# A Phase 1 Study of Oral SRA737 (formerly CCT245737) Given in Combination with Gemcitabine plus Cisplatin or Gemcitabine Alone in Patients with Advanced Cancer

**Abstract #TPS2613**

Ingles Garces A.[1], Chénard-Poirier M.[1], Jones R.H.[2], Quinton A.[2], Plummer E.R.[3], Drew Y.[3], Kowalski M.[4], Klencke, B.[4], Banerji U.[1].

Institute of Cancer Research, Royal Marsden Hospital, London, United Kingdom[1]; Velindre Cancer Centre, Cardiff, United Kingdom[2]; Freeman Hospital, Newcastle upon Tyne, United Kingdom[3]; Sierra Oncology, Inc., Brisbane, CA[4].

## SRA737 Investigational Drug

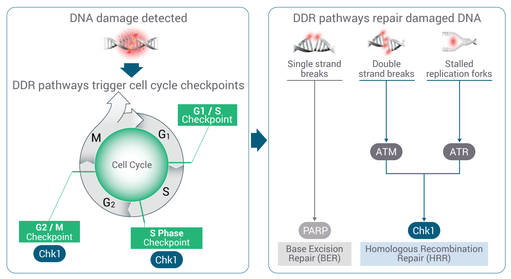
### SRA737 (FORMERLY CCT245737), A CHK1 INHIBITOR

- SRA737 is a potent, highly selective, orally bioavailable inhibitor of checkpoint kinase 1 (Chk1) with excellent pharmaceutical properties ($IC_{50}$: Chk1 = 1.4 nM).
- SRA737 demonstrates robust efficacy in numerous preclinical models as a single agent and in combination with selected cytotoxics and other novel anticancer agents.
- SRA737 was discovered and initially developed by the Cancer Research UK (CRUK) Cancer Therapeutics Unit at the Institute of Cancer Research (ICR).
- Sierra Oncology, Inc. licensed SRA737 in 2016 and became the sponsor of this first-in-human Phase 1 combination therapy study (SRA737-02) in January 2017.
- This clinical study employs an innovative clinical design, including a novel genetically-based prospective subject enrichment strategy.

## Chk1 is an Emerging Therapeutic Target in Cancer

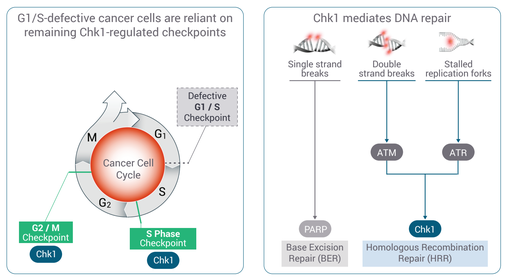
### THE DNA DAMAGE RESPONSE (DDR) NETWORK

The DDR network is a system of cellular pathways that detect DNA damage, pause the cell cycle, and repair damaged DNA to restore genomic integrity.




### CHK1 PLAYS AN IMPORTANT DUAL ROLE IN THE DDR

1. Chk1 is a key regulator of the cell cycle.
2. Chk1 is involved in homologous recombination repair of DNA.




**Chk1 inhibitors interfere with the biological role of Chk1 and induce Synthetic Lethality in selected genetically-mutated cancer cells. In addition, SRA737's activity is potentiated by chemotherapy such as gemcitabine, which could be further enhanced in the setting of genetic alterations predictive of Chk1 sensitivity.**

### GEMCITABINE IS A STRONG EXOGENOUS INDUCER OF REPLICATION STRESS AND POTENTIATES CHK1 INHIBITORS

- Replication Stress (RS) occurs during the process of cellular DNA replication and likely contributes to genomic instability, oncogenesis and tumor progression.
- RS is caused by a range of factors such as complex DNA secondary structure, damaged DNA, and a limiting dNTP pool.
- Gemcitabine is a potent inducer of RS and DNA damage via multiple mechanisms, and represents a rational and ideal drug combination with Chk1 inhibitors. Gemcitabine can induce DNA double strand breaks and stalled replication forks.
- Chk1 plays a critical role in the response to RS and DNA damage by mediating S and G2/M cell cycle arrest and homologous recombination repair, as well as by stabilizing replication forks and regulating origin firing in response to stalled replication.
- Profound mechanistic potentiation has been reported when SRA737 is combined with DNA damaging cytotoxic agents or radiation.
- Preclinical modeling demonstrates robust synergistic anti-tumor activity of SRA737 in combination with gemcitabine.

### GENETIC ALTERATIONS PREDICTIVE OF CHK1 SENSITIVITY

Preclinical and emerging clinical data have suggested that genetic alterations predictive of conferring enhanced susceptibility to Chk1 inhibition fall into four gene classes that are related to the multifunctional biological roles of Chk1:

| Gene Class | Biological Rationale |
|---|---|
| Tumor Suppressors (e.g. *RB1, TP53,* etc.) | Defective G1/S checkpoint should increase reliance on remaining Chk1-regulated DNA damage checkpoints. |
| Oncogenic Drivers (e.g. *MYC, KRAS,* etc.) | Oncogene-induced hyperproliferation and cell cycle dysregulation contribute to replication stress and could increase reliance on Chk1. |
| Replicative Stress (e.g. *ATR, CHEK1,* etc.) | Amplication of genes encoding ATR or Chk1 suggests greater reliance on Chk1 pathway to accomodate replication stress. |
| DNA Repair Machinery (e.g. *ATM, BRCA1/2,* etc.) | Mutated DNA repair genes result in excessive DNA damage, and may increase reliance on Chk1-mediated DNA repair and/or cell cycle arrest functions. |

## SRA737-02 Combination with Chemotherapy

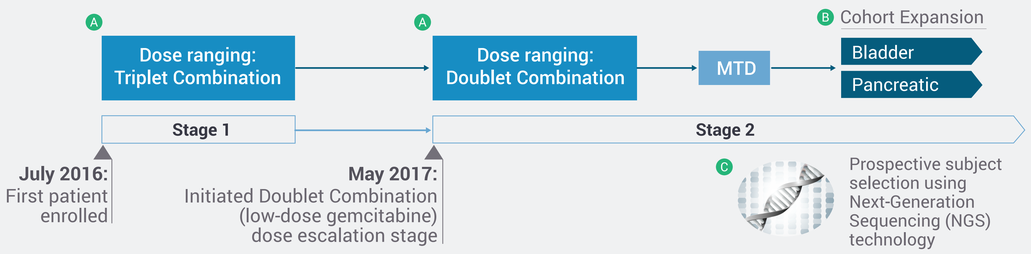
### RATIONALE

The study has been designed to investigate the safety and pharmacokinetics (PK) of SRA737 when given in combination with chemotherapy; to identify optimal dose, schedule, and maximum tolerated dose (MTD) of SRA737 in this setting; and to obtain preliminary evidence of therapeutic efficacy.

### STUDY DESIGN

**Phase 1, multicenter, first-in-human, open-label study in subjects with solid tumors.**

- Cohorts consisting of 3-6 subjects will receive escalating doses of SRA737.
- Intensive PK and pharmacodynamic assessments will be obtained on all subjects.
- Study includes 2 stages: Stage 1, Triplet Combination (SRA737 + gemcitabine + cisplatin) and Stage 2, Doublet Combination (SRA737 + gemcitabine). In Q2 2017, enrollment to the Doublet Combination was initiated.




**A Triplet Combination: SRA737 + gemcitabine + cisplatin**

- SRA737 orally on Days 2, 3, 9 & 10; gemcitabine IV on Days 1 and 8; cisplatin IV following gemcitabine on Day 1.
- Starting doses for Cohort 1: SRA737 20 mg, gemcitabine 1250 mg/m$^2$, cisplatin 80 mg/m$^2$.

**A Doublet Combination: SRA737 + low-dose gemcitabine**

- SRA737 orally on Days 2, 3, 9, 10, 16 & 17; gemcitabine IV on Days 1, 8, & 15.
- Starting doses for Cohort 1: SRA737 40 mg and gemcitabine 300 mg/m$^2$.

Prospective subject selection with NGS

B • After the dose escalation of the SRA737 + gemcitabine combination has been completed, a cohort expansion of genetically-defined bladder or pancreatic subjects will be enrolled.

C • Expansion cohort subjects must have tumors that harbor a minimum of two genomic alterations hypothesized to confer sensitivity to Chk1 inhibition and will be selected based on prospective genetic profiling.

### KEY STUDY OBJECTIVES

**Primary Objectives**

- To establish the safety profile of SRA737 administered in combination with gemcitabine ± cisplatin.
- To determine the MTD and a recommended Phase 2 dose of SRA737 administered in combination with gemcitabine.

**Secondary Objectives**

- To characterize the PK profile of SRA737 administered in combination with gemcitabine ± cisplatin.
- To explore the clinical activity of SRA737 in combination with gemcitabine ± cisplatin.

**Safety Evaluations**

- Assessment of adverse events and changes in laboratory tests.

**Efficacy Evaluations**

- Tumor assessments per RECIST v1.1 criteria.

### KEY ELIGIBILITY CRITERIA

No more than 3 previous lines of cytotoxic chemotherapy for metastatic disease.

**A Dose Escalation Phase**

Adults with locally advanced or metastatic solid tumors, relapsed after or progressing despite conventional treatment.

**B Cohort Expansion Phase**

Adults with genetically-defined, histologically or cytologically confirmed, locally advanced or metastatic **bladder cancer** or **pancreatic cancer** for which no other conventional therapy is considered appropriate.

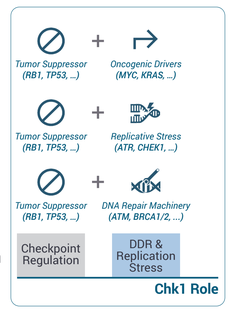
C Tumors must harbor the following genetic alterations:

- **A deleterious mutation in a key tumor suppressor gene** such as *RB1* or *TP53.*

And

One or more of the following:

- **A gain of function mutation/ amplification of an oncogenic driver** such as *MYC* or *KRAS*, or
- **A genetic indicator of replicative stress** defined as gain of function/ amplification of *CHEK1* or *ATR*, or
- **A loss of function/deleterious mutation in the DNA repair machinery** such as *ATM, BRCA1, or BRCA2*.




## Overall Summary

SRA737 is a potent, highly selective, orally bioavailable inhibitor of Chk1 with excellent pharmaceutical properties enabling potential broad clinical utility.

Targeted inhibition of Chk1 by SRA737 may have utility in a range of tumor indications.

- Replication Stress occurs during the process of cellular DNA replication and likely contributes to genomic instability, oncogenesis and tumor progression.
- RS is caused by a range of factors; Chk1 plays a critical role in the response to RS and DNA damage. Gemcitabine is a potent inducer of RS and DNA damage, and represents a rational and ideal drug combination with Chk1 inhibitors.
- Profound mechanistic potentiation has been reported when SRA737 is combined with gemcitabine.

Enrollment is ongoing in this novel Phase 1 dose escalation study combining SRA737, a potent Chk1 inhibitor, with **low-dose gemcitabine** and utilizing **a prospective genetically-based subject enrichment strategy**.

Subject Enrichment Strategy: Subjects with tumors that harbor a confirmed minimum of two different types of genomic alterations hypothesized to confer sensitivity to Chk1 inhibition, determined using NGS, will be prospectively enrolled into the indication-specific cohort.

**Contact**

Study sponsored by Sierra Oncology.
For more information, email info@sierraoncology.com or visit https://www.sierraoncology.com

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