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Program Update: Agenda

1. Introductions
   The DDR Network

2. SRA737 Development Program
   SRA737-01: Monotherapy
   SRA737-02: LDG Combination
   SRA737-03: PARPi Combination
   SRA737-04: I/O Combination

3. SRA141 Development Program
   SRA141-01: Monotherapy

4. Closing Remarks
   Q&A
## Sierra’s Management Team: Proven Leadership In Oncology Development

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nick Glover, PhD</td>
<td>President and CEO</td>
<td></td>
</tr>
<tr>
<td>Barbara Klencke, MD</td>
<td>Chief Development Officer</td>
<td></td>
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<tr>
<td>Mark Kowalski, MD, PhD</td>
<td>Chief Medical Officer</td>
<td></td>
</tr>
<tr>
<td>Angie You, PhD</td>
<td>Chief Business &amp; Strategy Officer and Head of Commercial</td>
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</tr>
<tr>
<td>Christian Hassig, PhD</td>
<td>Chief Scientific Officer</td>
<td></td>
</tr>
<tr>
<td>Sukhi Jagpal, CA, CBV, MBA</td>
<td>Chief Financial Officer</td>
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</tr>
</tbody>
</table>
• Professor Udai Banerji leads the Clinical Pharmacology and Trials team at the Cancer Research UK Cancer Therapeutics Unit at the ICR and is the Deputy Director of the Drug Development Unit at the ICR and The Royal Marsden. He heads the Clinical Pharmacodynamic Biomarker Group.

• Dr. Banerji has conducted crucial first-in-human studies of a rich pipeline of drugs discovered in collaboration with the ICR. His team has won prestigious awards such as the AACR team science award for drug discovery and the Cancer Research UK translational research award.

• Dr. Banerji is Chief Investigator for Sierra’s SRA737-01 and SRA737-02 clinical studies.
Distinguished Guest: Professor Alan D’Andrea, MD

• A recipient of numerous academic awards, Dr. D’Andrea is a Distinguished Clinical Investigator of the Doris Duke Charitable Trust, and a Fellow of the American Association for the Advancement of Science. He is the recipient of the 2001 E. Mead Johnson Award, and the 2012 G.H.A. Clowes Memorial Award from the American Association for Cancer Research.

• Dr. D’Andrea was recently elected to the National Academy of Medicine and is also a member of the National Cancer Institute's Board of Scientific Counselors in Basic Sciences.

• Dr. D’Andrea is Director of the Center for DNA Damage and Repair at the Dana-Farber Cancer Institute, and is a member of Sierra’s DDR Advisory Committee.
Sierra’s DDR Advisory Committee: Leading Experts In DNA Damage Response

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>Affiliation</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>
Sierra Oncology: Next Generation DDR Therapeutics

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

Shares (12/31/17):
- ~52.4M outstanding
- ~60.9M fully diluted

Cash and cash equivalents (12/31/17):
- ~$100.3M
Our Pipeline Of ‘Next Generation’ DDR Therapeutics: Current Status (Pre-Update)

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
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<tr>
<td>Five indications; prospective genetic selection; N=40 (8x5)</td>
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<tr>
<td><strong>Low-Dose Gemcitabine Combination</strong></td>
<td></td>
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<tr>
<td>Advanced solid tumors; two expansion cohorts; N=8</td>
<td></td>
<td></td>
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<tr>
<td><strong>PARPi Combination</strong></td>
<td></td>
<td></td>
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<tr>
<td>Potential clinical study in 2018</td>
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<td></td>
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<tr>
<td><strong>I/O Combination</strong></td>
<td></td>
<td></td>
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<tr>
<td>Potential clinical study in 2018</td>
<td></td>
<td></td>
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<tr>
<td><strong>IND enabling studies</strong></td>
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</tr>
</tbody>
</table>

Current Status (Pre-Update):
- Two active studies
- 7 indications
- Efficacy cohorts N=48
Introduction: DNA Damage Response (DDR) Network
Introduction:
The DNA Damage Response Network

DNA Damage

ENDOGENOUS

EXOGENOUS

Cell Cycle

G2/M Checkpoint

G1/S Checkpoint

S Phase Checkpoint

pause the cell cycle

monitor and detect DNA damage

Single strand breaks

Base Excision Repair (BER)

Cell metabolism

Oxygen radicals

Radiation

Viral infection

Chemotherapy

Double strand breaks

Stalled replication forks

Homologous Recombination Repair (HRR)

trigger DNA repair
Introduction:
The DDR In Cancer
SRA737: Our Chk1 Inhibitor Program
SRA737 Background: Originates From Renowned Drug Discovery Group

Discovered and advanced into the clinic by:

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

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

Drug discovery track record:

- ICR The Institute of Cancer Research

Originates From Renowned Drug Discovery Group
SRA737 Background: Potentially Superior Chk1 Inhibitor Profile

- SRA737’s potency, selectivity and oral bioavailability could potentially 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>Ph1/2</td>
<td>Ph2</td>
<td>Ph1/2</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>1.2 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>&gt;30x</td>
</tr>
</tbody>
</table>

- SRA737 selectivity:
  - 15/124 kinases at 10 µM
  - ERK8 = 100x
  - All other kinases >200x
  - CDK2 = 2750x
  - CDK1 = 6750x

- SRA737 patent protection to 2033+.
SRA737 Overall Development Strategy: Breadth Of Development Opportunities

**Current Clinical Trials**

- **Monotherapy -01**
  - Exploit synthetic lethality in genetically-defined patients across replication stress-driven tumors that have predicted high sensitivity to SRA737.

- **LDG Combo -02**
  - Exploit profound potentiating effects of low dose gemcitabine on SRA737 in genetically-defined patients.

**2018 Clinical Opportunities**

- **PARPi Combo -03**
  - Exploit synergy between SRA737+PARPi to address emerging issue of PARPi resistance and expand/enhance PARP inhibitor sensitivity.

- **I/O Combo -04**
  - Exploit empirical evidence of I/O-DDR interplay; explore PD-(L)1 combination and its potential to mechanistically synergize with Chk1i.
SRA737 Development Program

SRA737-01: Monotherapy Update
SRA737-01 Monotherapy: Clinical Development Strategy

Our monotherapy clinical development strategy employs an adaptive, seamless clinical trial design that follows a logical path from:

- **Dose Escalation:** First-in-human, establish safety, tolerability, PK, exposure, etc. (unselected ‘all-comer’ patients)
- **Cohort Expansion:** Efficacy oriented, broad survey for initial efficacy signals (NGS-selected patients in relevant indications)
- **Registration Oriented:** Expansion based on efficacy signals with defined genetic signature (by indication or by genetics / tissue agnostic)

Timeline:
- 2017
- 2018
- TBD
Fall 2016: CRUK-sponsored Ph1 monotherapy dose escalation initiated (advanced solid tumors)

Jan 2017: Sierra assumes sponsorship of SRA737

Q3 2017: Cohort expansions added

Dose escalation (non-selected)

Prospective patient selection using NGS technology

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

Actively enrolling expansion
Cohorts N=40 (8x5)
- Prostate
- Ovarian
- Non-Small Cell Lung
- Head & Neck
- Colorectal

Continued dose escalation to MTD (non-selected)
As of February 2018, successfully completed first-in-human Phase 1, and transitioned into efficacy-oriented Phase 2.

- First-in-human dose escalation Phase 1 conducted in ‘all-comers’; no genetic selection performed. Goal was establishing safety, tolerability and PK.
- Dose escalation proceeded rapidly and positively; currently dose optimizing - QD vs. BID schedule.
- Clinical data reinforce best-in-class potential of SRA737, as compared to competitor molecules.
- Cohort expansion Phase 2 in genetically-defined patients to determine preliminary efficacy signals in prospectively enrolled patients.
- Efficacy-oriented Phase 2 is still nascent; enrollment is early and ongoing.
- Preliminary data from the Phase 2 portion of the study expected to be presented at a medical conference in Q4 2018.
First-in-human study to establish basic drug parameters, and reinforce potential best-in-class properties of SRA737 in unselected, ‘all-comer’ patients.

Dose Escalation:
First-in-human, establish safety, tolerability, PK, exposure, etc. (unselected ‘all-comer’ patients)

Cohort Expansion:
Efficacy oriented, broad survey for initial efficacy signals (NGS-selected patients in relevant indications)

Registration Oriented:
Expansion based on efficacy signals with defined genetic signature (by indication or by genetics / tissue agnostic)
**SRA737-01 Monotherapy – Dose Escalation: Initial Focus On Safety, Tolerability & PK**

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

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

**Q3 2017:**
Cohort expansions added and screening initiated

**Prospective patient selection using NGS technology**

- Prostate
- Ovarian
- Non-Small Cell Lung
- Head & Neck
- Colorectal

**Continued dose escalation to MTD (non-selected)**

- Parallel MTD determination and cohort expansion in genetically-defined patient populations.
- Continuous daily oral administration.
• Accelerated design allowed single patient dose cohorts if related AEs Gr<2.
• Dose escalation has proceeded through multiple dose levels.
• Data reveal a broad potential therapeutic window as monotherapy.
• Once daily QD dosing through dose escalation up to DLT.
• Currently comparing 500 mg BID to 1000 mg QD.
SRA737-01 Monotherapy – Dose Escalation: Broad Potential Therapeutic Window

- Clinical $C_{\text{min}}$ exceeds the equivalent efficacious concentration from preclinical studies for at least 24 hours following $\geq 600$ mg QD dose; minimum efficacious concentration studies ongoing.
- Clinical $C_{\text{max}}$ enters the plasma concentration range shown to induce reversible hematological changes in the monkey at doses $\geq 1,000$ mg QD.
- Data reinforce potential for a broad therapeutic window.
- Mean terminal elimination half-life ($t_{1/2}$) at 1000 mg is $\sim 10$ hours; consistent with QD or BID dosing.

---

**Graph:**
- Onset of reversible hematological changes in monkey toxicology study
- Potential therapeutic window
- Effective monotherapy concentration in murine studies

*Preclinical dose decrements in progress*
SRA737-01 Monotherapy: Well-Tolerated Safety Profile To Date

- Overall, well-tolerated from 20 mg QD to 1000 mg QD as monotherapy*.
  - 2 Dose Limiting Toxicities (DLTs) were reported at the 1300 mg QD dose.
    - Each due to inability to receive 75% of the planned SRA737 dose due to GI intolerability.
  - Median duration of exposure: 2 cycles (Range <1 to 8 cycles).
    - No evidence of emergent or cumulative toxicity and/or declining tolerability with up to 8 cycles of drug administered, supportive of potential for extended dosing.

- Majority of reported AEs are Grade 1 or Grade 2 in severity.

- Most commonly observed AEs (≥20%; all reported causalities) are fatigue and GI events (diarrhea, nausea, vomiting).

- Related SAEs (at least possibly related by Investigator assessment).
  - Grade 3 neutropenia (highly probably related) at the 1300 mg QD dose level.
  - Grade 3 heart failure/cardiomyopathy (possibly related) in single subject with rapid disease progression at 1000 mg QD; possible Takotsubo cardiomyopathy.

*Data cutoff Feb 01, 2018. (N=31)
Hematologic and gastrointestinal (GI) toxicities are expected ‘on-target’ effects based on Chk1i mechanism of action, and are consistent with preclinical toxicology studies.

**Hematologic Toxicity**

- Grade 3 neutropenia reported in 2 patients to date (7%).
  - 1 subject dosed at 1300 mg QD and 1 subject dosed at 1000 mg QD.
  - Otherwise, only low grade (Grade 1 and Grade 2) hematologic toxicity observed (<20% incidence).

**GI Toxicity**

- Diarrhea, mostly Grade 1 and Grade 2, observed at 600-1300 mg QD dose levels.
  - Grade 3 diarrhea rate: 3% (1 subject).
  - Nausea and vomiting, primarily Grade 1 at the 600-1300 mg QD dose levels.
  - Grade 3 nausea rate: 7% (2 subjects).

- GI adverse effects appear to be dose related, and suggest a pharmacological ‘on-target’ effect consistent with other Chk1i.
  - High capsule burden (100 mg/capsule) and unoptimized FIH formulation may also contribute.
Prexasertib Published Safety Data: Reinforcing Differential Profile For SRA737

Prexasertib (Chk1i + Chk2i)*:

Most common Grade 3/4 AEs:
- neutropenia (93%)
- reduced WBC count (82%)
- thrombocytopenia (25%)
- anemia (11%)

Other frequent AEs (All Grades):
- nausea (64%)
- fatigue (53%)
- diarrhea (39%)
- vomiting (29%)
- fever (29%)
- abdominal pain (14%)

*Administered IV once every two weeks ~12 hour half-life.

- Precedent safety data show a confluence of both heme and GI toxicities with dual Chk1/Chk2 inhibitors, and largely GI AEs for more selective Chk1i, with minimal heme toxicity.

- GI effects are consistent with ‘on-target’ MOA-driven Chk1i activity.

- Heme toxicity manifests at high doses of SRA737, consistent with toxicology.

- Prexasertib’s significant dose limiting heme toxicity possibly related to Chk2i.

- Data reinforce potential best-in-class profile for SRA737.

Lee et al. Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study. Lancet Jan 16, 2018
Chk2 Inhibition: Potentially Exacerbates Toxicity In Healthy Cells

**Normal Cell**

- ATM → ATR → Chk2 → Chk1 → p53 → RS (Response)

**Normal Cell: Chk1/2 inhibition**

- ATM → ATR → Chk1 (inhibited) → p53 → RS (Response)

**Cancer Cell: Chk1/2 inhibition**

- ATM → ATR → Chk2 (inhibited) → p53

Normal activation of p53 via the ATM-Chk2 and ATR-Chk1 pathways to trigger repair of DNA damage.

Dual Chk1/2 inhibition in normal cells fully impedes p53’s activation, impacting repair of DSBs – potentially exacerbating hematological toxicity.

Inhibition of Chk2 in tumor cells with mutated p53 provides no additional therapeutic benefit. Chk1 inhibition drives anti-cancer activity.

TP53 gene encodes for p53 protein
SRA737-01 Monotherapy – Dose Escalation: First-in-human Phase 1 Summary

In our view, a safe, well tolerated, potent, selective, orally-administered Chk1i represents the optimal asset profile for further advancement, both as monotherapy and in a variety of combination settings.

**SRA737 first-in-human Phase 1 experience has been very encouraging:**

- Promising safety profile to date; mostly GI AEs, generally minimal low grade hematological adverse events.
- PK has been broadly dose-linear; very good exposures achieved.
- SRA737 appears to have a wide therapeutic window, as predicted from preclinical and toxicological modelling.
- Dose escalation complete; dose optimization in progress.
  - 2 DLTs observed at 1300 mg QD (<75% dose administered).
  - 1000 mg QD & 500 mg BID cohorts currently enrolling.
- Safety data reinforce that SRA737 has a differentiated and improved toxicity profile versus Lilly’s prexasertib, the most advanced Chk1i development candidate.
- These data support a potential best-in-class profile for SRA737.
SRA737-01 Monotherapy – Cohort Expansion: Efficacy Oriented Phase 2

Broad efficacy-oriented studies to establish initial activity in relevant indications in NGS-selected patients.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>2017</td>
<td>Dose Escalation: First-in-human, establish safety, tolerability, PK, exposure, etc. (unselected ‘all-comer’ patients)</td>
</tr>
<tr>
<td>2018</td>
<td>Cohort Expansion: Efficacy oriented, broad survey for initial efficacy signals (NGS-selected patients in relevant indications)</td>
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<td>TBD</td>
<td>Registration Oriented: Expansion based on efficacy signals with defined genetic signature (by indication or by genetics / tissue agnostic)</td>
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</table>
Replication Stress: Pathologic DNA Replication Is Fundamental To Cancer

“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 – A Hallmark of Cancer

- **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, CCNE1

- **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:**
- Excessive genomic instability results in cancer cell death
- Normal Cell
- Genomic Instability
- Cell Death
- Cancer cell survives with increased mutagenic capacity

---

**SIERRA ONCOLOGY**
Replication Stress: Chk1 Is A Master Regulator Of Replication Stress

**Cell Cycle**

Chk1 pauses the cell cycle to enable DNA repair

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

**DNA Damage Response**

Chk1 regulates origin firing to manage replication stress

- Chk1 stabilizes stalled replication forks
- Chk1 mediates DNA repair via HRR

**Checkpoints**

- G1/S Checkpoint
- G2/M Checkpoint
- S Phase Checkpoint

**Repair Mechanisms**

- HRR (Homologous Recombination Repair)
- BRCA 1/2
- ATM

**Stalled Replication Forks**

- Double strand breaks
  - Chk1

**Cancer Cell Cycle**

- M
- G1
- G2
- S
High Replication Stress (RS) Cancer Cells: Chk1 Inhibition Drives 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.

Chk1 regulates RS.

Excessive genomic instability results in cancer cell death.
RS Mutations & SRA737 Sensitivity: Proof-of-Concept Preclinical Data

- SRA737 active as monotherapy in RS-driven MYCN overexpressing neuroblastoma model, but not active in non-RS driven melanoma model.
- Reinforces MOA, and importance of RS-driving genetic mutations for activity; supports patient enrichment strategy.
Replication Stress Clinical Validation: Chk1i Monotherapy For Prexasertib In RS Cancers

AACR 2017 Poster:
Phase 1b monotherapy expansion cohort data in advanced head and neck squamous cancers and squamous cell carcinoma of the anus. Dosed IV once every two weeks.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Disease Control Rate (CR+PR+SD)</th>
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</thead>
<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 (*CCNE1*) proteolysis.
- Mutations and/or germline variants in DDR genes: *BRCA1, BRCA2, MRE11A* and *ATR*.

Clinical validation of:
- the target
- genetic selection strategy
- monotherapy
**SRA737-01 Monotherapy – Cohort Expansion: Efficacy Cohorts – Current Design**

- **Fall 2016:** CRUK-sponsored Ph1 monotherapy dose escalation initiated (advanced solid tumors)
- **Jan 2017:** Sierra assumes sponsorship of SRA737
- **Q3 2017:** Cohort expansions added and screening initiated
- **Prospective patient selection using NGS technology**
  - Prostate
  - Ovarian
  - Non-Small Cell Lung
  - Head & Neck
  - Colorectal
- **Continued dose escalation to MTD (non-selected)**
- **Actively enrolling expansion Cohorts N=40 (8x5)**
- **Parallel MTD determination and cohort expansion in genetically-defined patient populations.**
- **Continuous daily oral administration.**
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> (e.g. TP53, RAD50, etc.)</td>
<td>Defective G1/S checkpoint increases reliance on remaining Chk1-regulated DNA damage checkpoints.</td>
</tr>
<tr>
<td><strong>Oncogenic Drivers</strong> (e.g. MYC, KRAS, etc.)</td>
<td>Oncogene-induced replication and transcription results in transcription/replication collisions, dysregulation of replication and dNTP exhaustion, driving RS.</td>
</tr>
<tr>
<td><strong>DNA Repair Machinery</strong> (e.g. BRCA1/2, FA, etc.)</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><strong>Replicative Stress Response</strong> (ATR, CHEK1)</td>
<td>Amplification of genes encoding ATR or Chk1 suggests greater reliance on Chk1 pathway to accommodate RS.</td>
</tr>
</tbody>
</table>
Replication Stress: Patient Selection Algorithm For High RS Cancers

Genetic selection: Two or more mutations, from any class*

- Cell cycle dysregulation
  - Defective G1 / S Checkpoint
    - TP53
    - HPV

- Defective DNA damage repair
  - BRCA 1/2

- Oncogenic drivers
  - MYC
  - CCNE1

- Replicative Stress Response
  - ATR

Multiple genetic drivers of RS increases overall level of genomic instability, and associated reliance on Chk1.

Chk1i leads to excessive genomic instability resulting in cancer cell death.

*Illustrative genes depicted. e.g., TP53+MYC; TP53+ATR, etc.
<table>
<thead>
<tr>
<th>Tumor Suppressor Associated RS</th>
<th>HNSCC</th>
<th>HGSOC</th>
<th>mCRPC</th>
<th>CRC</th>
<th>NSCLC</th>
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<tbody>
<tr>
<td><strong>TP53</strong></td>
<td>74%</td>
<td>96%</td>
<td>53%</td>
<td>73%</td>
<td>68%</td>
</tr>
<tr>
<td>HPV+</td>
<td>~60%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>(Oropharyngeal)</td>
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<table>
<thead>
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<th>Oncogenic Driver Associated RS</th>
<th>HNSCC</th>
<th>HGSOC</th>
<th>mCRPC</th>
<th>CRC</th>
<th>NSCLC</th>
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<tbody>
<tr>
<td><strong>CCNE1 axis</strong></td>
<td>7%</td>
<td>21%</td>
<td>14%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>RAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MYC axis</strong></td>
<td>14%</td>
<td>30%</td>
<td>22%</td>
<td>5%</td>
<td>9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Defective DDR Associated RS</th>
<th>HNSCC</th>
<th>HGSOC</th>
<th>mCRPC</th>
<th>CRC</th>
<th>NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregated</td>
<td>10%</td>
<td>35%</td>
<td>31%</td>
<td>29%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Red = Higher Prevalence; Green = Lower Prevalence (TCGA)
Sierra is employing validated NGS technology from Foundation Medicine.
Enrollment tracking in line with predicted patient prevalence and coincident RS gene mutations.
Successfully enrolling patients with RS-driving mutations.
Pilot experience from three clinical sites supports broader rollout to drive enrollment.

<table>
<thead>
<tr>
<th>Genetic Class</th>
<th>HNSCC</th>
<th>HGSOC</th>
<th>mCRPC</th>
<th>CRC</th>
<th>NSCLC</th>
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<tbody>
<tr>
<td>Total Enrolled</td>
<td>(20)</td>
<td>5</td>
<td>2</td>
<td>11</td>
<td>2</td>
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<tr>
<td>Oncogenic Driver Associated RS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CCNE1 axis</strong></td>
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<td></td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Oncogenic Driver Associated RS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAS</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncogenic Driver Associated RS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MYC axis</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Aggregated</strong></td>
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</tr>
</tbody>
</table>
| | 4 | 1 | 1 | 1 |}

1 Other
Replication Stress & CCNE1: Emerging Evidence Of Key RS-Driving Role

- **CCNE1** gene encodes cyclin E protein, a critical activator of cyclin-dependent kinase CDK2 which is a direct regulator of DNA replication and the cell cycle.
- High levels of cyclin E, such as via genetic amplification of **CCNE1** locus in certain tumors, has been demonstrated to increase RS through several mechanisms.

![Diagram of Cancer Cell Cycle](image)

1. **CCNE1**^AMP^ and/or high cyclin E protein
2. DNA Replicative Helicase activation
3. Rb1 tumor suppressor inactivation
4. Loss G1/S cell cycle control
5. dNTP depletion
6. Aberrant transcription
7. Dysregulated DNA replication origin firing
8. High RS
• SRA737 has significant anti-tumor activity and a profound survival benefit in CCNE1 HGSOC preclinical models.
• PARPi inactive in this population.
• Supports our NGS patient selection strategy.

Research collaboration with Dr. F. Simpkins, UPenn
Approximately 20% of the high grade subtype of ovarian cancer (HGSOC) harbor CCNE1 amplifications.

BRCA1 and BRCA2 mutations are generally mutually exclusive to CCNE1 amplification.

CCNE1-amplified (& BRCA WT) ovarian cancers are commonly platinum-insensitive and are known to be PARPi insensitive.

Post-platinum population represents a significant unmet medical need; not addressable via PARPi.

Compelling biological and clinical rationale for Chk1i.
**CCNE1 In High Grade Serous Ovarian Cancer: Clinical Validation For Chk1i With Prexasertib**

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

**Efficacy**
- 33% ORR (8/24) Evaluable
- 42% ORR (8/19) CCNE1 (All)
- 33% ORR (4/12) CCNE1 amplification
- 32% ORR (6/19) Platinum resistant/refractory
- 58% DCR (11/19) Platinum resistant/refractory
CCNE1 In High Grade Serous Ovarian Cancer: Phase 2 Prexasertib Clinical Trial Announced

• New Lilly sponsored trial reported January 2018:
  “A Study of Prexasertib in Platinum-Resistant or Refractory Recurrent Ovarian Cancer”

• Enrollment of N=180 across 4 cohorts
  • 12 month projected enrollment timeline.
  • 43 global sites (US, EU including UK, Australia, Israel).

<table>
<thead>
<tr>
<th>Lilly</th>
<th>Platinum Resistant BRCA WT (≥3 lines prior therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=180</td>
<td>Platinum Resistant BRCA WT (&lt;3 lines prior therapy)</td>
</tr>
<tr>
<td></td>
<td>Platinum Resistant BRCA Mut+ (post-PARPi)</td>
</tr>
<tr>
<td></td>
<td>Platinum Refractory</td>
</tr>
</tbody>
</table>

• Further validates industry enthusiasm for Chk1i development.
• Unmet clinical and commercial need; PARPi insensitive/refractory population.
CCNE1 Overexpression: Significant Potential Across Multiple Tumors

Ovarian (HGSOC)
- CCNE1*: 21%
- MYC: 30%
- BRCA1/2: 22%
- HRD: 10%

Addressable Patients in US: ~24,000

Endometrial
- CCNE1*: 21%
- MYC: 6%
- KRAS: 17%

Addressable Patients in US: ~25,000

NSCLC
- CCNE1*: 9%
- DDR: 10%
- KRAS: 17%

Addressable Patients in US: ~162,000

Colorectal
- CCNE1*: 14%
- DDR: 10%
- KRAS: 45%

Addressable Patients in US: ~61,000

Bladder
- CCNE1*: 25%
- DDR: 17%
- EGFR: 9%

Addressable Patients in US: ~31,000

Cervical
- CCNE1*: 11%
- DDR: 13%
- KRAS: 6%

Addressable Patients in US: ~8,000

*CCNE1 + FBXW7 genetic alterations; Other ≥2% CRPC, SCLC, SCCHN (TCGA).
• Replication Stress concept is novel and differentiated:
  • Early clinical experience reinforces tractability of NGS selection for RS drivers.
  • Emerging preclinical and clinical data strongly support this approach.

• We are aggressively expanding the SRA737-01 monotherapy program:
  • First-in-human data supports SRA737’s potential best-in-class profile.
  • In Q1 2018, we will be amending the trial to add a new cohort to SRA737-01: **CCNE1**-driven high grade serous ovarian cancer.
  • We are expanding each cohort to 20 patients.
  • Aggregate of 120 patients will now be enrolled in Phase 2 expansion.
  • Preliminary data from the study are expected to be presented at a medical conference in Q4 2018.
SRA737-01 Monotherapy: Program Expansion & Amended Design

- **Focus on genetically-defined RS-driven patient populations.**
- **Continuous daily oral administration.**

**Target enrollment N=120 (20x6)**
- Prostate
- Ovarian (CCNE1)
- Ovarian (non-CCNE1)
- Non-Small Cell Lung
- Head & Neck + Anus
- Colorectal

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

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

**Q3 2017:** Cohort expansions added and screening initiated

**Q1 2018:**
- Cohorts enlarged & HGSOC CCNE1 cohort added
- Dose escalation (non-selected)
- Continued dose escalation to MTD (non-selected)

**Dose escalation (non-selected):**
- Prospective patient selection using NGS technology

**Continued dose escalation to MTD (non-selected):**
To support enrollment, we are expanding our clinical footprint.

Q3 2017:
- 3 active clinical sites
- Phase 2 cohorts initiated

Q1 2018:
- 15 active clinical sites
- Phase 2 cohorts expanded

20/120 enrolled

Cohort enrollment: 17%
### SRA737-01 Monotherapy Study Summary: Execution To Date & Where We Are Heading

<table>
<thead>
<tr>
<th>Execution and results to date</th>
<th>Dose Escalation Phase 1</th>
<th>Cohort Expansion Phase 2</th>
<th>Additional Cohort Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose escalation in ‘all-comers’ found drug well tolerated at predicted efficacious dose range.</td>
<td>Prospective screening in early stages (20 total enrolled) but have established confidence that selection algorithm for high RS patients is tractable and capable of enrolling a variety of desired genetic backgrounds.</td>
<td>Emerging data (preclinical and clinical) reinforces potential of targeting CCNE1-driven tumors.</td>
<td></td>
</tr>
</tbody>
</table>

| Implications – where we are heading | In final stages of optimizing the SRA737 dose regimen, including exploration of 500 mg BID vs. 1000 mg QD. | Expand monotherapy cohorts from N=8 to N=20 per cohort. | Conduct focused effort in promising genetic background by adding new CCNE1 cohort in ovarian cancer. Seek CCNE1 mutations in other cohorts. |
The adaptive design of SRA737-01 provides flexibility, and results in substantial optionality for future development. Determination of an RS signature could lead to focused development in a specific indication, or to a possible tissue agnostic approach:

Dose Escalation: First-in-human, establish safety, tolerability, PK, exposure, etc. (unselected ‘all-comer’ patients)

Cohort Expansion: Efficacy oriented, broad survey for initial efficacy signals (NGS-selected patients in relevant indications)

Registration Oriented: Expansion based on efficacy signals with defined genetic signature (by indication or by genetics / tissue agnostic)
SRA737 Development Program

SRA737-02: LDG Combination Update
GDC-0575: ESMO 2017 Poster - Phase 1 + gemcitabine (500-1000 mg/m²)

- GDC-0575 demonstrated 4 responses (DCR = 60%) including meaningful and 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 105 mg and a dose of 80 mg for the expanded enrollment.

Clinical validation of:
- the target
- genetic selection strategy
- gemcitabine potentiation
Initially advanced into clinical studies in a triplet study employing standard dose chemotherapy, Sierra’s revised approach represents a fundamental reimagining of Chk1i combination strategies: we are focused on potentiating SRA737, rather than augmenting activity of the combination agent:
SRA737-02 LDG Combination: Current Design

Jan 2017: Sierra assumes sponsorship of SRA737
May 2017: Amendment cleared by regulators

Cis/Gem combo dose escalation

Stage 1

Low dose gem combo dose escalation (non-selected)

Stage 2

Actively enrolling

N=8
Bladder
Pancreatic

Fall 2016:
CRUK-sponsored Phase1 cis/gem combination dose escalation initiated (advanced solid tumors)

Prospective patient selection using NGS technology

• Low dose gemcitabine (day 1) followed by intermittent oral dosing of SRA737 (days 2 & 3);
  Administer weekly for 3 weeks every 28 days.
Our LDG combination clinical development strategy:

- Exploits the combination of inducers (LDG) and regulators (Chk1 inhibition) of replication stress in a completely novel way.
- Dramatically improved safety observed in the LDG cohort vs. standard dose combinations; has allowed substantial escalation of SRA737 dose.
- Broad efficacy oriented studies in NGS selected patients to establish activity in relevant RS-driven indications.

**Diagram:**

- **Standard Dose Chemo + SRA737 Dose Escalation**
  - Establish safety, tolerability, etc.
  - (unselected patients)
  - Completed

- **Low Dose Gemcitabine + SRA737 Dose Escalation**
  - Establish safety, tolerability, etc.
  - (unselected patients)
  - Actively Enrolling

- **LDG Cohort Expansions**
  - Broad efficacy oriented survey for initial activity signals (NGS-selected patients in relevant indications)
  - ~Q2 2018
Gemcitabine profoundly depletes replication building blocks, inducing an exogenous form of 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
Revising Combination Clinical Trials: LDG Strategy Focuses On Chk1’s Core Biology

**Standard Strategy**

**Standard Dose Genotoxic Therapy Combination**

Standard Dose Chemo

DNA damage, double strand breaks (DSB) & overt cytotoxicity

+ Chk1i (low dose)

- Insufficient Chk1 inhibition
- Exacerbated toxicity
- Standard Chemo MOA

**Sierra Strategy**

**Low Dose Gemcitabine (LDG) Combination**

LDG

S-phase delay, stalled replication forks, high replication stress – Activated Chk1

+ Chk1i (active dose)

- Synergistic cytotoxicity
- Improved tolerability
- Novel anti-tumor MOA
SRA737 + LDG Proof Of Concept:
Synergistic Preclinical Activity Driven By SRA737

- SRA737 combined with low subtherapeutic doses of gemcitabine results in synergistic tumor growth inhibition in cancer models where single agent gemcitabine shows modest activity.
- Anti-tumor activity correlates with increased markers of RS (not shown).
SRA737-02 LDG Combination: Comparative Gemcitabine Doses

- Relative to standard-of-care, gemcitabine doses being tested in SRA737-02 are approximately 5-10% of a standard dose, and substantially lower than the doses of gemcitabine tested in clinical combination with GDC-0575.
**SRA737-02 LDG Combination: Current Focus On Dose Escalation**

- **Jan 2017:** Sierra assumes sponsorship of SRA737
- **May 2017:** Amendment cleared by regulators

**Cis/Gem combo dose escalation**

**Stage 1**

**Low dose gem combo dose escalation (non-selected)**

**Stage 2**

- **Actively enrolling**
- **N=8**
  - Bladder
  - Pancreatic

**Fall 2016:** CRUK-sponsored Phase1 cis/gem combination dose escalation initiated (advanced solid tumors)

- **Prospective patient selection using NGS technology**

- **Low dose gemcitabine (day 1) followed by intermittent oral dosing of SRA737 (days 2 & 3); Administer weekly for 3 weeks every 28 days.**
SRA737-02 LDG Combination – Dose Escalation: Promising Progress To Date

- Promising progress escalating SRA737 in combination with LDG.
  - No dose limiting toxicity observed to date.
- Currently dosing parallel cohorts of 300 mg SRA737 + 100 mg/m² & 50 mg/m² gem.
- The Cohort Expansion Phase 2 portion is anticipated to commence in Q2 2018.
  - Concurrent SRA737 escalation to MTD will continue in parallel, to optimize dosing.
• The clinical $C_{\text{min}}$ exceeds the active preclinical efficacious concentration for at least 24 hours following an oral 300 mg dose of SRA737 when given in combination with low dose gemcitabine.

• Confirmation of i) dosing in the predicted active range (achieved), and ii) tolerability at this dose (in progress) triggers cohort expansion phase; expected to commence in Q2 2018.
Overall, doublet regimen of intermittent SRA737 and low dose gemcitabine has been very well-tolerated in this ‘all-comer’, non-selected Phase 1 population*.

No DLTs have been reported in any LDG dose escalation cohort to date. Dose escalation continues.

The median duration of exposure currently is 2 cycles (Range <1 to 6+ cycles).
- No evidence of emergent or cumulative toxicity and/or declining tolerability over time, supportive of potential for extended dosing.

Majority of reported AEs are Grade 1 or Grade 2 in severity.

Most commonly observed AEs (≥20%; all reported causalities) are diarrhea, anemia, thrombocytopenia, fatigue, influenza-like illness, nausea, neutropenia and vomiting.

Only one Grade 3 treatment related AE (neutropenia) at 40/300 SRA737/gem.

Related SAEs include a Grade 1 fever (possibly related) and a Grade 2 DVT (possibly related).

*Data cutoff Feb 01, 2018 (N=16)
SRA737-02 LDG Combination – Dose Escalation: On-Target Hematologic And GI Adverse Events

• Hematologic and gastrointestinal (GI) toxicities are expected ‘on-target’ effects based on Chk1i mechanism of action, and are consistent with preclinical toxicology studies.

• Gemcitabine’s expected toxicities also include hematologic and gastrointestinal AEs; however, standard dose gemcitabine (≥1000 mg/m²) is 10-20 fold higher than doses used in the LDG combination.

• LDG combination design allows maximization of SRA737’s dose without undue potentiation of gemcitabine’s toxicity.

Hematologic Toxicity
• No Grade 3 hematologic toxicities have been observed in the LDG dose escalation stage with gemcitabine doses of 100 and 50 mg/m².
• Primarily low grade (Grade 1 & Grade 2) hematologic toxicity observed.

GI Toxicity
• No Grade 3 GI toxicity has been observed in the LDG dose escalation stage.
• Only low grade (Grade 1 & Grade 2) GI toxicities (diarrhea, nausea, vomiting) observed.
• Our focus for SRA737-02 moving forward will be enrichment for tumors that harbor drivers of intrinsic replication stress that we believe can be potentiated by deploying low dose gemcitabine in combination.
  • Original study design focused on tumors known to be sensitive to gemcitabine (pancreas & bladder; N=8 patients originally planned for expansion).

• RS clinical opportunities extend beyond traditional gemcitabine-sensitive indications; LDG is deployed as a Chk1i potentiator, not a cytotoxic!

• A compelling rationale for RS/LDG combination synergy exists in bladder cancer, cervical/anogenital cancer, sarcoma, and SCLC.

• We have amended SRA737-02 to enroll these four cohorts; 20 subjects/cohort (e.g., N=80).
  • One or more selected RS genetic variants required for NGS eligibility.

• Cohort Expansion Phase 2 portion is expected to commence in Q2 2018.
  • An update of the SRA737-02 study is expected to be presented in Q4 2018.
Low-dose gem combination

Prospective patient selection using NGS technology*

Target enrollment
N=80 (20x4)

- Bladder
- Small Cell Lung
- Sarcoma
- Cervical + Anogenital

* One or more mutations required for eligibility

Continued dose escalation

• Low dose gemcitabine (day 1) followed by intermittent oral dosing of SRA737 (days 2 & 3); Administer weekly for 3 weeks every 28 days.
SRA737 Development Program

SRA737-03: PARPi Combination Update
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 exist via ‘chemical synthetic lethality’. 
SRA737 + PARPi Combination Synergy: Compelling Biological Rationale

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

HRR Deficient  ‘Deepen Responses’

Post-PARPi Resistant  ‘Overcome Resistance’

HRR Proficient  ‘Expand Indications’
High Grade Serous Ovarian Cancer (HGSOC) Commonly Harbors DDR Alterations

![Pie chart showing various DDR alterations in HGSOC]

OTHER (some may be HR deficient via upregulation of miRNAs or other mechanisms)
- Other 21%
- NER mutations 4–8%
- MMR mutations 3%
- Cyclin E1 amplification 15%
- 

HR DEFICIENT
- BRCA1 germline mutations 8%
- BRCA1 somatic mutations 3%
- BRCA2 germline mutations 6%
- BRCA2 somatic mutations 3%
- BRCA1 promoter methylation 10%
- CDK12 mutations 3%
- RAD51C promoter methylation 2%
- FA gene mutations 2%
- Core RAD gene mutations 1.5%
- HR DNA-damage gene mutations 2%

HR PROFICIENT
- PTEN homozygous loss 7%
- EMSY amplification 6%

POSSIBLY HR DEFICIENT

Konstantinopoulos et al. Cancer Discov 2015
Functions Of BRCA1 And BRCA2 In Homologous Recombination Repair And In Protection Of Stalled Replication Forks

- BRCA1 Promotes End Resection
- BRCA2 Loads RAD51

Recombination pathway:
1. DSB
2. 5' to 3' end resection
3. Assembly of the RAD51 presynaptic filament by BRCA1–PALB2–BRCA2 complex
4. Invasion
5. PALB2–BRCA2 enhancing D-loop formation
6. Synthesis-dependent strand annealing
7. Second-end capture
8. Double Holliday-junction formation
9. Resolution
10. Crossover

BRCA1/FANCS
PALB2/FANCN
BRCA2/FANCD1

Fork Protection
- Mre11
- WRN
- Dna2
- BLM
- MUS81

Modified from Lee Zou
What Are The Known Mechanisms Of PARPi Resistance? Restoration Of HR Proficiency

1. Somatic reversion or restoration of ORF

Mutant protein → Functional protein

2. Epigenetic reversion of BRCA1 promoter hypermethylation

Reduced expression → Normal expression

3. Hypomorphic BRCA1 or BRCA2 allele

Mutant protein → Exon splicing (BRCA1Δ11)

New Mechanisms Of PARP Inhibitor Resistance: Protection Of The DNA Replication Fork

**ATR inhibition disrupts rewired homologous recombination and fork protection pathways in PARP inhibitor-resistant BRCA-deficient cancer cells**

Genes Dev. 2017

**EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation**

Nature Cell Biology, 2017
Reduced Tumor Growth In Mice Exposed To The Combination Of CHK1 Inhibitor And Olaparib
Ovarian Cancer PDXs For The Study Of PARPi Resistance And New Therapeutic Options

<table>
<thead>
<tr>
<th>PDX ID</th>
<th>subtype</th>
<th>chemotherapy</th>
<th>BRCA germline</th>
<th>PARPi</th>
<th>Rad51_foci</th>
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<td>DF59</td>
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<td>BRCA1 5385insC</td>
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<tr>
<td>DF68</td>
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<td>5</td>
<td>BRCA1 Q563X</td>
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<tr>
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<td>HGSOC</td>
<td>5</td>
<td>BRCA1 del exons 21-214</td>
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<tr>
<td>DF101</td>
<td>HGSOC</td>
<td>2</td>
<td>BRCA1 187del AG</td>
<td>resistant</td>
<td>positive</td>
</tr>
</tbody>
</table>

IHC for RAD51

- **No RAD51 Foci**
- **Positive RAD51 Foci**

Generation of Ovarian Cancer Organoid Cultures

Susan F. Smith Center for Women’s Cancers

1. Harvest tissue/obtain tissue biopsy
2. Dissociate tissue into functional units
3. Enrich for stem cells
4. Niche factors (R-spondin, WNT3A, Retinoic acid, GSK3β inhibitors, TGF-β inhibitors, EGF, FGF10, HGF, HDAC inhibitors, ROCK inhibitors, Noggin, Activin A, Gastrin, p38 inhibitors)
5. ECM factors (Collagen, Entactin, Fibronectin, Lamin)
6. Culture media
7. ECM
8. 7-10 days

Stem cells
Differentiated cells
Spherical/cyst-like
Branching
Budding
Analysis Of Ovarian Tumor Organoids From A BRCA1 Carrier With Acquired Olaparib Resistance

New Clinical Trial: Combination of Olaparib plus CHK1i for High Grade Serous Ovarian Cancer
Rapid Analysis Of Short Term Organoids For DNA Repair Capacity And Drug Sensitivity

CHK1 activity
Prexasertib (nM)

Fiber Assay: measure of fork stability

Therapeutic Sensitivity

Rad51 foci formation

Paired WES or targeted sequencing
SRA737 + PARPi Combination Synergy: Activity in Acquired PARPi Resistant HGSOC Cells

- SRA737 demonstrates inhibition of tumor cell colony formation in PARPi-resistant HGSOC as monotherapy, consistent with increased reliance of these tumors on Chk1.

- Combination of SRA737 plus PARPi results in synergistic inhibition of colony growth and survival.

- Results support combination of SRA737 with PARPi to treat patients with acquired PARPi resistance.

PEO1-PR is HGSOC cell line derived from PEO1 (BRCA2^MUT (c.C4965G)) that developed resistance to PARPi in vitro

[Research collaboration with Dr. F. Simpkins, UPenn]
Announcement Of Janssen Supply Agreement: Testing SRA737 + Niraparib In Prostate Cancer

Supply agreement facilitates the exploration of a novel and independent development path for SRA737, supported by both a promising scientific and a compelling commercial rationale.

- Janssen previously licensed world wide prostate cancer rights to TESARO’s PARPi, ZEJULA® (niraparib).
- We announced on February 27 2018 that Janssen will supply niraparib to Sierra to run a Phase 1b/2 study in combination with SRA737.
- Sierra intends to evaluate the combination in patients with metastatic castration-resistant prostate cancer (mCRPC).
Phase 1b/2, multicenter, open-label, dose-ranging study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of SRA737 given in combination with niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC).

- Strategic Objectives:
  - Expand clinical indications for PARPi in HR-proficient patients where PARPi monotherapy is ineffective.
  - Overcome emergent PARPi resistance.

- Study to be led by Chief Investigator Dr. Johann de Bono at The Royal Marsden, UK.

- SRA737-03 study anticipated to commence in Q4 2018.

“The combination of Chk1 inhibition with PARP inhibition potentially may expand the application of niraparib to patients with HRR proficient tumors or re-sensitize patients who have developed PARPi resistance.”
SRA737 Development Program

SRA737-04: I/O Combination Update
DNA Damage and Repair Biomarkers of Immunotherapy Response

Kent W. Mouw\textsuperscript{1,2,3}, Michael S. Goldberg\textsuperscript{2,4}, Panagiotis A. Konstantinopoulos\textsuperscript{2,5,6}, and Alan D. D'Andrea\textsuperscript{1,2,3,6}

How Does DNA Damage Modulate The Immune System?

**Sources of tumor genomic instability**
- Exogenous DNA damaging agents (chemo, IR)
- Endogenous damage sources (replicative/oxidative stress)
- Underlying tumor DNA repair defect

**Immune activating**
- Point mutations, indels
  - Altered protein product
  - Proteasomal processing
  - MHC presentation
  - TCR binding
  - T-cell activation
  - DC activation
    - ↑ PD-1/PD-L1
    - ↑ Type I IFN response

**Cytosolic DNA**
- cGAS binding
  - ATP
  - GTP
  - 2’-3’ cGAMP
  - STING activation
  - TBK1 activation
  - IRF3 activation
  - IRF3 activation

**Immune suppressive**
- Copy-number changes
  - Immune evasion:
    - ↓ Adaptive immune signaling
    - ↓ Cytotoxic T-cell activity
    - ↓ Cytokine signaling
    - Type I IFN response
• 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 correlate with patient responses:
  • 20-30% patient response rate without DDR mutations.
  • 70-80% patient response rate with DDR mutations.

• Chk1i could potentially induce the 'chemical equivalent' of an intrinsic DDR mutation, possibly enhancing I/O response rates.
SRA737 + I/O Combination: Synergy With Anti-PD-1 In Animal Models

- Anti-PD-1 displays limited single agent efficacy.
- Combination with SRA737 results in robust tumor growth inhibition.
- Data consistent with preclinical report of enhanced efficacy using prexasertib + anti-PD-L1.
- MOA studies ongoing.
- SRA737-04 CTA submission planned for Q4 2018.
SRA737: Program Summary
SRA737-01 Monotherapy:
Expanding to 120 Patients / Six Indications, Preliminary Data Q4 2018

- Dose escalation Phase 1 complete.
  - Dose-proportional exposure and linear PK; enrolling 1000 mg QD & 500 mg BID doses.
  - Generally very well tolerated.
  - Expected ‘on-target’ AE’s (GI/hematologic) observed at higher doses.
  - Data support potential best-in-class Chk1i positioning vs. competitor assets.
- Dose expansion Phase 2 underway across six indications.
  - Adding CCNE1-driven ovarian cancer cohort (high RS; significant unmet need).
  - 20/120 patients (17%) enrolled across the six 20-patient cohorts to date.

SRA737-02 Low-Dose Gem Combination:
Expanding to 80 Patients / Four Indications

- Low dose gemcitabine combo Phase 1 within predicted efficacious range.
  - Demonstrably improved combination tolerability vs. standard dose gemcitabine combination.
- Cohort Expansion Phase 2 anticipated to commence in Q2 2018.
  - Targeting enrollment of 80 patients across four indications.
  - On-track to report update in Q4 2018.
SRA737-01 & -02 Development Strategy: Exploiting Replication Stress

**SRA737-01**
Monotherapy
Target N=120
- Head & Neck + Anus
- Lung (NSCLC)
- Colorectal
- Prostate
- Ovarian
- Ovarian (CCNE1)

**SRA737-02**
LDG Combination
Target N=80
- Small cell lung (SCLC)
- Cervical + Anogenital
- Bladder
- Sarcoma

**Genomic Instability**
- Continuous daily oral SRA737 administration
- Low dose gemcitabine followed by intermittent oral dosing of SRA737
SRA737 PARPi Combination: Enabled for Initiation in Q4 2018

- Compelling POC preclinical data reported for SRA737 + PARPi combination.
  - Synergistic preclinical combination activity in HRD, HR-proficient, and PARPi resistant settings.
- Supply agreement executed with Janssen for niraparib.
- Phase 1b/2 trial in prostate cancer anticipated to begin Q4 2018.
  - Chief Investigator: Dr. Johann de Bono, The Royal Marsden, UK.

SRA737 I/O Combination: Preparing for CTA in 2018

- Compelling clinical data reported for I/O efficacy in DDR mutant tumors.
- Intriguing possible biological mechanisms underpin enthusiasm for SRA737 + I/O combination.
  - Synergistic preclinical combination activity in combination with PD-1
- Phase 1b/2 CTA planned for Q4 2018.
SRA141: Our Cdc7 Inhibitor Program

SRA141-01: Monotherapy
SRA141: Potent & Selective Cdc7 Inhibitor

- SRA141: potent, orally bioavailable, selective cell division cycle 7 (Cdc7) inhibitor.
- Key regulator of both DNA replication and DNA damage response, as well as mitosis.
- Sierra preclinical data & published literature suggest highly proliferative tumors, dependent on DNA replication, may be sensitive to Cdc7 inhibition.
- SRA141 has monotherapy and combination therapy development potential.
SRA141 Demonstrates Robust Efficacy: Rat MV-4-11 AML Xenograft

- SRA141 demonstrates significant activity in the AML MV-4-11 rat xenograft model.
- Tumor growth inhibition (TGI) = 86%.
- 2 PRs and 2 CRs were noted as best responses during the dosing period. 1 CR was maintained to study end at D42.

![Tumor Volume (mm³) vs Day graph]

- **Vehicle**
- **SRA141 (75 mg/kg)**
  - BID, 5 on, 2 off, p.o.

Very well-tolerated throughout dosing period.
SRA141 Demonstrates Robust Efficacy: Rat COLO-205 Colorectal Xenograft

- SRA141 demonstrates significant activity in the colorectal COLO-205 rat xenograft model at well-tolerated doses. TP53 & MSS - relevant genetics for Cdc7i.
- Tumor growth inhibition (TGI) = 99%.
- Complete tumor regressions in 4/7 (57%) rats at 75 mg/kg BID.

Biomarker studies consistent with potent, on-target activity.
SRA141 Clinical Trial: Development Opportunity In Colorectal Cancer

• Certain tumor suppressors (e.g. TP53) and/or oncogenes (e.g. KRAS) may confer tumor sensitivity to Cdc7 inhibition.

• Potential for biomarker-driven patient selection strategy in select indications.

• Emergent preclinical data & competitor development programs support advancement in colorectal cancer:

  **TAK931**
  
  Phase 2 trial announced Aug 2017 for the treatment of colorectal & pancreatic cancer. MSS patients only for the colorectal cohort.
  
  Preclinical data (AACR 2017) suggested KRAS mutation as a predictor of Cdc7i sensitivity; directly supports pancreatic & colorectal development.

  **LY3143921**
  
  Phase 1 trial announced June 2017.
  
  Tumors associated with TP53 LOF mutations, including colorectal cancer, squamous carcinomas, and pancreatic cancer.

• We anticipate submitting an IND for SRA141 in H2 2018.

• Phase 1/2 clinical program to be focused on colorectal cancer.
Closing Remarks

Q&A
**Our Pipeline Of ‘Next Generation’ DDR Therapeutics: Updated & Expanded Programs In 2018**

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<th>Preclinical</th>
<th>Phase 1</th>
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<td><strong>Monotherapy (Six Indications)</strong></td>
<td><strong>Low-Dose Gemcitabine Combination (Four Indications)</strong></td>
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<td>Target N=120 (20x6)</td>
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<td><strong>PARPi Combination (Prostate)</strong></td>
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**SRA737 Program:**
- Two active studies expanded
  - 10 indications
  - Efficacy cohorts target N=200
- Two new studies advanced in 2018
  - + PARPi (prostate cancer)
  - + I/O

**SRA141 Program:**
- IND expected to be filed H2 2018
  - Colorectal cancer
# Sierra Development Pipeline: Upcoming Anticipated Milestones

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*Sierra Oncology*
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; and best-in-class potential.

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 planned for 2018.

SRA141 IND filing expected in H2 2018; focus on colorectal cancer.