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A clinical-stage drug development company advancing next generation DNA Damage Response (DDR) therapeutics for the treatment of patients with cancer.

We are an ambitious oncology drug development company oriented to registration and commercialization.

We have a highly experienced management team with a proven track record in oncology drug development.

**NASDAQ: SRRA**

**Headquarters:** Vancouver, BC  
**Development:** San Francisco, CA

**Shares (03/31/17):**  
52.3M outstanding  
59.9M fully diluted

**Cash on hand (03/31/17):**  
$125.0M
The DNA Damage Response (DDR) network is an emerging biological target space for cancer, validated by the clinical success of PARP inhibitors. Lead program SRA737 targets Chk1, a clinically-validated target with potential for synthetic lethality in genetically-defined backgrounds. Our pipeline assets are potent, highly selective, oral kinase inhibitors against Chk1 (SRA737) and Cdc7 (SRA141), with excellent drug-like properties. SRA737 is in two active Phase 1 clinical studies employing a novel prospective patient enrichment strategy. Cash runway to mid-2019 delivers multiple data readouts, with preliminary data anticipated in early 2018.
# Our Pipeline of ‘Next Generation’ DDR Therapeutics

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<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td><strong>SRA737</strong></td>
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<td><strong>Phase 1</strong></td>
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<tr>
<td><strong>Chk1</strong></td>
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<td><strong>Monotherapy</strong></td>
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<td></td>
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<td>Advanced solid tumors, Currently enrolling</td>
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<tr>
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<td><strong>Phase 1</strong></td>
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<td><strong>Plan to file IND H2 2017</strong></td>
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**Targeting**

- **Cell division cycle 7**
- **Checkpoint kinase 1**
Beyond PARP: Our DNA Damage Response (DDR) Program
DDR Network: Detects DNA Damage, Pauses the Cell Cycle and Repairs DNA

- **DNA damage detected**
- **DDR pathways trigger cell cycle checkpoints**

**Diagram:**
- S Phase Checkpoint
- G2 / M Checkpoint
- S Phase Checkpoint

**DDR pathways repair damaged DNA:**
- Single strand breaks
- Double strand breaks
- Stalled replication forks

- ATM
- ATR
- PARP
- Chk1
- Base Excision Repair (BER)
- Homologous Recombination Repair (HRR)
- Cdc7
SRA737 Targeting Chk1
Chk1 is an Attractive Emerging Therapeutic Target in Cancer

Chk1 plays an important dual role:

1) as a key regulator of the cell cycle

G1/S-defective cancer cells are reliant on remaining Chk1-regulated checkpoints

2) in the repair of DNA double strand breaks

Chk1 mediates DNA repair

- Single strand breaks
- Double strand breaks
- Stalled replication forks

- PARP
- ATM
- ATR
- Chk1

Base Excision Repair (BER)
Homologous Recombination Repair (HRR)
SRA737 – Potential Best-In-Class Chk1 Inhibitor

**Clinically Validated Target**
- Clinical efficacy reported as monotherapy with LY2606368.
- Gemcitabine combination efficacy reported with GDC-0575.

**Superior Drug Profile**
- Potent, and superior selectivity for Chk1 vs. Chk2.
- Excellent oral bioavailability in man enables potential broad clinical utility.

**Differentiated Clinical Strategy**
- Aggressive clinical development focused on multiple tumor types.
- Novel genetically-driven, prospective patient selection strategy designed to demonstrate synthetic lethality.

**Near-term Data Readouts**
- R&D day showcasing preclinical and preliminary clinical data planned for early 2018.
- Medical conference data anticipated in H2 2018.

**Significant Commercial Potential**
- Genetic selection strategy applicable to multiple large market indications.
- Additional combination opportunities with other DDR agents (e.g. PARPi) and immuno-oncology agents.
SRA737: Originates from Renowned Drug Discovery Group with Proven Track Record

Discovered and advanced into the clinic by:

CRUK/ICR drug discovery track record:

- **Abiraterone (Zytiga)** for advanced prostate cancer: >$2B ww sales*
  - *2016

- **Temozolomide for glioblastoma**: >$1B ww sales*
  - *2008
SRA737 – Potentially Superior Chk1 Inhibitor Profile

- SRA737’s potency, selectivity and oral bioavailability could enable a superior efficacy and safety profile.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>SRA737</th>
<th>LY2606368</th>
<th>GDC-0575</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of development:</td>
<td>Ph1</td>
<td>Ph2</td>
<td>Ph1</td>
</tr>
<tr>
<td>Presentation:</td>
<td>Oral</td>
<td>i.v.</td>
<td>Oral</td>
</tr>
<tr>
<td>Biochemical IC$_{50}$: Chk1</td>
<td>1.4 nM</td>
<td>~1 nM</td>
<td>2 nM</td>
</tr>
<tr>
<td>Biochemical IC$_{50}$: Chk2</td>
<td>1850 nM</td>
<td>8 nM</td>
<td>unk</td>
</tr>
<tr>
<td>Selectivity: Chk1 vs. Chk2</td>
<td>1320x</td>
<td>~10x</td>
<td>unk</td>
</tr>
</tbody>
</table>

SRA737 selectivity:
- 15/124 kinases at 10 µM
- ERK8 = 100x
- All other kinases >200x
- CDK2 = 2750x
- CDK1 = 6750x
Chk1 Inhibition Induces Synthetic Lethality in Genetically-Mutated Cancer Cells

Protein “X” and Chk1 function in parallel compensatory pathways, for example in pathways regulating essential DDR functions required for survival.

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 tumor cells harboring a defective Protein “X” is expected to result in simultaneous abrogation of both pathways, leading to synthetic lethality and death of the mutated tumor cell.
Rapid Tumor Regression as Monotherapy in Neuroblastoma Model – Support for Synthetic Lethality

7 days consecutive dosing @ 150 mg/kg po

- **MYCN**-dependent proliferation of neuronal precursor cells is associated with replication stress.
- **MYCN**-transgenic mouse tumors are genetically unstable with chromosomal abnormalities reflective of the human disease.
- SRA737 treatment results in acute reduction of tumor burden in model of human **MYCN**-driven neuroblastoma, supporting the Chk1 synthetic lethality concept.
Profound Mechanistic Potentiation with DNA-Damaging Gemcitabine

- Gemcitabine is a potent inducer of replication stress and DNA damage, promoting DNA double strand breaks and stalled replication forks. Chk1 has a fundamental biological role in responding to replication stress.
- Preclinical modeling demonstrates extremely robust synergistic anti-tumor activity for SRA737 potentiated by gemcitabine.
- Potential to leverage both potentiation and synthetic lethality in genetically-defined combination studies.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Tissue Origin</th>
<th>SRA737 Potentiation of Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT29</td>
<td>Colon</td>
<td>7.9-fold</td>
</tr>
<tr>
<td>SW620</td>
<td>Colon</td>
<td>16.9-fold</td>
</tr>
<tr>
<td>Calu-6</td>
<td>NSCLC</td>
<td>9.1-fold</td>
</tr>
<tr>
<td>MiaPaCa</td>
<td>Pancreas</td>
<td>23-fold</td>
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</tbody>
</table>

[Sierra unpublished data: HT29 colorectal model; non-Chk1i synthetic lethal cell line]
Genes Impacting Cell Cycle & DNA Damage Linked to Chk1i Synthetic Lethality

Preclinical and emerging clinical data support that Chk1i sensitivity is associated with certain genetic backgrounds.

<table>
<thead>
<tr>
<th>Gene Class</th>
<th>Biological Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Suppressors (e.g. TP53, RAD50, etc.)</td>
<td>Defective G1/S checkpoint should increase reliance on remaining Chk1-regulated DNA damage checkpoints.</td>
</tr>
<tr>
<td>Oncogenic Drivers (e.g. MYC, KRAS, etc.)</td>
<td>Oncogene-induced hyperproliferation and cell cycle dysregulation contributes to replication stress and could increase reliance on Chk1.</td>
</tr>
<tr>
<td>Replicative Stress (e.g. ATR, CHEK1, etc.)</td>
<td>Amplification of genes encoding ATR or Chk1 suggests greater reliance on Chk1 pathway to accommodate replication stress.</td>
</tr>
<tr>
<td>DNA Repair Machinery (e.g. BRCA1/2, FA, etc.)</td>
<td>Mutated DNA repair genes results in excessive DNA damage, and may increase reliance on Chk1-mediated DNA repair and/or cell cycle arrest functions.</td>
</tr>
</tbody>
</table>
Sierra’s Patient Selection Algorithm is Based on Genetic Profiling for Synthetic Lethality

“Stack the deck” by requiring mutations in genes that impact both roles of Chk1 - cell cycle and DNA integrity - to maximally enhance potential SRA737 sensitivity.

- Tumor Suppressor (TP53, RAD50…)
- Oncogenic Drivers (MYC, KRAS…)
- Tumor Suppressor (TP53, RAD50…)
- Replicative Stress (ATR, CHEK1…)
- Tumor Suppressor (TP53, RAD50…)
- DNA Repair Machinery (BRCA1, FA…)

**Strategic goal:**
Enrich for patients with genetic profiles with high predicted SRA737 sensitivity.

Select tumor types with high genomic instability/replication stress.
Mutational frequencies in oncogenes associated with Chk1i synthetic lethality differ across cancer indications, facilitating rational patient selection strategies.
Clinical Validation of Chk1 Monotherapy with Emerging Data for LY2606368

ESMO 2016 Abstract:
Phase 2 study in sporadic high-grade serous ovarian cancer and germline BRCA mutation-associated ovarian cancer.

AACR 2017 Poster:
Phase 1b monotherapy expansion cohort data update in advanced head and neck squamous cancers and squamous cell carcinoma of the anus. Dosed 1 out of every 14 days.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Disease Control Rate (CR+PR+SD)</th>
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<tr>
<td>HNSCC</td>
<td>60% (28/47)</td>
</tr>
<tr>
<td>SCCA</td>
<td>75% (18/24)</td>
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</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Overall Response Rate (CR+PR)</th>
</tr>
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<tbody>
<tr>
<td>HGSOC</td>
<td>38% (5/13) (non-BRCA mutated)</td>
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</table>

Patients with favorable responses harbored:
- Loss of function mutations in \( FBXW7 \) and \( PARK2 \), two genes implicated in Cyclin E1 proteolysis.
- Mutations and/or germline variants in DDR genes: \( BRCA1 \), \( BRCA2 \), \( MRE11A \) and \( ATR \).

Clinical validation of:
- the target
- genetic selection strategy
- monotherapy
Clinical Validation of Chk1/Gemcitabine Combination with Emerging Clinical Data from Genentech

**GDC-0425: First generation Chk1 inhibitor**
- 40 patient Phase 1 combination study with gemcitabine.
- 21 patients had RECIST-evaluable disease and archival tissue for genetic assessment.
- 2 out of 3 PRs had TP53 mutations.

**GDC-0575: Currently in Phase 1 development**
- Genentech’s Phase 1 (EORTC 2016) saw meaningful responses in two sarcoma patients in combination with low-dose gemcitabine:
  - 1 CR (ongoing >9 months) in sarcoma with lung metastases.
  - 1 PR (lasted >1 year) in TP53 mutated leiomyosarcoma with extensive metastases.

Clinical validation of:
- the target
- genetic selection strategy
- chemopotentiation
Breadth of Development Opportunities Reflected in Sierra’s Development Strategy

**Current Clinical Trials**

- **Monotherapy**
  - Exploit synthetic lethality in genetically-defined patient populations across five tumor types that have predicted high sensitivity to SRA737.

- **Chemotherapy Combination**
  - Exploit profound potentiating effects of SRA737 with low dose gemcitabine plus synthetic lethality in genetically-defined populations in two tumor types.

**Potential Clinical Opportunities**

- **PARP Combo**
  - Exploit synergy between SRA737 + PARP inhibitor to expand/enhance PARP inhibitor sensitivity / overcome resistance.

- **I/O Combo**
  - Explore PD-(L)1 combination and its potential to drive neoantigen presentation in “double checkpoint” strategy.
Monotherapy Phase 1: Innovative Trial Design to Show Synthetic Lethality

Fall 2016: CRUK-sponsored Ph1 monotherapy dose escalation initiated (advanced solid tumors)

Jan 2017: Sierra assumes sponsorship of SRA737

May 2017: Amendment cleared by regulators

Continued dose escalation to MTD

• Parallel MTD determination and cohort expansion in genetically-defined patient populations.
• Continuous daily oral administration.

Prospective patient selection using NGS technology

Prostate
Ovarian
Non-Small Cell Lung
Head & Neck
Colorectal
Encouraging Initial Progress from Ongoing Phase 1 Monotherapy Trial

Preliminary observations from SRA737 Phase 1 monotherapy trial:

- Dose Escalation has efficiently advanced through six single patient dose cohorts (20, 40, 80, 160, 300 and 600 mg/day) under continuous daily oral dosing.

- SRA737 has been well tolerated to date:
  - No Grade 2 or higher SRA737-related Adverse Events reported
  - No dose-limiting toxicities observed
  - MTD not yet been reached

- Dose-proportional exposure:
  - Pharmacokinetic (PK) parameters for SRA737 have been generally linear across the dose range tested to date.

- Dosing in potentially active range:
  - Plasma concentrations of SRA737 exceeding the proposed minimum efficacious threshold (Cmin) of 100 nM were maintained for 24 hours post-dose at 160 mg/day dose level and above.

- Successfully surpassing Cmin enabled initiation of the ‘synthetic lethality’-oriented Cohort Expansion Phase focused on five indication-specific cohorts: colorectal, head and neck, non-small cell lung, ovarian, and prostate cancers.
Chemotherapy Combination Phase 1: Leverages Potentiation & Synthetic Lethality

**Fall 2016:** CRUK-sponsored Ph1 cis-gem combination dose escalation initiated (advanced solid tumors)

- *Low-dose gemcitabine combination.*
- *Intermittent oral dosing following each dose of chemotherapy.*

**Jan 2017:** Sierra assumes sponsorship of SRA737

**May 2017:** Amendment cleared by regulators

Later, a low-dose gem combo dose escalation was initiated. Prospective patient selection using NGS technology was also conducted for treatments targeting bladder and pancreatic cancers.

### Key Points
- **Low-dose gemcitabine combination.**
- **Intermittent oral dosing following each dose of chemotherapy.**
SRA737 Phase 1 Chemotherapy Combination trial has transitioned to Stage 2:

- Stage 1, evaluating SRA737 in combination with gemcitabine and cisplatin, has concluded enrolment.
- Stage 2, evaluating SRA737 with low-dose gemcitabine has been initiated, commencing with a Dose Escalation phase.
- Once an MTD and dosing schedule have been determined, the study will evaluate the preliminary efficacy of the combination in indication-specific cohorts of prospectively-selected, genetically-defined subjects with bladder or pancreatic cancer.

- Gemcitabine is a potent inducer of replication stress and DNA damage; Chk1 has a fundamental biological role in responding to such stressors.
- Low-dose gemcitabine potentiates the activity of SRA737.
- Preclinical modeling demonstrates robust synergistic anti-tumor activity of SRA737 in combination with low-dose gemcitabine.
SRA737 has Significant Commercial Potential Across Major Market Cancer Indications

Estimated 20-33% of patients in a given tumor type will be biomarker positive based on our genetic algorithm.

US Patient Population (‘000s) With Advanced Cancers

[Company Estimates]

- Colorectal: 61
- Ovarian: 24
- Prostate: 72
- Lung: 162
- Head & Neck: 31
- Bladder: 31
- Pancreatic: 38
- Total: 419

Monotherapy indications

Gemcitabine combination indications
SRA737: Upcoming Expected Milestones

<table>
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<tr>
<th>Q1 17</th>
<th>Q2 17</th>
<th>Q3 17</th>
<th>Q4 17</th>
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<td>Complete formal CTA transfer</td>
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<td>Preliminary R&amp;D update Early 2018</td>
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Potential Clinical Opportunities in 2018
- PARP Combo
- I/O Combo
SRA141 Targeting Cdc7
• SRA141: potent, orally bioavailable, highly selective cell division cycle 7 (Cdc7) inhibitor.

• Cdc7: key regulator of both DNA replication and DNA damage response.

• Potential development opportunities in solid and liquid tumors.

• Monotherapy and combination therapy development potential.
Cdc7: Key Function in DNA Replication

- Cdc7 activates DNA replication during S-phase in response to growth-promoting signals (e.g. cyclins, Myc, Ras)
- Cdc7 stabilizes stalled replication forks during replication stress.

Replication stress drivers:
- Cyclins
- Myc
- Ras

Diagram:
- DNA replication
- Stalled replication fork
- Homologous Recombination Repair (HRR)
- S Phase Checkpoint
- Replication stress drivers
  - Cyclins
  - Myc
  - Ras

Key proteins and pathways:
- SRA141
- CDK2
- Chk1
- ATR
- RAD51
- Fanconi Anemia
- SRA737

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SRA141: Potential First-In-Class/Best-In-Class Opportunity

- Preclinical data and published literature suggest a variety of indications with potential for response to Cdc7 inhibitors:
  - Solid tumors: breast, ovarian, pancreatic, melanoma, colorectal, uterine, thyroid, etc.
  - Hematological malignancies: AML, DLBCL, etc.
- SRA141’s selectivity profile offers possible differentiation and potential safety and efficacy advantages.
- A biomarker-driven patient selection strategy focusing on drivers of Cdc7 inhibitor sensitivity may help facilitate clinical trial execution.
Advancing Targeted Cancer Therapies
Proven Leadership in Oncology Development

Nick Glover, PhD
President and CEO

Barbara Klencke, MD
Chief Development Officer

Angie You, PhD
Chief Business & Strategy Officer and Head of Commercial

Sukhi Jagpal, CA, CBV, MBA
Chief Financial Officer

Mark Kowalski, MD, PhD
Chief Medical Officer

Keith Anderson, PhD
Senior Vice President, Technical Operations

Wendy Chapman
Senior Vice President, Clinical Operations

Diane Gardiner
Senior Vice President, Human Resources and Administration

Christian Hassig, PhD
Senior Vice President, Research

Chandra Lovejoy
Senior Vice President, Global Regulatory Affairs and Head of Quality

Emma McCann
Senior Vice President, Program Management

Gregg Smith, PhD, MBA
Senior Vice President, Preclinical
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