SRA737 (FORMERLY CCT245737), A CHK1 INHIBITOR

- SRA737 is a potent, highly selective, orally bioavailable inhibitor of checkpoint kinase 1 (Chk1) with excellent pharmaceutical properties (IC50 Chk1 = 1.4 nM).
- SRA737 demonstrates robust efficacy in numerous preclinical models as a single agent and in combination with select cytotoxics and other novel anticancer agents.
- A minimum efficacious plasma concentration (Cmin) of 100 nM has been proposed from preclinical models.
- 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 monotherapy study (SRA737-01) in January 2017.
- This clinical study employs an innovative design, including a novel genetically-based prospective subject enrichment strategy.

How CHK1 inhibition induces synthetic lethality in genetically-mutated cancer cells

In normal cells, inactivation of Chk1 is tolerated due to the redundant pathway mediated by Protein "X". In cancer cells, inactivation of Protein "X" by genetic mutation, provides a growth advantage to the tumor, but also increases its dependency on Chk1. Inactivation of Chk1 by SRA737 in tumors harboring a defective Protein "X" results in simultaneous abrogation of both pathways, leading to synthetic lethality and death of the mutated tumor cell.

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:

- Tumor Suppressors (e.g. RB1, TP53, etc.)
- Oncogenic Drivers (e.g. MYC, KRAS, etc.)
- Replication Stress (e.g. ATR, Chk1, etc.)
- DNA Repair Machinery (e.g. ATM, BRCA1/2, etc.)

KEY STUDY OBJECTIVES

Primary Objectives
- To establish the safety profile of SRA737.
- To determine the MTD and propose a RP2D of SRA737.
- To evaluate the preliminary efficacy of SRA737 including efficacy in subjects prospectively-enrolled into genetically-defined indication-specific expansion cohorts.

Secondary Objectives
- To characterize the PK profile of SRA737.
- To assess the relationship between response and the presence of selected genetic alterations in tumors.

Overall Summary

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

Chk1 is a key regulator of important cell cycle checkpoints and central mediator of the DDR network.

- In cancer cells, either replication stress induced by oncogenes (e.g., MYC or KRAS) or genetic mutations in DNA repair machinery (e.g., ATM or BRCA1) combined with loss of function in tumor suppressors (e.g., RB1 or TP53) results in persistent DNA damage and genomic instability leading to an increased dependency on Chk1 for survival.
- Targeted inhibition of Chk1 by SRA737 may therefore be synthetically lethal in certain genetically-defined backgrounds and have utility as a monotherapy in a range of tumor indications.

Enrollment is ongoing in this novel Phase 1 monotherapy study utilizing:

- An accelerated titration design during the dose escalation phase.
- A concurrent multi-indication cohort expansion phase being conducted at potentially active dose levels.
- A prospective genetically-based subject enrichment strategy.

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