A PHASE 1/2 TRIAL OF SRA737 (A CHK1 INHIBITOR) ADMINISTERED ORALLY IN SUBJECTS WITH ADVANCED CANCER

Sponsor protocol number:	SRA737-01
EudraCT number:	201500448686
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Compliance Statement:	This study will be conducted in accordance with Protocol SRA737-01, the International Conference on Harmonisation (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	02-March-2016	Addition of QTc exclusion criteria and amendments to contraceptive advice (made at the request of the MHRA prior to approval)
		Superseding version 2.0 was withdrawn prior to review in order to retain the current Investigational Medicinal Product name (CCT245737).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, SRA737 (formerly known as CCT245737). In addition, the study is being amended to assess preliminary efficacy in all subjects including 40 additional biomarker-selected and indication-specific subjects with tumors anticipated to be sensitive to inhibition of Chk1. Another new objective is to assess the relationship between drug exposure and any effects on the QT interval. Procedures are being revised to ensure appropriate subject selection, in accordance with the new and retained study objectives.
5.0	10-February-2017	Protocol Amendment Version 5.0 clarifies the frequency of bone scans for subjects with prostate cancer. In addition, a clarification was provided for the MSI testing criteria and ECG data collection.
6.0	18-May-2017	Protocol Amendment Version 6.0 removes the maximum number of prior regimens criteria for subjects participating in the Cohort Expansion Phase and circulating tumor cells requirement for metastatic castration-resistant prostate cancer subjects. In addition, the eligibility criteria for ovarian cancer subjects have been clarified.

Version No.	Date of issue	Reason for update
7.0	14-Sep-2017	Protocol Amendment Version 7.0 increases the size of each indication-specific cohort in the Cohort Expansion Phase from 8 to 20. The cohort enrolling subjects with squamous cell carcinoma of the head and neck was amended to also include squamous cell carcinoma of the anus. 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.
8.0	10-Jan-2018	A specific expansion cohort of approximately 20 subjects with high-grade serous ovarian cancer (HGSOC) with *CCNE1* gene amplification was added to the study. This is in addition to the expansion cohort of subjects with HGSOC with other eligible genetic profiles.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	AE	adverse event
	AML	acute myeloid leukemia
	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
C	CBC	Complete blood count (full blood count)
	Chk1 or 2	Checkpoint kinase 1 or 2
	CI	confidence interval
	C_{max}	maximum observed plasma concentration
	C_{min}	minimum observed plasma concentration
	CR	complete response
	CRA	Clinical Research Associate
	CT	computerized tomography
	CTC	circulating tumor cells
	CTCAE	Common Terminology Criteria for Adverse Events
	ctDNA	circulating tumor DNA
	CYP	Cytochrome P450
D	Day	cycle day
	DCR	disease control rate
	DDR	DNA damage response
	DLT	dose limiting toxicity
	DNA	deoxyribonucleic acid
	DOR	duration of response
E	EC	ethics committee
	ECG	Electrocardiogram
	ECHO	Echocardiogram
	eCRF	electronic case report form
F	5-FU	5-fluorouracil
	FDG	Fluorodeoxyglucose
G	GCP	Good Clinical Practice
	GI	Gastrointestinal
	GIT	Gastrointestinal Tract
	GLP	Good Laboratory Practice
H	h	Hour
	HGSOC	High-grade serous ovarian cancer
	HNSCC	Head and Neck Squamous Cell Carcinoma

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
I	IC_{50}	half maximal inhibitory concentration
	ICD	informed consent document
	ICH	International Conference on Harmonisation
	IMP	investigational medicinal product
	IRB	Institutional Review Board
	ITF	Investigator Trial File
	IV	Intravenous
L	LHRH	luteinizing hormone releasing hormone
	LV	Leucovorin
M	mCRPC	metastatic castration-resistant prostate cancer
	min	minute(s)
	MHRA	Medicines and Healthcare products Regulations Agency
	MRI	magnetic resonance imaging
	MSI	microsatellite instability
	MTD	maximum tolerated dose
N	NCI	National Cancer Institute
	NE	not evaluable
	NGS	Next generation sequencing
	NHL	non-Hodgkin lymphoma
	NSCLC	non-small cell lung cancer
	NYHA	New York Heart Association
O	ORR	overall response rate
	OS	overall survival
P	PBMC	peripheral blood mononuclear cells
	PCWG	Prostate Cancer Clinical Trials Working Group
	PD	progressive disease
	PDn	Pharmacodynamics
	PDX	Patient-derived xenograft
	PET	positron emission tomography
	PFS	progression-free survival
	PI	principal investigator
	PK	Pharmacokinetics
	PO	by mouth/orally
	PPI	proton pump inhibitors
	PR	partial response
	PSA	prostate-specific antigen
Q	QT, QTc	QT interval, corrected QT interval
	QTcF	QT interval corrected for heart rate using Fridericia's formula

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumors
	RP2D	recommended Phase 2 dose
S	SAE	serious adverse event
	SCCA	squamous cell carcinoma of the anus
	SD	stable disease
	SFU	safety follow-up
	Sierra Oncology	Sierra Oncology, Inc. (formerly ProNAi Therapeutics, Inc.)
	SRA737 (investigational medicinal product)	Previously known as CCT245737
T	$T_{1/2}$	terminal elimination half-life
	TCGA	The Cancer Genome Atlas
	T_{max}	time to reach C_{max}
U	ULN	upper limit of normal
	USM	urgent safety measure
W	WHO	World Health Organization
	WOCBP	Women of Childbearing Potential

PROTOCOL ACCEPTANCE PAGE

Title	A Phase 1/2 trial of SRA737 (a Chk1 inhibitor) Administered Orally in Subjects with Advanced Cancer
Protocol Number	SRA737-01
Version (Date)	Protocol Amendment Version 8.0 (10 Jan 2018)

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	A Phase 1/2 Trial of SRA737 (a Chk1 Inhibitor) Administered Orally in Subjects with Advanced Cancer
Short Title of Study	A Phase 1/2 Trial of SRA737 in Subjects with Advanced Cancer
Study objective(s):	Primary Objective**:** • To establish the safety profile of SRA737 • To determine the maximum tolerated dose (MTD) with 1 or more schedules of administration of SRA737 • To propose a recommended Phase 2 dose (RP2D) and schedule of SRA737 • To evaluate the preliminary efficacy of SRA737 including efficacy in prospectively-selected genetically-defined subjects enrolled into indication-specific expansion cohorts Secondary Objectives: • To characterize the pharmacokinetic (PK) profile of SRA737 • To assess the relationship between response and the presence of selected genetic alterations as detected in tumor tissue and/or circulating tumor deoxyribonucleic acid (ctDNA) Exploratory Objectives**:** • To investigate the pharmacodynamics (PDn) of SRA737 in tumor tissue • To investigate the PDn of SRA737 in surrogate tissue such as blood or peripheral blood mononuclear cell (PBMCs) • To explore possible predictors of response • To explore the relationship between exposure (PK) and QT/QTc, other electrocardiogram (ECG) parameters and cardiovascular safety findings
Study design:	This is a multicenter, first-in-human, Phase 1/2, open-label, dose-escalation and dose-expansion trial in subjects with advanced solid tumors or non-Hodgkin lymphoma (NHL). The trial will consist of 2 stages. Stage 1: A Dose Escalation Phase It is expected that between 30 and 50 subjects with solid tumors or NHL will be enrolled in the Dose Escalation phase of the study. Intensive PK and ECG monitoring for QTc assessments will be collected from all enrolled subjects, beginning with sampling before and after a single dose of SRA737 given on one day between Day -7 and Day -4. Tumor tissue (archival or fresh) and blood will be collected for retrospective biomarker analyses. Cohorts consisting initially of a single subject will receive escalating doses of SRA737, starting in Cohort 1 with 20 mg/day administered orally on a continuous daily dosing schedule in 28-day cycles. The dose will be escalated until the MTD has been identified, unless determined otherwise by the Sponsor in consultation with the Chief Investigator, for example, if an alternative schedule is pursued instead.

Study design (cont'd):	Once a SRA737-related, Grade 2 toxicity is observed in a dose escalation cohort during Cycle 1, that cohort will be expanded to 3 to 6 subjects, and subsequent dose level cohorts will follow a rolling 6 design (see Section 3.3 for additional details). Dose escalation with an alternative schedule may begin at any time and may either run either in parallel or instead of continued escalations in the continuous schedule. The final number of subjects enrolled into the trial is dependent on the number of dose levels explored in the Dose Escalation Phase. Patients who are not evaluable for assessment of dose limiting toxicity (DLT) may be replaced. <u>Stage 2: A Cohort Expansion Phase</u> The Cohort Expansion Phase consists of 6 indication-specific expansion cohorts of approximately 20 prospectively-selected genetically-defined subjects each (namely, subjects with previously treated metastatic colorectal cancer [CRC], high grade serous ovarian cancer [HGSOC] without *CCNE1* gene amplification, HGSOC with *CCNE1* gene amplification (or alternative genetic alteration with similar functional effect), metastatic castration-resistant prostate cancer [mCRPC], advanced non-small cell lung cancer [NSCLC], and squamous cell carcinoma of the head and neck [HNSCC] or squamous cell carcinoma of the anus [SCCA]). This allows for a preliminary exploration of the efficacy of SRA737. The goal of the expansion cohorts is to assess SRA737 across multiple tumor types in subjects who have a range of genomic profiles of interest as described in inclusion criterion 9. The Sponsor may choose to refine or select particular genomic profile requirements in each (or all) Expansion Cohort(s) 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 choose to select for alternative genomic profiles in the event profile(s) not associated with tumor responses are over-represented in subjects already enrolled. Intensive PK and ECG monitoring for QTc assessments will be collected until the Sponsor determines sufficient data have been collected and analyzed across the study as a whole. Tissue (archival or fresh) and blood will be collected for prospective genetic analysis to determine eligibility. See Section 7.1.1 for more details. Prospective screening of subjects within the selected indications to determine eligibility based on tumor genetics will begin prior to the completion of dose escalation. Eligibility will be determined by the Sponsor's review of genetic abnormalities detected in genes in the categories listed in inclusion criterion 9. Enrollment to Dose Escalation and Expansion Cohorts may occur in parallel. A subject that qualifies for the Cohort Expansion Phase will be enrolled into a Dose Escalation Cohort whenever possible. Any such subject will be considered to have enrolled in both phases simultaneously. Only when a dose escalation enrollment slot is not available for an eligible genetically-defined subject, that subject may be enrolled to an expansion cohort and treated with SRA737 at the highest dose level previously determined to be safe. Intra-subject dose escalation is allowed for these, and for all, study subjects.
Number ofinvestigational sites:	This is a multicenter study.

Planned number of subjects:	It is estimated that up to 50 subjects will be enrolled into the Dose Escalation Phase of the study. Six cohorts of approximately 20 subjects each (i.e. a total of approximately 120 subjects) will be enrolled into the Cohort Expansion Phase; the final number of subjects enrolled into the trial will depend on the number of dose levels, the number of subjects who participate in both the Dose Escalation and Cohort Expansion phases, and potentially alternative dose schedules explored.
Sample size justification:	The sample size for dose escalation is based on assumptions from allometric scaling and the number of dose levels required to establish the MTD. Six indication-specific expansion cohorts of approximately 20 prospectively-selected genetically-defined subjects each will permit confirmation that the 95% confidence intervals around an observed objective response rate (ORR) in each cohort is ± 16%.
Study population:	Dose Escalation Phase: Subjects with solid tumors or NHL. Cohort Expansion Phase: Prospectively-selected genetically-defined subjects with metastatic CRC, HGSOC without *CCNE1* gene amplification, HGSOC with *CCNE1* gene amplification, mCRPC, advanced NSCLC, or HNSCC/SCCA.
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 is 20 mg daily.
Treatment regimen(s):	SRA737 will be administered orally, daily of each 28-day cycle for subjects receiving the continuous dosing schedule. Alternate dosing schedules may also be explored. Subjects may continue to receive treatment as long as none of the treatment discontinuation criteria are met (Section 5.6). Intra-subject dose escalation(s) will be permitted.
Inclusion criteria:	**Dose Escalation Phase and Cohort Expansion Phase** 1. Written (signed and dated) informed consent and be capable of cooperating with treatment and follow up. 2a. For subjects in the Dose Escalation Phase: any locally advanced or metastatic, histologically or cytologically proven solid tumor or NHL, relapsed after or progressing despite conventional treatment and for which no other conventional therapy is considered appropriate by the investigator or has been declined by the subject. 2b. For subjects in the Cohort Expansion Phase: any locally advanced or metastatic, histologically or cytologically proven malignancy of the types specified in inclusion criterion 10, for which no other conventional therapy is considered appropriate by the investigator or has been declined by the subject. 3. Life expectancy of at least 12 weeks. 4. World Health Organization (WHO) performance status of 0–1 (Appendix 1).

Inclusion criteria (cont'd):

5. Hematological and biochemical indices within the ranges shown below, measured within one week prior to the subject receiving their first dose of investigational medicinal product (IMP).

Laboratory Test	Lower acceptable limit
Hemoglobin (Hb)	≥ 90 g/L
Absolute neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Bilirubin	≤ 1.5 x upper limit of normal (ULN) unless due to Gilbert's syndrome in which case up to 3 × ULN is permissible
Alanine aminotransferase and/or aspartate aminotransferase (and Alkaline Phosphatase	≤ 2.5 x ULN unless raised due to tumor in which case up to 5 x ULN is permissible
Serum Creatinine	≤ 1.5 x ULN

6. Subject has attained the age of 18 years 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 details.

Inclusion criteria (cont'd):	**Cohort Expansion Phase** 8. Subjects must have measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), or for mCRPC, evaluable disease per any of the following: a. Measurable disease per RECIST v1.1; b. Increasing prostate specific antigen (PSA, see Prostate Cancer Clinical trials Working Group [PCWG] Guidelines – Appendix 7); or c. circulating tumor cell (CTC) count of 5 or more cells per 7.5ml of blood. 9. Subjects must have tumor tissue or ctDNA evidence that their tumor harbors a combination of mutations which are expected to confer sensitivity to Chk1 inhibition. Eligibility will be determined by the Sponsor's review of genetic abnormalities detected in genes in the following categories, as listed in Appendix 6: a. Key tumor suppressor genes regulating G1 cell cycle progression/arrest such as *RB1*, *TP53*, etc. For patients with HNSCC or SCCA, positive HPV status is also considered for eligibility. b. The DNA damage response pathway including *ATM*, *BRCA1*, and *BRCA2*. For patients with CRC, mismatch repair genetic alterations and/or high microsatellite instability are also considered for eligibility. c. Genetic indicators of replicative stress such as gain of function/amplification of *Chk1* or *ATR* or other related gene. d. Oncogenic drivers such as *MYC*, *KRAS*, etc. e. *CCNE1* gene amplification (or alternative genetic alteration with similar functional effect) is required for the *CCNE1* gene amplification-specific HGSOC cohort.

Inclusion criteria (Cont'd):	10. Subjects must meet one of the following criteria (a-e): a. Metastatic CRC • Histologically and/or cytologically confirmed CRC • Must have received at least 1 prior regimen for advanced/metastatic disease b. HGSOC • Histologically confirmed high grade serous ovarian, fallopian tube or primary peritoneal cancer • Recurrent platinum-intolerant subjects, or those with platinum-resistant disease, defined as radiological evidence of disease progression within 6 months of the last receipt of platinum-based chemotherapy. Patients with platinum refractory disease (as defined by the European Society for Medical oncology [ESMO] Guidelines – Appendix 7) are not eligible. c. Advanced NSCLC • Locally advanced and recurrent or metastatic, histologically confirmed NSCLC • Must have received at least 1 prior regimen for advanced/metastatic disease d. mCPRC • Histologically or cytologically confirmed adenocarcinoma of the prostate that has progressed after androgen deprivation therapy e. NHSCC or SCCA • Histologically confirmed HNSCC from any primary site, or SCCA • For HNSCC: locally advanced disease (ie, persistent or progressive disease following curative-intent radiation, and not a candidate for surgical salvage due to incurability or morbidity), or metastatic disease • For SCCA: locally advanced disease or metastatic disease for which no curative intent therapy is available • Must have received at least 1 prior regimen for advanced/metastatic disease

Exclusion criteria:

1. Have received the following prior or current anticancer therapy:
   a. Radiotherapy within the last 6 weeks (except for symptom control and where the lesions will not be used as measurable disease)
   b. Endocrine therapy during the previous 4 weeks except for luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer
   c. Chemotherapy during the previous 4 weeks
   d. Immunotherapy during the previous 6 weeks
   e. Nitrosoureas or Mitomycin C during the previous 6 weeks
   f. Other IMPs during the 4 weeks before treatment
   g. Any prior treatment with a Chk1 inhibitor, or prior treatment with an ATR inhibitor within 6 months prior to receiving SRA737.
2. Other malignancy within the past 2 years with the exception of adequately treated tumors that are associated with an expected 5 year disease-free survival of approximately 95% or better.
3. 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 or Sponsor's designee monitor should not exclude the subject.

4a. For subjects in the Dose Escalation Phase that are not to be included in the Expansion Cohort, new or progressing brain metastases. Subjects with brain metastases that have been radiologically stable over an 8-week period may be included.

4b. For subjects in the Cohort Expansion Phase, present or prior brain metastases.

5. Women of childbearing potential (WOCBP) or women who are already pregnant or lactating. However, those patients who have a negative serum or urine pregnancy test before enrollment and agree to use two forms of contraception as per Appendix 4 or agree to sexual abstinence, effective from the first administration of SRA737, throughout the trial and for six months afterwards are considered eligible.
6. Male subjects with partners of childbearing potential (unless they agree to take measures not to father children by using a barrier method of contraception as per Appendix 4 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.
7. Major surgery from which the subject has not yet recovered.
8. At high medical risk because of nonmalignant systemic disease including active uncontrolled infection.
9. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

Exclusion criteria (cont'd):	10. 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. 11. Prior bone marrow transplant or extensive radiotherapy to greater than 25% of bone marrow within 8 weeks. 12. Peanut allergy. Refer to Section 6 for additional details. 13. QTcF > 450 msec in adult males and > 470 msec in adult females. 14. 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). 15. Not able to swallow capsules without chewing or crushing. 16. 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 or Sponsor's designee would be acceptable. 17. 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: consent will be obtained; availability of suitable archival tissue or planned biopsy of accessible tissue will be confirmed or submitted for tumor profiling, and MSI or HPV status will be determined if required (MSI for subjects with CRC and other subjects if clinically relevant; HPV for subjects with HNSCC or SCCA). Within 28 days prior to the first dose of SRA737, the following will be performed/obtained: demographic information, medical history, and concomitant treatment will be recorded; cardiac assessments (echocardiogram [ECHO] and electrocardiogram [ECG]), and radiological disease assessments will be performed; blood will be collected for CTCs (mCRPC subjects only), and ctDNA for tumor profiling; optional tumor biopsy for additional pharmacodynamic analysis; and collection of serious adverse events (SAEs) will be initiated. Within 7 days prior to the first dose of SRA737, the following assessments will be completed: SAEs and concomitant medications, WHO performance status, pregnancy test (WOCBP), and laboratory assessment of blood (hematology and biochemistry). Intensive PK collection will begin with a single dose administered between Day -7 to Day -4. 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. Also, central ECG assessments described below may be reduced in frequency or eliminated by the Sponsor once sufficient data have been collected and analyzed. If any of these occur, the modified requirements will be documented by an update to the appropriate study documents. At the single-dose PK run-in on the Day -7 to Day -4 visit (where applicable), subjects may remain as in-patients for at least 24 hours after their first dose of SRA737 to facilitate collection of study required assessments.

Overview of assessments (cont'd):	Temperature, height, weight, pulse rate, seated BP, replicate ECG, pregnancy test (WOCBP), urinalysis, and blood for hematology, biochemistry, troponin I or T, ctDNA for exploratory analyses, serum tumor markers, CTCs (mCRPC subjects only), additional exploratory analyses (mutational burden), and PK will be obtained predose. Additional blood will be collected postdose for up to 48 hours for PK. For Dose Escalation subjects; archival tumor tissue should be requisitioned by Cycle 1 Day 1. Adverse events will be collected starting at the administration of SRA737. If an optional tumor biopsy was taken at baseline for additional pharmacodynamic analysis, a second biopsy should be collected at one timepoint 2 to 8h after dosing from Cycle 1 Day 15 through Cycle 1 Day 22 (inclusive). Continuous daily dosing (or an alternative schedule dosing) will begin on Day 1 with the following procedures occurring at regular intervals. • AE and concomitant medication collection on an ongoing basis • Symptom-directed physical exam, if medically indicated, Day 1 of each cycle • Radiological assessment every 8 weeks after Day 1 • Subjects with bone metastases being followed by bone scans will have scans every 8–9 weeks for the first 6 months and then every 16 weeks thereafter. • Clinical disease assessment, serum tumor markers (if applicable) and CTCs (for mCRPC subjects only), every 4 weeks after Day 1 • Vital signs and WHO Performance Status, Day 1 of each cycle • Laboratory assessment of blood (hematology, biochemistry, troponin I or T) and urine (urinalysis): see Section 7.2.2 for detailed schedule • ECHO on Cycle 2 Day 1 • ECG (locally- and centrally-read): see Section 7.2.2 for detailed schedule • Blood collection for PK, ctDNA for exploratory analysis, and additional exploratory analyses (mutational burden): see Section 7.2.2 for detailed schedule • Compliance: review of diary card Hematology assessments to be repeated weekly for the cycle following an intra-subject dose escalation, where applicable. Subjects who discontinue treatment will complete the Safety Follow-up visit 30 days (± 7 days) after the last dose. Assessments required at the visit include AE and concomitant medication collection, vital signs, weight, WHO performance status, ECG, ECHO, radiological and clinical disease assessment (as clinically relevant), urinalysis, and laboratory assessment of blood for hematology, biochemistry, pregnancy (WOCBP), troponin I or T, ctDNA for exploratory analysis, CTCs (for mCRPC subjects only), serum tumor marker (if applicable), and additional exploratory analyses (mutational burden).

Overview of assessments (cont'd):	Subjects without progressive disease (PD) at the time of SRA737 discontinuation will continue in Long-term Follow-up to undergo disease evaluations every 16 weeks (± 2 weeks) and have the following collected: radiological and clinical disease assessments, SAEs assessed as related to SRA737 by the investigator, first subsequent anticancer therapy, and blood for serum tumor markers (if applicable) and CTCs (for mCRPC subjects only) 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 variables:	All subjects receiving at least 75% of planned doses of SRA737 within Cycle 1 and those subjects receiving less than these planned doses of SRA737 due to dose-limiting toxicities (DLTs) will be evaluable for dose review decisions.
Efficacy variables:	All subjects who have measurable disease, receive at least 75% of 1 cycle of study medication and have a baseline assessment of disease plus at least 1 post-baseline assessment of disease will be evaluable for response. All subjects enrolled into one of the 6 indication-specific expansion cohorts will be evaluable for response if they have measurable, prospectively-selected genetically-defined tumors as specified in Section 4, received at least 75% of 1 cycle of study medication, have a baseline assessment of disease and at least 1 post-baseline disease assessment. In addition, subjects who have measurable disease and received at least 75% of 1 cycle of study medication but develop PD, intolerable toxicity, or death prior to the post-baseline assessment will also be considered evaluable and will be classified as nonresponders.
Safety variables:	All subjects who receive at least one dose of SRA737 will be evaluable for safety.
Other:	Pharmacokinetics: All subjects who receive at least 1 dose of SRA737 and provide 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 the full dose and does not vomit within 4-hours postdose. PK/QTc: All enrolled subjects who receive at least 1 dose of SRA737 and for whom adequate QTc and ECG data are available will be evaluable for PK/QTc analyses. Pharmacodynamics: All enrolled subjects who receive at least 1 dose of SRA737 who 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. 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.

Statistical methods and analyses (cont'd):	The analysis of all efficacy endpoints will be based on the Response Evaluable Population and will be evaluated using RECIST v1.1 criteria, or for subjects with NHL, the revised International Working Group (IWG) criteria (Cheson 2007), or for subjects with mCRPC, using a composite response rate defined as any one of the following (Scher 2016): A) Response based on RECIST v1.1; B) PSA decrease of ≥ 50%; or C) CTC count conversion. Absolute values for PSA and CTCs will be recorded at baseline and response will be analyzed based on percentage of change. The ORR will be summarized using binomial proportions and confidence intervals computed by the method of Wilson. Duration of response (DOR) is defined as the interval from the first documentation of objective response (of partial response or complete response) to the earlier of the first documentation of PD or death from any cause. 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. Other efficacy variables will be further defined in the statistical analysis plan. The PK parameters will be determined using non-compartmental method(s). Parameters, such as AUC_{inf}, AUC_{tau}, C_{min}, C_{max}, T_{max}, $t_{½}$, will be estimated and reported, as appropriate. Pharmacodynamic parameters utilizing blood and tumor tissue to analyze biomarkers to identify possible predictors of clinical outcome will be further defined in the statistical analysis plan.

2 INTRODUCTION

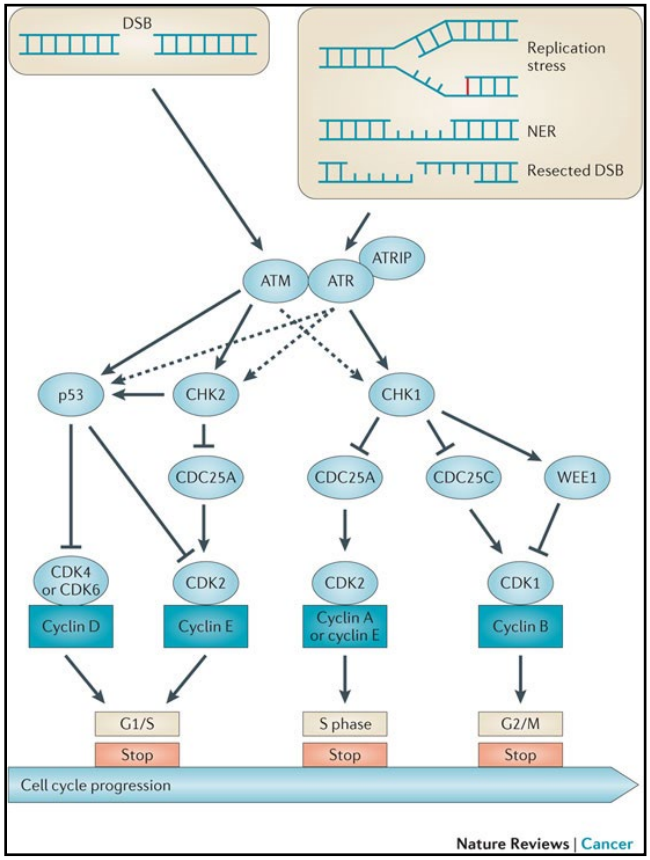
2.1 BACKGROUND

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, replication stress and 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 anti-tumor 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, whereas, the DDR to single strand breaks, stalled replication forks and DNA cross links are mediated mainly through 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, as shown in Figure 1,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). 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). Chk1 inhibitors (along with inhibitors of the upstream kinase ATR) are now in early phase trials both as monotherapies and in combination (see Section 2.4).

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



Source: Curtin 2012.

Mutations or genetic alterations in several classes of genes results in the development and maintenance of genomic instability, contributing to DNA damage and tumorigenesis (Hanahan 2011). These classes include activating mutations or amplification of growth promoting oncogenes such as *MYC, CCNE1* and *KRAS* (Negrini 2010), loss-of-function mutations or deletions in p53 and Rb tumor suppressor pathways controlling the G1/S checkpoint and defects in DDR signaling and DNA repair genes (eg, *ATM*, *BRCA1*).

While genomic instability of tumors provides a selective growth advantage by enabling adaptation, resistance and survival, these same tumor cells are dependent on remaining DDR factors and intact cell cycle checkpoints to sustain viability. An exciting therapeutic strategy is to deliberately target these remaining DDR pathways in genomically unstable tumor cells, leading to irreparable levels of DNA damage, mitotic catastrophe and subsequent tumor cell death. By targeting these remaining DDR components in the

presence of pre-existing deficits in cell cycle/DDR genes, one can achieve synthetic lethality in this highly sensitive genetic background. This approach has been validated by the recent clinical success of single agent PARP inhibitor therapy in ovarian, breast and prostate cancer patients harboring mutations in *BRCA1* and *BRCA2* (Underhill 2011).

The central role of Chk1 in DDR network signaling, including control of both S and G2/M cell cycle checkpoints, stabilization of replication forks, and aspects of homologous recombination repair, provides several avenues for achieving synthetic lethality in specific tumors. Synthetic lethality occurs when intrinsic alterations in one or more genes are coupled to targeted therapeutic inhibition of a second gene leading to cell death.

Against a variety of altered genetic backgrounds, Chk1 inhibition has demonstrated synthetic lethality as a single agent. As a widely recognized replication stress driving oncogene, *MYC* is frequently amplified in a range of tumors and has been strongly implicated in contributing to replication stress and potently enhancing sensitivity to Chk1 inhibitors (Gaillard 2015). Moreover, SRA737 (formerly known as CCT245737) and its analogues demonstrate robust single agent activity in tumor models with *MYC* or *MYCN* overexpression (Cole 2011; Derenzini 2015).

Activating mutations in *RAS* isoforms occur frequently in pancreatic, non-small cell lung cancer (NSCLC), colorectal, and other cancers and these mutations contribute to replication stress and genomic instability (Negrini 2010; Gaillard 2015). The ATR/Chk1 pathway suppresses replication stress in *RAS*-transformed cells and the Chk1 inhibitor, AZ7762, induces robust single-agent cytotoxicity in these cells (Zhang 2016). SRA737 potentiates chemotherapy-induced cytotoxicity in vivo in a lung cancer model harboring a *KRAS* activating mutation in the context of a p53 deficiency (Walton 2016). Correspondingly, *ATR* (and *Chk1* to lesser extent) is amplified in certain tumors, particularly in high-grade serous ovarian cancer (HGSOC), squamous non-small cell lung cancer (NSCLC) and head and neck squamous cell cancer (HNSCC) and may increase sensitivity to Chk1 inhibition.

Defective G1/S DNA damage checkpoints, arising through inactivation of the p53 and Rb pathways, result in synthetic lethality in the context of Chk1 inhibition. 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). Triple-negative breast

cancer and ovarian cancer cell lines with p53-deficiency display enhanced sensitivity to Chk1 inhibitors (Ma 2012). Moreover, a subject with metastatic urothelial cancer harboring a *RAD50* mutation (*ATM* deficiency) achieved a complete and durable response following treatment with a Chk1 inhibitor (AZD7762) and irinotecan (Al-Ahmadie 2014).

Lastly, genomic defects in components of the DNA repair machinery are implicated in both germline and somatic cancers and also contribute to genomic instability (Negrini 2010). Interestingly, similar to what is observed with PARP inhibitors, Chk1 phosphorylates *BRCA2* and inhibitors are synthetically lethal in cell lines deficient in *BRCA2* (Chen 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).

Collectively, these findings support the likelihood that tumors with genomic instability as a consequence of genetic alterations described above will display enhanced sensitivity to Chk1 inhibition, both as a single agent and in combination with DNA damaging agents or other DDR inhibitors.

2.2 RATIONALE FOR CHOICE OF TUMOR TYPES IN THE EXPANSION COHORTS

Preclinical xenograft data confirms the activity of SRA737 as a single-agent in diverse genetically-aberrant tumor settings including models of pediatric neuroblastoma, acute myeloid leukemia (AML), double-hit lymphoma and triple negative breast cancer. A number of genetic alterations are thought to predict sensitivity to SRA737 therapy including (i) activating mutations or amplification of growth promoting oncogenes; (ii) loss-of-function mutations or deletions in tumor suppressor pathways controlling the G1/S checkpoint; (iii) defects in DDR signaling and DNA repair genes; and (iv) gain of function mutations of replication stress genes. Tumor indications of high unmet medical need with high prevalence of these genetic aberrations include metastatic colorectal, ovarian, prostate, head and neck, and non-small cell lung cancer.

2.2.1 METASTATIC COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer worldwide, with 1,360,000 new cases diagnosed in 2012 and 693,000 deaths worldwide (Ferlay 2013).

Approximately 25% of patients present with metastatic disease at diagnosis and about 50% of patients with CRC will eventually develop metastases.

Until the last two decades, 5-fluorouracil (5-FU) with leucovorin (LV) remained the standard therapy in advanced CRC. The current approach to treating metastatic CRC (mCRC) favors the use of combination cytotoxic therapy including 5-FU, LV, and irinotecan (FOLFIRI); 5-FU, LV, and oxaliplatin (FOLFOX); capecitabine and oxaliplatin (XELOX); or 5-FU, LV, oxaliplatin, and irinotecan (FOLFOXIRI) in the first-line setting.

The treatment of mCRC has been further refined with the development of monoclonal antibodies that target the vascular endothelial growth factor (VEGF; bevacizumab) and epidermal growth factor receptor (EGFR; cetuximab and panitumumab) that have afforded improved outcomes in mCRC in the first-line and second-line setting (Gong 2016). Newest advances for previously treated patients include regorafenib, trifluridine-tipiracil and tipiracil. For example, regorafenib, an orally available multikinase inhibitor, prolonged median overall survival (OS) by 1.4 months compared with placebo (OS 6.4 months vs 5.0 months), hazard ratio (HR) = 0.77 [95% CI 0.64, 0.94]) (Grothey 2013).

Despite these recent advances, CRC remains an area of high unmet need where in late-stage disease, median OS remains less than 12 months.

Deficient mismatch repair (dMMR) of DNA is one of the genetic pathways that is involved in the development of CRC. DNA mismatch repair (MMR) is known to cause microsatellite instability (MSI). Hereditary non-polyposis colon cancer, the most common form of hereditary colon cancer, is a syndrome of deficient DNA MMR, but dMMR is also present in 10–20% of patients with sporadic CRC (Koopman 2009). Colorectal cancers with high frequency microsatellite instability (MSI-H) generally have a better prognosis and are more likely to respond to immunotherapy. To date, more than 300 different predisposing MMR gene mutations are known across 5 or possibly 6 human MMR genes, mainly affecting the MMR genes *MLH1*, *MSH2*, and *MSH6*. Universal screening in newly diagnosed CRC is recommended by many experts (Wang 2016).

Activating mutations or amplification of known oncogenic drivers such as *MYC* and *KRAS* are frequent in colorectal cancer at rates of 20% for *MYC* and 30-50% for *KRAS*. Aberrant activation of these oncogenic drivers have been strongly linked to sensitivity to Chk1 inhibition (Dietlein 2015, Gilad 2010).

Genetic mutations in CRC, in particular mutations of *KRAS*, p53, or in MMR genes allow for replication errors or instability in repeat DNA sequences in the cellular pathways of interest, which makes this indication an ideal therapeutic target for a Chk1 inhibitor, such as SRA737.

2.2.2 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 based on response greater than 6 months following, within 6 months following, or during platinum-based chemotherapy, respectively.

Patients with platinum-resistant disease have a poor prognosis with a short expected median 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 3–4 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 high-grade serous ovarian cancer (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). A specific expansion cohort of subjects with HGSOC and an eligible genetic profile including *CCNE1* amplification, in addition to a separate expansion cohort of subjects with HGSOC with other eligible genetic profiles, will be enrolled in this study of SRA737.

2.2.3 METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Prostate cancer is the fourth most common cancer worldwide, with 1,112,000 new cases diagnosed in 2012 and 307,000 deaths worldwide (Ferlay 2013).

In metastatic castration-resistant prostate cancer (mCRPC), patients have developed resistance to standard androgen deprivation therapies. There are several recent therapies that have demonstrated improved OS for patients with mCRPC including agents that target the androgen receptor pathway such as abiraterone acetate and enzalutamide, as well as cabazitaxel, a dendritic cell vaccine, Sipuleucel-T, and bone-targeted radiopharmaceutical treatment, radium Ra 223 dichloride (Beer 2014, Parker 2015, Ryan 2013, Tannock 2004). Abiraterone acetate and enzalutamide have become common first-line therapies for mCRPC because of their tolerability and efficacy in the pre-chemotherapy setting. Following androgen receptor-targeted therapy, systemic chemotherapy with docetaxel plus prednisone is also an available therapy, but it appears to be less effective in the post-abiraterone or enzalutamide setting, with median progression-free survival (PFS) of approximately 4.5 months (Suzman 2014) and carries with it toxicities of Grade 3 or Grade 4 neutropenia, sensory neuropathy, stomatitis, diarrhea and fatigue (Tannock 2004).

There is therefore a great need to develop novel therapeutic strategies to treat mCRPC, but also to develop biomarker strategies to stratify patients for optimal therapy. Key tumor suppressor proteins such as *TP53* and *RB1* were found to be mutated in 51 and 27% of over 50 patient samples, respectively. *MYC*, an oncogenic driver linked to Chk1 sensitivity was mutated in 20% of patient samples. BRCA2 was also found to be altered in roughly 12% of patient samples (Grasso 2012). Analysis of another cohort of 150 mCRPC patients revealed that approximately 90% of cases harbor actionable mutations, including aberrations in DNA repair genes such as BRCA1, BRCA2, and ATM in 19.3% of subjects (Geethakumari 2016). Genetic mutations in prostate cancer and the resulting alterations in the cellular pathways of interest, make this indication an ideal therapeutic target for a Chk1 inhibitor, such as SRA737.

2.2.4 NON-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). The predominant form of lung cancer is NSCLC which accounts for 70 to 80% of all lung cancers. NSCLC is further stratified into

squamous and adenocarcinoma subtypes. Unfortunately, a majority of patients with lung cancer are diagnosed with inoperable disease and they are treated with palliative chemotherapy.

The ESMO guidelines for the management of advanced/metastatic disease, suggest that treatment should take into account a range of factors including histology, molecular pathology, age, performance status (PS) and co-morbidities. Systemic therapy should be offered to all Stage 4 patients with PS 0–2 (Reck 2014).

For the vast majority of patients with advanced or metastatic disease (40–50% of all patients at time of diagnosis), platinum-based chemotherapy is associated with a median survival of about 10–11 months. Advances have been made with the introduction of targeted therapies in small subsets of patients with NSCLC with EGFR mutations (Maemondo 2010) and anaplastic lymphoma kinase (ALK) rearrangements (Solomon 2014) who are treated with EGFR and ALK inhibitors respectively. The use of newer cytotoxic agents such as pemetrexed, the introduction of maintenance therapy, and most recently, the use of immune therapies such as antagonist antibodies to programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) led to further improvement of OS. Nonetheless, even with these therapies, the majority of patients with NSCLC do not attain prolonged disease control (Dempke 2016).

Despite recent advances, finding new treatments for previously treated patients remains an area of unmet medical need. The Cancer Genome Atlas Project characterized over 175 lung squamous cell carcinoma patient samples for genetic signatures. The major tumor suppressor genes, *TP53* and *CDKN2A*, were found to be altered in 94% and 44% of patient samples, respectively. Additionally, roughly 16% of patients had gain of function mutations in key oncogenic drivers (*MYC*, *KRAS*, *CCNE1*). *ATR* was amplified in 18-19% of patient samples, and BRCA1 and BRCA2 were found to be mutated in roughly 6% of patients (TCGA 2012). Samples from patents with adenocarcinoma of the lung show generally lower but not insignificant rates of these mutations: *TP53* 47%; *CDKN2A* 24%; *MYC* 10%, *KRAS* 30-35%; *ATR* 5-6%, *BRCA*1 3%, and *BRCA2* 6% (TCGA 2014). Genetic mutations in NSCLC and the resulting alterations in the cellular pathways of interest, makes this indication an ideal therapeutic target for a Chk1 inhibitor, such as SRA737.

2.2.5 HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC) AND SQUAMOUS CELL CARCINOMA OF THE ANUS (SCCA)

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer worldwide, with approximately 550,000 new cases diagnosed in 2008 and 300,000 deaths worldwide (Jemal 2011).

The classification of sites in tumors of the oral cavity, oropharynx, pharynx, and hypopharynx varies in the literature. More than 90% of these tumors of the mucosal lining are classified as squamous cell carcinoma developed from premalignant lesions such as leukoplakia and erythroleukoplakia (Lambert 2011). Ninety percent of cancers that are known collectively as head and neck cancers are usually of squamous histology.

The prognosis of patients with recurrent or metastatic HNSCC is generally poor. The majority of HNSCC patients present with locally advanced disease for which multimodality therapeutic approach is employed. Despite advances in multimodality treatment, the 5-year progression-free survival rate of patients with HPV-negative locally advanced HNSCC does not exceed 40%–50% (Economopoulou 2016). The median OS for recurrent or metastatic HNSCC remains less than 1 year despite modern chemotherapy and targeted agents.

As per ESMO guidelines, options for fit patients with recurrent or metastatic HNSCC should include the combination of cetuximab with cisplatin or carboplatin plus 5-fluorouracil (Gregoire 2010). The recommendation to include cetuximab in combination with chemotherapy for patients with recurrent or metastatic disease is based on the results of the EXTREME study (Vermorken 2008) comparing cetuximab with chemotherapy (cisplatin or carboplatin and 5-FU) or chemotherapy alone. Patients receiving cetuximab with chemotherapy lived an average of 10.1 months, compared with 7.4 months for those receiving chemotherapy only ($p = 0.04$).

In patients for which polychemotherapy tolerability is anticipated to be poor, mono-chemotherapy such as weekly methotrexate or taxanes should be used. Cetuximab alone has a favorable toxicity profile with activity that is comparable to methotrexate alone (Gregoire 2010).

Recent therapeutic advances include nivolumab and pembrolizumab, PD-1 inhibitors which have shown clinically significant activity in patients who progressed on or after platinum-based regimens. In a pivotal Phase 3 trial of nivolumab versus standard, single-agent

systemic therapy (methotrexate, docetaxel, or cetuximab), the median OS was 7.5 months (95% CI, 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the group that received standard therapy. Overall survival was significantly longer with nivolumab than with standard therapy (HR for death, 0.70; 97.73% CI, 0.51 to 0.96; p = 0.01) (Ferris 2016).

Given the poor prognosis for most patients with recurrent or metastatic HNSCC and limited treatment options, novel approaches are needed. When over 250 clinical samples were profiled by The Cancer Genome Atlas Project for Head and Neck Squamous cell carcinomas, it was found that 50% of the samples had loss of function for the tumor suppressors *TP53* and *CDKN2A*. Additional mutations of interest were amplification of *MYC* (13%) and sporadic loss of key proteins within the DDR pathway (*BRCA1*, *BRCA2*, *ATM* 2-4%) (TCGA 2015). Genetic mutations in HNSCC and the resulting alterations in the cellular pathways of interest, makes this indication an ideal therapeutic target for a Chk1 inhibitor, such as SRA737.

In contrast to HNSCC, squamous cell carcinoma of the anus (SCCA) is rare. New cases of anal cancer in the USA were estimated at 8200 for 2017 (Siegel 2017) and 1300 new cases of SCCA were diagnosed in the UK in 2014 (Cancer Research UK 2017). Squamous cell carcinoma is the most common pathology for cancers of the anus and the incidence is increasing worldwide; estimated to have risen by 5.9% per year between 1992 and 2000 in the USA (Kang 2007). More than 90% of SCCA cases are associated with HPV infection and the high prevalence of HPV infection is implicated in the increase in SCCA (Nelson 2013, Julie 2016).

Therapy with a combination of cisplatin and 5FU is the standard for metastatic disease (NCCN guidelines 2017). Active investigation into improved therapies is ongoing. However, currently the 5-year OS rates for subjects with advanced disease are below 20% and there is an unmet need for effective therapies with active investigation into improved therapies ongoing (Julie 2016).

A Phase 1b expansion cohort study with the Chk1 inhibitor prexasertib included a subset of 24 patients with advanced SCCA (Martinez 2017). In this subset, the disease control rate based on RECIST Criteria v1.1 (ie, Complete Response [CR] + Partial Response [PR] + Stable Disease [SD]) was 75% (18/24) including one CR and 4 PRs. Next generation

sequencing of pretreatment tumor tissue identified genetic alterations corresponding to three pathways (cell cycle, DDR and PI3K) that were notably associated with favorable response. Known or likely loss-of-function mutations in FBXW7 and PARK2, two genes involved in Cyclin E1 proteolysis, were found in patients with a favorable response. Mutations and/or germline variants in multiple DDR genes (BRCA1, BRCA2, MRE11A and ATR) but not in FANC pathway genes were also found in patients with a treatment benefit. In addition, PIK3CA mutations were observed at a higher frequency in patients with SCCA who exhibited a treatment benefit. These clinical and genomic profile findings support the hypothesis that oncogene-induced replication stress in the context of attenuated DDR may sensitize patients to Chk1 inhibitor monotherapy and provide a rationale for treating SCCA patients with SRA737 monotherapy.

2.3 INVESTIGATIONAL MEDICINAL PRODUCT: SRA737

SRA737 is a potent, highly selective, orally bioavailable small molecule inhibitor of Chk1. The agent was developed through collaboration between The Institute of Cancer Research 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 combination therapy in subjects with solid tumors (NCT02797977).

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

2.3.1 MECHANISM OF ACTION OF SRA737

SRA737 is a highly selective, orally bioavailable small molecule inhibitor of Chk1, a serine-threonine kinase enzyme that acts as a central regulator of the DDR network. In cancer cells, replication stress induced by oncogenes (eg, *MYC* and *RAS* oncogenes) combined with loss of function in tumor suppressors (eg, *p53* and *ATM* tumor suppressor genes) results in persistent DNA damage and genomic instability. Chk1 has an important role in the S phase checkpoint where it stabilizes and preserves replication fork complexes following replication stress, preventing catastrophic replication fork collapse. Targeted inhibition of the remaining components of the DDR network such as by SRA737 may be synthetically lethal to cancer cells and have utility as a monotherapy in a range of tumor indications. Preclinical studies have demonstrated that SRA737 is a potent inhibitor of Chk1 which

abrogates etoposide-induced G2/M cell cycle checkpoint arrest in HT-29 colon cancer cells at nanomolar concentrations.

2.3.2 NON CLINICAL PHARMACOLOGY

2.3.2.1 Efficacy/Primary Pharmacology

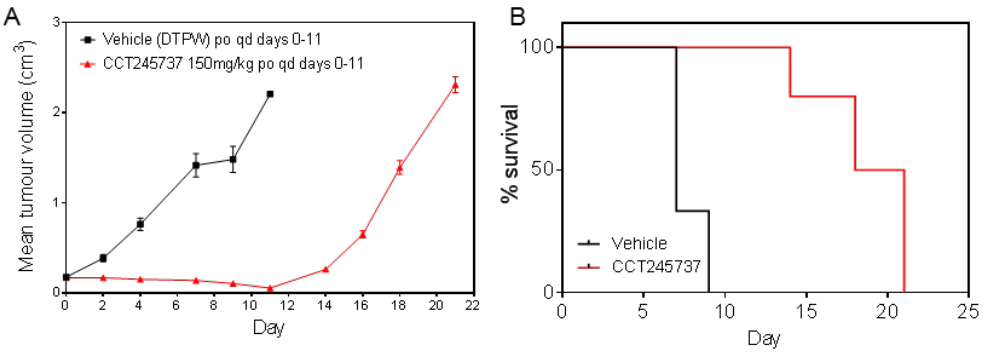
SRA737 is a potent and selective inhibitor of Chk1 (half maximal inhibitory concentration [IC_{50}] < 10 nM) with minimal activity against Chk2. Off-target kinase screening studies have also confirmed the selectivity of SRA737 across the broader kinome.

As previously mentioned, Chk1 inhibitors may exhibit single agent activity in defined tumor genetic backgrounds exhibiting high levels of replication stress including those with activating mutations in genes such as *MYC* or *KRAS*, loss-of-function mutations in tumor suppressor genes such as *TP53* or *ATM*, or defects in other DNA repair genes. This concept has been verified using siRNA knockdown of Chk1 and several Chk1 inhibitors in tumor types including AML, cMyc driven lymphomas, N-Myc regulated neuroblastomas and various solid tumors (Cavelier 2009, Ferrao 2012, Murga 2011, Cole 2011, Brooks 2013, Davies 2011, Hoglund 2011). Tumor cells deficient in homologous recombination and Fanconi anemia pathway genes were shown to be hypersensitive to Chk1 inhibition (Krajewska 2014, Chen 2009). Enhanced sensitivity to Chk1 inhibition may also be linked to loss-of-function in *ATM* or genes in the ATM DDR pathway such as *RAD50* (Al-Ahmadie 2014). Inactivation of ATM and CHK2 is associated with tumor growth, in contrast, amplification and activation of *ATR* and *CHEK1* is correlated with increased tumorigenesis (Manic 2015). In the context of monotherapy, prolonged inhibition of Chk1 is expected to be required rather than transient inhibition after genotoxic induced DNA damage. Accordingly, SRA737 is being investigated as a monotherapy for use in tumors exhibiting a high degree of replicative stress using a continuous daily schedule.

The single agent activity of SRA737 has been investigated in a number of murine xenograft models harboring genetic alterations likely to sensitize tumor cells to Chk1 inhibition, as follows:

The activity of SRA737 was assessed in the MOLM13 xenograft model of AML. Daily administration of SRA737 (150 mg/kg orally [PO] for 11 days) led to tumor regression and an approximate tripling of murine PFS compared to control animals (Figure 2).

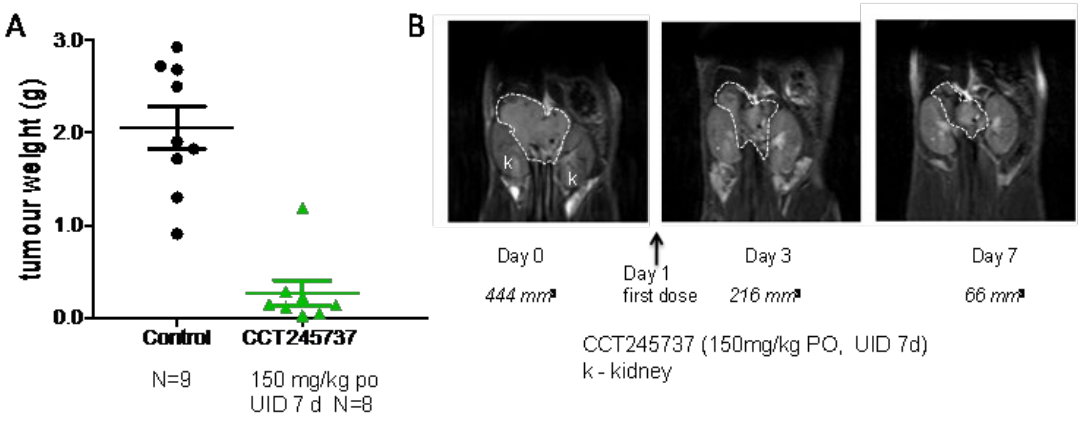
Figure 2. SRA737 (formerly CCT245737; 150 mg/kg/day PO) inhibits the growth of the MOLM 13 model of AML.



A) Tumor growth over the course of the study B) Kaplan Meier survival analysis

The activity of SRA737 was also assessed in a spontaneous, genetically-engineered murine model of N-Myc-driven neuroblastoma (Cole 2011). Administration of the compound at 150 mg/kg PO for 7 days resulted in significant reduction in tumor burden (Figure 3A). Magnetic resonance imaging (MRI) of a single tumor before and after treatment with SRA737, confirmed these findings with an 85% reduction in tumor volume (Figure 3B).

Figure 3. SRA737 (formerly CCT245737; 150 mg/kg PO) inhibits the growth of N MYC driven neuroblastoma in a genetically engineered mouse model

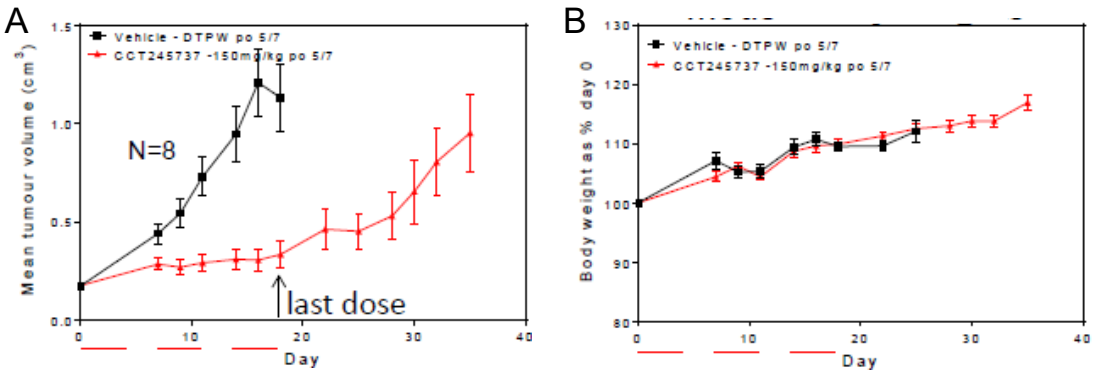


(A)Tumor growth (B) Tumor volume imaged by MRI pre and post treatment with SRA737 (150 mg/kg PO) in a single mouse

Similar findings were also noted in an Eu-Myc model of lymphoma where a significant reduction in tumor mass in the inguinal, brachial, mesenteric and cervical lymph nodes was observed (data not shown).

SRA737 has also shown activity as a single agent in an orthotopic solid tumor model (triple negative breast cancer MDA-MB-231). Significant antitumor activity of SRA737 (150 mg/kg PO for 3 cycles of 5 days) was noted during the extended dosing period as shown in Figure 4.

Figure 4. Antitumor efficacy of SRA737 (formerly CCT245737) in the MDA MB 231 orthotopic triple negative breast cancer xenograft model.

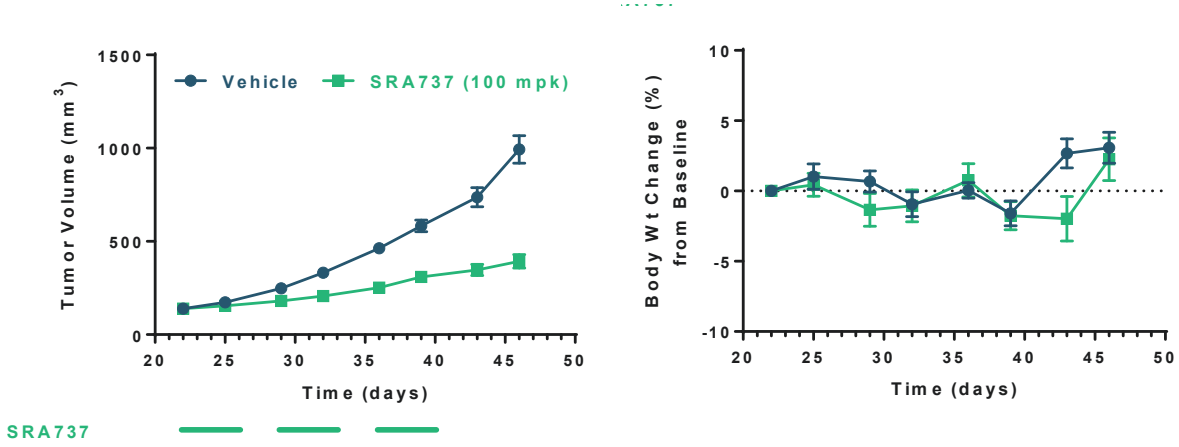


A) mean tumor volume

B) mouse body weight

The anti-tumor activity of SRA737 monotherapy was evaluated in the OVCAR-3 xenograft model of HGSOC. This tumor cell line was derived from a platinum insensitive patient and harbors an amplification of *CCNE1* (encoding cyclin E) and mutation in TP53 (encoding p53), two genomic alterations reported to contribute to Chk1 inhibitor sensitivity. Treatment of OVCAR-3 tumor-bearing mice with SRA737 (100 mg/kg for 3 cycles in a 5 days on, 2 days off schedule) was well tolerated as demonstrated by minimal body weight loss and resulted in tumor growth inhibition. On Day 46, a significant tumor growth inhibition of 60% relative to vehicle treated mice was observed ($P<0.0001$), as shown in) Figure 5.

Figure 5. Tumor growth inhibition with SRA737 in the OVCAR-3 tumor-bearing mouse model.



Note: Average tumor volume and body weight change (+/- SEM) with n=10 per treatment group.

In summary, SRA737 has demonstrated significant antitumor activity (including some tumor stasis and minor regression) in a variety of murine xenograft studies. Analysis of various DDR markers confirmed this activity was directly related to SRA737's mechanism of action. Initial pharmacokinetics/pharmacodynamics (PK/PDn) assessment suggests that sustained circulating plasma concentrations above 100 nM are required to significantly inhibit Chk1 autophosphorylation for a 24-hour period.

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 and induction 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 <u>In Vitro Metabolism</u>

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 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 (CYP) 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).

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 quantitative reverse transcription PCR. Minimal, concentration-dependent increases in CYP1A2 mRNA levels (up to 7-fold fold at 30 μM SRA737; EC_{50} = 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 (EC_{50} = 2.1 μM; 46% maximal effect of serotonin) likely renders this observation of limited toxicological significance in the intended subject 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-glycoprotein, and that favorable absorption following oral administration to humans is likely.

2.3.4 IN VIVO PHARMACOKINETICS

The pharmacokinetics (PK) of SRA737 have been determined in the mouse, rat, dog and monkey following oral and intravenous administration (Table 1). Very favorable absolute oral bioavailability (%F) was noted, particularly in the mouse (105%), dog (86%) 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 (≈ 3-5 h). Further studies in mice confirmed dose linearity in pertinent pharmacokinetic parameters over the range of 50 to 300 mg/kg orally administered.

Table 1. 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	-
	PO (10 mg/kg)	2.9	0.61	3.94	105
Rat	IV (5 mg/kg)	1.0	-	1.38	-
	PO (10 mg/kg)	4.6	0.19	1.17	42
Dog	IV (1 mg/kg)	2.8	-	0.20	-
	PO (10 mg/kg)	3.5	0.13	0.85	86
Monkey	IV (1 mg/kg)	5.3	-	1.52	-
	PO (2 mg/kg)	5.0	0.50	2.73	90
	PO (10 mg/kg)	5.1	2.64	15.8	104

%F = absolute oral bioavailability; $AUC_{(0-t)}$ = exposure; C_{max} = maximum observed plasma concentration; IV = intravenously; PO = orally; $t_{1/2}$ = terminal elimination half-life.

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 and 4.2 µM [2.4 and 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) in an isolated rabbit Purkinje fiber model 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 anaesthetized 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-clinical 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 oral 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 0.6 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), because of the sporadic natures 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 ECG waveform or intervals. Mean circulating plasma levels at the approximate time ECGs were recorded (≈ 4 h 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, cardiovascular safety assessments are included in the ongoing Phase 1/2 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's Brochure.

2.3.6.1 28-Day Mouse Study

The toxicity and population toxicokinetics 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 75mg/kg/day (≈ 30, 120, or 215mg/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, 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 tract in this 28-day study. It should be noted that apoptosis of cells in the gastrointestinal tract (GIT) 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 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 Maximum Tolerated Dose (MTD) in this study was 75 mg/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 toxicokinetics of SRA737 when administered in combination with intravenous gemcitabine and cisplatin on an intermittent schedule over 18 days. Male and female animals were administered SRA737 orally 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 white blood cell 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 total exposure (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 toxicokinetics of SRA737 following daily oral 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 (namely 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, GIT and lung, or septicemia was noted in the premature decedent animals.

A decrease in red blood cell 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 40 and 75 mg/kg 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 µg/mL to 0.6 µg/mL and total exposure (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 (≈ 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 were noted. These findings were reversible on cessation of drug administration.

Toxicological findings in the monkey, the most appropriate non-rodent toxicity species, indicated SRA737 had the potential to cause findings similar to those observed in mouse and minipig although at much higher doses.

Toxicological findings in the GIT 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 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.

2.3.7 RATIONALE FOR THE SELECTION OF THE STARTING DOSE AND SCHEDULE

The murine toxicity studies indicated a SRA737 MTD of 75 mg/kg/day (≈ 225 mg/m^2/day) as a single-agent. The International Conference on Harmonisation (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 (HED) of 22.5 mg/m^2/day (0.61 mg/kg/day) equating to an absolute dose of 36mg (for a 60 kg patient) could be utilized. For the further assurance of patient safety, a lower starting dosing of 20 mg was selected.

Using similar allometric scaling, pharmacologically-active concentrations of SRA737 may occur at clinical doses of approximately 80 mg to 160 mg. Based on the nonclinical toxicity studies, the most likely target organs for SRA737 toxicity are the bone marrow and GIT.

2.4 CLINICAL EXPERIENCE

SRA737 had not been administered to humans prior to the initiation of this 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 was the subject of 7 Phase 1 and 2 clinical studies both as monotherapy and in combination with various chemotherapeutic agents and radiotherapy as this current SRA737 study was activated. 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. Data from this study had not been reported at the time of activation of this current SRA737 study.

The proposed trial design for SRA737 as a monotherapy is consistent with several previous studies of Chk1 inhibitors. Based on the limited existing clinical data from second-generation clinical programs, myelosuppression may be anticipated to occur in the clinical trial of SRA737 as a monotherapy.

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

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, 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 define the RP2D for SRA737, while also evaluating which patients are most likely to benefit from treatment. Specific cohort expansion indications have been selected as being most likely to represent potential areas for SRA737 monotherapy efficacy, and the diagnostic test will be explored as a means to identify patients with 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. In cancer cells, replication stress induced by oncogenes (eg, *MYC* and RAS oncogenes) combined with loss of function in tumor suppressors (eg, TP53) results in persistent DNA damage and genomic instability, a trigger of the DDR network. Targeted inhibition of the remaining components of the DDR network such as Chk1 by SRA737 may be synthetically lethal to cancer cells and thus may have utility as a monotherapy in a range of tumor indications particularly in tumors with high rates of replication stress and genomic instability.

A body of experimental data supports the exploration of SRA737 as a single agent particularly in a molecularly-defined population. This first-in-human dose escalation study will be enriched in dose expansion cohorts with prospectively-selected genetically-defined subjects in tumor types that are known to have a high prevalence of genomic aberrations hypothesized to sensitize the tumor to Chk1 inhibition. Prospective selection of patients most likely to derive benefit from SRA737 will provide data to support the selection of specific indications and inform refinement of patient selection strategies in further clinical development. The indications for the expansion cohorts have been selected both on the scientific hypothesis of greater likelihood for benefit, as well as the high unmet medical need in these populations where alternative therapies are required.

Recent non-clinical toxicology data generated in the monkey, the most representative species for toxicity assessment of SRA737, indicate favorable tolerability at daily oral doses of 20 mg/kg, where mean C_{max} and AUC values reached 3.2 µg/mL (≈ 8 µM) and 24 µg.h/mL (≈ 65 µM.h), respectively. In contrast, clinical C_{max} and AUC values of 1.1 µg/mL and 9 µg.h/mL were observed in the 600mg clinical dosing cohort (n=1), indicating a favorable exposure safety margin with considerable opportunity for ongoing dose escalation during the clinical study.

The likely target organs for SRA737 toxicity are the bone marrow and the GIT, both of which will be closely monitored in the ongoing study. Although no significant nonclinical cardiac liabilities have been observed in the benchmark non-rodent toxicity studies, cardiovascular safety assessments are included in this Phase 1/2 clinical study as a precaution. The rationale for the starting dose and schedule of SRA737, based initially on preclinical data, is provided in Section 2.3.7.

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 (AEs, Section 5.4).

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

3 TRIAL DESIGN

3.1 CLINICAL TRIAL OBJECTIVES AND ENDPOINTS

3.1.1 PRIMARY OBJECTIVES AND ENDPOINTS

Primary objectives	Endpoints
To establish the safety profile of SRA737	Safety parameters (referencing National Cancer Institute – Common Terminology Criteria for Adverse Events [NCI-CTCAE] v4.03) including: incidence, seriousness, severity and causality of each AE to SRA737, 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 with 1 or more schedules of administration of SRA737	The highest dose at which ≤ 33% of subjects have a dose limiting toxicity (DLT) in a cohort of up to 6 subjects
To propose a recommended Phase 2 dose and schedule of SRA737	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
To evaluate the preliminary efficacy of SRA737 including efficacy in prospectively-selected genetically-defined subjects enrolled into indication-specific expansion cohorts	Objective response rate (ORR) Disease control rate (DCR) Time to response (TTR) Duration of response (DOR) Progression-free survival (PFS) Time to progression (TTP) Overall survival (OS)

3.1.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary objectives	Endpoints
To characterize the pharmacokinetic profile of SRA737	Plasma concentration-time profile based on PK parameters including, but not limited to: AUC_{inf}, AUC_{tau}, C_{max}, C_{min}, T_{max}, and $t_{1/2}$
To assess the relationship between response and the presence of selected genetic alterations detected in tumor tissue and/or circulating tumor deoxyribonucleic acid (ctDNA)	ORR and gene alterations in tumor tissue or ctDNA at baseline as measured by next generation sequencing (NGS)

3.1.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory objectives	Endpoints
To investigate the pharmacodynamics of SRA737 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 pharmacodynamics of SRA737 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: pS317 Chk1, pS345 Chk1, total Chk1, gammaH2AX and RAD51
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 explore the relationship between exposure (PK) and QT/QTc, other electrocardiogram (ECG) parameters and cardiovascular safety findings	Association of QT, QTc, blood pressure (BP), heart rate, other ECG intervals with time-matched PK concentrations. Profile of QTc over the dosing interval

3.2 DESIGN OF THE CLINICAL TRIAL

This is a multicenter, first-in-human, Phase 1/2, open-label, dose-escalation trial in subjects with advanced solid tumors or non-Hodgkin lymphoma (NHL), with cohort-expansion phase in 6 indication-specific expansion cohorts (Figure 6). The trial will consist of 2 stages:

- Stage 1: A Dose Escalation Phase.

  It is expected that between 30 and 50 subjects with solid tumors or NHL will be enrolled in the Dose Escalation Phase of the study.

  Intensive PK and ECG monitoring for QTc assessments will be collected from all enrolled subjects, beginning with sampling before and after a single dose of SRA737 given on one day between Day -7 and Day -4. Tissue (archival or fresh) and blood will be collected for retrospective biomarker analyses.

Cohorts consisting initially of a single subject will receive escalating doses of SRA737, starting in Cohort 1 with 20 mg/day administered orally on a continuous daily dosing schedule in 28-day cycles. The dose will be escalated until the MTD has been identified, unless determined otherwise by the Sponsor in consultation with the Chief Investigator, for example, if an alternative schedule is pursued instead.

Once a SRA737-related, Grade 2 toxicity is observed in a dose escalation cohort during Cycle 1, that cohort will be expanded to 3 to 6 subjects, and subsequent dose level cohorts will follow a rolling 6 design. See Section 3.3 for additional details.

Dose escalation with an alternative schedule may begin at any time and may either run in parallel or instead of continued escalations in the continuous schedule.

The final number of subjects enrolled into the trial is dependent on the number of dose levels explored in the Dose Escalation Phase.

- Stage 2: A Cohort Expansion Phase.

  Approximately 120 subjects will be enrolled into the Cohort Expansion Phase which consists of 6 indication-specific expansion cohorts of approximately 20 prospectively-selected genetically-defined subjects each (namely, subjects with previously treated metastatic CRC, HGSOC without *CCNE1* gene amplification, HGSOC with *CCNE1* gene amplification (or alternative genetic alteration with similar functional effect), mCRPC, advanced NSCLC, and HNSCC/SCC). This allows for a preliminary exploration of the efficacy of SRA737.

  Intensive PK and ECG monitoring for QTc assessments will be performed for subjects in the Cohort Expansion Phase. However, the Sponsor may reduce or modify the requirements for PK sampling, including elimination or modification of the Day -7 to Day -4 visit, once sufficient data to evaluate the PK of SRA737 have been collected and analyzed. If this occurs, the modified requirements will be documented by an update to the appropriate study documents.

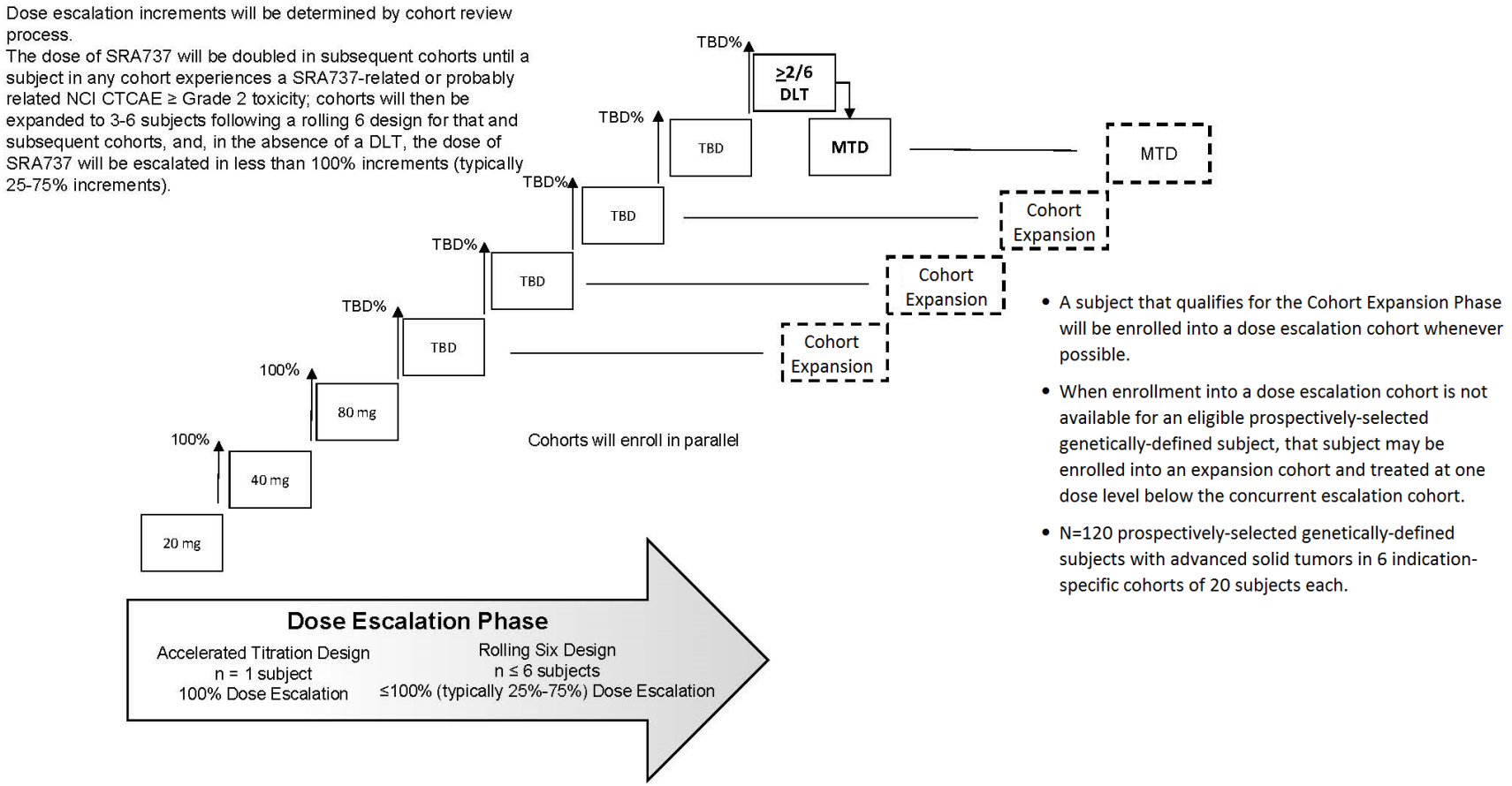
  Tissue (archival or fresh) and blood will be collected for prospective genetic analyses to determine eligibility. See Section 7 for more details.

  Prospective determination of tumor genetics to determine eligibility of subjects within the selected indications may begin prior to the completion of dose escalation. Enrollment to the Dose Escalation and Expansion Cohorts may occur in parallel. A subject that qualifies for the Cohort Expansion Phase will be enrolled into an Escalation Cohort whenever possible. Any such subject will be considered to have enrolled in both phases simultaneously. Only when a dose escalation enrollment slot is not available for an eligible prospectively-selected genetically-defined subject, that subject may be enrolled to an expansion cohort and treated with SRA737 at the highest dose level previously determined to be safe. Intra-subject dose escalation is allowed for these, and for all, study subjects when a higher dose level has been determined to be safe in a cohort of Dose Escalation subjects.

  Enrollment into the Expansion Cohorts requires that each subject's tumor has evidence of a combination of mutations which are expected to confer sensitivity to

Chk1 inhibition. Eligibility will be determined by the Sponsor's review of genetic abnormalities listed in Appendix 6.

Figure 6 Study Design



DLT= dose-limiting toxicity, NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, TBD = to be determined, MTD = maximum tolerated dose

3.3 DOSE ESCALATION PHASE

The Dose Escalation Phase will begin with an accelerated titration design which allows for single subject cohorts and 100% dose escalation increments if the previous dose level is determined to be safe by the cohort review process. The dose of SRA737 will be doubled in subsequent cohorts until a subject in any cohort experiences a SRA737-related or probably related National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 or greater toxicity during Cycle 1; cohorts will then be expanded to 3 to 6 subjects following a rolling 6 design for that and subsequent cohorts. In the absence of a DLT, the dose of SRA737 will be escalated in less than 100% (typically 25–75%) increments. The extent of the dose increase will be informed by the Cohort Review Committee.

Once the first subject in each rolling 6 cohort has completed an observation period of 7 days of continuous dosing (Days 1–7 inclusive), or a similar duration of observation on an alternative schedule, subsequent subjects may start treatment unless the Sponsor determines that safety findings in the first subject in that cohort warrants other action. With the exception of the single subject cohorts, a minimum of three evaluable subjects must have completed one cycle in order to decide to escalate the SRA737 dose. The minimum possible time between dose escalation cohorts is therefore 5 weeks.

Subjects who receive less than 75% of their planned doses in Cycle 1 for reasons other than SRA737-related toxicity will not be evaluable for assessment of DLT for dose review decisions and may be replaced in the cohort. Safety information for these subjects will, however, be considered to guide the extent of the dose increase.

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, and principal 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 the 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

as a minimum the chief investigator 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. DLTs will be the primary consideration for the purposes of dose escalation decisions; however, should cumulative toxicity become apparent this will also be taken into consideration.

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;
- Whether subjects receiving subsequent cycles of SRA737 at lower dose levels could be allowed to proceed with intra-subject dose escalation.

3.3.2 DOSE ESCALATION DECISION RULES

The dose level of SRA737 will be assigned according to the number of subjects already enrolled at the current dose level, the number of DLTs (and any other drug-related AEs) observed at the current dose level and the number of subjects enrolled who are at risk of developing a DLT. When sufficient data, as determined during the Cohort Review Meeting, are available to assess these in the rolling 6 cohorts, the subsequent SRA737 dose level will be assigned according to the following:

- 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 can be considered.
- If the data are available from 3 subjects who have been treated in a cohort and one DLT has been observed at that dose level, then the cohort will be expanded to up to 6 subjects.
- If two DLTs have been observed at any dose level, dose escalation will stop and this dose will be defined as the maximum administered dose for that schedule.
    - The dose will be de-escalated and the previous dose level will be expanded to up to 6 subjects. If the previous dose level already included a cohort of 6 subjects, then this could be identified as the MTD unless it is decided that an intermediate dose level would be tested.
    - An intermediate dose level between the previous and current dose level may be explored following full discussion between the Sponsor and Chief Investigator.
- The maximum administered dose could also equal the MTD in the event that dose escalation is stopped before 2 DLTs are observed at a given dose level, due to the expectation that higher dose levels would be too toxic to administer to subjects.

3.4 DEFINITION OF DOSE LIMITING TOXICITY

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

A DLT is defined as any highly probably or probably SRA737-related 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 per Cohort Review discussion:
  - Alopecia of any grade
  - Grade 3 or 4 nausea or vomiting in subjects that have not received optimal treatment with anti-emetics
  - Grade 3 or 4 diarrhea in subjects that have not received optimal treatment with anti-diarrheal medication
  - Transient, asymptomatic Grade 3 biochemical abnormalities if agreed by the Medical Monitor and the Chief Investigator
  - Grade 3 fatigue, unless there is an increase by at least 2 grades from baseline (classed as the grade prior to first dose)
- Inability to receive 75% of planned dose in the first cycle during the DLT window due to drug-related toxicity

DLTs 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 delegate 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 RECOMMENDED PHASE 2 DOSE AND SCHEDULE

If 2 out of up to 6 subjects at the same dose level experience a DLT, as defined above, the MTD will be determined as a lower dose level for that schedule.

The RP2D and schedule 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 for the selected schedule.

3.6 COHORT EXPANSION PHASE

Prospectively-selected genetically-defined subjects will be enrolled in 6 indication-specific expansion cohorts to establish the safety profile and preliminary efficacy of SRA737. Each expansion cohort will enroll approximately 20 subjects from the following indications: metastatic CRC, HGSOC without *CCNE1* gene amplification, HGSOC with *CCNE1* gene amplification, mCRPC, advanced NSCLC, or HNSCC/SCCA.

Screening for expansion cohorts will be initiated prior to the completion of dose escalation and determination of MTD or RP2D. If a slot is not available in the Dose Escalation Cohort, eligible prospectively-selected genetically-defined subjects will be enrolled in the Expansion Cohort 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.

The goal of the expansion cohorts is to assess SRA737 across multiple tumor types in subjects who have a range of genomic profiles of interest as described in inclusion criterion 9. The sponsor may choose to refine or select particular genomic profile requirements in each (or all) Expansion Cohort(s) 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 choose to 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 BRCAm and BRCAwt).

3.7 INTRA-SUBJECT DOSE ESCALATIONS

Once a higher dose level has been determined to be safe in a cohort of Dose Escalation subjects, subjects who have not experienced ≥ Grade 2 SRA737-related toxicity at the dose at which they are currently being treated, in the most recent prior cycle, are able to escalate to the next higher dose level for that schedule once the sponsor approves the escalation. Only one dose level increase can be undertaken each cycle.

This intra-subject escalation will be to a dose level already evaluated at a Cohort Review Meeting and found to be acceptable from a safety perspective. If the subject(s) then goes on to experience an event meeting the definition of DLT, this information will be taken into account for future dose escalation decisions.

3.8 SUBJECT EVALUABILITY

3.8.1 DLT EVALUABLE

All subjects receiving at least 75% of planned doses of SRA737 within Cycle 1 and those subjects receiving less than these planned doses of SRA737 due to DLT will be considered 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 less than 75% of planned doses of SRA737 during the DLT period for reasons other than drug-related toxicity.

In the Cohort Expansion Phase, subjects who are not response-evaluable may be replaced in order to achieve 20 response-evaluable prospectively-selected genetically-defined subjects per 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 system by site staff and be allocated a subject number by the electronic data capture system. Once the investigator or designated representative has confirmed the eligibility of the subject, the site must submit a completed eligibility checklist, and receive

confirmation of eligibility for a dose escalation cohort, an indication-specific cohort expansion, or both, 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

The study will enroll up to 170 subjects including an estimated 30–50 subjects during dose escalation and 6 expansion cohorts, each consisting of approximately 20 subjects. The final number of subjects enrolled into the trial will depend on the number of dose levels, the number of subjects who participate in both the Dose Escalation and Cohort Expansion phases, and potentially alternative dose schedules explored.

4.2 SUBJECT SELECTION CRITERIA

The subject must fulfil the eligibility criteria (listed in Sections 4.2.1 and Section 4.2.2).

4.2.1 INCLUSION CRITERIA

Dose Escalation Phase and Cohort Expansion Phase

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

2a. For subjects in the Dose Escalation Phase: any locally advanced or metastatic, histologically or cytologically proven solid tumor or NHL, that is relapsed after or progressing despite conventional treatment for which no conventional therapy is considered appropriate by the investigator or is declined by the subject.

2b. For subjects in the Cohort Expansion Phase: locally advanced or metastatic, histologically or cytologically proven malignancy of the types specified in inclusion criterion 10, for which no other conventional therapy is considered appropriate by the investigator or has been 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 one week prior to the subject receiving their first dose of investigational medicinal product (IMP).

Laboratory Test	Lower acceptable limit
Hemoglobin (Hb)	≥ 90 g/L
Absolute neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Bilirubin	≤ 1.5 x upper limit of normal (ULN) unless due to Gilbert's syndrome in which case up to 3 × ULN is permissible
Alanine aminotransferase and/or aspartate aminotransferase and Alkaline Phosphatase	≤ 2.5 x ULN unless raised due to tumor in which case up to 5 x ULN is permissible
Serum Creatinine	≤ 1.5 x ULN

6. Attained the age of 18 years 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 details.

Cohort Expansion Phase

8. Subjects must have measurable disease (per Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1]) or, for mCRPC, evaluable disease per any of the following:
   a. Measurable disease per RECIST v1.1;
   b. Increasing prostate specific antigen (PSA, see PCWG – Appendix 7); or
   c. Circulating tumor cell (CTC) count of 5 or more cells per 7.5ml of blood.
9. Subjects must have tumor tissue or ctDNA evidence that their tumor harbors a combination of mutations which are expected to confer sensitivity to Chk1 inhibition. Eligibility will be determined by the Sponsor's review of genetic abnormalities detected in genes in the following categories, as listed in Appendix 6:
   a. Key tumor suppressor genes regulating G1 cell cycle progression/arrest such as *RB1*, *TP53*, etc. For patients with NHSCC or SCCA, positive HPV status is also considered for eligibility.
   b. The DDR pathway including *ATM*, *BRCA1*, and *BRCA2*. For patients with CRC, MMR genetic alterations and/or high microsatellite instability are also considered for eligibility.
   c. Genetic indicators of replicative stress such as gain of function/amplification of *Chk1* or *ATR* or other related gene.
   d. Oncogenic drivers such as *MYC*, *KRAS*, etc.
   e. *CCNE1* gene amplification (or alternative genetic alteration with similar functional effect) is required for the *CCNE1* gene amplification-specific HGSOC cohort.
10. Subjects must meet one of the following criteria (a-e):

a. **Metastatic CRC, defined by the following:**

- Histologically and/or cytologically confirmed CRC, and
- Must have received at least 1 prior regimen for advanced/metastatic disease

b. **HGSOC, defined by the following:**

- Histologically confirmed high-grade serous ovarian, fallopian tube or primary peritoneal cancer, and
- Recurrent platinum-intolerant subjects, or those with platinum-resistant disease, defined as radiological evidence of disease progression within 6 months of the last receipt of platinum-based chemotherapy. Patients with platinum refractory disease (ESMO – Appendix 7) are not eligible

c. **Advanced NSCLC, defined by the following:**

- Locally advanced and recurrent or metastatic, histologically confirmed NSCLC, and
- Must have received at least 1 prior regimen for advanced/metastatic disease

d. **mCRPC, defined by the following:**

- Histologically or cytologically confirmed adenocarcinoma of the prostate that has progressed after androgen deprivation therapy

e. **HNSCC or SCCA, defined by the following:**

- Histologically confirmed HNSCC from any primary site, or SCCA:
  - For HNSCC: locally advanced disease (ie, persistent or progressive disease following curative-intent radiation, and not a candidate for surgical salvage due to incurability or morbidity), or metastatic disease
  - For SCCA: locally advanced disease or metastatic disease for which no curative intent therapy is available
- Must have received at least 1 prior regimen for advanced/metastatic disease

4.2.2 EXCLUSION CRITERIA

1. Have received the following prior or current anticancer therapy:
   a. Radiotherapy within the last 6 weeks (except for symptom control and where the lesions will not be used as measurable disease)
   b. Endocrine therapy during the previous 4 weeks except for luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer

c. Chemotherapy during the previous 4 weeks

d. Immunotherapy during the previous 6 weeks

e. Nitrosoureas or Mitomycin C during the previous 6 weeks

f. Other IMPs during the 4 weeks before treatment

g. Any prior treatment with a Chk1 inhibitor, or prior treatment with an ATR inhibitor within 6 months prior to receiving SRA737.

2. Other malignancy within the past 2 years with the exception of adequately treated tumors that are associated with an expected 5-year disease-free survival of approximately 95% or better.

3. 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 or sponsor's designee should not exclude the subject.

4a. For subjects in the Dose Escalation Phase that are not to be included in an Expansion Cohort: new or progressing brain metastases. Subjects with brain metastases that have been radiologically stable over an 8-week period may be included in this phase.

4b. For subjects in the Cohort Expansion Phase: present or prior brain metastases.

5. Women of childbearing potential (WOCBP) or women who are already pregnant or lactating. However, those patients who have a negative serum or urine pregnancy test before enrollment and agree to use two forms of contraception as per Appendix 4 or agree to sexual abstinence, effective from the first administration of SRA737, throughout the trial and for six months afterwards are considered eligible.

6. Male subjects with partners of childbearing potential (unless they agree to take measures not to father children by using a barrier method of contraception as per Appendix 4 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.

7. Major surgery from which the subject has not yet recovered.

8. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.

9. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

10. 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.

11. Prior bone marrow transplant or extensive radiotherapy to greater than 25% of bone marrow within 8 weeks.
12. Peanut allergy. Refer to Section 6 for additional details.
13. QTcF > 450 msec in adult males and > 470 msec in adult females.
14. 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).
15. Not able to swallow capsules without chewing or crushing.
16. 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 or Sponsor's designee would be acceptable.
17. 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 STARTING DOSE AND REGIMEN

SRA737 will be administered orally on a continuous daily schedule. The starting dose for Cohort 1 is 20 mg per day. Each cycle of continuous treatment will last 28 days, and subjects may continue as long as none of the treatment discontinuation criteria (see Section 5.6) are met.

5.2 ALTERNATIVE DOSING REGIMEN

Consideration may be given to alternative dosing schedules at any time during the study, following discussion between the Sponsor and investigators. It may be more likely that an alternative schedule will be needed if the C_{min} at the MTD of SRA737 is less than 100 nM (the concentration below which sustained Chk1 inhibition is not anticipated), and/or if safety and tolerability data, PK and/or PDn data (eg, time to onset and time to recovery of myelosuppression) indicate that an alternative dosing schedule would be more suitable. Alternative schedules may include, but are not limited to, the following examples: 5 days of dosing followed by 2 days of non-dosing each week; 1 week of daily dosing followed by 1, 2, or 3 weeks of non-dosing; 2 or 3 weeks of daily dosing followed by 1, or 2 weeks of non-

dosing; or twice daily dosing. Alternative dosing schedule cohorts may be recruited in parallel to or instead of the continuous schedule cohorts.

The initial starting dose for an alternate schedule will depend on the safety, tolerability and PK results from the previous schedule cohorts. If an alternative schedule is to be tested after an MTD has been identified with the previous schedule, the starting total weekly dose for the new schedule will not exceed the total weekly dose at the MTD for the previous schedules. If an MTD has not been identified with the previous schedule, a dose escalation step may occur; however, the dose escalation may not exceed 50% based on the total weekly dose.

5.3 DURATION OF TREATMENT

Treatment should continue until disease progression unless the subject meets one of the other treatment discontinuation criteria outlined in Section 5.6.

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 should be made conservatively, using the guidelines for the most severe AEs and the worst scenario of the recommended dose reduction(s). Once the dose has been reduced, it should not be re-escalated. 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 OR DELAYS

Guidelines for dose delays due to AEs are provided in Table 2**.**

Table 2. Dose Delay and Discontinuation Guidelines

Event	Recommended Action
Grade 3 neutropenia or Grade 3 thrombocytopenia	• Recommend twice weekly monitoring of blood tests if the subject is to continue dosing.

Grade 4 neutropenia or thrombocytopenia
or
Any non-hematologic ≥ Grade 3 SRA737-related toxicity*
	• Consider dose interruption
	• If toxicities have not resolved to ≤ Grade 1 or ≤ 1 grade worse than baseline with a dose interruption, continue to delay treatment for up to 4 weeks. If no recovery after 4-week delay, discontinue treatment.
	  • If toxicities have resolved to ≤ Grade 1 or ≤ 1 grade worse than baseline, treatment may be reinitiated.
	  Consider resumption of treatment at the next lowest dose level for the schedule under investigation or at a reduced dose at an alternative, intermittent schedule.

*Exceptions may include nausea, vomiting or diarrhea lasting < 48 hours, asymptomatic biochemical abnormalities lasting < 5 days, Grade 3 fatigue (unless there was an increase in severity of > 2 grades from baseline), or other event agreed with the Sponsor or Sponsor's designee.

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

Subjects should not be administered G-CSF prophylactically but may be administered as medically indicated.

5.5.1.2 Palliative Radiotherapy

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

5.5.1.3 Contraception Usage

To be eligible for this study, WOCBP (as defined per Appendix 4) and male subjects with partners of childbearing potential must use 2 forms of contraception or agree to sexual

abstinence effective from the first administration of SRA737 through the trial and for 6 months afterwards. See Appendix 4 for more information.

5.5.1.4 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 summary list of applicable drugs for this study is provided in Appendix 5.

5.5.1.5 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 H_2 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. PPIs should therefore be avoided if possible and used with caution if necessary.

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. Subjects requiring anticoagulation should change from warfarin to low molecular weight heparin while they are on study.

5.5.2 EXCLUDED CONCOMITANT MEDICATIONS

Subjects must not receive other anti-cancer therapy or investigational drugs while on the trial, with the exception of LHRH agonist therapy for the treatment of prostate cancer.

5.6 DISCONTINUATION FROM TREATMENT

Subjects can decline to continue receiving SRA737 but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from SRA737 and must discuss with the subject options for continuation of 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:

- Evidence of disease progression
- Unacceptable toxicity
- Noncompliance with study procedures
- Withdrawal by the investigator for clinical reasons not related to SRA737
- Treatment with prohibited concomitant medications
- Intercurrent illness that interferes with study assessments
- Pregnancy of a subject during the study
- Commencement 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.

5.7 DISCONTINUATION FROM THE 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 days ± 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 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 for the following reasons:

- Withdrawal of consent
- Death or loss to follow-up
- Sponsor's decision to terminate the study

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, 25, 50, 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 (#12; see Section 4.2.2) is required because the current manufacturing facility of the SRA737 cannot guarantee that 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 manufactured at the initial facility is depleted and no longer available for subject dosing. Refer to the SRA737 Pharmacy Manual for more information.

6.2 STORAGE CONDITIONS FOR SRA737

SRA737 must be stored according to the label (refrigerated at 2°C–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).

6.3 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.

6.4 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 5.5.1.5. Should a subject miss a scheduled dose due to an error, then the dose may be taken up to 6 hours after the scheduled dosing time. After this time the subject should wait until the next scheduled time before taking the dose. On clinic days, subjects must be counseled not to take their meds, but instead to bring their meds into clinic so that nursing staff may direct dosing to ensure the correct PK collections are made. Should a subject vomit the administered dose, the subject should not re-take the dose and should wait until their next scheduled dose.

6.5 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.

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-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: PRE-SCREEING AND WITHIN 28 DAYS PRIOR TO ADMINISTRATION OF SRA737

Repeat dosing will begin on Day 1, but subjects will also receive a single dose between Day -7 and Day -4 for the purpose of PK analysis until the sponsor determines sufficient data to evaluate the PK of SRA737 have been collected and analyzed. If this occurs, the modified requirements will be documented by an update to the Laboratory Manual.

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.

The following will be performed/obtained as part of Pre-Screening (no time restriction):

- Written informed consent (as detailed in Section 12.3)
- Determination of HPV status either from the subject's medical records, or assessment by local laboratory (subjects with HNSCC or SCCA only).
- Submission of, or confirmation of availability of, suitable archival tumor tissue or fresh tumor tissue (such as with fine needle aspirate) for tumor profiling.
    - 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 Cycle 1 Day 1.

- For subjects being considered for enrollment to the Cohort Expansion Phase, determination of tumor genetics (as confirmed by a validated method performed in a Central Laboratory selected by the sponsor) and MSI status (required for CRC subjects and other subjects if clinically relevant), will be used to determine eligibility for the Cohort Expansion Phase. Archival or fresh tumor 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 ability to collect fresh tumor tissue should be discussed with the sponsor.
- Suitable archival tumor tissue is defined as ≥ 40 µm tissue, of which a minimum of 20% is of malignant origin, on at least 10 and up to 20 unstained slides or in an FFPE block, plus one original (not recut) H&E slide.
- 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. For CRC patients, this could include MSI (high status). In cases where the data are approved as sufficient to support enrollment, archival or fresh tumor tissue must still be submitted for retrospective testing by the Central Laboratory after study entry, as noted in Section 7.2.1.

The following must be performed/obtained **within 28 days before** the subject receives their first dose of SRA737:

- Demographic details
- Medical history including current diagnosis, prior treatment, concomitant conditions/diseases, previous cancers (if appropriate), baseline signs and symptoms, and concomitant treatment
- Radiological disease assessments appropriate to the subject's disease must be performed. These may include, but are not limited to: radiological measurements (chest computerized tomography [CT] scan of the liver, abdomen or pelvis, MRI, x-ray; and/or a bone scan). 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.
- Echocardiogram (ECHO)
- ECG (locally-read)
    - QTcF is to be calculated according to the following formula:

      Fridericia's formula: $QT / (RR)^{0.33}$
      [Observed QT interval divided by cube root of RR interval]
- Laboratory tests (blood samples):
    - CTCs for mCRPC subjects only (Performed via CellSearch CTC Test)
- ctDNA for tumor profiling: If prospective tumor profiling by ctDNA at a Central Laboratory is available, then the blood sample will be obtained within 28 days prior to the first dose. If retrospective analysis will be performed, the sample may be obtained prior to the first dose between Day -7 and Day -4 dosing day. (See Laboratory Manual for details)
- Optional tumor biopsy material for exploratory PD assays (See Section 8.2.4) should optimally be collected within 7 days prior to the first dose of SRA737, but may be done at same time as biopsy for eligibility during Screening.

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).

7.1.2 SCREENING EVALUATIONS: WITHIN 7 DAYS PRIOR TO ADMINISTRATION OF THE FIRST DOSE OF SRA737

The following must be performed **within the 7 days before** the subject receives the first dose of SRA737 either between Day -7 to Day -4 or on Day 1, as applicable:

- Assessment of any SAEs experienced since signing of the consent and concomitant medications
- WHO performance status
- Complete physical examination including clinical disease measurements, as clinically relevant (ie, subjects with clinically assessable disease)
- Clinical disease evaluations
- Laboratory tests (blood/urine samples):
    - Hematology: complete blood count (CBC) with differential count
    - Biochemistry: sodium, potassium, chloride, magnesium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, direct and indirect bilirubin, LDH, alkaline phosphatase, alanine aminotransferase and/ or aspartate aminotransferase, non-fasting glucose
    - Pregnancy testing (WOCBP only): serum or urine test is acceptable
- Optional tumor biopsy material for exploratory PD assays (See Section 8.2.4) should optimally be collected within 7 days prior to the first dose of SRA737, but may be done at the same time as biopsy for eligibility during Screening.
- Enrollment of the subject on the study only once the investigator has confirmed eligibility and the Sponsor approves (see Section 4 for further eligibility details).

7.2 EVALUATIONS DURING THE TRIAL

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

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.

Intensive PK assessments are outlined in detail in Section 7.7 or the Laboratory Manual. 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.

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

- Optional tumor biopsy for exploratory PD assays, if not done during screening (See Section 8.2.4)
- AEs and concomitant medications. AEs must be monitored and recorded in the eCRF from the first dose of SRA737 administration. 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, WHO performance status, temperature, pulse rate, seated BP.
- Laboratory tests (blood/urine/tissue samples):
    - Hematology: CBC with differential count
    - Biochemistry: Sodium, potassium, chloride, magnesium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, direct and indirect bilirubin, LDH, alkaline phosphatase, alanine aminotransferase and/ or aspartate aminotransferase, non-fasting glucose
    - Urinalysis: glucose, protein and blood
    - Pregnancy testing (WOCBP only): serum or urine test is acceptable. More frequent pregnancy tests may be conducted if required per local regulations.
    - Troponin: Troponin T or I (subject should be followed for the same parameter)
    - Serum tumor markers (as clinically relevant, eg, CA-125 for ovarian cancer, PSA for prostate cancer, CEA for colorectal cancer, CA19-9 for pancreatic cancer, AFP for liver and other cancers, and others as clinically indicated.
    - CTCs for mCRPC subjects only.
    - PK time points: Predose, 1, 2, 4, 6, 8, 12, 24, and 48 hours after the first dose. For subjects in the Expansion Cohorts, the 12-hour time point may be omitted with sponsor's approval.
    - ctDNA for exploratory analyses (in a subset of up to 33 subjects).

- Blood sample should be collected and submitted for additional exploratory analyses (such as mutational burden).

- ECG (replicates, centrally-read):
  - ECGs will be performed at the intervals noted in Section 7.7) until the Sponsor has sufficient data to adequately explore the association of SRA737 exposure and QTc prolongation.
  - ECGs will be performed as a 5-minute continuous read in accordance with directions from sponsor or designee. At time points at which ECG and blood draws are required, the ECG will be performed first. The ECG must be transmitted electronically to a central laboratory and is to be centrally reviewed by an independent reviewer.

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

- Optional tumor biopsy for exploratory PD assays (See Section 8.2.4)
- Pregnancy testing (WOCBP only): serum or urine test is acceptable. More frequent pregnancy tests may be conducted if required per local regulations.
- Serum tumor markers (as clinically relevant, eg, CA-125 for ovarian cancer, PSA for prostate cancer, CEA for colorectal cancer, CA19-9 for pancreatic cancer, AFP for liver and other cancers, and others as clinically indicated.
- CTCs for mCRPC subjects only.
- ctDNA for exploratory analyses (in a subset of up to 33 subjects).
- Blood sample should be collected and submitted for additional exploratory analyses (such as mutational burden).
- Height and weight.

7.2.2 STANDARD EVALUATIONS FOR EACH CYCLE

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

- AEs and concomitant medications (detailed in Section 7.2.1): all visits
- Symptom directed physical examination, if clinically indicated: Day 1 of each cycle: predose
- WHO performance status: Day 1 of each cycle: predose
- Temperature, seated BP and pulse rate: Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of each cycle thereafter

- ECG (locally-read): Cycles 1, 2, and then every third subsequent cycle, Day 1 predose.
- ECG (replicates, centrally-read) –Cycle 1 Day 22 only: predose, 1, 2, 4, 6, and 24 hours postdose. Note: Centrally-read ECGs will be performed at the intervals noted above in addition to locally-read ECGs until the sponsor has sufficient data to adequately explore the association of SRA737 exposure and QTc prolongation. If the Sponsor stops collection of centrally-read ECGs, locally-read ECGs will continue to be performed.
- ECHO: Cycle 2, Day 1 only. All subsequent cardiac monitoring should be done at the investigator's discretion.
- Laboratory tests (blood/urine samples):

  Blood draws for laboratory tests will be performed predose. At time points at which both blood draws and ECGs are required, ECGs should be done first. Samples should be collected on the days indicated below, unless an acceptable window for sample collection is stated e.g. within 72 hours prior to the first dose of each cycle for hematology, biochemistry, and troponin. Subjects must be instructed not to take SRA737 before attending the clinic on those days they will attend for routine blood samples. SRA737 should only be taken once all clinic assessments have been completed:

  - Hematology (CBC with differential count): Hematology assessments should be repeated weekly for the cycle following an intra-subject dose escalation, where applicable.
    - Cycle 1 to Cycle 3: Days 1 (up to 72 hours predose), 8, 15, and 22
    - Cycle 4 onwards: Days 1 (up to 72 hours predose) and 15
  - Biochemistry (detailed in Section 7.1.2):
    - Cycle 1 and 2: Days 1 (up to 72 hours predose), 8, 15, and 22
    - Cycle 3 to Cycle 6: Days 1 (up to 72 hours predose) and 15
    - Cycle 7 onwards: Day 1 (up to 72 hours predose)
  - Troponin T or Troponin I (subject should be followed for the same parameter):
    - Cycle 1: Day 1 (up to 72 hours pre-dose), and Day 8
    - Cycle 2: Day 1 (up to 72 hours pre-dose)
    - Cycle 6: Day 1 (up to 72 hours pre-dose)
  - Urinalysis including glucose, protein and blood: Day 1 of each cycle (may be performed up to 72 hours prior to the first dose of each cycle)

- Blood sample for additional exploratory analyses (such as mutational burden): Cycles 3 and 6, Day 1 predose
- ctDNA for exploratory analyses (from a subset of up to 33 subjects): Cycle 3, Day 1 predose
- CTCs for mCRPC subjects only: End of every 4 weeks ± 1 week
- Serum tumor markers (if applicable, eg, CA-125 for ovarian cancer, PSA for prostate cancer, CEA for colorectal cancer, CA19-9 for pancreatic cancer, AFP for liver and other cancers, and others as clinically indicated): repeated every 4 weeks ± 1 week after Cycle 1 Day 1)
- Intensive PK schedule:

	Intensive PK Assessments
Continuous schedule	• C1 Days 1, 8, and 15: Predose • C1 Day 22: Predose, 1, 2, 4, 6, 8, 12, and 24 hours postdose. For subjects in the Expansion Cohorts, the 12-hour time point may be omitted with Sponsor's approval
	Subsequent cycles, Day 1: Predose
Alternate dosing schedules	• C1 Day 1: Predose • PK will also be collected on Cycle 1 Day 8 or at a day at the end of the first week's dosing as determined by the Sponsor in consultation with the investigator. Time points: Predose, 1, 2, 4, 6, 8, 12, and 24 hours postdose. For subjects in the Expansion Cohorts, the 12-hour time point may be omitted with Sponsor's approval
	Subsequent cycles, Day 1: Predose
Note: The Sponsor may reduce or eliminate the requirement for PK sampling once sufficient data to evaluate the PK of SRA737 have been collected and analyzed. If this occurs, the modified requirements will be documented by an update to the Laboratory Manual.	

- Repeat of clinical assessments (if applicable) performed at baseline: This must be repeated at the end of every 4 weeks (± 1 week) after Cycle 1 Day 1. Refer to Section 9.
- Repeat of radiological assessments performed at baseline: Radiological assessments must be repeated every 8 weeks (± 1 week) after Cycle 1 Day 1. Subjects with bone metastases being followed by bone scans will have scans every 8 weeks (± 1 week) for the first 6 months and then every 16 weeks (± 2 weeks) thereafter. Assessment may be discontinued if PD was shown on a previous scan. Refer to Section 9.
- 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.

- If an optional tumor biopsy was taken at baseline for additional PDn analysis, a second biopsy should be collected 2 to 8 hours after dosing at one timepoint from Cycle 1 Day 15 through Cycle 1 Day 22 (See Section 8.2.4).

7.3 SAFETY FOLLOW-UP (SFU) VISIT

If a subject discontinues the IMP for any reason, a Safety Follow-up (SFU) visit should be completed. Evaluations at the SFU visit should be performed 30 days ± 7 days after the last dose of SRA737. If the subject begins a new anticancer treatment within 30 days of the last administration of the IMP, 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 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.
- A symptom-directed physical examination including WHO performance status, temperature, pulse rate, seated BP and weight
- Laboratory tests (blood/urine samples):
    - Hematology tests: CBC with differential count detailed in Section 7.1.2
    - Biochemistry tests: detailed in Section 7.1.2
    - Troponin T or Troponin I: detailed in Section 7.1.2
    - Urinalysis: detailed in Section 7.1.2
    - Blood sample for additional exploratory analyses (such as mutational burden)
    - ctDNA for exploratory analyses (from a subset of up to 33 subjects)
    - CTCs for mCRPC subjects only unless PD was previously documented
    - Serum tumor marker (if applicable, eg, CA-125 for ovarian cancer, PSA for prostate cancer, CEA for colorectal cancer, CA19-9 for pancreatic cancer, AFP for liver and other cancers, and others as clinically indicated must be repeated) unless PD was previously documented
    - Urine or serum pregnancy test
- ECG (locally-read)
- ECHO

- Clinical (if applicable) and radiological assessment of disease, unless PD was indicated on a previous study scan or radiological disease assessments were conducted within the past 6 weeks.
- 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 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. 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:

- SAEs assessed by the investigator as related to SRA737
- First subsequent cancer therapy (if applicable)
- Laboratory tests (blood samples):
    - Serum tumor markers (if applicable), unless PD was previously documented
    - CTCs (for mCRPC subjects only), unless PD was previously documented
- Clinical disease evaluations, 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

Observation / Investigation	Screening evaluations – to be within [x] days of first dose (as noted)			First dose for Intensive PK	Treatment phase (28-day cycle) Evaluations for each day				Safety Follow-up	Long-term Follow-up
	N/A	28 days	7 days	Single day, Day -7 to Day -4	1	8	15	22	30 days ± 7 days after last dose of SRA737	Every 16 weeks ± 2 weeks
Written informed consent	X									
Demographics		X								
Medical history		X								
Adverse event evaluation	SAEs from informed consent. AEs from first dose of SRA737. Continually review								X (b)	X(c)
Concomitant treatments	From date of informed consent. Continually review									X(c)
Availability / Submission of tumor tissue and ctDNA for tumor profiling (d), and MSI status (e)	X									
Determination of HPV status (HNSCC and SCCA)	X									
Radiological disease assessment		X (f)			End of every 8 weeks (± 1 week) from C1D1				X (f, m)	X (f, m)
Clinical disease assessment (if applicable)			X		End of every 4 weeks (± 1 week) from C1D1				X (m)	X (m)
Disease and survival updates (where available)										X
Physical examination (g)			Complete		Symptom-directed, predose on D1 of each cycle - repeat as clinically indicated				Symptom-directed	
Temperature, seated BP, and pulse				X (a)	X	C1	C1	C1	X	
Height				X (a, n)						
Weight				X (a, n)					X	
WHO performance status			X	X (a)	X				X	
ECHO (h)		X			C2				X	

Observation / Investigation	Screening evaluations – to be within [x] days of first dose (as noted)			First dose for Intensive PK	Treatment phase (28-day cycle) Evaluations for each day				Safety Follow-up	Long-term Follow-up
	N/A	28 days	7 days	Single day, Day -7 to Day -4	1	8	15	22	30 days ± 7 days after last dose of SRA737	Every 16 weeks ± 2 weeks
ECG (i)		X (Locally-read)		Refer to Section 7.7 for time points (local and central)					X (Locally-read)	
Pregnancy test (j)			X	X (a, n)					X	
Serum tumor markers (if applicable, eg, CA-125, PSA, CEA, CA19-9, AFP, others as indicated)				X (a, n)	End of every 4 weeks (± 1 week) from C1D1				X	X (m)
Samples for biochemistry			X	X (a)	X (k)	X (k)	X (k)	X (k)	X	
Samples for hematology			X	X (a)	X (l)	X (l)	X (l)	X (l)	X	
Troponin T or I				X (a)	C1 C2 C6	C1			X	
Urine sample for urinalysis				X (a)	X				X	
Blood sample for CTCs (mCRPC subjects only)		X		X (a, n)	End of every 4 weeks (± 1 week)				X	X (m)
Blood sample for ctDNA for exploratory analysis	Refer to Section 7.7 for time points								X	
Blood sample for Exploratory Analyses (Mutational Burden)	Refer to Section 7.7 for time points								X	
Tumor Tissue for Optional Exploratory PD	Refer to Section 7.7 for time points									
Blood sample for PK				Refer to Section 7.7 for time points						
SRA737 administration				X (a)	Continuous daily dosing or as specified in alternate dosing schedule					
SRA737 Diary Card					Should be reviewed at each visit				X	

a. Assessments scheduled to occur for the first dose for PK (given on a single day between Day -7 to Day -4) will be conducted on the first day of dosing unless performed within 72 hours prior or noted otherwise for the specific assessment in Section 7.2.1. Dosing should be delayed if eligibility criteria are no longer met. 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 SFU visit. Monthly follow-up will continue until the event resolves, returns to baseline, stabilizes, or the subject discontinues from study.
c. Only new SAEs assessed by the investigator as related to SRA737 and first subsequent anticancer therapy will be collected.
d. Availability of suitable archival tumor tissue or planned biopsy for fresh tumor tissue acquisition for tumor profiling must be confirmed. When archival material was collected more than 18 months ago, the ability to collect fresh tumor tissue should be discussed with the sponsor. Submission prior to or during Screening (the 28-day window does not apply) with confirmation of positive results is required to determine eligibility for Expansion Cohort subjects. Archival tumor tissue should be requisitioned for submission by Cycle 1 Day 1 for Dose Escalation subjects. See Section 7.1.1 for more details.
A blood sample for ctDNA tumor profiling will be obtained from all screened subjects within 28 days prior to the first dose. If prospective analysis is performed, results must be available prior to the first dose of SRA737. If retrospective analysis will be performed, results are not required to be available prior to the first dose of SRA737.
e. For CRC subjects and other subjects as clinically relevant whose MSI status is unknown, determination of MSI status will be performed on archival tumor tissue or fresh tumor tissue submitted for tumor profiling during Screening.
f. Screening assessment to be conducted within 35 days of Cycle 1 Day 1. Follow-up radiological assessments must be repeated at the end of every 8 weeks (± 1 week) after Cycle 1 Day 1. Subjects with bone metastases being followed by bone scans will have scans every 8 weeks (± 1 week) for the first 6 months and then every 16 weeks (± 2 weeks) thereafter. During Long-term Follow-up, assessments will be done every 16 weeks, unless requested more frequently by the sponsor or investigator. Assessment may be discontinued if PD was shown on a previous scan.
g. Complete physical examination to be performed within 7 days of the first dose. Subsequent examinations on Day 1 of each cycle (and additionally as clinically indicated) may be symptom directed.
h. ECHO will be done at Screening, Cycle 2 Day 1 (± 3 Days), and at the SFU visit. All subsequent cardiac monitoring will be done at the investigator's discretion.
i. All subjects will have locally-read ECGs. Centrally-read ECGs will also be performed - see Section 7.7 for detailed time points. Centrally-read ECGs may be eliminated by the Sponsor once sufficient data have been collected and analyzed. If this occurs, the modified requirements will be documented by an update to the appropriate study documents.
j. Pregnancy test: For women of childbearing potential. More frequent pregnancy tests may be conducted if required per local regulations.
k. Biochemistry should be performed on Days 1, 8, 15 and 22, during Cycles 1 and 2. The frequency can be reduced to Days 1 and 15 from Cycle 3 onwards at the discretion of the investigator, and reduced again to once a month (predose on Day 1) from Cycle 7 onwards. Laboratory tests can be performed up to 72 hours prior to the first dose of each cycle (Day 1).
l. Hematology should be performed on Days 1, 8, 15 and 22, during Cycles 1 to 3. Hematology assessments will be repeated weekly for the cycle following an intra-subject dose escalation, where applicable. The frequency can be reduced to Days 1 and 15 from Cycle 4 onwards at the discretion of the investigator. Laboratory tests can be performed up to 72 hours prior to the first dose of each cycle.
m. Disease assessments will be discontinued in the case of PD or if subsequent anti-cancer therapy is initiated.
n. Assessment to be carried out on Cycle 1 Day 1 in the event the Day -7 to Day -4 visit is eliminated.

7.7 SCHEDULE OF SECONDARY AND EXPLORATORY ASSESSMENTS

		ctDNA for Exploratory Analyses (a)	Intensive PK (c)	Central ECG	Local ECG	Exploratory Analyses (Mutational Burden)	Optional Exploratory PD (Tumor Tissue)
Screening (-28 days of first dose)					X		Optimally within 7 days prior to first dose of SRA737. May also be done at Screening.
Day -7 to Day -4 (First dose for PK) (b)	Predose	X (f)	X	X		X (f)	
	1h ±15min		X				
	2h ±15min		X	X			
	4h ±15min		X				
	6h ±15min		X				
	8h ±15min		X (e)				
	12h ±15min		X (e)				
	24h ±1h		X				
	48h ±1h		X				
Cycle 1 Day 1	Predose		X		X		
Cycle 1 Days 8, 15	Predose		X				
Cycle 1 Day 22 (c)	Predose		X	X			
	1h ±15min		X	X			
	2h ±15min		X	X			2 to 8h post-dose at one timepoint from C1D15 through C1D22
	4h ±15min		X	X			
	6h ±15min		X	X			
	8h ±15min		X (e)				
	12h ±15min		X (e)				
	24h ±1h		X	X			
Subsequent cycles Day 1	Predose	C3	X		X(d)	C3, C6	
SFU Visit		X			X	X	

Note: Centrally-read ECGs will be performed at the intervals noted above in addition to locally-read ECGs until the Sponsor has sufficient data to adequately explore the association of SRA737 exposure and QTc prolongation. If the Sponsor stops collection of centrally-read ECGs, locally-read ECGs will continue to be performed. At time points at which both blood draws and ECGs are required, ECGs should be done first.

Refer to the Laboratory Manual for further instructions on all assay sample collection, specific timings, handling and storage.

a. Blood sample for exploratory ctDNA analysis will be collected for exploratory analyses for up to 33 subjects, prior to the first dose of SRA737, Cycle 3 Day 1, and SFU visit.

b. 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. 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.

c. The Sponsor may reduce the requirement for PK sampling once sufficient data to evaluate the PK of SRA737 have been collected and analyzed If this occurs, the modified requirements will be documented by an update to the Laboratory Manual. For Alternative Dosing schedules, instead of Cycle 1 Day 22, additional PK and centrally-read ECG will be collected on Cycle 1 Day 8 or at a day at the end of the first week's dosing as determined by the Sponsor in consultation with the investigator.

d. Locally-read ECGs will be performed at Screening; Cycle 1 Day 1, Cycle 2 Day 1, and then every third cycle Day 1; and at SFU.
e. For subjects in the Expansion Cohorts, the 12 hour time point may be omitted with Sponsor's approval.
f. Assessment to be carried out on Cycle 1 Day 1 in the event the Day -7 to Day -4 visit is eliminated.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

8.1 PHARMACOKINETICS

Approximately 2 mL of blood will be collected from all subjects at each time point. For the intensive PK schedule, up to 9 time points taken over a 48-hour time period on Day -7 to Day -4; predose sampling at Cycle 1 Days 1, 8, and 15; up to 8 time points taken over a 24 hour-time period at Cycle 1 Day 22; and all subsequent cycles at Day 1 will be collected. (See Section 7.2.2 for schedule for alternative dosing schedules).

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. If this occurs, the modified requirements will be documented by an update to the Laboratory Manual.

If one of these designated sampling times is missed a sample should be taken as soon as possible.

Please refer to the Laboratory Manual for further instructions on all assay sample collection, specific timings, handling and storage.

8.2 PHARMACODYNAMICS

8.2.1 TUMOR PROFILING

To identify genetic alterations 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 DNA damage response and repair, archival or fresh tumor tissue and ctDNA for tumor profiling will be collected during Screening. 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.

8.2.2 EXPLORATORY ANALYSES OF ctDNA

To evaluate changes in biomarkers between baseline and end of treatment, blood will be obtained serially throughout the study (Day -7 to Day -4 dosing day, Cycle 3 Day 1, and SFU visit) for an exploratory ctDNA assay for up to 33 subjects. Blood samples will be processed and analyzed at the Northern Institute for Clinical Research (NICR) laboratories.

8.2.3 ADDITIONAL EXPLORATORY ANALYSES

Additional exploratory analyses may be performed. Blood will be obtained serially throughout the study (Day -7 to Day -4 dosing day; Cycles 3 and 6, Day 1; and SFU visit) for assays which may include but not limited to the following: immune profiling, markers of genetic instability including microsatellite instability, neoantigens, and mutational burden.

8.2.4 ADDITIONAL PHARMACODYNAMIC ASSAYS

Optional tumor biopsies for additional pharmacodynamic analysis may be taken 2 to 8 hours after dosing at one timepoint from Cycle 1 Day 15 through Cycle 1 Day 22 (inclusive) if a biopsy was taken at baseline (within 7 days of the first dose).

Where applicable, assays for inhibition of Chk1 and other PD markers associated with induction of replication stress and ATR/Chk1 signaling in tumor samples will follow agreed upon SOPs and validated methods. Markers to be evaluated include, but are not limited to: total Chk1 and evidence of DNA damage (pSer296Chk1, pSer317Chk1, pSer345Chk1, total H2A.X and gamma-H2A.X).

Refer to the laboratory manual for specific details on sample collection, handling, storage, and shipping requirements.

9 ASSESSMENT OF EFFICACY

9.1 MEASUREMENT OF DISEASE

Disease must be measured according to the RECIST v1.1 criteria provided in Appendix 2 for subjects with solid tumors, according to the revised IWG criteria (Cheson 2007) for subjects with NHL, and for subjects with mCRPC, using a composite of any one of the following: A) Measurable disease per RECIST v1.1; B) Increasing PSA; or C) CTC count of 5 or more cells per 7.5ml of blood.

9.2 TIMING AND TYPE OF TUMOR 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. 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. The interval between the last anti-cancer therapy and these measurements should be at least 4 weeks when possible. All clinical measurements and serum tumor markers that may be utilized to assess response must be performed within **1** week prior to the first dose of SRA737.

The determination of CR and PR requires confirmation by a subsequent assessment at least 4 weeks after the original determination. Stable Disease (SD) determination requires that the relevant criteria be met at least once, a minimum of 6 weeks after study entry.

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

9.2.1 BASELINE EVALUATIONS

Baseline evaluations must include radiological measurements of lesions appropriate to the nature of the malignancy. This may include: CT scan, liver CT scan, abdominal CT scan, 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 dimensions 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, Assessment of disease response).

9.2.2 EVALUATIONS DURING AND AFTER THE END OF TREATMENT

Tumor assessments must be repeated every 8 weeks or more frequently, when clinically indicated. Subjects with bone metastases being followed by bone scans will have scans every 8 weeks (± 1 week) for the first 6 months and then every 16 weeks (± 2 weeks) thereafter. During Long-term Follow-up, assessments for subjects who have not yet progressed and who have not initiated alternative anti-cancer therapy will be done every 16 weeks, unless requested more frequently by the sponsor or investigator. All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent. All subjects, who are removed from the study treatment for reasons other than PD, should be re-evaluated at the time of treatment discontinuation, unless a tumor assessment was performed within the previous four weeks. Subjects will be followed for PD until disease progression 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 selected and recorded at baseline and comment on the non-target lesions in accordance with RECIST v 1.1 criteria or the revised IWG criteria, as applicable.

9.3 TUMOR RESPONSE

All subjects who have measurable disease, receive at least one cycle of SRA737 and have a baseline plus at least 1 post-baseline 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. Stable Disease (SD) determination requires that the relevant criteria be met at least once, a minimum of 6 weeks after the initial dose of SRA737 is given.

Should rapid tumor progression occur before the completion of 4 weeks of treatment 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.
- AEs occurring from an overdose of an IMP, whether accidental or intentional
- AEs 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 study drug.

10.1.2 SERIOUS ADVERSE EVENTS

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

- results in death
- is life-threatening*
- requires in-patient hospitalization *or* prolongs existing in-patient 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 SRA737 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 of SRA737 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 of SRA737.
- Medication error (any unintentional error in the dispensing or administration of SRA737).

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 relevant regulatory authorities relating to suspected unexpected serious adverse reactions consistent with relevant legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), 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	• Starts within a time related to the IMP administration and • No obvious alternative medical explanation
Probable	• Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the subject's clinical state
Possible	• Starts within a time related to the IMP administration and • A causal relationship between the IMP and the AE is at least a reasonable possibility
Unlikely	• 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	• 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 PK 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. 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's 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 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 Safety Follow-up 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) all SAE and any AEs that have been assessed as related to the IMP. 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 <u>faxed or e-mailed</u> 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: GlobalSAEInbox@chiltern.com	Refer to your country-specific contact information in the Study Manual for the Sponsor Medical Monitor Email: medicalmonitorSRA737-01@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, 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 Ethics Committee/Institutional Review Board (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.

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: GlobalSAEInbox@chiltern.com	Refer to your country-specific contact information in the Study Manual for the Sponsor Medical Monitor Email: medicalmonitorSRA737-01@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, Medicines and Healthcare Products Regulatory Agency) 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 subject or a partner of a subject does not become pregnant during the trial and for 6 months after their final dose of SRA737. 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.

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, 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 provides consent.

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 patient safety. There will be no adjustment to significance levels for reviews of the accumulating data during the trial. The planned reviews will occur at the following time points:

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

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 POPULATON

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

11.1.2 RESPONSE EVALUABLE POPULATON

All enrolled subjects who have measurable disease, receive at least 75% of 1 cycle of study medication, and have a baseline assessment of disease plus at least 1 post-baseline disease assessment will be evaluable for response. All subjects who were enrolled into one of the 6 indication-specific expansion cohorts will be evaluable for response if they have measurable, prospectively-selected genetically-defined tumors as specified in Section 4, received at least 75% of 1 cycle of study medication, have a baseline assessment of disease and at least 1 post-baseline disease assessment.

In addition, subjects who have measurable disease and receive at least 75% of 1 cycle of study but develop disease progression, intolerable toxicity, or death prior to the post-baseline assessment will also be considered evaluable and will be classified as nonresponders.

11.1.3 PHARMACOKINETICS EVALUABLE POPULATON

All subjects who receive at least 1 dose of SRA737 and provide 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 the full dose and does not vomit within 4-hours postdose.

11.1.4 PHARMACOKINETICS/CORRECTED QT INTERVAL EVALUABLE POPULATON

All enrolled subjects who receive at least 1 dose of SRA737 and for whom adequate QTc and ECG data are available will be evaluable for PK/QTc analyses.

11.1.5 PHARMACODYNAMICS EVALUABLE POPULATON

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

11.2 STATISTICAL ANALYSES

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 informed consent. Safety variables will be summarized by descriptive statistics. Laboratory variables will be described using the NCI-CTCAE v4.03. The MTD for each schedule tested, if reached, and the RP2D and schedule will be described.

Treatment-emergent AEs will be reported for each dose level and coded using a current version of the MedDRA thesaurus, presented as tables of incidence of AEs by body system and by worst 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.

Efficacy endpoints will be evaluated using RECIST v1.1 criteria, or for subjects with NHL, the revised IWG criteria (Cheson 2007), or for subjects with mCRPC, a composite response rate defined as any one of the following (Scher 2016):

- Best response based on RECIST v1.1
- PSA decrease of ≥50%

- CTC count conversion

Absolute values for PSA and CTCs will be recorded at baseline and response will be analyzed based on percentage of change.

Descriptive analyses of the distribution of ORR, DCR, DOR, TTR, TTP, PFS per RECIST v1.1, the revised IWG criteria, or a composite of any one of the following: A) Response based on RECIST v1.1; B) PSA decrease of ≥ 50%; or C) CTC count conversion, as applicable, and OS will be prepared.

The ORR will be summarized using binomial proportions and confidence intervals computed by the method of Wilson. The examples below display the CI estimates for response within each indication-specific group of approximately 20 enrolled to an expansion cohort. i.e. at the 95% CI, 0 of 20 responses observed excludes an ORR of 16%.

Numerator	Denominator	Proportion	Lower	Upper
0	20	0	0	0.161
1	20	0.05	0.009	0.236
2	20	0.10	0.028	0.301
3	20	0.15	0.052	0.360
4	20	0.20	0.081	0.416
5	20	0.25	0.112	0.469
6	20	0.30	0.145	0.519
7	20	0.35	0.181	0.567
8	20	0.40	0.219	0.613
9	20	0.45	0.258	0.658
10	20	0.50	0.299	0.701
11	20	0.55	0.342	0.742
12	20	0.60	0.387	0.781
13	20	0.65	0.433	0.819
14	20	0.70	0.481	0.855
15	20	0.75	0.531	0.888
16	20	0.80	0.584	0.919
17	20	0.85	0.640	0.948
18	20	0.90	0.699	0.972
19	20	0.95	0.764	0.991
20	20	1	0.839	1

The distribution of DOR, in the subset of subjects responding will be summarized using Tukey's five number summary, including the minimum, mean, median, maximum and

standard deviation. Time to response will be summarized using Tukeys' five 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 next-generation sequencing (NGS) techniques, either retrospectively or prospectively, subjects enrolled into one of the indication-specific cohort expansions, and subjects defined by dose level to which they were enrolled. Additional subgroups of interest may also be identified, and the ORR will be estimated, as described in the Statistical Analysis Plan.

Duration of response is defined as the time from first evidence of PR or better to disease progression or death. 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.

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

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

11.2.4 PK/QTC

Time-matched ECG measurements and PK samples will be collected after a single dose of SRA737 on Day -7 to Day -4 and during Cycle 1 (See Section 7.7 for the Schedule of Secondary and Exploratory Assessments).

A concentration-effect model will evaluate the relationship between plasma concentrations and the mean change from Baseline in QTcF for all subjects in the PK/QTc study.

Plasma concentrations of SRA737 will be determined using a validated bioanalytical method and summarized using descriptive statistics. Pharmacokinetic parameters, including but not limited to C_{min}, C_{max}, T_{max}, AUC, $t_{½}$, total body clearance, and apparent volume of distribution, will be determined using non-compartmental method(s). PK 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. These data 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 tumor profiling will be obtained at Screening 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 relationship between the presence and type of genetic alteration and clinical outcome (response) will be explored.

11.2.5.2 Exploratory Analyses of ctDNA

Blood will be collected from a subset of approximately 33 subjects for exploratory analyses of ctDNA for mutations relating to resistance to Chk1 inhibitor therapy. Based on the timing and availability of the ctDNA results, a separate statistical analysis plan may be prepared for the analysis of resistance to Chk1 inhibitor therapy.

11.2.5.3 Additional Exploratory Analyses

Blood obtained serially for the purposes of additional exploratory analyses may be analyzed for but not limited to the following: immune profiling, markers of genetic instability including microsatellite instability, neoantigens, and mutational burden.

11.2.5.4 Additional Pharmacodynamic Assays

For subjects who had optional tumor biopsies for additional pharmacodynamic analysis taken at baseline and 2 to 8 hours after dosing at one timepoint from Cycle 1 Day 15 through Cycle 1 Day 22 (inclusive). Inhibition of Chk1 and other PD markers in tumor samples will be measured. Markers to be evaluated include but are not limited to: total Chk1, evidence of DNA damage (pSer296Chk1, pSer317Chk1, and Gamma-H2AX).

Based on the timing and availability of the PDn assay analyses, a separate statistical analysis plan may be prepared for these analyses.

11.3 SAMPLE SIZE

The study will enroll up to 170 subjects in total including an estimated 30–50 subjects during dose escalation and 6 indication-specific expansion cohorts each consisting of approximately 20 prospectively-selected genetically-defined subjects. The sample size for dose escalation is based on assumptions of the likely MTD based on allometric scaling and will depend on the number of dose levels required to establish the MTD and RP2D. The final number of subjects enrolled into the trial will depend on the number of dose levels, the number of subjects who participate in both the Dose Escalation and Cohort Expansion phases, and potentially alternative dose schedules explored.

A sample size of 20 subjects enrolled in each indication-specific expansion cohort will permit confirmation that the 95% confidence intervals around an observed ORR in each cohort is ± 16%.

12 STUDY ADMINISTRATION

This trial is conducted under a clinical trial authorization, and approval from the MHRA and 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 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, the 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 must be received before the amendment can be implemented and incorporated into the protocol if necessary.

12.2 SERIOUS BREACH OF GOOD CLINICAL PRACTICE (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 MHRA within seven 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 safety information becomes available during the study, 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 signed copy of the 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 regulation and guidelines 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 Safety Follow-up visit or the long-term follow-up visit (whichever is later).

It is the responsibility of the Sponsor to inform the relevant Health Authorities 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:

- The drug is considered too toxic to continue treatment before the required number of subjects has 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 a Clinical Research Associate (CRA) will be responsible for monitoring data quality in accordance with applicable 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
- 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 on-site audits.

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 referenced in 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 Good Clinical Practice (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 receive the favorable opinion of the assigned REC.

It is the Principal Investigator'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, Chief Investigator, and Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles, all applicable local regulations, and the ICH GCP guidelines.

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 (Eisenhauer 2009) or for any subject with NHL, using the revised International Working Group (IWG) criteria (Cheson 2007).

Revised RECIST guideline (v 1.1)

Note that this is an abridged version of the RECIST criteria. Please refer to the Eisenhauer 2009 article for detailed appendices and if in doubt.

Measurability of tumor at baseline

1.1. Definitions

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

1.1.1. Measurable

Tumor 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 caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers 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:

- Tumor 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 calipers 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 characterize 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 calipers (eg, skin nodules). For the case of skin lesions, documentation by color 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 (eg, for body scans). More details concerning the use of both CT and MRI for assessment of objective tumor 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 utilization of these techniques for objective tumor 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.

Tumor markers:

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize 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 tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, 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 tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumor response evaluation

2.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor 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 (2009).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. 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 tumor. 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, sagittal 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 characterize any objective tumor 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 (eg, '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 (eg, 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 normalization of tumor 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 tumor 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 tumor 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 tumor 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 localized 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 tumor (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:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. 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 Prod. 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 = not evaluable.

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 = not evaluable.
(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 'early progression, 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 (eg, 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 randomized trials, from date of randomization) 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 dyspnea (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 dyspnea (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 dyspnea (or fatigue, palpitation or anginal pain)

Class IV subjects with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnea (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 PARTNERS OF WOCBP

The risks of treatment with SRA737 during pregnancy have not been evaluated. Please refer to the latest version of the Investigator's Brochure 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 for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months). Of note, amenorrhea following cancer therapy does not rule out childbearing potential.

Contraceptive Requirements for Females and Female Partners of Male Subjects

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 after the last dose of SRA737.

WOCBP partners of male subjects should use a reliable form of birth control from the date of the male partner's 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.

** Vasectomized 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 vasectomized 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 first administration of SRA737 throughout the trial and for 6 months after administration of the last dose of SRA737. 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 administration of the last dose of SRA737. 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 after the first administration of study drug and for at least 6 months after the last dose.

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. LIST OF QT PROLONGATION DRUGS AND DRUG METABOLIZED BY CYP1A2

List of known QT 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

Generic Name	Brand Names (Partial List)	Drug Class
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic
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

Generic Name	Brand Names (Partial List)	Drug Class
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic
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

Generic Name	Brand Name (Partial List)
riluzole	Rilutek, Teglutik
ropivacaine	Naropin
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

A combination of gene mutations documented or predicted to enhance sensitivity to Chk1 inhibition/loss is required for enrollment into the Cohort Expansion Phase of this study. 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
[redacted]			

1. Amplification or gain of function mutations are desired for this gene
2. *CCNE1* gene amplification (or alternative genetic alteration with similar functional effect) is required for the *CCNE1* gene amplification-specific HGSOC cohort
3. Loss of function mutations are desired for this gene

Other genetic predictors can be added to this list, including 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 MSI.

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.

APPENDIX 7 PROSTATE CANCER CLINICAL TRIALS WORKING GROUP (PCWG) AND EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) GUIDANCE

Definition of increasing PSA per PCWG 2 and 3:

For patients who manifest disease progression solely as a rising PSA level, a sequence of rising values at least 1 week apart with a minimum level of 2.0 ng/mL are required for trial entry.

Reference: Scher HI, Halabi S, Tannock I, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148–1159

Definition of platinum refractory disease (in ovarian cancer) per ESMO guidance:

The GCIG 4th Ovarian Cancer Consensus Meeting, defines:

'platinum-refractory' as patients progressing during therapy or within 4 weeks after the last dose;

'platinum-resistant' patients progressing within 6 months of platinum-based therapy.

Reference: Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013;24(Suppl6):vi24–vi32