifferentiated pleomorphic sarcoma) (Cousin 2016).

Further progress in STS management will rely on subtype-specific therapies and validation of biomarkers to tailor therapy (In 2017).

Genetic alterations in the p53 pathway are common for STS not harboring translocations. For example, over 50% of leiomyosarcomas and undifferentiated pleomorphic sarcomas have defects in TP53 (Zehir 2017). Certain classes of liposarcomas have also shown very high rates of p53 pathway dysfunction. As such, genetic mutations in non-translocated STS make this indication an ideal therapeutic target for a Chk1 inhibitor such as SRA737, in particular in combination with gemcitabine, which is hypothesized to further enhance the activity of SRA737.

2.2.4 CERVICAL/ANOGENITAL CANCER (HUMAN PAPILLOMA VIRUS RELATED CANCERS)

Human papilloma virus (HPV) is the most common sexually transmitted virus that affects the genital tract of males and females. Cervical cancer is the most prevalent HPV-related cancer and the fourth most common cancer in women, with approximately 528,000 new cases and more than 266,000 deaths resulting from cervical cancer annually worldwide (Globocan 2012). The biology of HPV has been extensively studied and its link with malignancies has been well established, specifically with cancers involving the anogenital (cervical, vaginal, vulvar, penile, anal) tract and also those involving the head and neck. HPV, including high-risk types, such as

HPV genotypes 16 and 18, cause approximately 30% of all cancers worldwide (de Martel 2012) and are the estimated cause of 100% cervical cancer cases, 90% of anal cancers, 35% of oropharyngeal cancers and 40% of vaginal cancers, vulvar cancers, and penile cancers worldwide (Gilison 2008).

Not only are the biology and histology of anogenital cancers similar, but so are the treatment options and outcomes for those who are not cured with surgery or multi-modality therapy. Early-stage cervical cancer, like other early-stage HPV-related cancers, may be appropriately treated with either radical surgery and/or chemoradiation.

In metastatic or recurrent cervical cancer, paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen. In patients progressing following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated, but response rates are low and no recommendation has been given concerning the most effective second-line treatment (Marth 2017).

Similar treatment dilemmas exist for other metastatic or recurrent HPV-related cancers and very few recent advances have been reported. However, encouraging preliminary results have been observed in an early phase trial of the PD1 inhibitor nivolumab in metastatic cervical cancer (Hollebecque 2017).

Also notable were recent reports of single agent activity in anal cancer for the Chk 1 inhibitor LY2606368 (Bendell 2015). Following the initial report of a response in an anal cancer patient in the Phase 1 study, a Phase 2 study in 24 anal cancer patients was conducted that demonstrated 5 objective responses including 1 CR and 4 PRs in an otherwise unselected patient population (Martinez 2017). LY2606368 differs from SRA737 in that it is not selective for Chk1 and equipotent against both Chk1 and Chk2, despite the lack of anticancer activity associated with inhibition of Chk2.

Chk1 functions as an essential effector kinase in the cellular response to endogenous RS, and tumor cells with elevated RS become highly reliant on Chk1 for survival. Chk1 inhibitors, such as SRA737 have been shown to exacerbate RS and result in replication catastrophe. Non-genetic alterations, such as HPV infection, also induce the high RS phenotype through the action of viral proteins including E6 and E7. This synergy makes these cancers an ideal

therapeutic target for a Chk1 inhibitor, such as SRA737, in particular in combination with gemcitabine, which is hypothesized to further enhance the activity of SRA737.

2.3 INVESTIGATIONAL MEDICINAL PRODUCT: SRA737

SRA737 (the investigational medicinal product [IMP] formerly known as CCT245737) is a potent, highly selective, orally bioavailable small molecule inhibitor of Chk1, a serine-threonine kinase enzyme that acts as a central regulator of the DDR network.

The agent was developed through collaboration between The Institute of Cancer Research (ICR) Cancer Therapeutics Unit, Sareum Ltd and Cancer Research Technology Ltd. SRA737 was acquired by Sierra Oncology, Inc. in September 2016. The agent is also being investigated as monotherapy in subjects with solid tumors (NCT02797964).

2.3.1 STARTING DOSE RATIONALE: SRA737

Murine toxicity studies indicated a SRA737 MTD of 75 mg/kg/day (~ 225 mg/m^2/day) as a single-agent or in combination with cisplatin and gemcitabine. The ICH S9 guidance suggests using an equivalent dose 1/10th that of the rodent MTD as an initial clinical dose. Consequently, a Human Equivalent Dose of 22.5 mg/m^2/day (0.61 mg/kg/day) equating to an absolute dose of 36 mg (for a 60 kg subject) could be utilized. For the further assurance of subject safety, a lower starting dose of 20 mg was selected.

Using similar allometric scaling, pharmacologically-active concentrations of SRA737 are expected at clinical doses of approximately 80 to 160 mg.

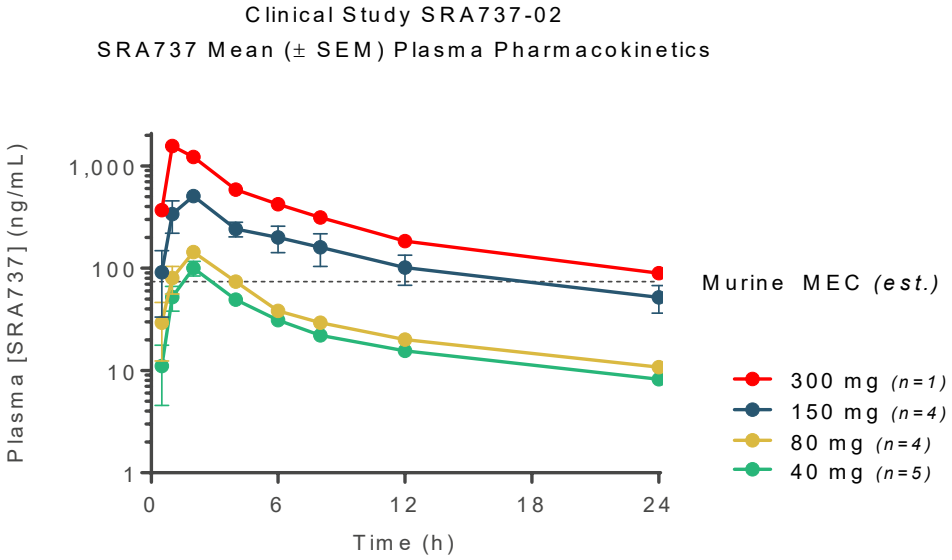
For additional information concerning SRA737, refer to the Investigator's Brochure.

2.3.1.1 Dose Justification for Stage 2 Expansion Phase

Data from murine efficacy studies investigating the activity of various doses of SRA737 in combination with low-dose gemcitabine (40 mg/kg) indicate profound activity at the minimum administered SRA737 dose of 25 mg/kg (IMPD v3.0; Section 2.2.1.2.2.1.1 p33; Figure 2.2.1-10).

The C_{min} (C_{24h}) of 200 nM (~76 ng/mL) modelled following administration of this dose of SRA737 to mice has been determined as the minimum effective concentration (MEC) for the SRA737/low-dose gemcitabine combination dosing regimens examined thus far, noting that further SRA737 murine dose decrement studies are ongoing.

Preliminary clinical PK data from the SRA737-02 study, supported by modelling of the more extensive SRA737-01 PK dataset, suggests that the murine MEC will be exceeded for approximately 18 hours post-dosing at 150 mg and for 24 hours at doses of 300 mg or greater (again, noting the ongoing murine efficacy studies designed to determine whether the MEC is lower than that presently estimated).



Data from patients enrolled in the Dose Escalation cohorts receiving SRA737 in combination with low-dose gemcitabine (Stage 2 of this study) indicate that the administration of 500 mg SRA737 in combination with 100 mg/m^2 gemcitabine was well-tolerated and no DLTs have been observed in patients in Stage 2 of this study to date (refer to Section 2.4.2 for details). Based on the preliminary PK data from the Stage 2 escalation cohorts, the efficacious concentration has been achieved at these clinical doses. Together these safety and PK data supported the initiation of expansion cohorts at the 500 mg SRA737 + 100 mg/m^2 gemcitabine dose level, or a higher dose level based on emerging clinical data from the ongoing escalation phase.

2.3.2 NON-CLINICAL PHARMACOLOGY

2.3.2.1 Efficacy/Primary pharmacology

SRA737 is a potent and selective inhibitor of Chk1 (half maximal inhibitory concentration [IC_{50}] < 10 nM) with minimal activity against Chk2. Off-target kinase screening studies has also confirmed the selectivity of SRA737 across the broader kinome.

In vitro, SRA737 at 0.1 to 0.5 μM inhibited Chk1 autophosphorylation induced by genotoxic chemotherapy and prevented downstream signal transduction. Dose-dependent inhibition of chemotherapy-induced checkpoint arrest (data not shown) and a potentiation of these agents was observed (Table 1). SRA737 alone caused cytotoxicity; however, at concentrations approximately 10-fold higher than those shown to be synergistic in these cell lines.

Table 1. Potentiation of DNA-damaging agents in cancer cells by SRA737

Human Cancer Cell Line	Tissue of Origin	Genotoxic drug	Potentiation (fold)
HT29	Colon	**Gemcitabine**	**7.9 (±2.1, n=6)**
HT29	Colon	SN38[a]	1.8 (±0.3, n=3)
SW620	Colon	**Gemcitabine**	**16.9 (±3.4, n=7)**
SW620	Colon	SN38[a]	3.1 (±0.9, n=3)
Calu6	NSCLC	**Gemcitabine**	**9.1 (±1.5, n=3)**
Calu6	NSCLC	SN38	1.3 (±0.08, n=3)
MiaPaCa-2	Pancreas	**Gemcitabine**	**23 (±10, n=3)**
MiaPaCa-2	Pancreas	SN38[a]	3.1 (±0.4, n=3)

a = The active metabolite of irinotecan.

In the colon cancer cell lines, exposure to gemcitabine or SN38 alone increased ATR-mediated Chk1 phosphorylation, autophosphorylation of Chk1, downstream phosphorylation of CDK1 and resulted in a small increase in γH2AX foci.

Consistent with its mechanism of action, the administration of SRA737 with these agents inhibited Chk1 autophosphorylation and CDK1 phosphorylation, induced a large increase in γH2AX foci and cleaved PARP as a result of abrogation of the DDR response to chemotherapy. Little effect on ATR-mediated Chk1 phosphorylation was noted, supporting SRA737's pathway selectivity.

Subsequently, SRA737 was combined in an optimized dose combination matrix with gemcitabine in a 15-cell line panel including: 5637, TCCSUP, and J82 (bladder); HT29 and SW620 (colon); CAL-27 and FaDu (head and neck squamous carcinoma); Calu-6 and NCI-H520 (lung); KURAMOCHI, OV90, and OVCAR-3 (ovarian); MIA PaCa-2, Panc 03.27, and SNU-324 (pancreatic). Combination indices (CI) values were calculated as determined by Chou and Talalay (1984) across the combination dose matrix and the mean and range best CI values across the panel were 0.25 (0.06 – 0.87). CI values <0.7 indicate synergy, CI values between 0.7 and 1.3 indicate additivity, and CI values >1.3 are antagonistic. Fourteen of the 15 cell lines

had best CI values less than 0.7 indicating the profound synergy of the combination verses either agent alone across numerous types of cancer cell lines.

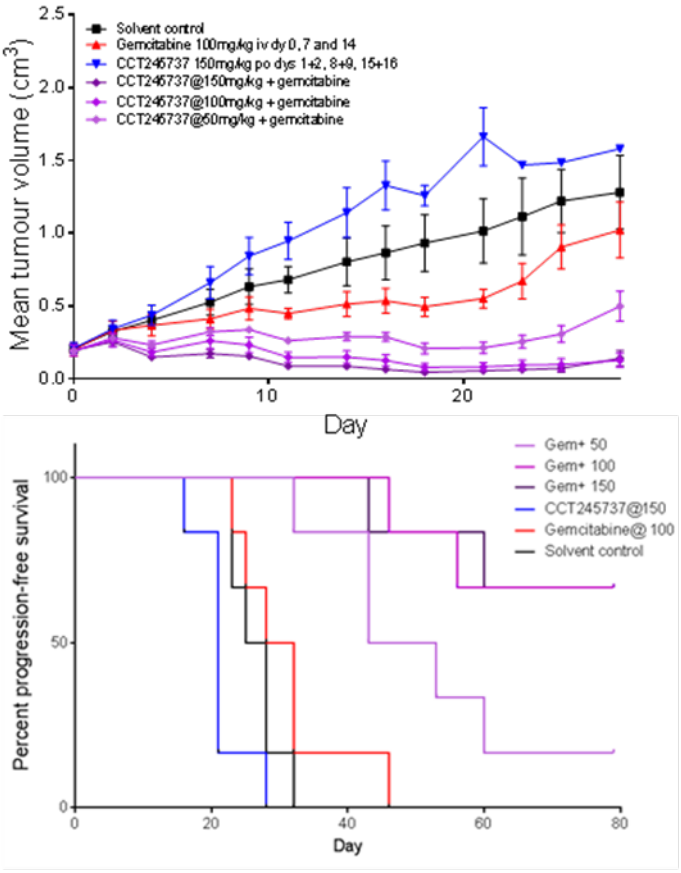
The efficacy of SRA737 in combination with cytotoxic agents was then examined in various mouse tumor xenograft studies, including in combination (i) with gemcitabine in HT29 and SW620 colon cancer and Calu6 NSCLC models; (ii) with gemcitabine and carboplatin in the Calu6 model; (iii) with irinotecan in the HT29 model and (iv) with ionizing radiotherapy in the HT29 and SW620 models. The efficacy of SRA737 in combination with gemcitabine was also investigated in gemcitabine-resistant bladder carcinoma patient-derived xenograft model.

For all combinations with cytotoxic chemotherapy SRA737 was administered at 24 and 48 hours after the cytotoxic agent (Walton 2012) at doses ranging variously from 50 to 150 mg/kg.

Importantly, some degree of increased antitumor efficacy over cytotoxic chemotherapy alone was observed in all combinations but, as observed in the in vitro cytotoxicity studies, the potentiation of cytotoxicity by SRA737 appeared greater in combination with gemcitabine than irinotecan.

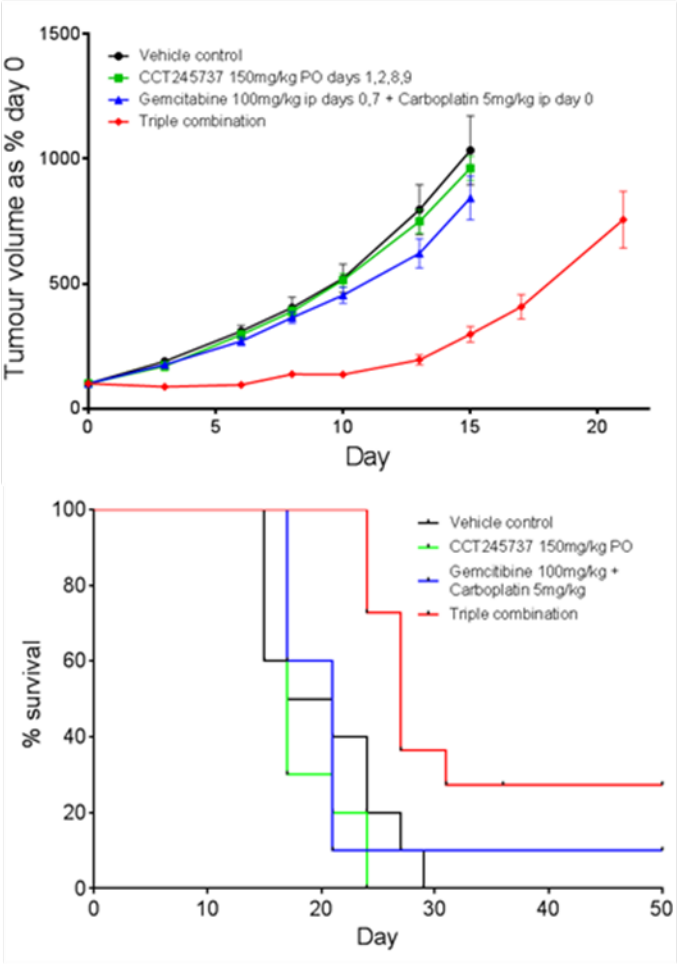
Data from a gemcitabine combination study in an HT29 colon cancer model, showed a striking dose dependent potentiation of gemcitabine efficacy by SRA737, including complete tumor stasis or minor regression at the higher investigated doses (Figure 3). Progression-free survival was also substantially improved in subject animals receiving the SRA737 plus gemcitabine combination therapy.

Figure 3. SRA737 (formerly CCT245737) potentiates the efficacy of gemcitabine in HT29 xenografts in mice in a dose dependent manner



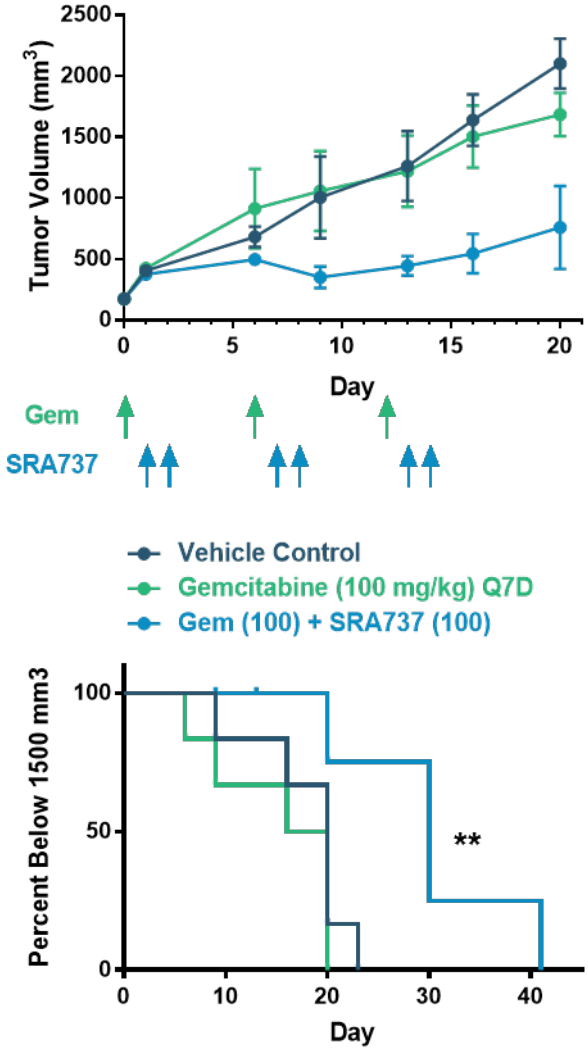
A further murine xenograft study investigating the activity of SRA737 in combination with gemcitabine and cisplatin in the Calu6 NSCLC model was also performed. Markedly improved tumor growth inhibition was noted in subject animals receiving the triple combination therapy compared with the gemcitabine/cisplatin doublet combination or SRA737 alone (Figure 4). An approximate 50% increase in PFS for the triplet combination was also noted.

Figure 4. SRA737 (formerly CCT245737) potentiates the efficacy of a single cycle of the combination of gemcitabine and carboplatin in Calu6 NSCLC xenografts



Gemcitabine plus or minus SRA737 was examined in a bladder carcinoma patient-derived xenograft model. The combination of SRA737 with gemcitabine resulted in 64% tumor growth inhibition compared to vehicle treatment and significantly increased survival in a highly aggressive gemcitabine-resistant bladder carcinoma PDX model (Figure 5). These results suggest that this combination may be substantially more efficacious than gemcitabine alone in certain settings.

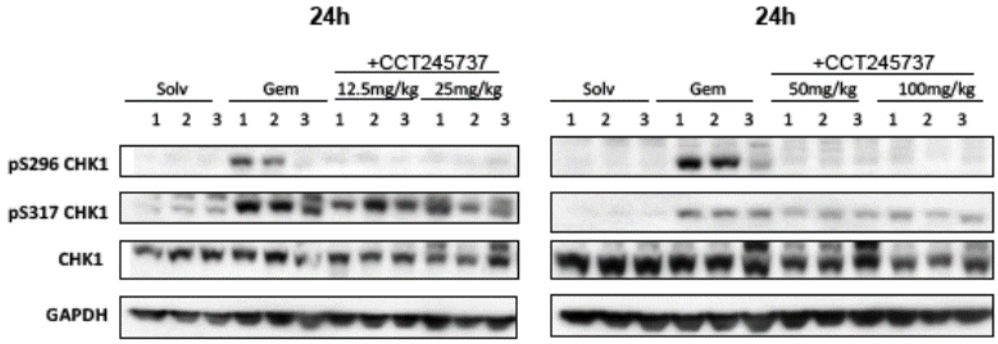
Figure 5. SRA737 plus gemcitabine inhibits tumor growth and extends survival in a gemcitabine-insensitive patient-derived xenograft model of bladder cancer.



Note, ** = Log-rank (Mantel-Cox) test Gem(100)+SRA737(100) vs Gem(100) (P=0.011) or Vehicle (P=0.016). One mouse was found dead on D9 and another sacrificed on D13 in the combination treatment group. SRA737 dosed as scheduled in combination resulted in no tumor growth inhibition or improvement in time to tumor volumes 1500 mm^3 compared to vehicle.

A PDn assessment of HT29 and SW620 xenografts tumors demonstrated that gemcitabine induced tumor Chk1 autophosphorylation (pS296). This autophosphorylation was significantly inhibited by administration of SRA737 at doses as low as 12.5 mg/kg (Figure 6).

Figure 6. Effect of SRA737 (formerly CCT245737; 12.5 to 100 mg/kg PO) on gemcitabine-induced Chk1 S296 autophosphorylation in HT29 human tumor xenografts in mice (ICR EXP 1569)



An exploratory correlation of these PDn findings with pharmacokinetic (PK) data, suggests that a total circulating plasma concentration above 100 nM (equating to a free (unbound) concentration of ~ 20 nM) may be required to significantly inhibit Chk1 in vivo for an entire 24-hour period in mice. Continuous inhibition of Chk1 activity in combination with gemcitabine for a period of 48 hours is necessary for maximal potentiation (Garrett 2011).

In summary, SRA737 has demonstrated significant antitumor activity (including some tumor stasis and minor regression) in a variety of murine and patient-derived xenograft studies in combination with gemcitabine, gemcitabine and carboplatin and irinotecan and radiotherapy (data not shown). Analysis of various DDR markers confirmed this activity was directly related to SRA737's mechanism of action.

2.3.3 IN VITRO ADMET AND NONCLINICAL PHARMACOKINETICS

SRA737 has been assessed in an initial package of in vitro absorption, distribution, metabolism, elimination, and toxicity (ADMET) studies, including comparative metabolism in nonclinical species and human hepatocytes; inhibition of human cytochrome P450 (CYP) enzymes; profiling in the CEREP pharmacological off-targets panel; plasma protein binding and Caco-2 permeability assessment. In vitro cardiac channel studies were also undertaken. More detailed information on these various studies is available in the current version of the Investigator's Brochure.

2.3.3.1 In Vitro Metabolism

The in vitro metabolism of SRA737 has been compared in human, mouse, rat, dog, minipig, and monkey hepatocytes.

The rank order of stability from most stable to least stable for the species was rat ≈ mouse > monkey ≈ human >> dog >> minipig. In the human hepatocyte preparation, approximately 66% of the parent remained after 4 hours of incubation compared to 75% and 7% in the rat and minipig preparations, respectively.

Twelve components were identified as putative metabolites of SRA737 formed by oxygenation, dehydrogenation, N-dealkylation, glucuronidation, sulfation, acetylation, or a combination thereof. The metabolic profile in monkey hepatocytes was most similar to human hepatocytes with all eight human SRA737 metabolites also observed in the monkey, with six at equal or greater abundance. No human-specific metabolites were observed.

2.3.3.2 In Vitro Safety and Developability Assessments

2.3.3.2.1 Cytochrome P450 inhibition

No significant inhibition of major CYP enzymes (1A2, 2A6, 2C9, 2C19, 2D6 and 3A4) was observed at the highest concentration of SRA737 investigated (IC_{50} > 10-50 µM), suggesting that the compound is unlikely to mediate significant metabolic drug-drug interactions.

2.3.3.2.2 CYP Induction

The ability of SRA737 to induce the major inducible CYP enzymes (1A2, 2B6 and 3A4) in cultured human hepatocytes was assessed by qRT-PCR. Minimal, concentration-dependent increases in CYP1A2 mRNA levels (up to 7-fold at 30 µM SRA737; EC50 = 3-7 µM) were observed. While the response was less than 10% of the positive control (omeprazole, 50 µM), these in vitro data suggest SRA737 may minimally affect the metabolism of concomitantly administered drugs that are predominately metabolized by CYP1A2.

2.3.3.2.3 Off-target Profiling Screen

The potential off-target binding activity of SRA737 against a range of 80 pharmacological targets (including the hERG and related cardiac channels) was determined in the CEREP Express Profiler assay package.

Partial agonism of the $5HT_{2B}$ receptor was the only finding of note, although an absence of particularly potent nor complete agonist activity (half maximal efficacious concentration [EC_{50}] = 2.1 µM; 46% maximal effect of serotonin) likely renders this observation of limited toxicological significance in the intended patient population.

2.3.3.2.4 Plasma Protein Binding

Moderate, concentration-independent plasma protein binding of SRA737 (1 and 10 µM) has been noted in minipig (f_{bound} = 80%), dog (69%), monkey (87%), and human plasma (87%). High protein binding was observed in mouse plasma (94%).

2.3.3.2.5 Permeability

SRA737 displays high permeability (A > B = 25 × 10-6 cm/s; 10 µM) and a low efflux ratio (0.80) in a standard Caco-2 cell model of human intestinal permeation. These data suggest that the compound is not an avid substrate for efflux transporters such as P-gp, and that favorable absorption following oral administration to humans is likely.

2.3.4 IN VIVO PHARMACOKINETICS

The PK of SRA737 have been determined in the mouse, rat, dog, and monkey following oral (PO) and intravenous (IV) administration (Table 2). Very favorable absolute oral bioavailability (%F) was noted, particularly in the mouse (105%) and monkey (90-104%), consistent with the moderate metabolism and favorable permeability noted in in vitro models. An acceptable terminal elimination half-life ($t_{1/2}$) was also observed in each species. Further studies in mice confirmed dose linearity in pertinent PK parameters over the range of 50 to 300 mg/kg PO.

Table 2. Non-Clinical Pharmacokinetics of SRA737

Species	Dose	$t_{1/2}$ (h)	C_{max} (µg/mL)	AUC (0-t) (µg•h/mL)	%F
Mouse	IV (10 mg/kg)	2.9	-	3.77	105
	PO (10 mg/kg)	2.9	0.61	3.94	
Rat	IV (5 mg/kg)	1.0	-	1.38	42
	PO (10 mg/kg)	4.6	0.19	1.17	
Dog	IV (1 mg/kg)	2.8	-	0.20	86
	PO (10 mg/kg)	3.5	0.13	0.85	
Monkey	IV (1 mg/kg)	5.3	-	1.52	-
	PO (2mg/kg)	5.0	0.50	2.73	90

	PO (10 mg/kg)	5.1	2.64	15.8	104

Taken together, the compound's favorable solubility, permeability, metabolic stability, and demonstrable oral bioavailability in nonclinical species is suggestive of favorable oral absorption in humans.

2.3.5 SAFETY PHARMACOLOGY

An extensive program of safety pharmacology studies designed to investigate the cardiac safety of SRA737 has been undertaken.

2.3.5.1 In Vitro Cardiac Safety Assessments

Initial data from human cardiac ion patch clamp assays indicated moderate inhibition of the hERG channel (IC_{50} = 6.2 µM [2.4 µg/mL] and 4.2 µM [1.6 µg/mL] free drug concentration), with no significant inhibition of the other ion channels at 10 µM (3.8 µg/mL).

A subsequent study of SRA737 (3–30 µM [1.1-11.4 µg/mL]) in an isolated rabbit Purkinje fiber model was demonstrated a statistically-significant increase in action potential duration and an increase in V_{max} at 30 µM.

2.3.5.2 In Vivo Cardiac Safety Assessments

The cardiac safety of SRA737 (0, 0.3, 3 and 30 mg/kg; administered sequentially via 10-minute IV infusion) was assessed in anesthetized female guinea pigs (n = 5). A single animal died following administration of 30 mg/kg and QT prolongation (> 10% compared to baseline) was noted at the highest dose. Poor control of anesthesia was noted in this study.

The cardiac safety of SRA737 was further assessed in a benchmark, non-Good Laboratory Practice (GLP) study in conscious, telemetered female beagle dogs (0, 30 and 80 mg/kg PO; n = 3 per dose). No adverse effects on cardiovascular parameters were noted at doses up to and including 80 mg/kg, corresponding to a mean circulating plasma concentration of 3,4 µg/mL (~ 8,700 nM; 3 hours postdose).

The effect of SRA737 on cardiac parameters was also investigated in male and female minipigs following single PO administration at 50 or 75 mg/kg (n = 2/sex/dose level). One male animal (50 mg/kg) experienced multiple frequent premature ventricular complexes at approximately 1 hour postdose. although these findings were thought unrelated to drug. No other SRA737-

related changes were noted. Significant maximal plasma exposure (C_{max}) of approximately 0.64 µg/mL and 2.3 µg/mL in male and female animals, respectively, at the 50 mg/kg dose, and 2.3 µg/mL and 2.9 µg/mL in male and female animals, respectively, at the 75 mg/kg dose can be inferred from other studies.

The cardiovascular effect of SRA737 was also investigated in male and female cynomolgus monkeys following single and repeat oral administration at 2, 10 or 20 mg/kg/day (n=3-5/sex/dose level) in a GLP 28-day toxicity study. Although there were instances of sinus tachycardia and bradycardia-(both of which are known findings in cynomolgus monkeys), due to the sporadic nature of these findings and the absence of a treatment or dose relationship, these observations were considered unrelated to SRA737. There were no other SRA737-related effects on electrocardiogram (ECG) waveform or intervals. Mean circulating plasma levels at the approximate time ECGs were recorded (~ 4 hours post-dose) were 1.6 µg/mL in males and females.

2.3.5.3 Cardiovascular Safety Summary

When taken together, data from this program of in vitro and in vivo studies suggests that SRA737 possesses no significant nonclinical cardiac liabilities at likely free therapeutic plasma concentrations, including in the benchmark in vivo studies in jacketed minipigs and telemetered beagle dogs, and in the 28-day GLP monkey toxicity study. Consequently, there appears minimal risk that SRA737 will mediate clinically meaningful cardiac liabilities in humans. Nonetheless, standard cardiovascular safety assessments are included in the ongoing Phase I clinical studies.

2.3.6 TOXICOLOGY

The toxicology of SRA737 has been assessed in a number of clinical-trial enabling studies including 28-day repeat-dose toxicity studies in the mouse, minipig, and monkey and a triple combination study in the mouse. More detailed information on this suite of studies is available in the current version of the SRA737 Investigator Brochure.

2.3.6.1 28-Day Mouse Study

The toxicity and population toxicokinetics (TK) of SRA737 were assessed in a GLP 28-day, repeat-dose, oral toxicology study in CD-1 mice. Subject animals were administered compound daily at doses of 0, 10, 40 or 75 mg/kg/day (~ 30, 120 or 215 mg/m^2/day).

The findings of this study were broadly consistent with those expected for a compound with SRA737's cell cycle mechanism; namely, dose-dependent hematological changes, including significantly decreased red and white blood cell parameters (RBC, WBC), atrophy of the femoral and sternal marrow, decreased thymic weight, and a concordant increase in splenic weight likely due to compensatory extramedullary hematopoiesis. Partial or complete reversal of these findings was noted over the 14-day recovery period. Of note, given the compound's mechanism of action, was the absence of adverse macro- or microscopic findings in the gastrointestinal (GI) tract in this 28-day study. (It should be noted that apoptosis of cells in the GI tract was noted at high drug doses [> 150 mg/kg] in an earlier dose-range finding study).

An apparently irreversible tubular atrophy of the testis was also observed at the high dose. Although considered an adverse finding, the relevance of these changes to adult human cancer patients appears limited.

Drug exposure was broadly dose proportional, with the mean maximal circulating plasma concentrations of SRA737 (C_{max}) of 4.0 and 5.5 µg/mL (~ 10.6 and 14.5 µM), and total exposure (AUC_{0-t}) of 45.5 and 68.6 µg•h/mL in female and male animals respectively at the 75 mg/kg dose (Day 28).

The MTD in this study was 75mg/kg/day.

2.3.6.2 Three-Cycle Mouse Triple Combination Study

A further study was conducted in CD-1 mice to investigate the toxicity and TK of SRA737 when administered in combination with IV gemcitabine and cisplatin on an intermittent schedule over 18 days. Male and female animals were administered SRA737 PO at 40, 75 or 150 mg/kg/day on Days 2, 3, 9, 10, 16 and 17 of dosing, in combination with cisplatin (12 mg/kg IV Day 1) and gemcitabine (100 mg/kg IV on Days 1, 8 and 15; "triplet combination").

The toxicological findings in this combination study mirrored those noted in the monotherapy toxicity study, namely a decrease in RBC parameters (although of a magnitude less that observed previously); decreased eosinophils; sporadic marrow pallor and hypocellularity; decreased thymic weight and evidence of extramedullary hematopoiesis including increased spleen and liver weights and testicular changes. Partial or complete recovery of these findings was observed over the 28-day recovery period, with some minor exceptions. Reversible intestinal epithelial degeneration was also noted in the high dose triplet combination group. No changes in WBC or clinical chemistry parameters was observed.

Importantly, only the reversible marrow toxicity, consequent splenomegaly, and the high-dose intestinal observations were deemed to have been exacerbated by administration of SRA737 over those observed following administration of the cisplatin/gemcitabine control group alone.

The MTD of SRA737 in combination with cisplatin and gemcitabine on an intermittent schedule was 75 mg/kg/day, equivalent to its MTD when administered as a single agent (daily for 28 days).

At this dose, the PK of the compound was broadly equivalent to those observed in the single-agent toxicology study, suggesting an absence of profound drug-drug interactions with gemcitabine and cisplatin. Mean maximal plasma concentrations (C_{max}) of 4.4 and 5.1 µg/mL, and AUC_{0-t} of 46.2 and 59.7 µg•h/mL were noted in female and male animals respectively at the 75 mg/kg dose (D16).

2.3.6.3 28-Day Minipig Study

This GLP study was designed to assess the toxicity and TK of SRA737 following daily PO administration to minipigs for 28 consecutive days at doses of 0, 10, 40 or 75 mg/kg/day (~ 350, 1,400 or 2,625 mg/m^2). No recovery animals were included.

Toxicological findings in this study were broadly consistent with those observed in the mouse study (including hematological and lymphoid changes), and in keeping with the compound's mechanism of action, although often at a greater severity than previously noted.

Six animals were prematurely terminated over the course of the study due to moribundity (viz: all high dose and two mid dose males terminated in Week 4, and one high dose female terminated in Week 3). Significant lymphoid depletion predisposing to secondary infection of the liver, GI tract, and lung, or septicemia was noted in the premature decedent animals.

A decrease in RBC parameters (including hemoglobin, RBC and reticulocyte count, and packed cell volume) were noted in male and female animals at 40 or 75 mg/kg/day at the end of the dosing period. A slight to minimal increase in hematopoiesis was also noted in the femur, sternum, spleen and liver of most animals in these dose groups.

Decreased white blood cell counts were also observed at the higher doses in female animals as was lymphoid atrophy of the spleen, thymus and other organs. Minimal single cell necrosis in the gastrointestinal tract of these animals was also noted.

Low grade tubular atrophy of the testis and of the prostate was noted sporadically in male animals, with minimal to moderate ovarian toxicity noted in females. Again, the toxicological relevance of these findings in immature minipigs to adult cancer patients is not considered development limiting.

The highest non-severely toxic dose in this study was 10 mg/kg/day (~ 350 mg/m^2/day).

At this dose, maximal plasma concentrations ranged from 0.5–0.6 µg/mL and AUC_{0-t} approximated 6.5 µg•h/mL in the male and female animals collectively on Day 28.

2.3.6.4 28-Day Monkey Study

This GLP study was designed to assess the toxicity and toxicokinetics of SRA737 following daily oral administration to monkeys for 28 consecutive days at doses of 0, 2, 10, or 20 mg/kg/day (~ 0, 24, 120, or 240 mg/m^2/day). A subset of animals in the control, and mid and high dose groups were retained on study for a two-week non-dosing recovery period.

SRA737 was well tolerated at all dose levels with SRA737-related findings limited to a minimal non-regenerative decrease in red cell mass in males at doses ≥10 mg/kg/day and females at 20 mg/kg/day, and reversible minimal decreases in lymphocytes and transient minimal increases in glucose concentration in females at 20 mg/kg/day; none of these changes had correlating microscopic findings and were considered to be non-adverse. There were no SRA737-related effects on any other parameter evaluated in this study.

The no-observed-adverse-effect-level (NOAEL) was 20 mg/kg/day (~ 240 mg/m^2/day). At this dose, mean maximal plasma concentrations (C_{max}) of 3.2 and 2.3 µg/mL, and total exposure (AUC_{0-t}) of 20.7 and 24.2 µg.h/mL were noted in male and female animals, respectively, on Day 28.

2.3.6.5 Toxicology Summary

In summary, the toxicology findings were broadly similar between the mouse and minipig and consistent with SRA737's mechanism of action. Specifically, dose-dependent toxicological findings related to bone marrow toxicity, including variously decreased red and white cell parameters with increased medullary or extramedullary hematopoiesis and atrophy of lymphatic organs including the thymus was noted. These findings were reversible on cessation of drug administration.

Toxicological findings in the monkey indicated SRA737 had the potential to cause findings similar to those observed in mouse and minipig, although at much greater plasma exposures.

Toxicological findings in the GI tract were also observed in the minipig and in early mouse and monkey studies and changes in reproductive organs, particularly the testes, were also observed in the minipig and mouse, but not the monkey. These latter changes were not reversible in the mouse; however, the relevance of these findings in sexually immature animals to adult cancer patients appears limited.

As the combination agents in this study (gemcitabine ± cisplatin) also possess known hematological and GI toxicities, and some exacerbation of myelosuppression was observed in the murine triple combination toxicity study, the clinical combination of SRA737, gemcitabine and cisplatin may lead to augmented hematological and other toxicities in patients.

2.4 CLINICAL EXPERIENCE

SRA737 had not been administered to humans prior to the concurrent initiation of this study and the ongoing monotherapy study.

Several Chk1 and Chk1/2 inhibitors have however previously been investigated clinically. The development of several first generation inhibitors was terminated due to unfavorable pharmaceutical properties and/or unmanageable toxicities including off-target cardiovascular liabilities. Several second-generation Chk1 inhibitors are now in development.

LY2606368, an unselective Chk1/Chk2 inhibitor administered by intravenous infusion is currently the most advanced second-generation agent. This compound is currently the subject of a number of Phase 1 and 2 clinical studies both as monotherapy and in combination with various chemotherapeutic agents and radiotherapy. Interim data from a number of these studies suggests that (putatively on-target) myelosuppression including high-grade neutropenia, is dose-limiting. Favorable initial activity has also been noted with a PR rate of 38% in a study of 13 patients with HGSOC (Lee 2016).

GDC-0575 an orally available Chk1 inhibitor is also currently being investigated in a Phase 1 clinical trial in refractory solid tumors and lymphoma (refer to Section 2.2.3).

Dose escalation is ongoing in the SRA737 Phase 1 monotherapy trial and has been safely advanced through six single patient dose cohorts of 20, 40, 80, 160, 300 and 600 mg/day, administered on a continuous daily oral dosing regimen in 28-day cycles.

Further information on SRA737 is available in the current version of the Investigator's Brochure.

2.4.1 SRA737-01 (MONOTHERAPY)

The SRA737-01 trial is a first-in-human (FIH) trial of SRA737 administered orally with continuous daily dosing as monotherapy.

As of 02 July 2018, 69 subjects have been enrolled and received at least a single dose of SRA737. Dose level cohorts at 20, 40, 80, 160, 300, 600 and 1000 mg once daily were completed without DLTs. Two DLTs have been observed at the 1300 mg once daily dose, each being an inability to receive 75% of the planned SRA737 dose due to Grade 1/2 GI intolerability. After 1000 mg once daily dose level cohort was completed without DLT, a cohort receiving 500 mg twice daily was added to determine if a twice daily dosing schedule can improve GI tolerability, given the half-life of SRA737 is approximately 10 hours. One DLT was experienced by a subject in the 500 mg twice daily cohort; this was inability to receive 75% of the planned SRA737 dose due to grade 4 thrombocytopenia with grade 3 neutropenia and anemia. Cohort expansion subjects initially received 1000 mg once daily, however based on overall tolerability and gastrointestinal AEs (nausea, vomiting, and diarrhea), new subjects enrolled in expansion cohorts are receiving a dose of 800 mg once daily as of 15 Jun 2018.

At the time of this amendment (7.0), AE data were available for a total of 61 subjects treated up to 02 July 2018. The majority (>90%) of the reported AEs were Grade 1 or Grade 2 in severity and the most commonly observed treatment emergent AEs (≥ 20%; all reported causalities) were fatigue and GI events (diarrhea, nausea, vomiting). Additional AEs observed in ≥ 15% but < 20% of subjects included constipation and decreased appetite. Serious AEs that were at least possibly related to SRA737 by investigator's assessment and occurred in single subjects included: at the 1300 mg once daily dose level: Grade 3 neutropenia; at the 1000 mg once daily dose level: Grade 3 heart failure/cardiomyopathy (possible stress-related cardiomyopathy), asymptomatic Grade 3 QTc prolongation, Grade 3 pyrexia and Grade 2 nausea; at the 500 mg twice daily dose level: Grade 4 thrombocytopenia with Grade 3 neutropenia and anemia. Serious AEs of Grade 3 skin rash that were at least possibly related to SRA737 occurred in 2 subjects, one at the 1000 mg once daily dose level and the other at 500 mg twice daily.

2.4.2 SRA737-02 (IN COMBINATION WITH GEMCITABINE AND CISPLATIN OR GEMCITABINE ALONE)

The SRA737-02 trial is a FIH trial of SRA737 administered orally intermittently in combination with cytotoxic chemotherapy.

Enrollment to Stage 1 has concluded with 10 subjects enrolled across 3 cohorts. Enrollment is currently proceeding in the low-dose gemcitabine combination in Stage 2 Dose Escalation cohorts.

In Stage 1, DLTs (hematology toxicities/rash) in Cohorts 1 and 2 led to the reduction in the gemcitabine dose from a starting dose of 1250 mg/m^2 in Cohort 1 to 875 mg/m^2 in Cohort 2 and subsequently to 600 mg/m^2 in Cohort 3. Each of the 3 cohorts also received cisplatin at a dose of 80 mg/m^2 and SRA737 at a dose of 20 mg. No DLTs were observed in Cohort 3 of Stage 1.

Further enrollment to Stage 1 was superseded by the activation of Stage 2 following Amendment 5.0 which introduced the low-dose approach to the gemcitabine combination. As of 06 Jul 2018, no DLTs have been observed in Stage 2 across the 35 subjects treated in dose escalation cohorts with dose levels as described in “Trial Status” contained in Section 2.

At the time of this amendment (7.0), AE data were available for 33 subjects treated in Stage 2 up to 27 June 2018. The majority (94%) of the reported AEs were Grade 1 or Grade 2 in severity. Most commonly observed treatment-emergent AEs (≥ 20% of subjects) were: nausea, diarrhea, vomiting, fatigue, anemia, ALT increased, headache, influenza-like illness, neutropenia, back pain, and thrombocytopenia. Two SAEs were considered by the investigator to be at least possibly related to SRA737: a Grade 1 fever (80 mg SRA737 + 100 mg/m^2 gemcitabine dose level cohort) which the subject recovered after 1 day and continued on treatment, and a Grade 2 deep vein thrombosis (150 mg SRA737 + 100 mg/m^2 gemcitabine dose level cohort) which was resolved with sequalae after 2 days and SRA737 was withdrawn.

The 500 mg SRA737 + 100 mg/m^2 gemcitabine and 500 mg SRA737 + 50 mg/m^2 gemcitabine dose level cohorts were completed in May 2018 without a DLT and the dose escalation proceeded to open a 500 mg SRA737 + 150 mg/m^2 cohort in parallel with a 600 mg SRA737 + 100 mg/m^2 cohort.

2.5 RATIONALE FOR THE PROPOSED TRIAL:

Although progress has been made in many areas of clinical oncology, the treatment options for patients with cancer remain limited and continue to represent an area of high unmet medical need. In the continually evolving science of cancer drug development, combination therapies that leverage the mechanism of action of each agent represent a potentially important strategy for treating the highly complex biology of cancer. In addition, the ability to select patients for treatment based on relevant underlying genetic components of their disease provides a means for improving the potential for patient benefit without increasing overall risk.

Consistent with this paradigm, this clinical trial has been designed to evaluate SRA737 in combination with low-dose gemcitabine. The recommended Phase 2 dose (RP2D) for the combination will be defined, while also evaluating which patients are most likely to benefit from the combination. Four indications have been selected as being most likely to represent potential areas for SRA737/gemcitabine efficacy, and the diagnostic test will be explored as a means to identify patients with the greatest likelihood of benefit from treatment.

2.6 BENEFIT/RISK ASSESSMENT

SRA737 is a highly selective, orally bioavailable small molecule inhibitor of Chk1, a central regulator of the DDR network. The compound abrogates gemcitabine-induced G2/M arrest of HT29 human colon cancer cells at nanomolar concentrations and potentiates the anti-proliferative and apoptotic activities of a range of DNA-damaging agents in human lung, pancreatic and colon cancer cell lines. SRA737 has also shown chemosensitizing efficacy of gemcitabine or gemcitabine + carboplatin in a number of murine xenograft models. In addition, the compound possesses the requisite PK, toxicological, and pharmaceutical properties for further clinical investigation.

As described in Section 2.1.4, gemcitabine has the ability to greatly potentiate the cytotoxicity observed with SRA737 and other Chk1 inhibitors in preclinical models. This effect is retained even when very low doses of gemcitabine are used. Although tolerability of the combination of SRA737 and gemcitabine has been studied in mice and in a formal toxicology study in mini-pigs, the optimal doses of gemcitabine and SRA737 when administered together in humans is not known and is the focus of this current study. It is hypothesized that a very low dose of gemcitabine, well below what might be considered active as a single agent, might be sufficient to develop an active combination regimen with an optimal benefit-risk profile.

Given the strength of the data, the safety and preliminary activity of escalating doses of SRA737 in combination with gemcitabine ± cisplatin in subjects with advanced solid tumors will be investigated. The safety and activity of SRA737 in combination with gemcitabine will be further evaluated in expansion cohorts of prospectively-selected genetically-defined subjects with HGSOC, SCLC, STS and cervical/anogenital cancer. The indications selected for the expansion cohorts have been identified 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.

In a Phase 1 monotherapy trial of SRA737 (SRA737-01), subjects receive continuous daily doses in 28-day cycles. This trial is ongoing, and dose level cohorts of up to 1000 mg once daily have been completed without any DLT (refer to Section 2.4.1). These initial clinical findings are supported by the favorable tolerability and broad implied therapeutic window observed in the pivotal monkey toxicology study. The most likely target organs for SRA737 toxicity are the bone marrow and GI tract, which will be closely monitored in the ongoing studies. Although no significant nonclinical cardiac liabilities have been observed during the pivotal toxicity studies, cardiovascular safety assessments are included in the clinical study.

During the conduct of the study, the sponsor is committed to perform ongoing review of safety data with careful oversight of the subject's safety by the Cohort Review Committee. The protocol includes guidelines for the reduction, interruption and discontinuation of study treatment in the event of adverse events (Section 5.4 and Section 5.6).

Based on the non-clinical and clinical information currently available, the balance between anticipated efficacy/benefits and the potential safety risks for SRA737 in combination with gemcitabine remains favorable.

3 TRIAL DESIGN

3.1 CLINIAL TRIAL OBJECTIVES AND ENDPOINTS

3.1.1 PRIMARY OBJECTIVES AND ENDPOINTS

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 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 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.

3.1.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary Objectives	Endpoints
To characterize the PK profile of SRA737 administered in combination with gemcitabine ± cisplatin.	Plasma concentration-time profiles of SRA737 based on PK parameters including but not limited to AUC_{inf}, AUC_{tau}, C_{min}, C_{max}, time to reach C_{max} (T_{max}), $t_{½}$.
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.	• 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) • PFS • Time to Progression (TTP) • OS

3.1.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory Objectives	Endpoints
To assess the relationship between response and the presence of selected genetic alternations 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.

3.2 DESIGN OF CLINICAL TRIAL

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

The trial will consist of 2 stages:

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

  Upon implementation of Amendment v5.0, dose escalation in Stage 1 was halted. Ten subjects with solid tumors in cohorts of 3 to 6 subjects were enrolled in Stage 1 of the study. Subjects receiving the triplet combination when Amendment v5.0 was implemented continued to follow the treatment regimen and schedule of assessments for Stage 1 defined in Section 5 and Section 7, respectively.

- **Stage 2:** SRA737 + gemcitabine Dose Escalation and Cohort Expansion Phases

  Stage 2 began upon activation of Amendment v5.0.

  In the Dose Escalation Phase, approximately 30-40 subjects with solid tumors in cohorts of 3 to 6 subjects will 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 has been achieved or evidence of anti-tumor activity observed), gemcitabine may be escalated to a maximum dose of 600 mg/m^2 (with corresponding decreases in the SRA737 dose, as necessary for safety).

In the Cohort Expansion Phase, approximately 20 prospectively-selected genetically-defined subjects will be enrolled in each of the 4 indication-specific cohorts: HGSOC, SCLC, STS, or cervical/anogenital cancer. These subjects will be treated at the MTD or a lower dose selected by the sponsor.

The original study design schema is presented in Figure 7,an amended study design schema (with implementation of Amendment v5.0) is presented in Figure 8, and a further amended study design schema (with implementation of Amendment v6.0) is presented in Figure 9.

Figure 7. Original Study Design Schema (Protocol v1.0-4.0)

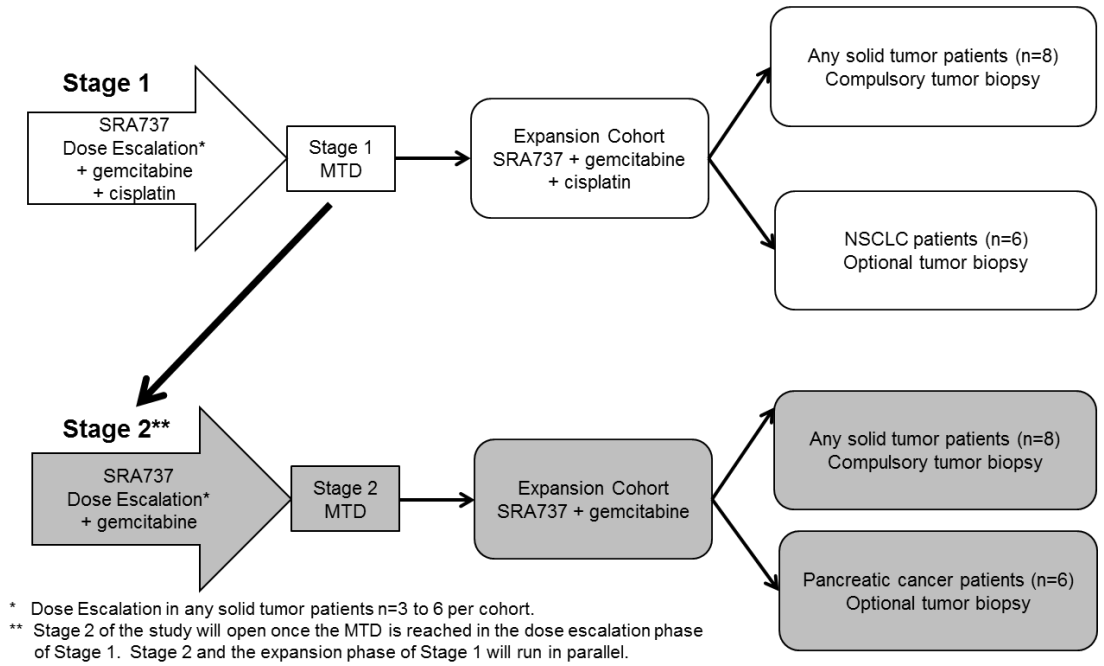
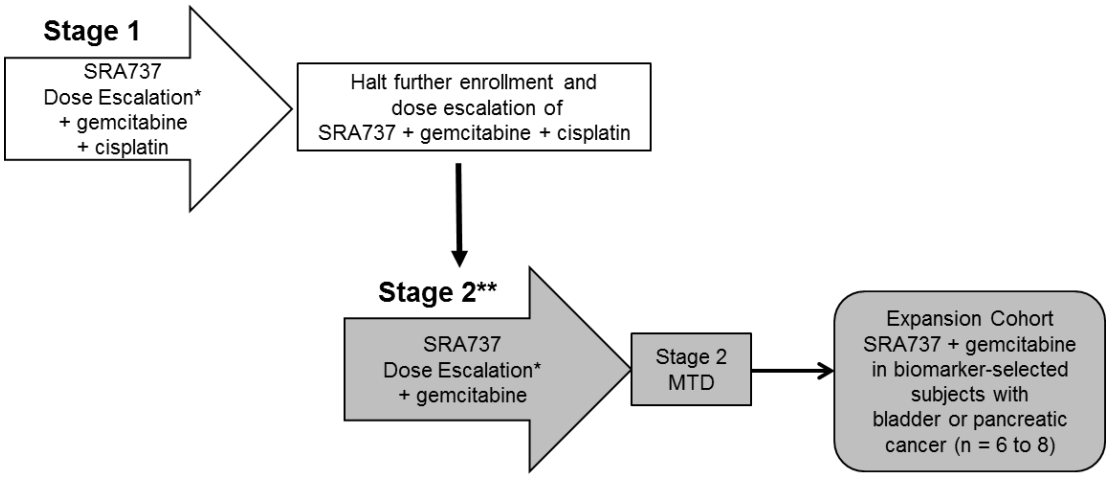
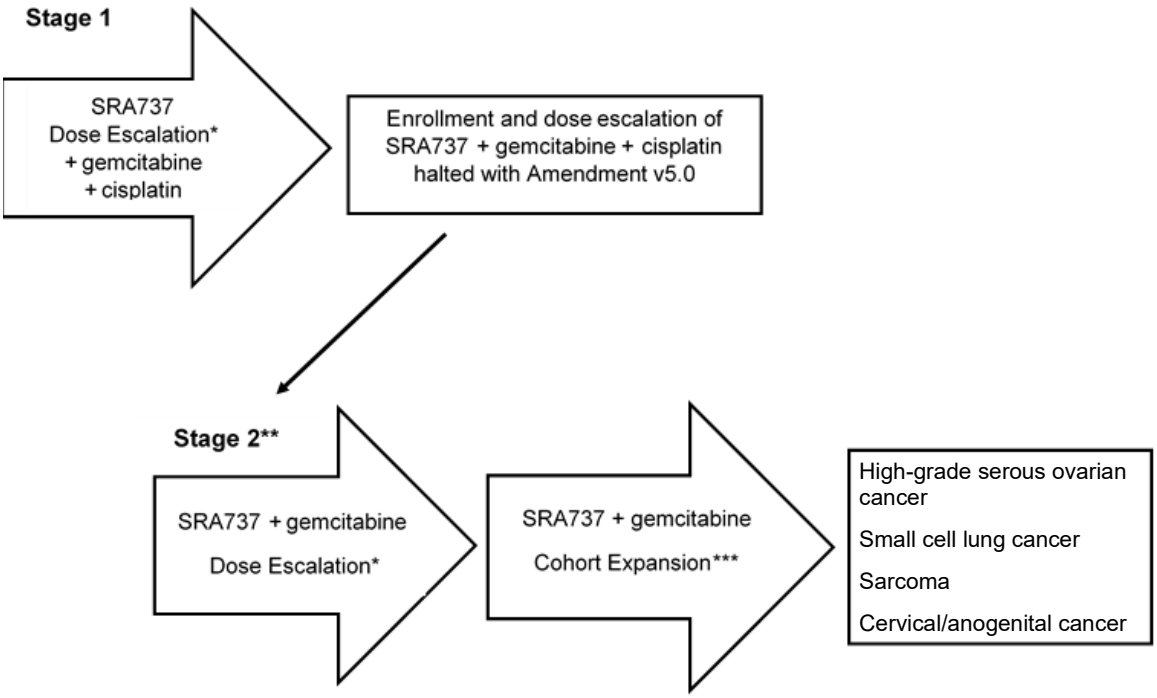


Figure 8. Amendment v5.0 Study Design Schema



* Dose Escalation in any solid tumor patients n=3 to 6 per cohort.
* Note: The 1st subject of each cohort must complete 7 days of dosing before others can start.
** Upon activation of Amendment v5.0, Stage 2 will open immediately. Upon reaching Stage 2 MTD, a dose expansion cohort consisting of 6 to 8 biomarker-selected bladder or pancreatic cancer subjects will be enrolled and treated at the SRA737+gemcitabine MTD.

Figure 9. Amendment v6.0 Study Design Schema



* Dose Escalation in subjects with any solid tumor; n=3 to 6 per cohort.
* Note: the 1st subject of each dose escalation cohort must complete 7 days of dosing before others can start.
** Stage 2 opened upon activation of Amendment v5.0.
*** Cohort Expansion in prospectively-selected genetically-defined subjects; n= up to approximatey 20 per cohort. Cohort expansion may begin prior to determination of MTD.

3.3 DOSE ESCALATION SCHEME

Dose escalation rules are described in Section 3.3.2. The goal of Stage 1 and Stage 2 Dose Escalation is to identify the doses and schedule of these agents given in combination that provide the optimal balance of safety and potential for efficacy. The main objective is to escalate the dose of SRA737 across sequential cohorts until an MTD is reached. Depending on emerging safety, PK, PDn, and preliminary efficacy data, the cytotoxic dose(s) (gemcitabine and/or cisplatin in Stage 1; gemcitabine in Stage 2) may be de-escalated or the frequency of their administration reduced. For example, this approach could be pursued if toxicity precludes further escalation at dose levels with insufficient SRA737 exposure to produce the desired PDn effects. This approach could also be pursued in the absence of toxicity sufficient to preclude further escalation, that is, simultaneous with SRA737 dose escalation.

Subjects will be recruited to cohorts according to a rolling 6 design. In Stage 2, 3 to 6 evaluable subjects will be entered at each dose level and receive escalating or varying doses of SRA737 and gemcitabine for the determination of MTD and safety and toxicity profile. Alternative schedules of either agent in Stage 2 may also be tested if deemed appropriate. Once the first subject has completed the observation period of 7 days after the first dose of gemcitabine subsequent subjects may start treatment at the same time, unless otherwise determined by the sponsor, based on emerging data from the study.

- If a DLT (in 1 of 6 subjects) occurs at a concentration of SRA737 below 100 nM at C_{min} 24 hour (level below which we would not expect to see Chk1 inhibition from preclinical models), the dose of SRA737 may continue to be escalated in 100% increments. After reaching a concentration of SRA737 above 100 nM at C_{min} 24 hour, the dose of SRA737 will be escalated in less than 100% increments, typically 25-75% increments, depending on the clinical data. Dose escalation of SRA737 will cease once the MTD has been reached (defined in Section 3.5), unless the sponsor elects to stop prior to this. Refer to Section 3.3.2 for dose escalation rules.

- The sponsor may elect to escalate the dose of gemcitabine, for example if the minimum efficacious dose range for SRA737 has been reached or evidence of anti-tumor activity observed. The maximum possible dose of gemcitabine will be 600 mg/m^2.

- Alternative dosing/schedules for SRA737 and gemcitabine may be considered, as described in Section 5.1.

Subjects who receive fewer than 5 of the 6 (< 83%) planned doses of SRA737 in Stage 2 in Cycle 1 (from Cycle 1 Day 1 [C1D1] onwards) or do not receive all doses of gemcitabine in Cycle 1 for reasons other than IMP-related toxicity will not be evaluable for assessment of DLT and may be replaced in the cohort unless the sponsor elects to evaluate an alternative dosing schedule. Reported safety information for these subjects will, however, be considered to guide the percentage change in dose levels.

3.3.1 COHORT REVIEW PROCESS

A review of safety data and other supporting data required to make a recommendation with regard to dose escalation will be conducted prior to opening any new cohort. Dose assignment for each cohort will be carried out, using all available data, by the sponsor in conjunction with the chief investigator (CI), and principle investigators (PIs). Cohort Review Meetings will be held to determine if the dose level has been tolerated by the subjects, to determine if it is safe to escalate to a higher dose, and to determine the next dose level. These reviews will be triggered when sufficient subjects have completed their first cycle of treatment at a particular dose. These meetings will be led by the sponsor and will include, at a minimum, the CI or his designee and a representative from each site with a subject in the cohort under discussion. The safety data, including a list of DLTs and all AEs, will be reviewed along with all other available data such as PK and/or PDn data.

Other topics to be discussed could include, but are not limited to whether the data suggest that testing of an alternative schedule should begin and if so, what initial dose and schedule would be tested.

3.3.2 DOSE ESCALATION DECISION RULES

Dose levels of SRA737 and gemcitabine (and, for Stage 1, cisplatin) for subsequent cohorts will be determined, following a Cohort Review Meeting held when at least 3 evaluable subjects have completed the DLT observation window, or earlier if required for the safety of the subjects (eg, 2 subjects with DLTs observed in the first 2 subjects).

Decision criteria for dose escalation for Stage 2 are as follows:

- If the data are available from a minimum of 3 subjects who have been treated in a cohort and no DLTs have been observed at that dose level, then dose escalation of SRA737 or gemcitabine can be considered. Electively, a simultaneous reduction of the gemcitabine dose may also be undertaken.

- If the data are available from 3 subjects who have been treated in a cohort and 1 DLT has been observed at that dose level, then the cohort will be expanded to include 6 subjects.
- If 2 DLTs have been observed at any dose level, the dose of gemcitabine, SRA737, or both will be de-escalated. This could be accomplished with a lower dose for each administration or a less frequent administration of either agent during a cycle (eg, gemcitabine on Days 1 and 15, and SRA737 on Days 2, 3, 16, and 17).
- The next lower dose level will be expanded to include up to 6 subjects. If this dose level is confirmed to be tolerable:
    - It may be defined as the MTD.
    - Alternatively, if the gemcitabine dose had been de-escalated and if the lower dose level of gemcitabine with SRA737 is confirmed to be safe in 3 to 6 subjects, further escalation of SRA737 is allowed for subsequent cohorts.
    - Or, if the SRA737 dose had been de-escalated to the next lower dose level or an intermediate dose level and confirmed to be safe in 3 to 6 subjects, further escalation of gemcitabine is allowed for subsequent cohorts.

Table 3. Dose Escalation Decision Making

Number of Subjects with DLT(s)	Action
0/3	Increase to next SRA737 or gemcitabine dose level
1/3	Treat up to 3 more subjects at same SRA737 and gemcitabine dose level
≥2/3*	Stop enrollment at that dose level, de-escalate and test a lower dose level. Define the MTD or pursue an alternative dose escalation strategy as described above.
Once a DLT has been seen or the cohort expanded up to 6 subjects	
1/6	Continue dose escalation with up to 100% increment if SRA737 below 100 nM at C_{min} 24 hour, or For SRA737 above 100 nM at C_{min} 24 hour, escalated in less than 100% increments (typically 25-75%), depending on the clinical data.
≥2/6*	Stop enrollment at that dose level, de-escalate and test a lower dose level; Define the MTD or pursue an alternative dose escalation strategy as described above.

*No additional subjects will be added to a cohort after a second DLT is observed.

3.4 DEFINITION OF DOSE-LIMITING TOXICITY

Due to anticipated overlapping hematological toxicities with chemotherapy and SRA737, hematological toxicities assessed as associated with chemotherapy should also be assessed for the relationship to SRA737.

The DLT window is defined from the first Day -7 to -4 dose until the end of Cycle 1 (up to 35 days).

A DLT is defined as any highly probably or probably IMP-related (SRA737, gemcitabine, cisplatin) event of:

- Grade 4 neutropenia or thrombocytopenia that lasts for > 7 days despite withholding dosing and/or providing supportive care (eg, hematopoietic growth factors)

  Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 7 after the onset of the event to determine if a DLT has occurred. The investigator must continue to monitor the subject closely until resolution to ≤ Grade 3.
- Febrile neutropenia
- A ≥ Grade 3 thrombocytopenia with ≥ Grade 3 bleeding
- A ≥ Grade 3 nonhematological toxicity with the following possible exceptions if agreed by the sponsor after discussion during the Cohort Review Meeting:
  - Alopecia of any grade
  - Grade 3 or 4 nausea or vomiting, in subjects that have not received optimal treatment with antiemetics
  - Grade 3 or 4 diarrhea, in subjects that have not received optimal treatment with antidiarrheal medication
  - Transient, asymptomatic Grade 3 biochemical abnormalities if agreed by the sponsor's Medical Monitor and the CI
  - Grade 3 fatigue, unless there is an increase by at least 2 grades from baseline (classed as grade prior to first dose of SRA737 [or gemcitabine if the SRA737 dose for PK is omitted])
- Inability to receive all doses (Stage 2) of gemcitabine dose in Cycle 1 due to IMP-related toxicity (unless not applicable due to the sponsor having elected to evaluate an alternative dosing schedule)
- Inability to receive 5 of the 6 (83%, Stage 2) planned doses of SRA737 (or the equivalent if the sponsor elects to evaluate an alternative dosing schedule) in Cycle 1 due IMP-related toxicity

Dose-limiting toxicities defined above will be considered for the purposes of dose escalation decisions; however, should cumulative toxicity become apparent this will also be taken into consideration when determining either the next dose level or the RP2D(s).

All DLTs must be reported to the sponsor or sponsor's designee within 24 hours of site staff becoming aware of the DLT, including any change made to the grade or causality of an AE that may alter its DLT status, as this may affect dose escalation decision making.

3.5 DEFINITION OF MAXIMUM TOLERATED DOSE AND RECOMMENED PHASE 2 DOSE

If 2 out of up to 6 subjects at the same dose level experience a DLT, as defined in Section 3.4, the MTD will be determined as a lower dose level.

The R2PD will be defined at the end of the study and will take all clinically relevant toxicity, PK and PDn data into account. The RP2D will be a dose equal to or less than the MTD.

3.6 COHORT EXPANSION SCHEME

To further evaluate the safety profile and to preliminarily explore efficacy, prospectively-selected genetically-defined subjects will be enrolled in 4 indication-specific expansion cohorts to be treated with SRA737 and gemcitabine at the MTD or a lower dose selected by the sponsor. Each expansion cohort will enroll approximately 20 subjects from the following indications: HGSOC, SCLC, STS, and cervical/anogenital cancer.

Determination of the MTD is likely to occur prior to the initiation of the expansion cohorts; however, enrollment for expansion cohorts may begin prior to the completion of dose escalation and determination of MTD or RP2D, if there is evidence of anti-tumor activity or the minimal plasma concentration of SRA737 is maintained above a threshold of 100 nM (the level at which sustained Chk1 inhibition is anticipated) at 24 hours after dosing (C_{min} 24h). Eligible subjects may be enrolled in the Cohort Expansion at the highest dose level determined to be safe and tolerable in the Dose Escalation Phase. If a subject who meets the eligibility criteria for the expansion cohorts enrolls to a Dose Escalation Cohort, that subject will count toward the sample size of 20 for that indication specific cohort. Subjects in expansion cohorts may be able to undergo intra-subject dose escalation to receive higher doses of SRA737 and/or gemcitabine depending on results from the ongoing escalation phase (see Section 3.7).

The goal of the expansion cohorts is to assess SRA737 in combination with gemcitabine across subjects who have a range of genomic profiles of interest as described in inclusion criterion 10. As this is an early stage clinical trial, the role of diagnostic testing is being explored and refined in an effort to improve likelihood of patient benefit. In order to ensure the genetic selection component reflects the current scientific understanding and is also consistent with an effective exploration of the testing as it relates to patient benefit, the sponsor may refine particular genomic profile requirements in any expansion cohort based on observations of tumor response and clinical benefit in the ongoing study and/or other emerging clinical and nonclinical data.

The sponsor may also select for alternative genomic profiles in the event profile(s) not associated with tumor responses are overrepresented in subjects already enrolled. For example, if no responses have been seen in subjects with deleterious KRAS and TP53 mutations across tumor types, the sponsor may elect to restrict further enrollment of subjects with this particular genomic profile. Also, the sponsor may select subjects such that sufficient numbers of genetic variants within an indication are studied (for example BRCA mutant and BRCA wild-type). The maximum enrollment in each of these indication cohorts will be maintained at approximately 20 subjects total.

3.7 INTRA-SUBJECT DOSE ESCALATION FOR STAGE 2

Any subject that remains on treatment at a lower dose level of SRA737 may, at the discretion of the investigator and with the agreement of the sponsor, be offered treatment at the higher dose of SRA737 once that higher dose level in combination with the corresponding dose of gemcitabine has been shown to be safe. While a specific safety threshold has not been defined by the protocol, subjects who are permitted to escalate their SRA737 dose must not have experienced significant SRA737-related toxicity at the prior dose level. There is no limit on the number of intra-subject dose escalations of SRA737 for a subject although only one dose level increase can be undertaken each cycle. Similar intra-subject dose escalation may be undertaken for gemcitabine should gemcitabine escalation be carried out as described in Section 5.2.

3.8 SUBJECT EVALUABILITY

3.8.1 DLT EVALUABLE

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 evaluable for dose review decisions.

3.8.2 REPLACEMENT OF SUBJECTS

In the Dose Escalation Phase, if agreed by the sponsor, subjects will be replaced if they receive fewer than 5 of the 6 (83%) planned doses of SRA737 and/or not all doses of gemcitabine (or the equivalent if the sponsor elects to evaluate an alternative dosing schedule) during the DLT period for reasons other than IMP-related toxicity.

In the Cohort Expansion Phase, subjects who are not response evaluable (as defined in Section 11.1.2) will be replaced in order to achieve approximately 20 response-evaluable prospectively-selected genetically-defined subjects in each indication-specific expansion cohort.

4 SUBJECT SELECTION AND ENROLLMENT

Subjects who have consented to participate in the trial must first be entered in the electronic data capture (EDC) system by site staff and be allocated a subject number by the EDC system. Once the investigator or designated site representative has confirmed the eligibility of the subject, the site must submit a completed eligibility checklist, and receive confirmation of eligibility and confirmation of the assigned dose level from the sponsor or sponsor's designee before the subject may be enrolled.

4.1 NUMBER OF SUBJECTS

Approximately 140 subjects will be enrolled in this study.

4.2 SUBJECT SELECTION CRITERIA

Subjects must fulfill the eligibility criteria listed in Sections 4.2.1 and 4.2.2 in order to participate in this study.

4.2.1 INCLUSION CRITERIA

Dose Escalation and Cohort Expansion:

1. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up.
2. In the Dose Escalation Phase, subjects with 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 (Appendix 1).
5. Hematological and biochemical indices within the ranges shown below measured within 1 week prior to the subject receiving their first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted).

Laboratory Test	Value Required
Hemoglobin	≥ 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 and 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 subject beginning study treatment. Supplement use should continue while on study as appropriate.

6. Subjects who are 18 years or older at the time consent is given.
7. Subjects must have archival tumor tissue for tumor profiling OR accessible tumor and willingness to consent to a biopsy for the collection of tumor tissue. Refer to Section 7.1.1 for more information.

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 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 will be 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 will be determined by the sponsor's review of genetic abnormalities detected in genes in the following categories, as detailed in Appendix 6:

        - 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 in Section 2.2.1), or intolerance of 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 approved otherwise for the 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 approved otherwise for the 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 approved otherwise for the sponsor.

4.2.2 EXCLUSION CRITERIA

1. 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:

   a. Radiotherapy (except for symptom control and where the lesions will not be used as measurable disease), chemotherapy, 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 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 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 child-bearing potential, unless they agree to take measures not to father children by using a barrier method of contraception defined per Appendix 4, 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 (eg, condom plus spermicidal gel) to prevent exposure of a 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] - refer to Appendix 3), 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 is removed by the sponsor (refer to Section 6.1 for additional details).
16. QTcF > 450 msec in adult males and > 470 msec in adult females.
17. Impairment of 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.

5 DOSAGE AND TREATMENT ADMINISTRATION

5.1 TREATMENT SCHEDULE

In both study stages, subjects will take a single PO dose of SRA737 prior to the start of Cycle 1, on a single day between Day -7 and Day -4 to assess PK parameters up to 48 hours postdose.

The treatment schedule starting with Cycle 1 for Stage 1 and Stage 2 regimens is described in Table 4.

Table 4. Treatment Schedules

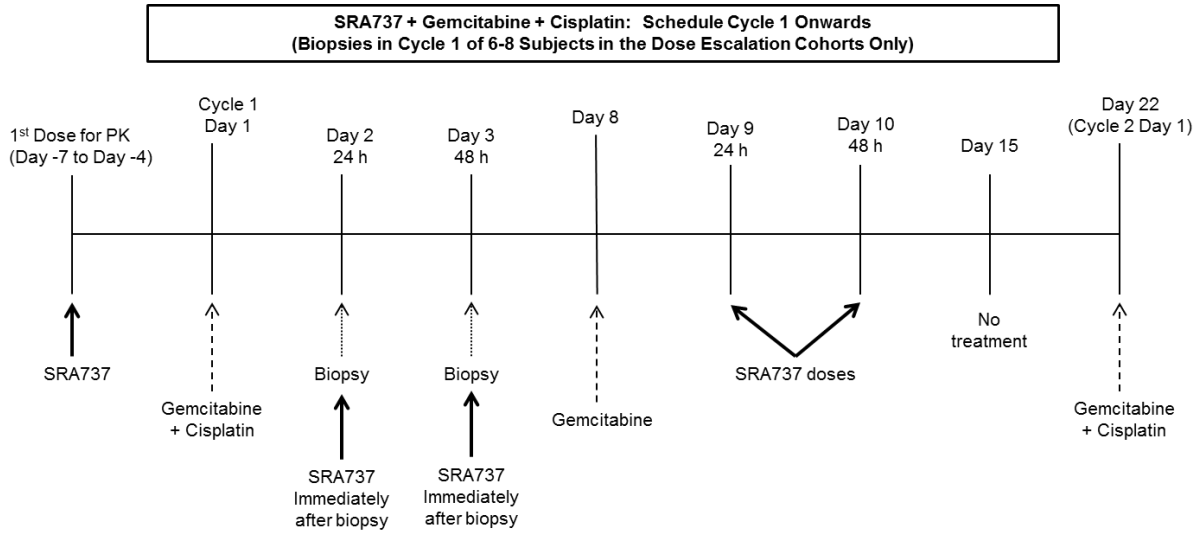
	Cycle Duration	SRA737 Dosing	Gemcitabine Dosing	Cisplatin Dosing
Stage 1 SRA737+GC	21 days	Days 2, 3, 9 and 10	Days 1 and 8	Day 1
Stage 2 SRA737+G	28 days	Days 2, 3, 9, 10, 16 and 17	Days 1, 8, and 15	Not applicable

SRA737+GC = SRA737 in combination with gemcitabine and cisplatin; SRA737+G = SRA737 in combination with gemcitabine alone.

Stage 1 consists of SRA737 administered in combination with gemcitabine and cisplatin on a 21-day cycle (Figure 10). Subjects in Stage 1 have received:

- Gemcitabine, administered IV over 30 minutes on Days 1 and 8. The starting dose of gemcitabine for Cohort 1 was 1250 mg/m^2/day
- Cisplatin, administered IV over 2 hours following gemcitabine on Day 1 of each cycle with pre- and post-infusion hydration. The starting dose of cisplatin for Cohort 1 was 80 mg/m^2/day.
- SRA737, taken PO as described in Section 6.1.3, approximately 24 and 48 hours after the end of the Day 1 and Day 8 gemcitabine infusions (ie, on Days 2, 3, 9, and 10). The starting dose of SRA737 for Cohort 1 was 20 mg/day.
    - **If the dose of gemcitabine is not administered or is delayed by more than 7 days, the doses of SRA737 will also be omitted or delayed by the same number of day to start 24 hours after the end of the gemcitabine infusion**.

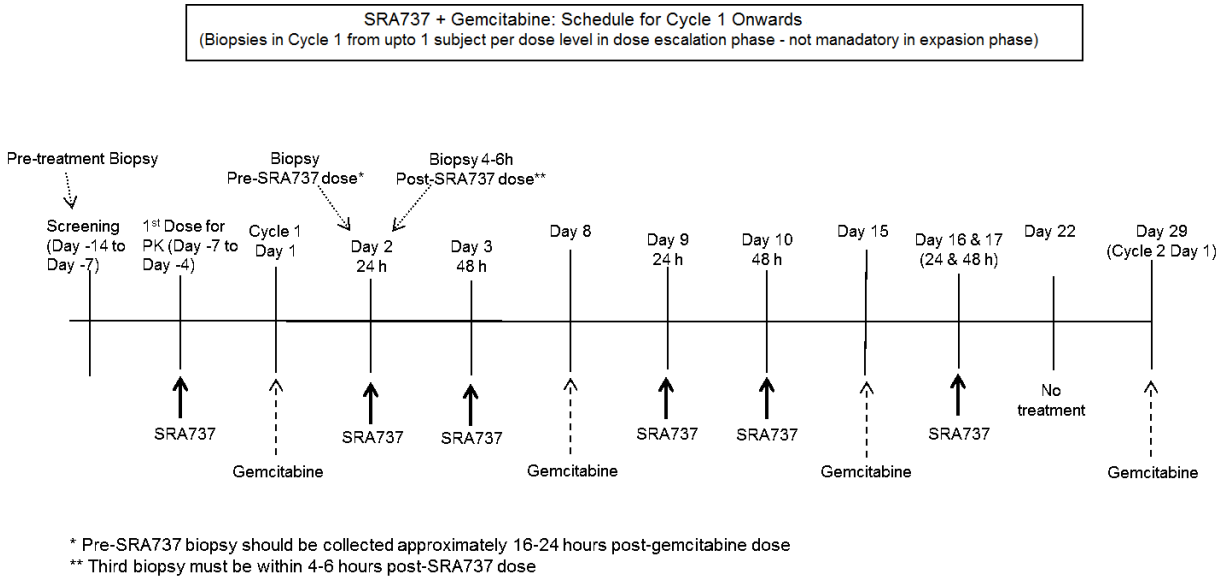
Figure 10. Stage 1 Treatment Schedule (SRA737/Gemcitabine/Cisplatin)



Stage 2 consists of SRA737 administered in combination with gemcitabine on a 28-day cycle (Figure 11). Subjects in Stage 2 will receive:

- Gemcitabine, administered IV over 30 minutes on Days 1, 8 and 15. Gemcitabine will be administered at a starting dose for Cohort 1 of 300 mg/m^2. The dose and schedule may be modified based on accumulating data.
- SRA737, taken PO as described in Section 6.1.3, approximately 24 and 48 hours after the end of the Day 1, 8, and 15 gemcitabine infusions (ie, on Days 2, 3, 9, 10, 16, and 17). The starting dose for dose escalation Cohort 1 was 40 mg/day.
    - **If the dose of gemcitabine is not administered or delayed, the doses of SRA737 will also be omitted or delayed to start 24 hours after the end of the gemcitabine infusion.**

Figure 11. Stage 2 Treatment Schedule (SRA737/Gemcitabine)



* Pre-SRA737 biopsy should be collected approximately 16-24 hours post-gemcitabine dose
** Third biopsy must be within 4-6 hours post-SRA737 dose

Treatment with SRA737 may continue until discontinuation of either gemcitabine + cisplatin or gemcitabine alone, PD, withdrawal of consent, unacceptable toxicity, or the investigator believes treatment with SRA737 should cease for any other reason. Treatment duration for Stage 2 is further described in Section 5.3.

Alternative dosing/schedules for SRA737 and gemcitabine including but not limited to those listed below will be considered by the sponsor based on emerging safety, PK, and PDn data during the study and following a discussion between sponsor, CI and PIs.

- Gemcitabine on Days 1 and 15, and SRA737 at current dose level on Days 2, 3, 16, and 17.
- Start dosing of SRA737 earlier, such as at 12 and 36 hours after the end of the gemcitabine infusion.
- Reduce the frequency of dosing of SRA737 to 1 day rather than 2 days following chemotherapy.
- Increase the frequency and/or duration of dosing of SRA737.
- Twice-daily dosing of SRA737.

5.2 DOSE LEVELS

The dose level of SRA737 will be assigned following discussion of all clinically relevant toxicity and available PK/PDn data from previous dose level(s) between the sponsor, the CI, and PIs.

Dose levels of SRA737 will be guided by the dose escalation rules as described in Section 3. With the implementation of Amendment v5.0, no further dose escalations were attempted in Stage 1.

In Stage 2, the starting dose of SRA737 was 40 mg/day and the starting dose of gemcitabine was 300 mg/m^2. Lower doses of gemcitabine will be permitted if necessary to allow for the maintenance of SRA737 dosing or the continuation of SRA737 dose escalation. The de-escalated gemcitabine dose level and schedule will be determined after a review and discussion of all clinically relevant safety data between the sponsor, CI, and PIs.

Growth factor support will be permitted to allow for continued dose escalation of SRA737.

Once the dose escalation of SRA737 is complete, or earlier, it may be decided to explore further dose escalation cohorts with a stepwise escalation of gemcitabine dose to a maximum of 600 mg/m^2, if fewer than 2 DLTs were observed at the previous dose level. If this is pursued, prophylactic or early interventional use of granulocyte-colony stimulating factor (G-CSF) could be considered as well as enrolling only those subjects whose baseline absolute neutrophil count is $\geq 2.0 \times 10^9$/L.

5.3 DURATION OF STUDY TREATMENT

5.3.1 SRA737

Treatment with SRA737 may continue until discontinuation of either gemcitabine + cisplatin or gemcitabine alone, PD, withdrawal of consent, unacceptable toxicity, or the investigator believes treatment with SRA737 should cease for any other reason. Subjects will undergo the Safety Follow-up (SFU) visit 30 days after discontinuation of SRA737.

5.3.2 GEMCITABINE AND CISPLATIN

Treatment with chemotherapy (gemcitabine alone or gemcitabine + cisplatin) may continue until discontinuation of SRA737, PD, withdrawal of consent, unacceptable toxicity, or the investigator believes treatment with chemotherapy should cease for any other reason. The duration of chemotherapy treatment should follow local treatment guidelines specific to the subject's indication, although, in general, cisplatin should be limited to 6 cycles or less to avoid cumulative toxicity. While there is no protocol mandated cap on the number of gemcitabine cycles allowed, once a subject discontinues SRA737, his/her participation in the study will end after the SFU visit. For subjects with an objective response who do not start new anticancer

therapy and remain on gemcitabine, they should stay in long-term follow-up (LTFU) until PD or start of another anticancer therapy.

5.4 DOSE MODIFICATIONS

The schedule and/or dose may be reduced for all subjects depending on emerging safety information. Decisions regarding treatment modification for individual subjects will be based on the following assessments:

- Laboratory values and AE observations from the day of dosing, to determine if treatment can be administered or should be withheld;
- Lowest (nadir) laboratory values and worst grade AE observations since the previous dose of study drug(s), to determine if a dose reduction is recommended.

Decisions to delay or adjust the dose of SRA737 and/or gemcitabine ± cisplatin should be made conservatively, using the guidelines for the most severe AEs and the worst scenario of the recommended dose reduction(s). Following dose reductions made due to hematological toxicity, the dose may be re-escalated when toxicity has resolved to appropriate levels (refer to Table 6). If the dose is reduced for reasons other than hematological toxicity it may be re-escalated if clinically appropriate, in consultation with the sponsor. If any subject requires a delay in dosing for more than 28 days, the subject should be discontinued from treatment (see Section 5.6).

5.4.1 DOSE REDUCTIONS OF SRA737

Granulocyte-colony stimulating factor may be administered for treatment of neutropenia to avoid dose delays and reductions of SRA737 and/or gemcitabine. If G-CSF and/or reduction in the doses or frequency of chemotherapy is not successful or is not considered appropriate, consideration will be given to reducing the dose or frequency of SRA737 (eg, from 2 days to 1 day following each dose of gemcitabine).

If toxicity occurs at a concentration of SRA737 below 100 nM at C_{min} 24 hour (level below which we would not expect to see Chk1 inhibition from preclinical models), no reduction of SRA737 is required.

5.4.2 DOSE MODIFICATIONS FOR GEMCITABINE AND CISPLATIN

Standard dose reductions are provided below for common hematological and nonhematological toxicities for gemcitabine and cisplatin.

Following dose reductions made due to hematological toxicity, the dose may be re-escalated when toxicity has resolved to appropriate levels (refer to Table 6). If the dose is reduced for reasons other than hematological toxicity it may be re-escalated if clinically appropriate, in consultation with the sponsor.

5.4.3 TREATMENT MODIFICATIONS ON DAY 1

If treatment is withheld on Day 1 in response to toxicity, all agents must be withheld. Hematological dose modification recommendations for SRA737 in combination with gemcitabine (± cisplatin) at Day 1 are described in Table 5.

Table 5. Gemcitabine/Cisplatin and Gemcitabine Alone Dose Modifications for Hematologic Toxicity

Observation	Recommended Action
Observation on Day 1	
• WBC ≥ 3.0 × 10^9/L AND • Neutrophils ≥ 1.5 × 10^9/L AND • Platelets ≥ 100 × 10^9/L	Treat on time; For Cycle 2 and beyond, chemotherapy doses will be based on AEs observed in the previous cycle as described below
• WBC < 3.0 × 10^9/L AND/OR • Neutrophils < 1.5 × 10^9/L AND/OR • Platelets < 100 × 10^9/L	Withhold all study drugs for at least 1 week, or up to 28 days if required, until • WBC ≥ 3.0 × 10^9/L AND • Neutrophils ≥ 1.5 × 10^9/L AND • Platelets ≥ 100 × 10^9/L, • Then resume dosing per guidelines below
Lowest (Nadir) Counts and AEs in Previous Cycle	
• Neutrophils ≥ 0.5 × 10^9/L OR < 0.5 × 10^9/L for ≤ 7 days AND • Platelets ≥ 25 × 10^9/L	No Change
• Neutrophils < 0.5 × 10^9/L for > 7 days AND/OR • Platelets < 25 × 10^9/L	First Occurrence: Reduce gemcitabine to 75% of the previous dose and cisplatin by 1 dose level; no change to SRA737 dose. Second Occurrence: Reduce gemcitabine to 75% of the previous dose and/or SRA737 to the dose level previously explored depending on whether toxicities have occurred at a concentration of SRA737 above 100 nM at C_{min} 24 hours[a]; reduce cisplatin by 1 dose level. Third Occurrence: Reduce SRA737 to the dose level previously explored or reduce SRA737 frequency. Fourth Occurrence: Permanently discontinue study drugs unless the investigator considers continuation of treatment to be in the best interest of the subject and the sponsor's Medical Monitor or designee approves continued treatment. Alternative dosing schedules may be utilized to allow improved tolerability.
• Febrile neutropenia	
• Grade 3 or Grade 4 infection with ≥ Grade 3 neutropenia	
• Thrombocytopenic bleeding (≥ Grade 3 bleeding with ≥ Grade 3 thrombocytopenia)	

Note: Dose levels for cisplatin include 80, 60, and 40 mg/m^2.
a. As communicated at the prior cohort review meeting.

5.4.4 TREATMENT MODIFICATIONS ON DAY 8 (AND DAY 15 IN STAGE 2)

When treatment with gemcitabine is administered on Day 8 (and Day 15 in Stage 2), adjustment guidelines are described in Table 6.

Table 6. Recommendations for Modifying Study Drug on Day 8 in Stage 1 and Day 15 in Stage 2 for Hematologic Toxicity

Observation on Day 8 / 15	Recommended Action
Neutrophils ≥ 1.0 × 10^9/L AND Platelets ≥ 100 × 10^9/L	Treat on time and administer full dose of gemcitabine and SRA737
Neutrophils ≥ 0.5 to < 1.0 × 10^9/L AND/OR Platelets ≥ 50 to < 100× 10^9/L	Treat on time and reduce gemcitabine dose to 75% of the previous dose; no change to SRA737 dose
Neutrophils < 0.5 × 10^9/L AND/OR Platelets < 50 × 10^9/L AND/OR Febrile neutropenia AND/OR Thrombocytopenic bleeding (≥ Grade 3 bleeding with ≥ Grade 3 thrombocytopenia)	Withhold both study drugs for 1 week, or longer if required. • If neutrophils ≥ 1.0 × 10^9/L AND Platelets ≥ 100 × 10^9/L within 7 days, resume dosing and reduce gemcitabine to 75% of the previous dose level. • If not recuperated within 7 days, re-assess at the time of the next scheduled dose, ie, either on Day 1 of the next cycle.

Note: Following dose reductions made due to hematological toxicity, the dose may be re-escalated when toxicity has resolved to appropriate levels. If the dose is reduced for reasons other than hematological toxicity it may be re-escalated if clinically appropriate, in consultation with the sponsor.

5.4.5 TREATMENT MODIFICATIONS DUE TO NONHEMATOLOGIC ADVERSE EVENTS

On any day of any cycle, the presence of specific nonhematologic AEs should result in treatment modification in accordance with the guidelines provided below (Table 7).

Table 7. Dose Modifications for Toxicities of Stomatitis or Diarrhea

Grade	Stomatitis	Diarrhea	Dose Reductions
1	Painless ulcers, erythema or mild soreness	Increase of 2-3 stools/day or mild increase in loose watery colostomy output	100% doses
2	Painful erythema, edema, or ulcers but can eat	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Omit gemcitabine, cisplatin if relevant, and SRA737 until resolved, then resume at 100% doses
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7-9 stools/day or incontinence, malabsorption, or severe increase in loose watery colostomy output	Omit all IMPs until resolved, then reduce gemcitabine to 75% of previous dose and cisplatin (except for mucositis) by 1 dose level. Consider reducing SRA737 to the dose level previously explored
4	Mucosal necrosis, requires parenteral support	Increase of 10 or more stools/day or grossly bloody diarrhea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support, dehydration	Omit all IMPs until resolved, then reduce gemcitabine by 50% of the original dose, cisplatin (except for mucositis) by 1 dose level, and SRA737 to the dose level previously explored

- Doses reduced for toxicity may be re-escalated if clinically appropriate, in consultation with the sponsor.
- If doses must be omitted for Grade 2 toxicity twice in previous cycles, then commence next cycle chemotherapy at 75% lower dose level when treatment is resumed.

5.4.5.1 Renal Impairment

Gemcitabine should be used with caution in subjects with a creatinine clearance (CrCl) < 30mL/min; however, no specific dosing recommendations for gemcitabine have been made.

Dosing with cisplatin should be withheld if calculated CrCl is less than 60 mL/min. Cisplatin induced nephrotoxicity is dose related and cumulative. It manifests early by elevations in blood urea, creatinine, and wasting of potassium and magnesium. Renal function, fluid and electrolyte balance must return to normal prior to subsequent doses. Renal toxicity may be irreversible and is more prolonged and severe with repeated courses. Avoid concomitant use of other nephrotoxic drugs.

5.4.5.2 Neurotoxicity

Grade 2 neurotoxicity requires a 50% dose reduction of cisplatin. For Grade 3 or 4 neurotoxicity, treatment should be discontinued.

5.4.5.3 Other Nonhematologic Toxicities

For all other Grade 3 nonhematologic toxicities other than events assessed as related primarily to the underlying condition, withhold therapy for at least for 1 week and up to 28 days. Once recovery occurs to Grade ≤ 1 or within 1 Grade of baseline, resume with a 75% dose of gemcitabine or 75% of gemcitabine dose and 1 reduced level of cisplatin unless the event was assessed as unlikely or not IMP-related. Consider resuming SRA737 at the dose previously explored.

For all other Grade 4 nonhematologic toxicities, withhold therapy for at least 1 week and up to 28 days. Therapy may be resumed if the event was assessed as unlikely or not IMP-related, the toxicity has recovered of to Grade ≤ 1 or within 1 Grade of baseline, and sponsor approval is granted. If therapy is to be resumed, consider reducing the chemotherapy and/or SRA737 dose levels. Consider discontinuing therapy if the above conditions are not met.

5.5 SUPPORTIVE CARE, CONCOMITANT MEDICATIONS, AND STUDY RESTRICTIONS

5.5.1 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Concomitant medication may be given as medically indicated. Details (including name and start and stop dates of the concomitant medication given) must be recorded in the subject's medical records and details entered into the electronic case report form (eCRF).

5.5.1.1 Granulocyte-colony Stimulating Factor

Granulocyte-colony stimulating factor may be administered as medically indicated. Treatment with G-CSF for subjects with ≥ Grade 3 neutropenia is recommended. If G-CSF is not started for ≥ Grade 3 neutropenia, neutrophil levels must be closely monitored.

5.5.1.2 Palliative Radiotherapy

Palliative radiotherapy may be given concomitantly for the control of bone pain or other symptoms. These irradiated lesions will not be evaluable for response.

5.5.1.3 Acid-reducing Agents

Preliminary in vitro studies suggest that the SRA737 citrate drug product may possess some minimal to moderate pH-dependent solubility over the physiological range. The effect of acid-reducing agents on the oral bioavailability of SRA737 in preclinical species or in humans is currently not known. Consequently, administration of antacids or H2 antagonists should occur 4 hours before or 2 hours after administration of SRA737. Due to the long-acting duration of proton pump inhibitors (PPIs), there is no utility in separating SRA737 and PPI dose administrations. Proton pump inhibitors should therefore be avoided if possible and used with caution if necessary.

5.5.1.4 Contraception Usage

To be eligible for this study, WOCBP (as defined per Appendix 4) and male subjects with partners of child-bearing potential must follow the contraceptive requirements as described in Appendix 4, from the first administration of SRA737 through the trial and for 6 months afterwards.

5.5.1.5 QT Prolonging Drugs

Preclinical data indicates that SRA737 possesses a minimal risk of clinically relevant prolongation of the QTc interval. The potential for QT prolongation has not yet been evaluated in the clinical setting. As a result, caution should always be used when continuing or initiating administration of QT prolonging drugs (https://www.crediblemeds.org) and the sponsor should be consulted for guidance in specific cases. A summary list applicable for this study is provided in Appendix 5.

5.5.1.6 Drugs Metabolized by Cytochrome P450 (CYP) Isoforms

Preliminary in vitro data suggests SRA737 may minimally induce cytochrome P450 CYP1A2 (Section 2.3.3.2.2). Consequently, investigators should be aware of this when continuing or initiating administration of drugs predominately metabolized by CYP1A2 while the subject is receiving SRA737. A summary list of such drugs is provided in Appendix 5.

5.5.1.7 Sun Protection

SRA737 has a theoretical potential to elicit phototoxicity; therefore, subjects should use sun protection measures (eg, sunscreen, adequate garments) and avoid direct exposure to sunlight while receiving treatment.

5.5.1.8 Treatment for Rash

If rash develops following administration of study drug (SRA737 and gemcitabine), prompt treatment with antihistamines and/or topical or systemic steroids is recommended, as indicated.

5.5.2 EXCLUDED CONCOMITANT MEDICATIONS

Subjects must not receive other anticancer therapy or investigational drugs while on the trial, with the exception of luteinizing hormone releasing hormone agonist therapy for the treatment of prostate cancer.

Gemcitabine can cause increased prothrombin time in subjects treated with warfarin, however the exact mechanism of drug interaction, if any, is not clear. Nevertheless, subjects requiring anticoagulation should change from warfarin to low molecular weight heparin while they are on study.

The following medication is not allowed and must be discontinued before starting study treatment and throughout therapy:

- Warfarin
- For subjects receiving cisplatin the following medications are not allowed and must be discontinued before starting study treatment and throughout therapy: nephrotoxic drugs, aminoglycoside antibiotics, phenytoin and carbamazepine

Refer to the summary of product characteristics (SmPC) for cisplatin and gemcitabine for further details.

5.6 DISCONTINUATION FROM TREATMENT

Subjects can decline to continue receiving IMP but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IMP and must discuss with the subject the options for continuation of Safety Follow-up and Long-term Follow-up assessments as described in Section 7.3 and Section 7.4 including different options for collection of data, including endpoints and AEs.

Subjects may discontinue study treatment for the following reasons:

- Disease progression
- Unacceptable toxicity
- Noncompliance with study procedures

- Treatment with prohibited concomitant medications
- Intercurrent illness that interferes with study assessments
- Withdrawal by the investigator for clinical reasons not related to SRA737
- Pregnancy (of a subject during the study)
- Start of new anticancer therapy
- Treatment delay of more than 28 days

The sponsor or sponsor's designee should be notified within 24 hours if a subject is discontinued from study treatment.

If the reason for discontinuation is the occurrence of an AE, the subject will be followed by the investigator for at least 30 days after discontinuation of study drug until such event(s) resolve, stabilize, and according to the investigator's judgment, there is no need for further follow-up. Subjects who discontinue study treatment for reasons other than disease progression or death may continue on study until disease progression or death. The reason for discontinuation from study treatment will be documented on the eCRF.

5.7 DISCONTINUATION FROM STUDY

Subjects will be followed according to the procedures described in Section 7.4 until disease progression, initiation of subsequent cancer therapy, or the subject is discontinued from the study for any of the reasons described below.

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. All study related assessments and data collection will cease.

The investigator must make every reasonable effort to complete study-specified Safety Follow-up assessments at 30 ± 7 days after last SRA737 administration. However, if the investigator removes a subject from the study or if the subject declines further participation prior to the planned Safety Follow-up visit, the Safety Follow-Up assessments should be performed before withdrawal from the study whenever possible. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the study, must be recorded in the medical records and in the eCRF.

Subjects may be discontinued from the study due to the following reasons:

- Sponsor's decision to terminate the trial
- Death or lost to follow-up
- Withdrawal of consent

6 PHARMACEUTICAL INFORMATION

6.1 SRA737

For information on SRA737 (the IMP previously known as CCT245737) including storage, handling, labelling, dispensing, and supply ordering, refer to the SRA737 Pharmacy Manual.

SRA737 is supplied as its citrate salt in capsules containing 20 mg, 25 mg, 50 mg, and 100 mg of drug and higher dosage strengths when available (on a free base equivalent basis). The capsules are presented in blister strips. The primary and secondary packaging for the IMP will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice.

Note: The peanut allergy exclusion criterion (#15) is required because the current manufacturing facility of the SRA737 drug product cannot guarantee it is free from contact with nut products. Drug manufacturing will be transitioned to a different facility in the future. This exclusion criterion will not be applicable when the SRA737 drug product manufactured at the current facility is depleted and no longer available for subject dosing. Refer to the SRA737 Pharmacy Manual for more information.

6.1.1 STORAGE CONDITIONS FOR SRA737

SRA737 must be stored according to the label (refrigerated at 2°C to 8°C) in its original packaging in a secure, limited access storage area in the site pharmacy. Please refer to the labelling on the carton (primary package) and blister strip for the expiry date of the IMP.

Subjects must be instructed to ensure that SRA737 is kept refrigerated and out of sight and reach of children (refer to the SRA737 Pharmacy Manual for more information).

6.1.2 DISPENSING

Subjects are to be supplied with the required quantity of SRA737 capsules **in the original blister pack** to cover the prescribed dose until the next scheduled dispensing visit. Blister packs must **not** be altered to reduce capsule numbers at dispensing.

6.1.3 SRA737 ADMINISTRATION

The SRA737 capsules must be swallowed whole (with water) and not chewed, crushed, dissolved or opened.

SRA737 capsules should be taken on an empty stomach, at the same time each day. Subjects should fast for 2 hours before administration and for 1 hour after administration. Acid reducing medications should be avoided as described in Section 5.5.1.3. SRA737 doses should be taken at the scheduled dosing time (ie, 24 hours after the preceding gemcitabine dose on the 2nd, 9th, and 16th day of each cycle and 24 hours after the preceding SRA737 dose on the 3rd, 10th, and 17th day of each cycle) wherever possible. However, if necessary, it is acceptable for the dose to be taken 22-30 hours after the preceding dose of gemcitabine orSRA737. After this time the subject should wait until the next scheduled time before taking the dose. Subjects must be counseled to take their doses on time, without delay, on days prior to PK sampling. Should a subject vomit after taking a scheduled dose, the subject should not re-take the dose and should wait until their next scheduled dose.

6.2 SRA737 ACCOUNTABILITY

Accurate records of all IMP shipments, capsules dispensed, all IMP returned by subjects, depot returns, and IMP destruction must be maintained by sites. This inventory record must be available for inspection at any time by the sponsor or sponsor's designee. The IMP supplies are to be used only in accordance with this protocol and under the supervision of the investigator.

Subjects will be asked to complete a study diary to document drug administration and to bring any remaining capsules with them to each study visit. The investigator should make every effort to ensure subjects' compliance to treatment.

Destruction of IMP and depot returns are described in the SRA737 Pharmacy Manual.

6.3 GEMCITABINE AND CISPLATIN

Gemcitabine and cisplatin will both be considered IMPs as subjects will not be prescribed either drug before enrollment on this trial. Both drugs are available commercially. The investigators will be responsible for supplying gemcitabine and cisplatin. Prior to dispensing, the gemcitabine and cisplatin will be labelled by the Pharmacy according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the EU Guide to Good Manufacturing Practice. Sufficient

quantities of either gemcitabine and/or cisplatin will be dispensed to cover the prescribed dose (as per Section 5.4.3).

Gemcitabine and cisplatin will be dispensed from the hospital pharmacy on a per subject basis.

Please refer to the relevant SmPC for the particular presentation of gemcitabine and cisplatin used for information on the formulation, administration, storage, stability and handling of the IMP.

6.3.1 GEMCITABINE RECONSTITUTION, STABILITY AND ADMINSTRATION

Gemcitabine should be administered as per standard institutional guidelines. For reconstitution and stability, please see the gemcitabine SmPC for more details.

6.3.2 CISPLATIN RECONSTITUTION, STABILITY AND ADMINSTRATION

Cisplatin should be administered as per standard institutional guidelines. For reconstitution and stability, please see the cisplatin SmPC for more details.

6.4 GEMCITABINE AND CISPLATIN ACCOUNTABILITY

Pharmacy records are to be kept of the gemcitabine and cisplatin dispensed to study subjects, the expiry date and batch number used should be recorded. These records must be available for inspection by the sponsor or sponsor's designee at any time.

7 INVESTIGATIONS SCHEDULE

In cases where a subject has investigations at a different hospital, for example weekly blood samples, then it is the investigator's responsibility to ensure he/she receives and reviews the reported results. These results must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used, and updated if changed.

7.1 PRE-TREATMENT ENROLLMENT EVALUATIONS

All required procedures must be performed only after obtaining informed consent unless the assessment was already performed within the allowable window as standard of care. Details of all evaluations/investigations for enrolled subjects, including relevant dates, required by the protocol must be recorded in the medical records.

Please also refer to the tabulated Schedule of Events in Section 7.6.

7.1.1 SCREENING EVALUATIONS: WITHIN 28 DAYS PRIOR TO ADMINISTRATION OF SRA737 (FIRST DOSE OF SRA737 FOR PK BETWEEN DAY -7 AND DAY -4)

Existing results such as radiological measurements may be used even where these investigations were performed prior to the subject's provision of informed consent for the study if they were performed within the required time window.

In Stage 2, the following will be performed/obtained as part of Pre-Screening (no time restriction relative to the start of dosing):

- Written informed consent (as detailed in Section 12.3).
- Submission of, or confirmation of availability of, suitable archival tumor tissue or fresh tumor tissue (such as with fine needle aspirate) for tumor profiling is required for all subjects.
    - For subjects being considered for enrollment to the Dose Escalation Phase, confirmation of the availability of suitable (as defined below) archival tumor tissue or planning for the acquisition of fresh tumor tissue after enrollment and before the start of treatment for **retrospective** tumor profiling is required. If the subject is enrolled, archival tissue should be requisitioned for submission by C1D1. A decision to enroll a subject into the escalation phase, for whom no archival tissue is available for retrospective tumor profiling, may be made on a case by case basis after approval by the sponsor.
    - Subjects being considered for enrollment to the Cohort Expansion Phase 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 will be performed prospectively if required to evaluate Chk1 sensitivity or otherwise performed retrospectively. If required, archival or fresh tissue should be submitted for **prospective** testing at the central laboratory as early as possible.
        - When archival material was collected more than 18 months ago, the need to collect fresh tumor tissue for participation in the study should be discussed with the sponsor.
        - Fresh tissue from triplet biopsies may also be collected from subjects during Cohort Expansion, if available, within 28 days prior to receiving the first SRA737 dose. Note: Triplet biopsies in Cohort Expansion are not mandatory.
        - Suitable archival tissue is defined as ≥ 40µm tissue, of which a minimum of 20% is of malignant origin, on approximately 11 unstained slides or in an FFPE block.

- Cytology would be an acceptable alternative to pathology for genomic analysis when clinically appropriate and technically feasible.

- If results from a previously performed determination of tumor genetics are already available for a subject, the sponsor or sponsor's designee must review and approve that data as being sufficient, based on both the type of assay used and the spectrum of genetic information available, to support enrollment without prospective confirmation by this study's central laboratory. In cases where the data is approved as sufficient to support enrollment, archival or fresh tumor tissue must still be submitted for retrospective testing by the central laboratory.

The following evaluations must be completed within **28 days before** the subject receives their first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), unless specified otherwise.

- Demographic details.
- Medical history including current diagnosis, prior treatment, concomitant conditions/diseases, previous cancers if appropriate, and baseline signs and symptoms, and concomitant treatment.
- Radiological disease assessments appropriate to the subject's disease must be performed. This may include: radiological measurements (chest computerized tomography [CT] scan, liver CT scan, abdominal CT scan, magnetic resonance imaging [MRI], x-ray; a bone scan at Screening only, if clinically indicated). Scans may be collected for potential central review.
    - Imaging should include all areas of known, suspected, or likely sites of disease.

  Note: Radiological measurements should in general be conducted within 35 days of C1D1, and thus, should be repeated when the interval is > 35 days due to a delay in start of C1D1, or for any other reason.
- ECG performed on any day within 28 days prior to administration of SRA737 for PK analysis. The QTc is to be calculated according to Fridericia's formula: $QTcF=QT / (RR)^{0.33}$ (observed QT interval divided by cube root of RR interval).
- Echocardiogram (ECHO) scan conducted within 28 days before the subject receives the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted).
- Blood for exploratory ctDNA analysis will be collected from all subjects during Screening. When prospective ctDNA tumor profiling is performed to determine eligibility, blood samples for tumor profiling may be collected during Screening, or prior to Screening if necessary.
- Tumor markers from serum or urine; if applicable (Stage 1 only)
- All serious adverse events (SAEs) must be monitored and recorded in the eCRF from the time the subject consents to any protocol specific procedure (see Section 10 for further details).
- Triplet biopsies (3 separate core needle biopsies) will be performed in subjects with accessible tumor and who provide additional consent for this procedure. Biopsies will be

taken in up to 1 subject, if available, per dose level in Dose Escalation, and subjects with accessible tumor and willingness to consent to a biopsy in Cohort Expansion. Biopsies should be obtained at the following time-points: Screening - up to 28 days prior to the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), Cycle 1 Day 2, immediately before SRA737 dosing (which should occur approximately 16-24 hours after the Cycle 1 Day 1 gemcitabine dose), Cycle 1 Day 2 at 4-6 hours post-SRA737 dose. Note: Triplet biopsies in Dose Escalation and Dose Expansion are not mandatory.

7.1.2 SCREENING EVALUATIONS: WITHIN 7 DAYS PRIOR TO ADMINISTRATION OF SRA737 (THE FIRST DOSE OF SRA737 FOR PK BETWEEN DAY -7 AND DAY -4)

The following must be performed **within 7 days before** the subject receives the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted):

- Serious AEs (an assessment of any SAEs experienced since signing of the consent).
- Concomitant treatment.
- WHO performance status.
- Complete physical examination including clinical disease assessment, as clinically relevant (ie, for subjects with clinically assessable disease).
- Laboratory tests (blood/urine/tissue samples):
    - Hematology – complete blood count (CBC) with differential count.
    - Biochemistry – sodium, potassium, adjusted calcium, phosphate, chloride, magnesium, urea, creatinine, total protein, albumin, direct and indirect bilirubin, LDH, alkaline phosphatase, alanine aminotransferase and/ or aspartate aminotransferase, glucose (non-fasting), renal function (calculated creatinine clearance [Cockroft-Gault]).
    - Pregnancy testing (WOCBP only): Serum or urine test is acceptable.
- Enrollment of the subject on the study only once the investigator has confirmed eligibility and the sponsor approves (see Section 4.2).

7.2 EVALUATIONS DURING THE TRIAL

Subjects should fast for 2 hours before and 1 hour after each dose of SRA737.

7.2.1 FIRST DOSE OF SRA737 FOR PK (DAY -7 TO DAY -4)

The sponsor may eliminate or modify the requirements for the Day -7 to Day -4 visit once sufficient data to evaluate the single-dose PK of SRA737 have been collected and analyzed. If this occurs, the modified requirements will be documented by an update to the Laboratory Manual.

Subjects will remain as in-patient for 24 to 48 hours (if required to facilitate the collection of PK draws) after their first dose of SRA737 between Day -7 and Day -4.

The following assessments will be conducted on the first day of SRA737 dosing unless performed within the preceding 3 days or unless noted otherwise below. Dosing should be delayed if eligibility criteria are no longer met.

- Adverse events and concomitant medications: Adverse events must be monitored and recorded in the eCRF from the first dose of SRA737 administration (or gemcitabine if the SRA737 dose for PK is omitted). At each visit, before each SRA737 administration, an assessment of any AE experienced since the previous visit must be made by the investigator, Research Nurse or suitably qualified member of the investigator's team.
    - The start and stop dates of the AE together with the relationship of the event to the SRA737 must be recorded in the medical records.
    - All AEs must be graded according to NCI-CTCAE v4.03. (See Section 10 for further details regarding AE reporting requirements).
    - Any concomitant treatment must be recorded in the medical records. (See Section 10 for further details regarding AE reporting requirements.)
- Height, weight, body surface area (BSA) will be required for gemcitabine and cisplatin dose calculation, WHO performance status, temperature, seated blood pressure (BP) and pulse rate. If a subject's BSA is > 2.2 m^2, the dose can be calculated using a BSA of 2.2 m^2 or the actual BSA can be used, depending on Institutional guidelines.
- Laboratory tests (blood/urine/tissue collection for):
    - Hematology: detailed in Section 7.1.2. Predose.
    - Biochemistry: detailed in Section 7.1.2. Predose.
    - Troponin: Troponin T or I (subject should be followed for the same parameter). Predose.
    - Tumor markers (serum or urine), if applicable based on standard institutional practice for the type of malignancy being followed (for example, PSA and CTCs for subjects with prostate cancer, CA-125 for subjects with ovarian cancer). Predose.
    - Urine pregnancy testing (WOCBP only): Serum or urine test is acceptable. Predose.
    - Urinalysis – glucose, protein, and blood. Predose.
    - Blood collected and submitted for retrospective, exploratory Comet assay in up to 3 subjects in Dose Expansion Cohort. Schedule in Section 7.7.
    - For subjects without adequate archival tissue, a biopsy to obtain fresh tumor tissue for tumor profiling must be performed prior to the first dose of SRA737 (or

gemcitabine if the SRA737 dose for PK is omitted), unless it was performed during Screening as described in Section 7.1.1. For subjects with archival tissue, requisition of archival tissue for tumor profiling is required and submission of suitable archival tumor tissue should occur by C1D1, unless submitted during Screening. Tumor profiling may include exploratory determination of microsatellite instability status, where relevant.

- PK Assessments: 0 (predose), 1, 2, 4, 6, 8, 12, 24, and 48 hours after the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted). For subjects in the Dose Expansion Cohort, the12-hour time point may be omitted with sponsor's approval.

If the Day -7 to Day -4 visit is eliminated, the following assessments and sample collections should be added pre-dose on Cycle 1 Day 1:

- Tumor markers (serum or urine), if applicable based on standard institutional practice for the type of malignancy being followed (for example, PSA and CTCs for subjects with prostate cancer, CA-125 for subjects with ovarian cancer).
- Urine pregnancy testing (WOCBP only): Serum or urine test is acceptable.
- Height, weight, body surface area (BSA) will be required for gemcitabine and cisplatin dose calculation. If a subject's BSA is > 2.2 m^2, the dose can be calculated using a BSA of 2.2 m^2 or the actual BSA can be used, depending on Institutional guidelines
- For subjects without adequate archival tissue, a biopsy to obtain fresh tumor tissue for tumor profiling must be performed prior to the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), unless it was performed during Screening as described in Section 7.1.1. For subjects with archival tissue, requisition of archival tissue for tumor profiling is required and submission of suitable archival tumor tissue should occur by C1D1, unless submitted during Screening. Tumor profiling may include exploratory determination of microsatellite instability status, where relevant.

7.2.2 STANDARD EVALUATIONS FOR EACH CYCLE

The standard evaluations and sample collections for each cycle are listed below:

- Adverse events and concomitant medications (detailed in Section 7.2.1).
- Symptom directed physical examination: if clinically indicated, predose Day 1 of each cycle.
- WHO performance status at predose Day 1 of each cycle.
- Temperature, pulse rate, seated BP at predose Day 1 and 8 of each cycle in Stage 1 or predose Day 1, 8 and 15 of each cycle Stage 2.
- Weight and BSA must be repeated prior to Day 1 of each cycle to calculate the dose required for gemcitabine plus cisplatin or gemcitabine administration. The dose of gemcitabine and cisplatin will only need to be recalculated should there be a 10% or greater

change in weight (unless required by local pharmacy procedures) or where doses are reduced because of toxicity.

- Compliance: Subjects will be provided with a diary card and will be instructed to record the time they take SRA737 as well as details of any missed doses. At each visit, the subject's most recent diary card should be collected and checked for completeness and compliance in taking SRA737.
- ECG (locally read): Day 1 predose for Cycles 1, 2, and then every third subsequent cycle. Also required in first cycle of intra-subject dose escalation.
- ECHO scan: Cycle 2 Day 1 only and then all subsequent cardiac monitoring should be done at investigator's discretion. The modality for this assessment should be consistent with the modality used at baseline (prior to the first dose of SRA737 [or gemcitabine if the SRA737 dose for PK is omitted]).
- Laboratory tests (blood/urine samples): Blood draws for laboratory tests will be performed at predose. Samples should be collected on the days indicated below, unless an acceptable window for sample collection is stated, eg, within 72 hours prior to the first dose of gemcitabine each cycle for hematology, biochemistry, and troponin. Subjects must be instructed not to take SRA737 prior to attending the clinic on those days they will be required to attend for routine blood samples. SRA737 should only be taken once all clinic assessments have been completed:
    - Hematology and Biochemistry (detailed in Section 7.1.2): 72 hours prior to the first dose of gemcitabine of each cycle
        - Stage 1 Cycle 1 onwards: Days 1 and 8.
        - Stage 2 Cycle 1 onwards: Days 1, 8, and 15.

      Note: Clinical hematology laboratory assessments should also be performed at Days 3, 10, and 18 or 19 in Cycle 1 only. These samples may also be collected in subsequent cycles if clinically indicated due to toxicity. In the case of intra-subject dose escalation, more frequent hematology laboratory assessments should be considered during the first cycle following escalation utilizing the same Cycle 1 assessment schedule.
    - Troponin: Troponin T or I
        - Cycle 1 Days 1 (within 72 hours prior to dose) and on Day 8.
        - Cycle 2 Day 1 (within 72 hours prior to dose).
        - Cycle 6 Day 1 (within 72 hours prior to dose).
    - Urinalysis (glucose, protein and blood): Day 1 of each cycle (may be performed up to 72 hours prior to the first dose of gemcitabine of each cycle).
    - Tumor markers (serum or urine), if applicable based on standard institutional practice for the type of malignancy being followed: every 6 weeks (± 1 week) for Stage 1 and every 4 weeks (± 1 week) for Stage 2.

- Follow-up triplet biopsies (3 separate core needle biopsies) will be performed for appropriate subjects (Refer to “Triplet biopsies” in Section 7.1.1) on Cycle 1 Day 2, immediately before SRA737 dosing (which should occur approximately 16-24 hours after the Cycle 1 Day 1 gemcitabine dose), Cycle 1 Day 2 at 4-6 hours post-SRA737 dose. Note: Triplet biopsies in Dose Escalation and Dose Expansion are not mandatory. See Section 8.3 for more information.
- PBMC for exploratory biomarker analyses in up to 3 subjects per dose level in Dose Escalation at Cycle 1 Days 1, 2, and 3.
- Blood for exploratory Comet assay in up to 3 subjects per dose level in Dose Escalation at Cycle 1 Days 1, 2, and 3.

- PK Assessments (see Section 7.7): Cycle 1 Day 1 at pre-dose, Cycle 1 Day 10 at pre-dose, and 1, 2, 4, 6, 8, and 12 hours after SRA737 dose. For subjects in the Dose Expansion Cohort, the 12-hour time point may be omitted with sponsor’s approval. For subjects in Stage 2, additional PK samples will be taken at Cycle 1 Day 8 at pre-dose and Cycle 1 Day 15 at pre-dose.
- Radiological disease assessments: The same method of assessment as recorded at baseline is required throughout the trial (refer to Section 9 for more information) repeated every 8 weeks (± 1 week) (every 6 weeks for Stage 1).
- Clinical disease assessments (if applicable): Repeated at every 6 weeks for Stage 1 and every 4 weeks (± 1 week) for Stage 2.

7.3 SAFETY FOLLOW-UP VISIT

If a subject discontinues investigational product for any reason, the SFU visit evaluations should be performed 30 ± 7 days after the last dose of SRA737. If the subject begins a new anticancer treatment within 30 days of the last administration of study drug, the SFU Visit should be performed prior to initiation of the new anticancer treatment, if possible. The following investigations should be performed wherever possible:

- Assessment of AEs (also see Section 7.2.1) and review of concomitant medications
    - Monthly follow up required ONLY for those AEs and SAEs considered drug related (highly probable, probable or possible) and present at Safety Follow-up visit. Monthly follow-up to continue until resolution, return to baseline, stabilization or subject discontinues from study.
- A symptom directed physical examination including WHO performance status, temperature, pulse rate, seated BP and weight;
- Laboratory tests (blood/urine samples):
    - Hematology tests (detailed in Section 7.1.2).
    - Biochemistry tests (detailed in Section 7.1.2).

  - Troponin T or Troponin I (where applicable, detailed in Section 7.1.2).
  - Urinalysis (detailed in Section 7.1.2).
  - Urine or serum pregnancy test.
  - Tumor markers (serum or urine), if applicable based on standard institutional practice for the type of malignancy being followed.
- ECG (locally read).
- ECHO scan (modality for this assessment should be consistent with the modality used at baseline).
- Clinical and radiological (if applicable) assessment of disease: Continue clinical disease assessments at every 4 weeks and radiological disease assessments at every 8 weeks unless PD was indicated on a previous study scan.
- Compliance: the subject's most recent diary card must be collected and checked for completeness and compliance in taking SRA737.

7.4 LONG TERM FOLLOW-UP

For subjects who have stopped study treatment but have not progressed and have not initiated subsequent cancer therapy, clinical, serum, and radiological disease assessments will continue to be captured every 16 weeks (± 2 weeks) until the subject withdraws from the study or until documented disease progression, or until the initiation of new anticancer therapy. Additional contact may be made as requested by the sponsor or the investigator to obtain disease and survival updates on an as-needed basis until the subject discontinues from the study. The following data will be collected:

- Serious adverse events assessed by the investigator as related to SRA737.
- First subsequent cancer therapy (if applicable).
- Tumor markers (serum or urine; if applicable), unless PD was previously documented.
- Clinical disease assessments, unless PD was previously documented.
- Radiographic disease assessments, unless PD was previously documented.
- Disease and survival updates, where available

7.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the originally scheduled date as possible. Based on the investigator's judgment, an exception can be made when rescheduling becomes medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation may be omitted.

7.6 SCHEDULE OF EVENTS

The schedule of events for Stage 1 is provided in Table 8, and the schedule of events for Stage 2 is provided in Table 9.

Table 8. Schedule of Events for Stage 1

Observation/Investigation	Pre-treatment evaluations		First dose for PK	Treatment phase - Triple Combination (Stage 1) Evaluations for each day/ **21**-day cycle						Safety Follow-Up	LTFU
	-28 days of 1st dose for PK (Screening)	**-7 days of 1st dose for PK (Screening)**	**Day -7 to Day -4**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 9**	**Day 10**	**30 ±7 days after last IMP dose**	**Every 8 ± 3 Weeks**
Written informed consent	X										
Demographics	X										
Medical history	X										
Adverse event evaluation	SAEs from consent. AEs from first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted). Continual Review									X (a)	X (b)
Concomitant treatments	X	X	Continually review							X	X (b)
Radiological disease assessment (c)	X			End of every 6 weeks (±1 week)						X	X
Tumor markers (serum or urine; if applicable)	X			End of every 6 weeks (±1 week)						X	X
Availability of historical tumor biopsy (d)	X										
Pregnancy test (e)		X		C1						X	
Clinical disease assessment (if applicable)		X		End of every 6 weeks (±1 week)						X	X
Physical examination (f)		Complete		Symptom-directed, repeat as clinically indicated						X	
Temperature, blood pressure and pulse rate		X	X	X			X			X	
Height		X									
Weight		X		X						X	
Body surface area (BSA) (g)		X		X							
WHO performance status		X		X						X	
Bloods for hematology and biochemistry (h, i)		X	X	X			X			X	
Troponin T or I (j)		X	X	X	C1	C1	C1	C1	C1	X	
Urine sample for urinalysis		X		X						X	
Renal Function		X		X							
Electrocardiogram (ECG) (k)		X	X	X	C1	C1	C1	C1	C1	X	
Echocardiogram (ECHO)		X		C2D1, then as clinically indicated						X	
Gemcitabine administration				X			X				
Cisplatin administration				X							
SRA737 administration			X		X	X		X	X		
Tumor biopsy (l)					C1	C1					
Blood for PK (m)			X	Refer to laboratory manual							
Blood for PDn (m)			X	Refer to laboratory manual							

a. Monthly follow up is required for all SAEs and for those AEs considered drug related (highly probable, probable or possible) and present at the Safety Follow-up visit. Monthly follow-up will continue until the event resolves, returns to baseline, stabilizes, or the subject discontinues from study.
b. SAEs assessed by the investigator as related to SRA737 and start of new anticancer therapy will also be collected.
c. Radiological disease assessment: Unless performed within previous 28 days or PD seen on previous study scan (one bone scan will be done at Screening only, if clinically indicated).
d. Historical tumor biopsy: If historical or pre-study biopsy material is available and P53 expression status is not known, this will be requested for retrospective analysis of P53 either during or after the end of the study.
e. Pregnancy test: For female patients of child bearing potential to be performed within 7 days of the first dose of SRA737 for PK
f. Physical exam: Complete physical examination to be performed at baseline. For all subsequent examinations, a symptom directed physical examination is to be performed on Day 1 of each cycle before gemcitabine/cisplatin or gemcitabine administration if clinically indicated.
g. BSA: Screening weight can be used to calculate BSA for Cycle 1
h. Hematology and Biochemistry: Clinical laboratory assessments should be performed on Days 1 and 8 in Stage 1 and on Days 1, 8 and 15 in Stage 2. Laboratory tests can be performed up to 72 h prior to the first dose of gemcitabine of each cycle.
i. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 7 after the onset of the event to determine if a DLT has occurred. Continue close monitoring until resolution to Grade 3 or less.
j. Troponin: Subjects should follow the same parameter (troponin T or I) assessed at baseline. Troponin assessment should be performed within 7 days of the first dose of SRA737 for PK, before first dose of SRA737 for PK, before dosing on Cycle 1 Days 1, 2, 3, 8, 9, and 10, then on Day 1 of all subsequent cycles, and at the SFU visit.
k. ECGs: All ECGs will be conducted at Screening and then pre-dose at Day 1 of Cycles 1 and 2, and then pre-dose Day 1 at each third subsequent cycle and end of study. For Stage 1: Cycle 1 Day 1 (pre-dose), Cycle 1 Days 2 and 3 (4 h post-dose), Cycle 1 Day 8 (pre-dose), Cycle 1 Days 9 and 10 (4 h post-dose). Then pre-dose on Day 1 of all subsequent cycles. The Cycle 1 ECG schedule should also be followed for the first cycle of intra-subject dose escalation.
l. Tumor biopsies (Expansion cohorts only): Biopsies for PDn assessment will be taken on Cycle 1 Days 2 and 3 in Stage 1. Biopsies will be mandatory for all subjects in the ‘All Solid Tumor’ expansion cohorts and optional for subjects in the NSCLC (Stage 1) cohort.
m. PK/PDn assessments: Refer to the Laboratory Manual for specific timings of PK and PDn sample collection.

Table 9. Schedule of Events for Stage 2 (Dose Escalation and Cohort Expansion)

Observation/Investigation	Screening evaluations – to be within noted window of first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted)			First SRA-737 Dose (a)	Treatment phase - Double Combination (Stage 2) Evaluations for each day/ 28-day cycle									Safety Follow-Up	LTFU
	N/A	28 days	7 days	Single Day Day -7 to Day -4	D1	D2	D3	D8	D9	D 10	D 15	D 16	D 17	30 ± 7 days after last dose of IMP	Every 16 ± 2 Weeks
Written informed consent	X														
Demographics		X													
Medical history		X													
Adverse event evaluation	SAEs from consent. AEs from first dose of SRA737. Continual Review													X (b)	X (c)
Concomitant treatments		X	X	Continually review										X	X (c)
Radiological disease assessment (d)		X			End of every 8 weeks (±1 week)									X	X
Tumor markers (serum or urine; if applicable)				X	End of every 4 weeks (±1 week)									X	X
Submission/avail. of archival tumor tissue - tumor profiling (e)	X			X											
Blood for ctDNA (f)	X														
Pregnancy test (g)			X	X										X	
Clinical disease assessment (if applicable)			X		End of every 4 weeks (±1 week)									X	X
Physical examination (h)			Complete		Symptom directed, repeat as clinically indicated										
Temperature, BP and pulse			X	X	X			X			X			X	
Height				X											
Weight				X	X									X	
Body surface area (i)				X	X										
WHO performance status			X	X	X									X	
Bloods for hematology and biochemistry (j, k)			X	X	X		C1	X		C1	X			X	
Troponin (l)				X	C1 C2 C6			C1						X	
Urine sample for urinalysis				X	X									X	
Electrocardiogram (ECG) (m)		X			X									X	
Echocardiogram (ECHO) (n)		X			C2									X	
Gemcitabine administration					X			X			X				
SRA737 administration				X		X	X		X	X		X	X		

Observation/Investigation (continued)	Screening evaluations – to be within noted window of first dose of SRA737			First SRA-737 Dose (a)	Treatment phase - Double Combination (Stage 2) Evaluations for each day/ 28-day cycle									Safety Follow-Up	LTFU
	N/A	28 days	7 days	Single Day Day -7 to Day -4	D1	D2	D3	D8	D9	D 10	D 15	D 16	D 17	30 ± 7 days after last dose of IMP	Every 8 ± 3 Wks
Triplet Tumor biopsy(o)		X				C1									
Blood for PK (p)				Refer to Section 7.7 and Laboratory Manual											
Blood for PDn (q)					Refer to Section 7.7 and Laboratory Manual										
SRA737 Diary Card					Should be reviewed at each visit									X	

a. Assessments scheduled to occur for the first dose of SRA737 (given on a single day between Day -7 and Day -4) will be conducted on the first day of dosing unless performed within the 3 days prior or unless noted otherwise for the specific assessment. The sponsor may eliminate or modify the requirements for the Day -7 to Day -4 visit once sufficient data to evaluate the single-dose PK of SRA737 have been analyzed.

b. Monthly follow up is required for all SAEs and for those AEs considered drug related (highly probable, probable or possible) and present at the Safety Follow-up visit. Monthly follow-up will continue until the event resolves, returns to baseline, stabilizes, or the subject discontinues from study.

c. SAEs assessed by the investigator as related to SRA737, and start of new anticancer therapy will also be collected.

d. Radiological disease assessment: assessments will be performed every 8 weeks (± 1 week) and then in long-term follow-up every 16 weeks (± 2 weeks). Assessments will stop when PD is seen on previous study scan.

e. Availability of suitable archival tumor tissue or planned biopsy for fresh tumor tissue acquisition for tumor profiling must be confirmed: Fresh tissue is strongly preferred when historical material was collected more than 18 months ago. Submission prior to or during Screening (the 28-day window does not apply) with confirmation of positive results is required for Cohort Expansion subjects; Archival tissue should be requisitioned for submission by C1D1 for Dose Escalation subjects. See Section 7.1.1 for more information.

f. Blood for exploratory ctDNA analysis will be collected from all subjects during Screening. When prospective ctDNA tumor profiling is performed to determine eligibility, blood samples for tumor profiling may be collected during Screening, or prior to Screening if necessary.

g. Pregnancy test: For WOCBP, must be performed within 7 days prior to the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), predose for the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), and at SFU visit. More frequent pregnancy tests may be conducted per local regulatory requirements. Urine or blood test is acceptable.

h. Physical exam: Complete physical examination to be performed at baseline. For all subsequent examinations, if clinically indicated, a symptom directed physical examination may be performed on Day 1 of each cycle before gemcitabine administration.

i. BSA: Screening weight can be used to calculate body surface area for Cycle 1.

j. Hematology and Biochemistry: Clinical laboratory (hematology and biochemistry) assessments should be performed within 7 days of the first dose of SRA737, at predose of first dose of SRA737 (where applicable), and on Days 1, 8 and 15 of each cycle. In addition, clinical hematology laboratory assessments should also be performed at Days 3, 10, and 18 or 19 in Cycle 1 only; these samples may also be collected in subsequent cycles if clinically indicated due to toxicity. Laboratory tests can be performed up to 72 hours prior to the first dose of gemcitabine of each cycle. In

the case of intra-subject dose escalation, more frequent hematology laboratory assessments should be considered during the first cycle following escalation utilizing the same Cycle 1 assessment schedule

k. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 7 after the onset of the event to determine if a DLT has occurred. Continue close monitoring until resolution to Grade 3 or less.

l. Troponin: Subjects should follow the same parameter (troponin T or I) assessed at baseline. Troponin assessment should be performed predose for first dose of SRA737 (where applicable), before gemcitabine dosing on Cycle 1 Days 1 and 8, on Day 1 of Cycles 2 and 6, and at the SFU visit.

m. ECGs: All ECGs must be conducted within 28 days of first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), at predose of gemcitabine Day 1 of Cycles 1 and 2, and then predose of gemcitabine Day 1 at each third subsequent cycle, the first cycle of any intra-subject dose escalation, and at SFU visit.

n. ECHO: ECHO must be conducted within 28 days of first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), at Cycle 2 Day 1 (± 3 days) and repeated as clinically indicated, and at SFU visit. The modality for this assessment should be consistent with the modality used at baseline.

o. Triplet biopsies (3 separate core needle biopsies) will be performed in subjects with accessible tumor and who provide additional consent for this procedure. Biopsies will be taken in up to 1 subject, if available, per dose level in Dose Escalation, and subjects with accessible tumor and willingness to consent to a biopsy in Cohort Expansion. Biopsies should be obtained at the following time-points: Screening - up to 28 days prior to the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), Cycle 1 Day 2, immediately before SRA737 dosing (which should occur approximately 16-24 hours after the Cycle 1 Day 1 gemcitabine dose), Cycle 1 Day 2 at 4-6 hours post-SRA737 dose. Note: Triplet biopsies in Dose Escalation and Dose Expansion are not mandatory. Refer to the Laboratory Manual and protocol Sections 7.7 and 8.3 for more information.

p. PK assessments: Refer to the Laboratory Manual for specific timings of PK sample collection (see Section 7.7 also).

q. PDn assessments: Refer to the Laboratory Manual for more information (see Section 7.7 also).

7.7 STAGE 2 SCHEDULE OF SECONDARY AND EXPLORATORY ASSESSMENTS

Table 10. Schedule for Stage 2 Secondary and Exploratory Assessments

SRA737+Gem		Triplet Biopsy (PDn Biomarker)[a]	PBMC (PDn Biomarker)[a]	Comet Assay PDn	SRA737 PK (Blood)[b]
Within 28 days prior to the first dose of SRA737	Predose	X			
Day -7 to Day -4 (First dose of SRA737 for PK)[b, c]	Predose			X [e]	X
	1h ±15min				X
	2h ±15min				X
	4h ±15min				X
	6h ±15min				X
	8h ±15min				X
	12h ±15min			X [e]	X [d]
	24h ±1h			X [e]	X
	48h ±1h			X [e]	X
Cycle 1 Day 1	Predose		X	X [e]	X
	6h post-Gem		X	X [e]	
Cycle 1 Day 2	Pre-SRA737	X (16-24 h post-Gem)	X	X [e]	
	4-6h ±15min post-SRA737	X	X	X [e]	
Cycle 1 Day 3	Predose		X	X [e]	
	4-6h ±15min post-SRA737		X	X [e]	
Cycle 1 Day 8	Predose				X
Cycle 1 Day 10	Predose				X
	1h ±15min				X
	2h ±15min				X
	4h ±15min				X
	6h ±15min				X
	8h ±15min				X
	12h ±1h				X [d]
Cycle 1 Day 15	Predose				X

Note: Pharmacodynamic and PK assessments for Stage 1 can be found in the Laboratory Manual.

(a) Triplet biopsies (3 separate core needle biopsies) will be performed in subjects with accessible tumor and who provide additional consent for this procedure. Biopsies will be taken in up to 1 subject, if available, per dose level in Dose Escalation, and subjects with accessible tumor and willingness to consent to a biopsy in Cohort Expansion. Biopsies should be obtained at the following time-points: Screening - up to 28 days prior to the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted), Cycle 1 Day 2, immediately before SRA737 dosing (which

should occur approximately 16-24 hours after the Cycle 1 Day 1 gemcitabine dose), Cycle 1 Day 2 at 4-6 hours post-SRA737 dose. Note: Triplet biopsies in Dose Escalation and Dose Expansion are not mandatory. Refer to the Laboratory Manual and protocol Sections 7.7 and 8.3 for more information.

(b) The sponsor may reduce the requirement for PK sampling once sufficient data to evaluate the PK of SRA737 have been collected and analyzed. Any modified requirements will be documented by an update to the Laboratory Manual.

(c) If required to facilitate the collection of PK, subjects may remain as in-patients for at least 24 hours after their first dose of SRA737 between Day -7 and Day -4.

(d) With sponsor's approval, subjects in the Cohort Expansion may elect to not participate in the 12 hour PK draws during the first dose of SRA737 for PK (where SRA737 is administered on 1 day between Day -7 and -4) and at Cycle 1 Day 10.

(e) Blood for Comet assay will be collected at up to 4 time points during the first dose of SRA737 for PK (where SRA737 is administered on 1 day between Day -7 and -4) in up to 3 subjects in the Cohort Expansion. Blood for Comet assay will be collected during Dose Escalation at Cycle 1 Days 1-3 in up to 3 subjects per dose level.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Pharmacokinetic and PDn assessments for Stage 1 can be found in the Laboratory Manual.

8.1 SRA737 PHARMACOKINETICS

Subjects will undergo PK evaluation at several time points throughout the study (see Section 7.7 for timing).

Approximately 2 mL of blood will be collected from all subjects at up to 10 time points taken over a 48-hour time period on Day -7 to -4 (First dose of SRA737 for PK) and up to 8 time points taken over a 24-hour period at Cycle 1 Day 10 for Stage 2. On Day 1 of Cycle 1 a PK sample will be taken prior to chemotherapy dosing. If an alternative schedule of SRA737 is tested, the time points for PK assessments may need to be altered. If this occurs, the number of PK assessments will not exceed 20 time points between Day 1 and Day 22 in Cycle 1, or 10 within a 24-hour period. The alternative sampling schedule will be provided in the Laboratory Manual.

The sponsor may reduce the requirement for PK sampling, including elimination of the Day -7 to Day -4, visit once sufficient data to evaluate the PK of SRA737 have been collected and analyzed. Any modified requirements will be documented by an update to the Laboratory Manual.

If one of the time points detailed in the in Section 7.7 (or Laboratory Manual) is missed, a sample should be taken as soon as possible.

Please see Laboratory Manual for more information on the sample collection, specific timings, handling, and storage.

8.2 GENETIC ALTERATIONS IN TUMOR TISSUE OR CIRCULATING TUMOR DNA

To identify genetic alternations implicated in the Chk1 pathway sensitivity including genetic indicators of loss of the integrity of the G1/S checkpoint and replicative stress, oncogenic drivers, or genetic alterations in components of the DDR and repair, archival or fresh tumor tissue will be collected during Screening or at Baseline. For the Dose Escalation Phase, samples may be stored and tumor profiling may be performed retrospectively. For the Cohort Expansion Phase, tumor profiling results must be available to determine eligibility. Blood for ctDNA will be collected from all subjects during Screening for future retrospective analysis.

Subjects enrolled prior to the implementation of Amendment v5.0 were required to submit blood for gemcitabine and cisplatin PK assessments and hair follicles for PDn assessments. As of Amendment v5.0, these specimens were no longer collected. The schedule of assessments for triplet biopsies, PBMCs, and COMET analysis has been modified as described in the subsequent sections below.

8.3 TRIPLET BIOPSIES

Triplet biopsies (3 separate core needle biopsies) will be performed in subjects with accessible tumor and who provide additional consent for this procedure. Biopsies will be taken in up to 1 subject, if available, per dose level in Dose Escalation, and subjects with accessible tumor and willingness to consent to a biopsy in Cohort Expansion. Biopsies should be obtained at the following time-points:

- Screening - up to 28 days prior to the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted)
- Cycle 1 Day 2, immediately before SRA737 dosing (which should occur approximately 16-24 hours after the Cycle 1 Day 1 gemcitabine dose)
- Cycle 1 Day 2 at 4-6 hours post-SRA737 dose.

Note: Triplet biopsies in Dose Escalation and Dose Expansion are not mandatory.

Inhibition of Chk1 in triplet tumor samples will be measured in fresh frozen tumor samples according to agreed SOPs and validated methods. One biopsy per time point will be used for markers including but not limited to pSer296Chk1, pSer317Chk1, and total Chk1.

8.4 PBMCS FOR EXPLORATORY BIOMARKERS ANALYSES

Immunofluoresence and confocal microscopy will be used to measure a range of PDn biomarkers in PBMCs indicative of Chk1 inhibition and DNA damage. Blood for these assays will be collected in Dose Escalation at Cycle 1 Days 1 to 3 from up to 3 subjects per dose level. See Section 7.7 for specific sample timings and the Laboratory Manual for more information on the sample collection, handling, and storage.

8.5 COMET ASSAY

The Comet assay, a single cell gel electrophoresis assay, will be used as an exploratory analysis to measure DNA damage response in blood. Blood for this assay will be collected in Dose Escalation at Cycle 1 Days 1 to 3 from up to 3 subjects per dose level and, in up to 3 Cohort Expansion subjects, at the first dose of SRA737 for PK (single dose of SRA737 given between Day -7 and Day -4). See Section 7.7 for specific sample timings and the Laboratory Manual for more information on the sample collection, handling, and storage.

9 ASSESSMENT OF EFFICACY

9.1 MEASUREMENT OF DISEASE

Disease must be measured according to the RECIST v1.1 criteria in Appendix 2 or the most appropriate method for the subject's indication. For example, subjects with metastatic castration resistant prostate cancer should be followed with PSA and CTCs every 4 weeks ± 1 week.

9.2 TIMING AND TYPE OF TUMOUR ASSESSMENTS

A thorough clinical and radiological evaluation of the malignancy, as judged appropriate by the investigator, and consistent with the protocol, must be performed before a subject receives their first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted). The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

All radiological assessments must be performed within 4 weeks before starting treatment with SRA737 on Day -7 to -4. All clinical measurements and serum tumor markers to assess response must be performed within **1** week of their first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted).

The determination of CR or PR is required to be confirmed by a subsequent assessment at least 4 weeks after the original determination. Stable disease determination requires that the relevant criteria be met at least once, a minimum of 6 weeks after study entry.

Copies of any radiological assessment must be available for external independent review if requested by the sponsor or sponsor's designee.

9.2.1 BASELINE EVALUATIONS

These must include radiological measurements of lesions appropriate to the subject's disease. This may include: chest CT scan, liver CT scan, abdominal CT scan, magnetic resonance imaging (MRI), X-ray, bone scan and/or other radiological measurements as clinically indicated or clinical measurements as appropriate (eg, assessment of palpable lesions or measurement of tumor markers). All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by color photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses (see Section 1.2.1 of Appendix 2)

9.2.2 EVALUATIONS DURING STUDY

Tumor assessments must be repeated every 6 weeks (± 1 week) in Stage 1. In Stage 2, assessments will be performed every 8 weeks (± 1 week) and then in long-term follow-up every 16 weeks (± 2 weeks). Assessments may be performed more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly on the scan reports. All nonmeasurable lesions noted at baseline must be noted on the scan report as present or absent.

All subjects who discontinued treatment for reasons other than PD must be re-evaluated at the time of treatment discontinuation, unless a tumor assessment was performed within the previous 4 weeks. Subjects will be followed for progression until disease progression, the start of alternative anticancer therapy, or withdrawal from trial.

It is the responsibility of the PI to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the nontarget lesions in accordance with RECIST v1.1 criteria.

9.3 TUMOUR RESPONSE

All subjects who have measurable disease, receive at least one cycle of SRA737 and have a baseline and at least 1 postbaseline assessment of disease will be evaluable for response. Subjects who develop clear evidence of PD without a formal disease assessment and those without a formal disease assessment before study withdrawal will be considered non-responders. Complete responses and PRs are required to be confirmed by a subsequent assessment at least 4 weeks later. To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once and at least 6 weeks after the initial dose of the SRA737 is given.

Should rapid tumor progression occur before the completion of 3 weeks of treatment in Stage 1 and 4 weeks of treatment in Stage 2, the subject will be classified as having early progression.

Tumor response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by the sponsor may undertake an independent review of the investigator’s assessed objective responses (CR and PR). Any independent reviewer’s assessment will also be documented in the final clinical study report along with the assessment made by the investigator. The eCRF will reflect the investigator’s opinion.

9.3.1 RECORDING OF RESPONSE IN THE ECRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF.

9.3.2 OTHER DEFINITIONS OF OUTCOME

- Toxic death: Any death to which drug toxicity is thought to have a major contribution.
- Early death: Death during the first 28 days of treatment.

10 ASSESSMENT OF SAFETY

10.1 ADVERSE EVENT DEFINITIONS

10.1.1 ADVERSE EVENT

An AE is any untoward, undesired or unplanned medical occurrence in a subject administered an IMP, a comparator product or an approved drug.

An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- Any recurrence of an intermittent preexisting condition at a frequency or severity that differs from the subject's historical experience.
- Any injury or accident occurring during the screening, on-treatment, or post-treatment periods. If a medical condition is known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs.
- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (eg, clinical chemistry, hematology, urinalysis) or investigational abnormality (eg, ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (eg, anemia) not the laboratory result (eg, decreased hemoglobin) should be recorded.
- An AE occurring from an overdose of an IMP, whether accidental or intentional.
- An AE occurring from lack of efficacy of an IMP, for example, if the investigator suspects that a drug batch is not efficacious or if the investigator suspects that the IMP has contributed to disease progression.
- An AE occurring from misuse of a sponsor study drug.
- An AE associated with the discontinuation of the use of a sponsor study drug.

Note: A preexisting condition is a clinical condition that is diagnosed before the subject receives the first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted).

10.1.2 SERIOUS ADVERSE EVENTS

A SAE is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life threatening*;
- requires in subject hospitalization or prolongs existing in subject hospitalization (some hospitalizations are exempt from SAE reporting – eg, hospital admissions planned prior to

the subject entering the trial; overnight stays for planned procedures such as blood transfusions (Section 10.3.1);

- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect in the offspring of a subject who received the investigational medicinal product;
- is any other medically important event**.

*A life threatening event is defined as an event when the subject was at substantial risk of dying at the time of the AE, or use or continued use of the device or other medical product might have resulted in the death of the subject.

**A medically important event is defined as any event that may jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

For fatal SAEs, wherever possible report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term. When available the autopsy report will be provided to the sponsor.

Other reportable events that must be treated as SAEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a subject or a subject's partner during treatment with an IMP or occurring within 6 months of the last IMP administration, must be reported to the Pharmacovigilance Department in the same timelines as an SAE. These should be reported even if the subject is withdrawn from the trial.
- Overdose with or without an AE.
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.
- Abuse or misuse.
- Medication error (any unintentional error in the dispensing or administration of an IMP).

10.1.3 SUSPECTED, UNEXPECTED, SERIOUS ADVERSE REACTIONS

All AEs and SAEs will be assessed by the sponsor for seriousness, causality and expectedness. The study sponsor is required to expedite reports to regulatory authorities worldwide relating to suspected unexpected serious adverse reactions consistent with relevant legislation or

regulations, including the applicable US FDA Code of Federal Regulations, the European Commission Clinical Trials Directive (2001/20/EC, and revisions), and other country specific legislation or regulations.

10.1.4 DETERMINING ADVERSE EVENT CAUSALITY

The relationship of an AE to the IMP is determined as follows:

Highly probable	1. Starts within a time related to the IMP administration and 2. No obvious alternative medical explanation
Probable	3. Starts within a time related to the IMP administration and 4. Cannot be reasonably explained by known characteristics of the subject's clinical state
Possible	5. Starts within a time related to the IMP administration and 6. A causal relationship between the IMP and the AE is at least a reasonable possibility
Unlikely	7. The time association or the subject's clinical state is such that the trial drug is not likely to have had an association with the observed effect
Not related	8. The AE is definitely not associated with the IMP administered

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The investigator must endeavor to obtain sufficient information to determine the causality of the AE (ie, IMP, other illness, progressive malignancy, etc.) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken in to account when assessing the causality of an AE:

- Previous experience with the IMP and whether the AE is known to have occurred with the IMP;
- Alternative explanations for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding effects;
- Timing of the events between administration of the IMP and the AE;
- IMP blood levels and evidence, if any, of overdose;
- De-challenge, that is, if the IMP was discontinued or the dosage reduced, what happened to the adverse reaction?;
- Re-challenge, that is, what happened if the IMP was restarted after the AE had resolved?

10.1.5 EXPECTEDNESS

Assessment of expectedness for SRA737 will be made by the sponsor or sponsor designee's Pharmacovigilance Department against the current version of the investigator's Brochure.

10.2 EVALUATING AND RECORDING ADVERSE EVENTS

10.2.1 SCREENING FAILURES

For subjects who fail screening, SAEs must be reported to the sponsor or sponsor designee's Pharmacovigilance Department, from the date of consent until the date the subject is confirmed as ineligible.

10.2.2 DOCUMENTATION OF ADVERSE EVENTS

For eligible subjects, SAE collection and monitoring will commence at the time the subject gives their written consent to participate in the trial, while AE collection and monitoring will commence at the time the subject receives their first dose of SRA737 (or gemcitabine if the SRA737 dose for PK is omitted). SAE and AE collection and monitoring will continue until 30 days after the last administration of SRA737.

Should an investigator become aware of any drug related SAEs after this 30-day period, these must also be reported to the sponsor or sponsor designee within the expedited timelines in Section 10.3.

10.2.3 MONITORING AND FOLLOW-UP OF AES AND SAES

All subjects will be monitored for AEs from the start of treatment through 30 days after the last dose of study therapy. Additionally, monthly follow up is required for all SAEs and for those AEs considered drug related (highly probable, probable or possible) and present at the SFU visit. Monthly follow-up will continue until the event resolves, returns to baseline, stabilizes, or the subject discontinues from study.

After a study participant's completion or discontinuation from the study treatment, the investigator remains responsible to follow (through an appropriate health care option) any AEs that are serious or that caused the study participant to discontinue before completing the study. Events will be followed for outcome (resolution, with or without sequelae; stabilization of the event in those cases where the condition is expected to be chronic; or death).

The reporting period for SAEs that the investigator considers to be related to a study procedure begins at the time the subject signs the informed consent document. Any SAE that occurs outside the time period specified above for AE monitoring (ie, through 30 days after the last dose of study therapy) that the investigator considers to be possibly, probably, or definitely related to study drug must be reported (refer to Section 10.1.2).

Follow-up information relating to an SAE must be reported to the sponsor designee's Pharmacovigilance Department within 24 hours of site staff becoming aware of the new information.

The sponsor designee's Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow up request. For fatal or life threatening cases, follow up information must be reported to the sponsor designee's Pharmacovigilance Department as soon as possible.

10.3 IMMEDIATE ADVERSE EVENT REPORTING

All SAEs, regardless of causality, must be reported to the sponsor designee's Pharmacovigilance Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be faxed or e-mailed to the sponsor designee's Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

Primary Contact	Secondary Contact
Refer to your country-specific fax number in the Study Manual for the sponsor designee's Pharmacovigilance team contact. Email: GlobalSAE.Inbox@chiltern.com	Refer to your country-specific contact information in the Study Manual for the sponsor Medical Monitor Email: medicalmonitorSRA737-02@sierraoncology.com

Each episode of an SAE must be recorded on a separate SAE report form. The NCI-CTCAE v4.03 must be used to grade the severity of each SAE. If new or amended information on a previously reported SAE becomes available, the investigator should report this to the sponsor or sponsor designee's Pharmacovigilance Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the fax cover sheet when sending the SAE report form to the sponsor or sponsor designee's Pharmacovigilance Department.

Should the investigator become aware of any drug-related SAEs after the subject stops treatment with IMP(s), these must also be reported to the sponsor or sponsor designee's Pharmacovigilance Department within the specified timelines specified above.

If required by local regulations, SAEs must also be reported on an expedited basis to the EC/IRB of the study center.

10.3.1 EVENTS EXEMPT FROM BEING REPORTED AS SAES TO THE PHARMACOVIGILANCE DEPARTMENT

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalization is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the eCRF.

Elective admissions – Elective admissions to hospital for procedures which were planned prior to entering the trial are not SAEs. Hospitalization for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE.

10.4 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS IN ECRFS

All AEs, including SAEs, must be recorded in the eCRF for eligible subjects. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The sponsor or sponsor's designee and the investigator(s) will regularly review the safety data from both the safety and the clinical database.

If known, the diagnosis of the AE or disorder should be recorded using standard medical terminology, rather than its individual symptoms. The following AE information must be included: dates of occurrence; severity; causal relationship; action taken; and outcome. When possible, the NCI-CTCAE v4.03 definitions should be used to assess the severity of an AE.

10.5 URGENT SAFETY MEASURES

The sponsor/sponsor's designee or investigator may take appropriate urgent safety measures (USMs) in order to protect the subject of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect subjects from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorization from the competent authority.

The Medicines and Healthcare products Regulations Agency (MHRA), the Research Ethics Committee (REC), and/or other appropriate Regulatory Authorities and Ethics Committees (EC)/Institutional Review Boards (IRB) must be notified within 3 days of such measures being taken.

Should the site initiate a USM, the investigator must inform the sponsor or sponsor's designee immediately either by:

Primary Contact	Secondary Contact
Refer to your country-specific fax number in the Study Manual for the sponsor designee's Pharmacovigilance team contact. Email: GlobalSAE.Inbox@chiltern.com	Refer to your country-specific contact information in the Study Manual for the sponsor Medical Monitor Email: medicalmonitorSRA737-02@sierraoncology.com Phone: 1-604-558-6575

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The sponsor or sponsor's designee will then notify the applicable regulatory authority(ies) (eg, MHRA) and the applicable RECs within the required timeframes (eg, 3 days of USM initiation in the UK).

10.6 PREGNANCY REPORTING

Female subjects who become pregnant during the trial or treatment period, must have study treatment stopped immediately.

The investigator must make every effort to try and ensure that a clinical trial subject or a partner of a clinical trial subject does not become pregnant during the trial or for 6 months afterwards. This should be done as part of the consent process by explaining clearly to the subject the potential dangers of becoming pregnant and also providing each subject with information about appropriate medically approved contraception. Two forms of medically approved contraception must be used as described in Appendix 4.

It should be explained to the subject that if his partner is pregnant or breast feeding when he is enrolled on the trial, the subject should use barrier method contraception as described in Appendix 4 to prevent the unborn baby or the baby being exposed to the SRA737.

However, if a subject or a partner of a subject does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a subject or a subject's partner during treatment with an IMP or occurring within 6 months of last IMP administration must be reported to the sponsor or sponsor designee's Pharmacovigilance Department within 24 hours of the site staff becoming aware of it using a Pregnancy Notification Report (provided in the Investigator Trial File [ITF]).

It is the investigator's responsibility to obtain consent for follow-up from the subject or subject's partner. The sponsor or sponsor designee's Pharmacovigilance Department will follow up all pregnancies for the pregnancy outcome via the investigator, using a Pregnancy Follow-up Report.

The investigator must ensure that all subjects are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to 6 months after the last IMP administration. The investigator should offer counseling to the subject and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject and the baby should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this.

11 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

As this is an open label, first-in-human study, data trends will be reviewed in real time. There will also be 2 planned interim reviews on the accumulating data. These are not formal statistical interims and the reviews are conducted in part for subject safety. There will be no adjustment to

significance levels for these planned reviews of the accumulating data during the trial, at the following time points:

- At the end of cohort expansion
- At the completion of subject follow-up for the last subject enrolled at the end of the dose escalation

The final analysis will be conducted after one of the following conditions is met:

- The trial is terminated early.
- The end of trial as defined in Section 12.5 has been reached.

Additional analysis may be conducted for regulatory, publication, or decision making purposes.

11.1 ANALYSIS POPULATIONS

11.1.1 SAFETY EVALUABLE POPULATION

All enrolled subjects who receive at least 1 dose of SRA737 will be evaluable for safety.

11.1.2 RESPONSE EVALUABLE POPULATION

All enrolled subjects who have measurable disease, receive at least 75% or 83% of SRA737 in 1 cycle (Stages 1 and 2, respectively), and have a baseline assessment of disease plus at least 1 post-baseline disease assessment will be evaluable for response. All subjects who will be enrolled into the Cohort Expansion will be evaluable for response if they have measurable disease, receive at least 1 cycle of study medication as defined above, have a baseline assessment of disease plus at least 1 post-baseline disease assessment and are confirmed as having met the genetic selection eligibility requirements.

In addition, subjects who have measurable disease and received at least 83% of SRA737 in 1 cycle but developed PD, intolerable toxicity, or death prior to the post-baseline assessment will also be considered evaluable and will be classified as nonresponders.

11.1.3 PHARMACOKINETIC EVALUABLE POPULATION

All subjects who receive at least 1 dose of SRA737 and provided at least 1 evaluable PK concentration will be included in the PK analysis. Concentrations will be eligible for inclusion into PK analyses if the subject receives all doses and does not vomit within 4 hours postdose prior to the relevant PK sampling day(s).

11.1.4 PHARMACODYNAMIC EVALUABLE POPULATION

All enrolled subjects who receive at least 1 dose of SRA737 and have evaluable data for each specific PDn assessment will be evaluable for PDn.

11.2 STATISTICAL ANALYSIS

11.2.1 PRESENTATION OF DATA

Data will be presented in a descriptive fashion. Variables will be analyzed to determine whether the criteria for the trial conduct are met. This will include a description of subjects who did not meet all the eligibility criteria, an assessment of protocol deviations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarized for all enrolled subjects.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

11.2.2 SAFETY

Safety data will be collected from the date of written consent. Safety variables will be summarized by descriptive statistics. Laboratory variables will be described using the NCI-CTCAE v4.03. The MTD for the SRA737 and gemcitabine tested, if reached, and the RP2D and schedule will be described.

Treatment-emergent adverse events (also referred to as AEs) will be reported for each dose level and coded using a current version of the MedDRA thesaurus, presented as tables of frequency of AEs by body system and by worse severity grade observed. Additional tables will be prepared to summarize incidence of AEs reported as related and unrelated events.

11.2.3 EFFICACY ANALYSES

The analysis of all efficacy endpoints will be based on the Response Evaluable Population.

Descriptive analyses of the distribution of objective response rate (ORR), duration of response (DOR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), time to progression (TTP) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), and OS will be prepared.

Objective response rate, defined as the proportion of evaluable subjects with a best overall response of PR or CR per RECIST v1.1, will be summarized using binomial proportions and confidence intervals computed by the method of Wilson. The distribution of DOR, in a subset of subjects responding will be summarized using Tukey's 5 number summary, including the minimum, mean, median, maximum, and standard deviation. Time to response will be summarized using Tukey's 5 number summary.

The ORR and DCR will be summarized for the Response Evaluable Population and for important subgroups including, but not limited to, genetically-defined subjects selected by the NGS techniques, either retrospectively or prospectively, subjects enrolled into each of the indication-specific expansion cohorts, and subjects enrolled to Stage 1 or Stage 2. Additional subgroups of interest may also be identified, and the ORR will be estimated, as described in the Statistical Analysis Plan. Responses will be defined using the RECIST v1.1, and will also be summarized as best absolute change from baseline.

Duration of response is defined as the time from first evidence of PR or better to disease progression or death. Duration of response will be right-censored for subjects who at least achieve a PR based on the censoring conventions defined for PFS in the Statistical Analysis Plan. Analysis of DOR will be performed using the Kaplan-Meier method. Medians and other quartiles for DOR will be estimated in addition to the corresponding 2-sided 95% confidence intervals.

All other efficacy variables listed below will be further defined in the statistical analysis plan.

Although an analysis of OS is not a planned endpoint for the purposes of efficacy evaluation, survival information will be captured as death is also a safety variable. Statistical analysis of OS will include data from all subjects, and data from subjects alive at the end of the study will be included in the Kaplan Meier Analysis as a censored observation with censoring at the last available visit where survival status was ascertained.

Progression-free survival will include data from all subjects including subjects who did not progress and were alive at the end of the study. Censoring will be defined using the algorithm below and included in the Kaplan Meier analysis.

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Cycle 1 Day 1	Censored
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than 1 missed visit	Date of last radiological assessment of measured lesions	Censored

The statistical analysis of OS and PFS will be prepared using the Kaplan Meier estimator, and variance estimated using the Greenwood Estimator.

Binomial proportions will be summarized with a confidence interval estimated by the method of Wilson. The evaluation of binomial proportions, for example from ORR may use confidence intervals for binomial proportions computed by the method of Wilson.

11.2.4 PHARMACOKINETICS

Pharmacokinetic parameters will be determined using non-compartmental method(s). Pharmacokinetic parameters including but not limited to C_{min}, C_{max}, T_{max}, AUC_{inf}, AUC_{tau}, $t_{½}$, total body clearance, and apparent volume of distribution will be estimated and reported, as appropriate. Pharmacokinetic data generated from this study may be used in conjunction with PK data from other clinical studies in future meta-analyses for population PK assessment and will be reported separately.

11.2.5 PHARMACODYNAMICS

11.2.5.1 Tumor Profiling

Archival and/or fresh tumor biopsy samples and blood samples for ctDNA will be obtained at screening or baseline and analyzed using NGS to characterize the mutational status of a pre-specified panel of genes. The proportion of subjects with evaluable tissue and blood based assays will be described. The frequency of each genetic alteration will be characterized. The proportion of subjects with mutations within each of the categories of genetic alterations 1) activating mutations or amplification of growth promoting oncogenes; 2) loss-of-function mutations or deletions in tumor suppressor pathways controlling the G1/S checkpoint; 3) defects in DDR signaling and DNA repair genes; 4) gain of function mutations of replication stress genes) will be characterized. The association between the presence and type of genetic alteration and clinical outcome (response) will be explored.

11.2.5.2 Triplet Tumor Biopsies

The tumor biopsy lysates will be analyzed using ELISAs including but not limited to pS296 Chk1, pS317 Chk1, and total Chk1. The PDn parameters to be determined are absorbance, extrapolated concentrations, data normalized as a percentage of the Screening (Stage 2) and Cycle 1 Day 2 (Stage 2) biopsies and phosphorylated biomarker levels normalized to total biomarker levels.

11.2.5.3 PBMCs

The fixed PBMCs will be analyzed using immunofluorescence and confocal microscopy in order of priority (which may be altered as data emerges) including but not limited to: pS296 Chk1, pS317 Chk1, pS345 Chk1, total Chk1, gamma H2AX, and RAD51. The PDn parameters to be determined for the Chk1 biomarkers are nuclear fluorescence intensity per cell and mean fluorescent intensity. The PDn parameter to be determined for the gamma H2AX biomarker is percentage of cells with over 5 foci. For all biomarkers the data will also be normalized as a percentage of Day1 predose.

11.2.5.4 Comet Assay

The Comet assay, a single cell gel electrophoresis assay, will be used as an exploratory assay to measure DNA damage response in blood. A separate statistical analysis plan may be prepared for the analysis of DNA damage in blood.

11.2.5.5 Additional PDn Assays

Subjects enrolled prior to the implementation of Amendment v5.0 were required to submit blood and hair follicles for the purposes of exploratory PDn assessments. The following assessments will be performed:

- Samples for cell death markers will be taken from subjects in expanded cohorts in the dose escalation phase and the cohort expansion phase, i.e., will not be taken from subjects in the early dose escalation single subject cohorts. M30 and M65 ELISA assays will be used to measure markers of cell death in plasma according to agreed SOPs and validated methods.
- Immunofluoresence and confocal microscopy will be used to measure the PDn biomarker gamma H2AX in hair follicles, which is indicative of DNA damage.

A separate statistical analysis plan may be prepared for PDn assay analyses.

11.3 SAMPLE SIZE

This study will enroll approximately 140 subjects in total including 10 subjects in Stage 1, approximately 30-40 subjects during Stage 2 Dose Escalation, and another approximately 90 subjects in Stage 2 Cohort Expansion (up to 8 subjects in the original expansion cohort plus approximately 20 prospectively-selected genetically-defined subjects in each of 4 indication-specific expansion cohorts added with Amendment v6.0). The sample size for dose escalation is based on assumptions for allometric scaling and the estimated number of dose levels required to establish MTD. For the cohort expansion, the sample size of 20 subjects enrolled in each indication-specific expansion cohort was chosen such that 0 of 20 responses observed excludes an ORR of 16% in the 95% confidence interval (CI).

12 ADMINISTRATION

This trial is conducted under the appropriate clinical trial authorization and approval from the relevant REC(s), Regulatory Authorities, and ECs/IRBs will be obtained before the start of this trial. This trial is sponsored and monitored by Sierra Oncology, Inc. and its designee. Applicable regulatory requirements are described in this section.

12.1 PROTOCOL DEVIATIONS AND AMENDMENTS

The protocol should be adhered to throughout the conduct of the study, if a situation arises where the conduct of the study may not be in line with the protocol, then site should contact the sponsor or sponsor’s designee to discuss this.

Amendments to the protocol may only be made with the approval of the sponsor. A protocol amendment may be subject to review by the assigned REC(s), Regulatory Authorities (eg, MHRA), and ECs/IRBs Committees. Written documentation of the approval must be received before the amendment can be implemented and incorporated into the protocol if necessary.

12.2 SERIOUS BREACH OF GCP

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

In order that the sponsor can fulfil their obligations in terms of reporting serious breaches of GCP to the Regulatory Authorities within 7 calendar days of identification, site staff must inform the sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the sponsor.

12.3 OBTAINING WRITTEN INFORMED CONSENT

Written informed consent must be obtained from the subject before any protocol-specific procedures are carried out.

The subject must be given adequate time to think about their commitment to the study. If new information has been issued, subjects must be informed of this and re-consented if appropriate.

Only the site staff with delegated responsibility by the PI, and who have signed the Delegation Log, are permitted to obtain informed consent from subjects and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8). The date of the signatures of both the subject and the individual obtaining informed consent should be the same.

The delegated site staff member must inform the subject about the background to, and present knowledge of the normal management of their disease and SRA737 and must also ensure that the subject is aware of the following points:

- That SRA737 is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The known toxicity of SRA737 and the possibility of experiencing side effects.

- The potential dangers of becoming pregnant (or the subject's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception (refer to Appendix 4).
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.
- Who to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the signed informed consent document (ICD) must be given to the subject to keep and the original ICD, must be filed in the ITF (unless otherwise agreed that the original document will be filed in the medical records and a copy kept in the ITF).

12.4 COMPLETION OF THE ELECTRONIC CASE REPORT FORM

Electronic CRFs approved by the sponsor will be used to collect the data. The investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the investigator and those personnel who have signed the Delegation Log provided by the sponsor or sponsor's designee and have been authorized by the investigator should enter or change data in the eCRFs. Authorized users will be included on a user list in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The investigators must retain all original reports, traces and images from these investigations for future reference.

The collection and processing of personal data from the subjects enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial. The data must be collected and processed with adequate precautions to ensure subject confidentiality and compliance with applicable data privacy protection according to the applicable regulations. The data collected will comply with applicable local regulations on the protection of individuals with regard to the processing of personal data.

Data will be entered directly into electronic screens by authorized site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorized personnel must answer the queries by making relevant amendments to data and/or providing a response. Answered queries will be closed or reissued as appropriate.

Once the subject is 'off study' and the eCRF has been fully completed, the investigator must provide an electronic signature to authorize the complete subject casebook.

At the end of the trial all eCRFs are retained and archived by the sponsor and a portable document format copy provided to the investigator who is responsible for archiving at site.

12.5 END OF STUDY

The 'end of trial' is defined as the date when the last subject has completed the SFU visit or the final long-term follow-up visit (whichever is the latter).

It is the responsibility of the sponsor to inform the Medicines and Healthcare Products Regulatory Agency (MHRA), the Research Ethics Committee (REC), and other appropriate Regulatory Authorities and ECs/IRBs within 90 days of the 'end of the trial' that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the sponsor, the sponsor or sponsor's designee will notify the MHRA, the REC and other appropriate Regulatory Authorities and ECs/IRBs within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

Recruitment will cease when any of the following occur:

- The drug is considered too toxic to continue treatment before the required number of subjects have been recruited.
- The stated number of subjects to be recruited has been reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for subjects at the time of discontinuation of follow up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, the sponsor and the investigators must ensure that adequate consideration is given to the protection of the subject's interest.

12.6 TRIAL PERFORMANCE, MONITORING, AUDITING AND INSPECTION

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organizational preparations made with the trial center. The sponsor or sponsor's designee must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial, the CRA will be responsible for monitoring data quality in accordance with sponsor or sponsor designee's standard operating procedures.

Before the study start, the investigator will be advised of the anticipated frequency of the monitoring visits. The investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check PK and PDn samples and storage;
- discuss the conduct of the trial and the emerging problems with the investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

At the end of the trial all unused SRA737 supplies must be destroyed at site (only once authorized to do so by the CRA) or if authorized by the sponsor or sponsor's designee returned to the supplier.

It is the responsibility of the sponsor to notify the REC of the 'end of the trial' (See definition in Section 12.5). Principal investigators are responsible for notifying their local ECs/IRBs, as appropriate.

During the course of the trial, the sponsor or sponsor's designee, may conduct an on-site audit.

Principal Investigators conducting this trial accept the potential for inspection by the MHRA or other Regulatory Authorities.

12.7 SOURCE DOCUMENT VERIFICATION

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore, it is the investigator's responsibility to ensure that both he/she and his/her study team

records all relevant data in the medical records. The investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with subjects' medical records and the verification will be recorded in the eCRF.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF.

12.8 RECORD RETENTION

During the clinical trial and after trial closure the investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and SAE report forms, shall show whether the investigator has complied with the principles and guidelines of GCP.

All essential documents required to be held by the investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or sponsor, for the minimum period required by national legislation or for longer if needed by the sponsor. Records must not be destroyed without prior written approval from the sponsor.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

12.9 ETHICAL CONSIDERATIONS

Before starting the trial, the protocol and subject ICD must go through the Sierra Oncology review process and receive the favorable opinion/approval of the assigned REC/ECs/IRBs.

It is the PI's responsibility to update subjects (or their authorized representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the subject's willingness to continue in the trial. The PI must ensure this is documented in the subject's medical notes and the subject is re-consented.

The sponsor and CI/PI must ensure that the trial is carried out in accordance with the GCP principles and requirements of applicable ICH GCP and local regulations.

12.10 PUBLICATION POLICY AND PRESS RELEASES

Sierra Oncology, Inc. (Sierra Oncology) is committed to the publication and widespread dissemination of the results of this study.

This study represents a joint effort between Sierra Oncology and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Sierra Oncology for review before submission for publication or presentation. If the proposed publication or presentation contains patentable subject matter, which, at Sierra Oncology's sole discretion, warrants intellectual property protection, Sierra Oncology may delay any publication or presentation for the purpose of pursuing such protection.

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14 APPENDICES

Appendix 1. WHO Performance Scale

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

APPENDIX 2: ASSESSMENT OF DISEASE RESPONSE

Assessment of disease response in this study should be performed according to the RECIST criteria specified below.

New response evaluation criteria in solid tumours (RECIST criteria): Revised RECIST guideline (version 1.1)
E.A. Eisenhauer et al. (2009) European Journal of Cancer 45: 228-247

Note that this is an abridged version of the RECIST criteria. Please refer to the above article for detailed appendices and if in doubt.

Measurability of tumour at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal

masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in the publication from Eisenhauer et al.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent

review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy:

The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers:

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a subject to be considered in complete response.

Cytology and histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1).

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. An example in Fig. 3 of the publication by Eisenhauer et al.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis

<10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease

This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to

widespread, or may be described in protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. Should a response not be documented until after the end of therapy in this trial, post-treatment assessments may be considered in the determination of best overall response as long as no alternative anti-cancer therapy has been given. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1. Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the subject is known.

Best response determination in this trial (in which confirmation of complete or partial response IS NOT required):

Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable. A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Table 1 – Time point response: subjects with target (+/–non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: subjects with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD(a) NE
Not all evaluated	No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
(a) 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of 'zero' on the case report form (CRF).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in Tables 1 to 3.

Conditions that define 'EP, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar

to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 3. NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I subjects with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II subjects with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III subjects with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV subjects with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

APPENDIX 4. CONTRACEPTIVE GUIDANCE FOR WOMEN OF CHILDBEARING POTENTIAL (WOCBP) AND MALE PARTNER OF WOCBP

The risks of treatment with SRA737 during pregnancy, given in combination with gemcitabine plus cisplatin or gemcitabine alone, have not been evaluated. Please refer to the latest version of the Investigator's Brochure for SRA737 as well as to the regional prescribing information for Gemcitabine and Cisplatin for additional information.

Women of Childbearing Potential

This protocol defines a women of childbearing potential (WOCBP) as a sexually mature woman who:

- Has not undergone a hysterectomy or bilateral oophorectomy, or
- Has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Contraceptive Requirements for Females

In order to be eligible for the clinical trial, WOCBP planning to participate must agree to use 2 forms of contraception (one reliable form plus a barrier method) effective from the date of the first administration of SRA737 (ie, at least 7 days prior for hormonal methods) throughout the trial and for 6 months afterwards. The investigator should counsel subjects on appropriate methods for avoiding pregnancy during the study. These include the following:

- Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, implants) and condom;
- Intra-uterine device (IUD) or intrauterine system (IUS) and condom;
- Diaphragms with spermicidal gel and condom

The following highly effective methods (failure rate <1% per year), are also acceptable as single methods:

- Vasectomy**
- Tubal sterilization*

Abstinence is only considered an acceptable method of contraception if it is a pre-existing part of a subject's lifestyle. Symptom-thermal methods (basal body temperature, cervical mucous, or calendar/rhythm) or withdrawal are not considered adequate forms of contraception for the purposes of this study.

* Tubal sterilization via the Essure procedure is not considered a reliable form of contraception unless tubal blockage is verified by hysterosalpingogram (HSP) approximately 3 months after microinsertion. Prior to verification, another contraception method described above should be used.

** Vasectomised partner is also considered a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical confirmation of the surgical success. Prior to verification, another contraception method described above should be used.

Contraceptive Requirements for Male Subjects with Female Partners of Childbearing Potential

All male study participants must agree to consistently and correctly use a condom plus spermicidal gel from the date of the first administration of SRA737 throughout the trial and for 6 months after the last dose of study drug. If their female partner is a WOCBP (as defined above), additionally, male subjects must be willing to ensure that their partner uses 1 of the methods of birth control listed above effective from the date of the first administration of SRA737 (ie, at least 7 days prior to the first dose for hormonal methods) throughout the trial and for 6 months after the last dose of study drug. Male subjects with pregnant or lactating partners must be advised to use condom plus spermicidal gel to prevent exposure of the fetus or neonate.

Male subjects must agree to refrain from sperm donation from the first administration of study drug for at least 6 months after the last dose of study drug.

Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they, or the partners of male subjects become pregnant at any time during the study, or if they become pregnant within 6 months] of the last dose of study drug. Subjects who become pregnant or who suspect that they are pregnant must report the information to the investigator. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the investigator. All pregnancies (subjects and their partners) should be followed until resolution if possible.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 10.6.

APPENDIX 5. QT PROLONGING DRUGS AND DRUGS METABOLIZED BY CYP1A2

List of known QTc prolongation drugs from www.crediblemeds.com. Reprinted on 16 November 2016.

Generic Name	Brand Names (Partial List)	Drug Class
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Trisenox	Anticancer
Astemizole (Removed from Market)	Hismanal	Antihistamine
Azithromycin	Zithromax, Zmax	Antibiotic
Bepridil (Removed from Market)	Vascor	Antianginal
Chloroquine	Aralen	Antimalarial
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic
Cisapride (Removed from Market)	Propulsid	GI stimulant
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Clarithromycin	Biaxin, Prevpac	Antibiotic
Cocaine	Cocaine	Local anesthetic
Disopyramide	Norpace	Antiarrhythmic
Dofetilide	Tikosyn	Antiarrhythmic
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea
Donepezil	Aricept	Cholinesterase inhibitor
Dronedarone	Multaq	Antiarrhythmic
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryt, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic

Generic Name	Brand Names (Partial List)	Drug Class
Fluconazole	Diflucan, Trican	Antifungal
Gatifloxacin (Removed from Market)	Tequin	Antibiotic
Grepafloxacin (Removed from Market)	Raxar	Antibiotic
Halofantrine	Halfan	Antimalarial
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic
Ibogaine (Only on Non US Market)	None	Psychedelic
Ibutilide	Corvert	Antiarrhythmic
Levofloxacin	Levaquin, Tavanic	Antibiotic
Levomepromazine (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic
Levomethadyl acetate (Removed from Market)	Orlaam	Opioid agonist
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic
Mesoridazine (Removed from Market)	Serentil	Antipsychotic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic
Oxaliplatin	Eloxatin	Antineoplastic Agent
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary
Pentamidine	Pentam	Antifungal
Pimozide	Orap	Antipsychotic
Probucol (Removed from Market)	Lorelco	Antilipemic
Procainamide	Pronestyl, Procan	Antiarrhythmic
Propofol	Diprivan, Propoven	Anesthetic, general
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar,	Antibiotic

Generic Name	Brand Names (Partial List)	Drug Class
	Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	
Sevoflurane	Ulane, Sojourn	Anesthetic, general
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic
Sparfloxacin (Removed from Market)	Zagam	Antibiotic
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical
Terfenadine (Removed from Market)	Seldane	Antihistamine
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic
Vandetanib	Caprelsa	Anticancer

List of drugs known to be metabolized by CYP1A2 from

http://medicine.iupui.edu/CLINPHARM/ddis/main-table. Reprinted on 01 September 2017.

Generic Name	Brand Name (Partial List)
amitriptyline	Elavil
caffeine	
clomipramine	Anafranil
clozapine	Clozaril
cyclobenzaprine	Flexeril
duloxetine	Cymbalta
estradiol	
fluvoxamine	
haloperidol	Haldol
imipramine N-DeMe	Tofranil
mexiletine	
nabumetone	Relafen, Relifex, Gambaran
naproxen	Aleve, Naprosyn
olanzapine	Zyprexa
ondansetron	Zofran
phenacetin→acetaminophen→NAPQI	Tylenol, Paracetamol
propranolol	Inderal
riluzole	Rilutek, Teglutik
ropivacaine	Naropin

Generic Name	Brand Name (Partial List)
tacrine	Cognex
theophylline	
tizanidine	Zanaflex, Sirdalud, Relentus
triamterene	Dyrenium, Maxzide, Dyazide
verapamil	Calan, Covera-HS
(R)warfarin	Coumadin
zileuton	Zyflo
zolmitriptan	

APPENDIX 6. GENETIC PREDICTORS OF SRA737 SENSITIVITY

Subjects must have predicted sensitivity to Chk1 inhibition for enrollment 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 2011). Note, this list is not exhaustive as scientific discoveries and technology continue to evolve.

Tumor Suppressor	DNA Damage Repair	Replicative Stress	Oncogenic Driver

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 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 1 peer reviewed article documenting its relationship or sensitivity to genetic alterations with a Chk1 or ATR mutation.
- Data from PDX studies performed by the sponsor or its collaborator demonstrating evidence of genetic sensitivity.
- Data of similar quality that has been reviewed by the sponsor but is 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 and when genes are added to or removed from this list.