Next Generation DDR Therapeutics
Q1 2018
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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.

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

NASDAQ: SRRA

Headquarters: Vancouver, BC

Shares (09/30/17):
52.3M outstanding
60.0M fully diluted

Cash on hand (09/30/17):
$107.8M
Proven Leadership in Oncology Development

Nick Glover, PhD
President and CEO

Barbara Klencke, MD
Chief Development Officer

Mark Kowalski, MD, PhD
Chief Medical Officer

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

Christian Hassig, PhD
Chief Scientific Officer

Sukhi Jagpal, CA, CBV, MBA
Chief Financial Officer
### Our Pipeline of ‘Next Generation’ DDR Therapeutics

<table>
<thead>
<tr>
<th>Targeting Checkpoint kinase 1</th>
<th>Targeting Cell division cycle 7 kinase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SRA737</strong></td>
<td><strong>SRA141</strong></td>
</tr>
<tr>
<td>Chk1</td>
<td>Cdc7</td>
</tr>
</tbody>
</table>

#### Preclinical
- **Monotherapy**
  - Five indications; prospective genetic selection
- **Low-Dose Gemcitabine Combination**
  - Advanced solid tumors
- **PARPi Combination**
  - Potential clinical study in 2018
- **I/O Combination**
  - Potential clinical study in 2018
- **IND enabling studies**
SRA737: Our Chk1 Inhibitor Program
The DNA Damage Response Network

- **Endogenous:**
  - Replication stress
  - Cell metabolism
  - Oxygen radicals
  - Radiation
  - Viral infection
  - Chemotherapy

- **Exogenous:**

  - DNA Damage
  - Monitor and detect DNA damage

- **Cell Cycle:**
  - G1 / S Checkpoint
  - S Phase Checkpoint
  - G2 / M Checkpoint
  - Pause the cell cycle

- **DNA Repair:**
  - Single strand breaks
  - Base Excision Repair (BER)
  - Double strand breaks
  - Homologous Recombination Repair (HRR)
  - Stalled replication forks
  - Trigger DNA repair
“Cancer... is a genome that becomes pathologically obsessed with replicating itself. . . .”

Dr. Siddhartha Mukherjee, Oncologist
Pulitzer Prize winning author of The Emperor of All Maladies & The Gene

Replication Stress (RS)

Hyperproliferation and dysregulated DNA replication result in **Replication Stress** manifested by stalled replication forks and DNA damage, leading to increased genomic instability, a fundamental hallmark of cancer.
Replication Stress Drives Genomic Instability

Cell cycle dysregulation
- e.g. Loss of G1/S
- Defective G1 / S Checkpoint
  - TP53
  - HPV

Oncogenic drivers
- e.g. Dysregulation of replication, transcription/replication collision
  - MYC
  - RAS

Defective DNA damage repair
- e.g. Single strand breaks, double strand breaks
  - BRCA 1/2

Depleted replication building blocks
- e.g. Chemotherapy induced

High RS results in:

Cancer cell survives with increased mutagenic capacity

Excessive genomic instability results in cancer cell death

Normal Cell

Genomic Instability

Cell Death
Chk1 is a Master Regulator of the Replication Stress

Cell Cycle Regulation
Chk1 pauses the cell cycle to enable DNA repair

DNA Damage Response
Chk1 regulates origin firing to manage replication stress
Chk1 stabilizes stalled replication forks
Chk1 mediates DNA repair via HRR

G1/S-defective cancer cells are reliant on Chk1-regulated cell cycle checkpoints
Chk1 Inhibition Drives High-RS Cancer Cells Into Catastrophic Genomic Instability

Cancer cells are dependent on Chk1 to manage high levels of RS and survive.

Chk1 inhibition results in catastrophic dysregulation of replication, leading to cancer cell death.

RS increases genomic instability in cancer cells. Chk1 regulates RS.

SRA737 inhibits Chk1, leading to excessive genomic instability and cell death.
### Chk1i Synthetic Lethality Associated with RS Genes

Preclinical and emerging clinical data support that Chk1i sensitivity is associated with genetic backgrounds linked to increasing replication stress.

<table>
<thead>
<tr>
<th>Gene Class</th>
<th>Biological Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysregulated Cell Cycle</strong></td>
<td>Defective G1/S checkpoint increases reliance on remaining Chk1-regulated DNA damage checkpoints</td>
</tr>
<tr>
<td>(e.g. TP53, RAD50, etc.)</td>
<td></td>
</tr>
<tr>
<td><strong>Oncogenic Drivers</strong></td>
<td>Oncogene-induced replication and transcription results in transcription/replication collisions, dysregulation of replication and dNTP exhaustion, driving RS</td>
</tr>
<tr>
<td>(e.g. MYC, KRAS, etc.)</td>
<td></td>
</tr>
<tr>
<td><strong>DNA Repair Machinery</strong></td>
<td>Mutated DNA repair genes results in excessive DNA damage, increased RS and increase reliance on Chk1-mediated DNA repair and/or cell cycle functions</td>
</tr>
<tr>
<td>(e.g. BRCA1/2, FA, etc.)</td>
<td></td>
</tr>
<tr>
<td><strong>Replicative Stress Response</strong></td>
<td>Amplification of genes encoding ATR or Chk1 suggests greater reliance on Chk1 pathway to accommodate RS</td>
</tr>
<tr>
<td>(ATR, CHEK1)</td>
<td></td>
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</tbody>
</table>
SRA737: Originates from Renowned Drug Discovery Group with Proven Track Record

Discovered and advanced into the clinic by:

Drug discovery track record:

- Temozolomide for glioblastoma
  >$1B ww sales*
  *2008

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

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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>Prexasertib</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$_{50}$:</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chk1</td>
<td>1.4 nM</td>
<td>~1 nM</td>
<td>2 nM</td>
</tr>
<tr>
<td>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>&gt;30x</td>
</tr>
</tbody>
</table>

- SRA737 patent protection to 2033+.
SRA737 Phase 1/2 Monotherapy Synthetic Lethality Trial
Clinical Validation of Chk1i Monotherapy with Emerging Data for Prexasertib (LY2606368)

Lancet Oncology 2018:
Phase 2 study in high-grade serous ovarian cancer. Heavily pre-treated. BRCA wild type (PARP insensitive). Dosed 1 out of every 14 days.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGSOC (BRCAwt)</td>
<td>33% ORR (8/24) Evaluable</td>
</tr>
<tr>
<td></td>
<td>32% ORR (6/19) Platinum resistant</td>
</tr>
<tr>
<td></td>
<td>58% DCR (11/19) Platinum resistant</td>
</tr>
</tbody>
</table>

Tumor Type Efficacy:
- HGSOC (BRCAwt):
  - 33% ORR (8/24) Evaluable
  - 32% ORR (6/19) Platinum resistant
  - 58% DCR (11/19) Platinum resistant
Clinical Validation of Chk1i Monotherapy with Emerging Data for Prexasertib (LY2606368)

**AACR 2017 Poster:**
Phase 1b monotherapy expansion cohort data 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>
</tr>
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<tbody>
<tr>
<td>HNSCC</td>
<td>60% (28/47): 3 PRs</td>
</tr>
<tr>
<td>SCCA</td>
<td>75% (18/24): 1 CR, 4 PRs</td>
</tr>
</tbody>
</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
Our clinical studies target promising indications associated with genetically-driven replication stress and high genomic instability.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Replicated Cell Cycle (TP53, RAD50…)</th>
<th>Oncogenic Drivers (MYC, RAS…)</th>
<th>DNA Repair Machinery (BRCA1/2, FA…)</th>
<th>Replicative Stress Response (ATR, CHK1…)</th>
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<tbody>
<tr>
<td>Bladder</td>
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<td>Ovarian (HGSOC)</td>
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<td>Squamous NSCLC</td>
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<td>Prostate</td>
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<td>Colorectal*</td>
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<td>Head &amp; Neck</td>
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<td>Lung Adenocarcinoma</td>
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<td>Pancreatic</td>
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<td>Cholangiocarcinoma</td>
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<td>Invasive Breast</td>
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<tr>
<td>AML</td>
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(Red = most frequently mutated; Green = least frequently mutated)

- Cancer-related alterations in genes associated with Chk1i synthetic lethality differ across cancer indications, facilitating rational patient selection strategies.
Monotherapy Phase 1/2: 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

- **Mid-2017:** Amendment active

- **Q3 2017:** Actively Enrolling
  - Prostate
  - Ovarian
  - Non-Small Cell Lung
  - Head & Neck
  - Colorectal

- **Prospective patient selection using NGS technology**

- **Parallel MTD determination and cohort expansion in genetically-defined patient populations.**

- **Continuous daily oral administration.**

- **Dose escalation (non-selected)**

- **Continued dose escalation to MTD (non-selected)**
Preliminary observations from SRA737 Phase 1 monotherapy trial (as of June 2017):

- 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.
  - Plasma exposure in patients exceed SRA737 levels that achieve anti-tumor activity in preclinical models as monotherapy.

Program update planned for February 2018 and interim clinical results anticipated in the second half of 2018.
SRA737 Phase 1/2 Low-Dose Gemcitabine (LDG) Combination Trial
Clinical Validation of Chk1i/Gemcitabine Combination with Emerging Clinical Data from Genentech

GDC-0575: ESMO2017 Poster - Phase 1 + high/mid dose gemcitabine
- GDC-0575 demonstrated 4 responses (DCR = 60%) including meaningful & durable partial responses in TNBC, NSCLC and sarcoma:
  - Biological rationale: Chk1 inhibition augments gemcitabine's cytotoxic activity.
  - 1 PR (lasted >1 year) in TP53 mutated leiomyosarcoma with extensive metastases.
  - 1 PR (ongoing >6 months) in sarcoma.
  - However, gemcitabine-related toxicity limited GDC-0575 to a max dose of 105mg.

Clinical validation of:
- the target
- genetic selection strategy
- gemcitabine potentiation
Gemcitabine is a Potent Inducer of Replication Stress

Gemcitabine profoundly depletes replication building blocks inducing additional replication stress, further enhancing sensitivity to Chk1 inhibition.

- Intrinsic genetic RS drives genomic instability
- Low-dose gemcitabine induces additional RS without cytotoxicity, further increasing genomic instability
- Excessive genomic instability results in cancer cell death
SRA737 Synergizes with Sub-Therapeutic Doses of Gemcitabine *In Vivo*

- Typical combination approaches seek to augment the cytotoxic activity of full dose chemotherapy, exacerbating tolerability and limiting the dose of the combination agent.
- Conversely, our novel approach employs very low doses of chemotherapy to augment the activity of SRA737.
- Preclinical models demonstrate that SRA737 can be potentiated by sub-therapeutic doses of gemcitabine.

Sierra data presented in a poster at the 2017 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.
Low-Dose Gemcitabine Combination Phase 1/2: Leverages Potentiation & Synthetic Lethality

- **Jan 2017:** Sierra assumes sponsorship of SRA737
- **May 2017:** Amendment cleared by regulators
- **Fall 2016:** CRUK-sponsored Phase 1 cis/gem combination dose escalation initiated (advanced solid tumors)
- **Actively Enrolling**
  - Low-dose gem combo dose escalation (non-selected)
  - Prospective patient selection using NGS technology

- **Low dose gemcitabine (day 1) followed by intermittent oral dosing of SRA737 (days 2 & 3) for three consecutive weeks per each 28 Day Cycle**
PARPi synthetic lethality is associated with HRR deficiency, particularly induced by BRCA1/2 genetic mutations.

- Chk1 has a fundamental role regulating the HRR machinery.
- Rational PARPi + Chk1i combination opportunities via ‘chemical synthetic lethality’.
Compelling Biological Rationale for Potential Synergy Between SRA737 + PARPi

- Chk1’s role regulating HRR facilitates various SRA737 + PARPi therapeutic scenarios.

**HRR Deficient**
‘Deepen Responses’

**Post-PARPi Resistant**
‘Overcome Resistance’

**HRR Proficient**
‘Expand Indications’
SRA737 Potential Synergy With I/O
• ASCO 2017 presentation (Abstract #4509) highlighted results of retrospective analysis linking DDR alterations to I/O response rates in Urothelial Carcinoma.
• DDR alterations were found to significantly affect I/O responses:
  • 20-30% response rate without DDR mutations.
  • 70-80% response rate with DDR mutations.
• Chk1i could potentially induce the 'chemical equivalent' of an intrinsic DDR mutation, possibly enhancing I/O response rates.
Rationale for SRA737 + I/O Combinations

• Emerging preclinical and clinical data demonstrate that dual targeting of the DDR network (via certain genetic backgrounds or small molecule inhibitors) in conjunction with I/O can result in synergistic efficacy.

• There are several developing mechanistic rationales to explain the potential synergistic activity of Chk1i and I/O:
  • Inhibition of Chk1 with SRA737 leads to modulation of innate immune signaling pathways (e.g. STING, interferon). This results in the release of cytokines and chemokines that recruit immune cells potentially rendering I/O therapy more effective.
  • Inhibition of Chk1 with SRA737 leads to increased mutational burden and a higher prevalence of neoantigens, resulting in additional stimulation of the immune system, which could render I/O therapy more effective.
Sierra Oncology: Advancing Targeted Cancer Therapies
**SRA737: Upcoming Expected Milestones**

### Monotherapy

<table>
<thead>
<tr>
<th>Q1 17</th>
<th>Q2 17</th>
<th>Q3 17</th>
<th>Q4 17</th>
<th>H1 18</th>
<th>H2 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal CTA transfer Q1 2017 ✓</td>
<td>Protocol amendment Q2 2017 ✓</td>
<td>Expansion cohorts Q3 2017 ✓</td>
<td></td>
<td>Preliminary Program Update Feb 2018</td>
<td>Medical conference data H2 2018</td>
</tr>
</tbody>
</table>

### Low-Dose Gemcitabine Combination

<table>
<thead>
<tr>
<th>Q1 17</th>
<th>Q2 17</th>
<th>Q3 17</th>
<th>Q4 17</th>
<th>H1 18</th>
<th>H2 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formal CTA transfer Q1 2017 ✓</td>
<td>Protocol amendment Q2 2017 ✓</td>
<td>Advance to stage 2 Q3 2017 ✓</td>
<td></td>
<td>Preliminary Program Update Feb 2018</td>
<td>Medical conference data H2 2018</td>
</tr>
</tbody>
</table>

### Potential Clinical Opportunities in 2018

- PARP Combo
- I/O Combo
Represented by leading experts in DDR biology, chemistry and medicine. Focused on maximizing the potential clinical and commercial deployment of our DDR drug candidates.

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/University</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eric Brown, PhD</td>
<td>Perelman School of Medicine, University of Pennsylvania</td>
</tr>
<tr>
<td>Karlene Cimprich, PhD</td>
<td>Stanford University School of Medicine</td>
</tr>
<tr>
<td>Alan D'Andrea, MD</td>
<td>Harvard Medical School &amp; Dana-Farber Cancer Institute</td>
</tr>
<tr>
<td>Alan Eastman, PhD</td>
<td>Norris Cotton Cancer Center at Dartmouth</td>
</tr>
<tr>
<td>Michelle Garrett, PhD</td>
<td>School of Biosciences at the University of Kent and ICR UK</td>
</tr>
<tr>
<td>Thomas Helleday, PhD</td>
<td>Karolinska Institute, Stockholm, Sweden</td>
</tr>
<tr>
<td>Leonard Post, PhD</td>
<td>Former CSO BioMarin, developer of PARP inhibitor talazoparib</td>
</tr>
</tbody>
</table>
Next Generation DDR Therapeutics

The DDR network is an emerging biological target space in oncology, validated by the clinical success of PARP inhibitors.

Our pipeline assets are potent, highly selective, oral kinase inhibitors against Chk1 (SRA737) and Cdc7 (SRA141), with excellent drug-like properties.

Lead program SRA737 targets Chk1, a clinically-validated target with a fundamental role regulating replication stress in cancer. Potential for synthetic lethality in genetically-defined backgrounds.

SRA737 is in two active Phase 1/2 studies (monotherapy and low-dose gemcitabine combination) employing novel prospective patient enrichment strategies. PARPi and I/O combination studies are also planned.

Expected cash runway to mid-2019 delivers multiple data readouts, with a program update planned for February 2018 and interim clinical results anticipated in the second half of 2018.