Charting the path from pioneering biology to impactful therapeutics

AACR 2019: Late-Breaking Data for SRA737+LDG with Immunotherapy

NASDAQ: SRRA
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Sierra is Advancing Two Drug Candidates Targeting the DNA Damage Response (DDR)

**SRA737**
TARGETING Chk1

THERAPEUTIC FOCUS
High Grade Serous Ovarian Cancer, Squamous Cell Carcinoma, SCLC & Other Solid Tumors

**SRA141**
TARGETING Cdc7

THERAPEUTIC FOCUS
Colorectal Cancer
Our Pipeline* Of ‘Next Generation’ DDR Therapeutics

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Focus</th>
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<tbody>
<tr>
<td>SRA737-01 Monotherapy</td>
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<td>Solid Tumors</td>
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<tr>
<td>SRA737-02 LDG Combination</td>
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<td>Solid Tumors</td>
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<td>PARP Inhibitor Combination</td>
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<td>Prostate</td>
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<td>I/O Combination</td>
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<td>Monotherapy</td>
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<td>Colorectal</td>
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*Sierra is also developing its Phase 3 asset, momelotinib, for the treatment of myelofibrosis.
Executive Summary

• SRA737 is potentially the best-in-class Chk1 inhibitor, with preclinical and clinical drug properties (selectivity, PK, safety) that support it as a viable clinical combination partner

• Chk1 is a master regulator of both the DDR network and tumor response to Replication Stress, making it an important emerging biological target for therapeutic intervention in oncology

• SRA737 in combination with low dose gemcitabine (LDG), an external inducer of replication stress, has emerged as a novel and compelling approach, where LDG potentiates the activity of SRA737

• For some indications, immunotherapy (IO) single agent response rates have been modest and while numerous IO combination studies are underway, many lack a compelling biological / mechanistic basis

• A growing body of evidence supports a synergistic interplay between the DDR network and tumor immune response; targeting the DDR network can enhance immune checkpoint blockade (ICB) response rates

• Sierra has determined a strong rationale for Chk1i synergy with ICB; SRA737 leads to micronuclei formation, activation of STING, and induction of a type I interferon signature and immune anti-tumor response

• SRA737+LDG demonstrates profound synergy with ICB in preclinical models of ICB-insensitive SCLC, suggesting potential clinical opportunities exist for SRA737 in combination with ICB
Chk1, a Master Regulator of Replication Stress
Replication Stress: Uncontrolled 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.
Chk1: A next-generation DDR target that acts as a master regulator of replication stress

Cell Cycle

Chk1 pauses the cell cycle to enable DNA repair

Defective G1/S Checkpoint

S Phase Checkpoint

Chk1

Cancer Cell Cycle

G2/M Checkpoint

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

Double strand breaks

BRCA 1/2

ATM

HRR = Homologous Recombination Repair

Chk1 stabilizes stalled replication forks

Chk1 mediates DNA repair via HRR

Chk1 regulates origin firing to manage replication stress

Chk1 stabilizes stalled replication forks

Chk1 mediates DNA repair via HRR
Internal and External Inducers of Replication Stress (RS)
Both Increase Tumor Cell Reliance on Chk1

**INTRINSIC RS INDUCERS**

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

- **Oncogenic drivers**
  - Dysregulation of replication, transcription/replication collision
  - e.g. MYC* CCNE1*

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

- *Illustrative genes and drivers only

**EXTRINSIC RS INDUCERS**

- **Depleted replication building blocks**
  - Low dose gemcitabine (LDG)

**High RS results in:**

- Increased reliance on Chk1 in tumor

Chk1 regulates RS
SRA737+LDG Combination: Comparative Gemcitabine Doses

Relative to standard-of-care, the non-cytotoxic gemcitabine doses employed in the SRA737-02 Phase 1/2 clinical trial are approximately 10-20% of a standard cytotoxic dose.

Current doses, in combination with SRA737, in SRA737-02 study
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>
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<tbody>
<tr>
<td>Stage of development:</td>
<td>Ph2</td>
<td>Ph2</td>
</tr>
<tr>
<td>Presentation:</td>
<td>Oral</td>
<td>i.v.</td>
</tr>
<tr>
<td>Biochemical IC$_{50}$: Chk1</td>
<td>1.4 nM</td>
<td>~1 nM</td>
</tr>
<tr>
<td>Biochemical IC$_{50}$: Chk2</td>
<td>1850 nM</td>
<td>8 nM</td>
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<tr>
<td>Selectivity: Chk1 vs. Chk2</td>
<td>1320x</td>
<td>~10x</td>
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<tr>
<td>Clinical toxicity: G3/4 Neutropenia</td>
<td>LOW</td>
<td>HIGH</td>
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</table>

SRA737 selectivity:
- 15/124 kinases at 10 µM
- ERK8 = 100x
- All other kinases >200x
- CDK2 = 2750x
- CDK1 = 6750x
Linking Immune Checkpoint Blockade (ICB) Responses and the DDR Network
MSKCC Retrospective Analysis in Bladder Cancer: Clinical Evidence Linking DDR Alterations & ICB Efficacy

- A retrospective analysis by Memorial Sloan Kettering* links tumor DDR alterations to higher response rates for ICB agents in Urothelial Carcinomas in Phase II studies
  - 34 gene panel of DDR genes analyzed
  - Chk1 and other genes implicated in Replication Stress were included in the panel

<table>
<thead>
<tr>
<th>Mismatch Repair (MMR)</th>
<th>Nucleotide Excision Repair (NER)</th>
<th>Homologous Recombination (HR)</th>
<th>Fanconi Anemia (FA)</th>
<th>Checkpoint</th>
<th>Others</th>
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<tbody>
<tr>
<td>MLH1</td>
<td>ERCC2</td>
<td>BRCA1</td>
<td>BRCA2</td>
<td>ATM</td>
<td>POLE</td>
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<td>MSH2</td>
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<td>RAD50</td>
<td>PALB2</td>
<td>CHEK2</td>
<td>RECQL4</td>
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<tr>
<td>PMS2</td>
<td></td>
<td>RAD51</td>
<td>RAD51C</td>
<td>MDC1</td>
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<td>RAD51B</td>
<td>BLM</td>
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<td>RAD51D</td>
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<td></td>
<td></td>
<td>RAD52</td>
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<tr>
<td></td>
<td></td>
<td>RAD54L</td>
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- 47% of 60 patients analyzed had an alteration in ≥1 of the DDR genes (25% had deleterious mutation(s))

In these bladder cancer studies, patient response to ICB agents was found to depend on the presence of DDR mutations:

- **80% ORR** in patients with DDR mutations known or likely deleterious
- **54% ORR** in patients with DDR mutations of unknown significance
- **19% ORR** in patients without a DDR mutation

OS and PFS were significantly improved in patients harboring DDR mutations.

Additional Support Linking the DDR and ICB: Recent Combination Clinical Trial Results

- Emerging clinical data exploring novel DDR-targeted therapies and ICB further validates the interplay between cancer immunity and the DNA damage repair network
  - In certain indications, addition of targeted DDR therapeutics have the potential to improve upon the modest single agent response rates of ICB agents

<table>
<thead>
<tr>
<th>ICB Combination Examples and Results</th>
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<tbody>
<tr>
<td><strong>PARP Inhibitors</strong></td>
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<tr>
<td>• All approved PARPi are currently in clinical trials combined with ICB across variety of solid tumors</td>
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<tr>
<td>• Durable responses observed, but efficacy primarily limited to tumors with underlying HRD defects (e.g., BRCA1/2, same population as PARPi monotherapy)</td>
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<td><strong>ATR Inhibitors</strong></td>
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<tr>
<td>• AZD6738 + durvalumab Phase 1: 3/17 responses, 2CRs in NSCLC and HNSCC</td>
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<tr>
<td>• All 3 responders noted as BRCAwt, suggesting that ATR/Chk1 axis ICB combination efficacy may be independent of underlying HRD defects (unlike PARPi)</td>
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<tr>
<td><strong>Chk1 Inhibitors</strong></td>
</tr>
<tr>
<td>• Prexasertib + PD-L1 inhibitor Phase 1 is ongoing; results not yet available</td>
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</table>
Preclinical Support Linking the DDR and ICB: Mechanistic Rationale for Chk1 Combination

- Recently, numerous preclinical publications (including from Sierra and our collaborators) have provided mechanistic data that strongly links the DDR network and cancer immunity.

### Recent Preclinical Mechanistic Publications

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Details</th>
</tr>
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<tbody>
<tr>
<td>2017</td>
<td><strong>Chk1i + PD-L1</strong> results in remarkable tumor regression in a SCLC model (Sen)</td>
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<td>ATRi enhances micronuclei formation in HNSCC models (Magnus)</td>
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<td>Models of innate immune activation following S-phase DNA damage and G2/M progression via micronuclei formation and STING activation (Harding) (Parkes)</td>
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<td>2018</td>
<td><strong>SRA737</strong> induces STING activation and type I IFN signaling and demonstrates anti-tumor activity in combination with anti-PD-L1 (Sen)</td>
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<td></td>
<td>PARPi elicits STING-dependent immunity in BRCA1-deficient HGSOC models (Ding)</td>
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<tr>
<td></td>
<td>PARPi treatment promotes CD8+ T-cells and generates immunological memory in BRCA1-null mouse models but not in BRCA WT models (Robillard)</td>
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<tr>
<td></td>
<td>Gemcitabine and ICB significantly enhances survival in mouse models of mesothelioma (RN5) and overcomes resistances of either agent alone (Tallon de Lara)</td>
</tr>
<tr>
<td>2019</td>
<td><strong>Chk1i</strong>-mediated anti-tumor activity is dependent on STING activation and CD8 T-cell infiltration (Sen)</td>
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<tr>
<td></td>
<td><em>Combination treatment of the CHK1 inhibitor, SRA737, and low dose gemcitabine demonstrates profound synergy with anti-PD-L1 inducing durable tumor regressions and modulating the immune microenvironment in small cell lung cancer (Sen)</em></td>
</tr>
</tbody>
</table>

*Oral presentation disclosed at AACR 2019*
Biological Rationale for the Combination of SRA737 (Chk1i) + ICB
Chk1 Inhibition + High RS Environment = Intrinsic and Immune-Mediated Anti-Tumor Activity

Genetically-driven RS +/- LDG

- Genomic Instability
  - Excessive DNA damage
  - Replication / mitotic catastrophe
  - Tumor Cell Death

Intrinsic RS-mediated anti-tumor activity

- Moderate DNA damage
- Micronuclei formation
- STING activation
- IFN signaling / chemokine release
- T cell, APC recruitment

Immune-mediated anti-tumor activity
Intrinsic RS-mediated Anti-Tumor Activity

Genetically-driven RS +/- LDG

Chk1 regulates RS

Genomic Instability

Intrinsic RS-mediated anti-tumor activity

Excessive DNA damage

Replication / mitotic catastrophe

Tumor Cell Death

Immune-mediated anti-tumor activity

Moderate DNA damage

Micronuclei formation

STING activation

IFN signaling / chemokine release

T cell, APC recruitment
SRA737 Has *In Vitro* Anti-Tumor Activity as Monotherapy and in Combination with LDG

- SRA737 induces DNA damage (γH2AX) and intrinsic cytotoxicity in sensitive SCLC cell lines
- Low dose gemcitabine (LDG) induces replication stress and greatly potentiates cytotoxicity in combination with SRA737

**Intrinsic RS-Mediated Anti-Tumor Activity**

Excessive DNA damage → Replication / mitotic catastrophe

**SRA737 IC₅₀s in SCLC panel**

**HT-29 colon cancer cells**
SRA737 Has *In Vivo* Anti-Tumor Activity as Monotherapy and in Combination with LDG

**Intrinsic RS-Mediated Anti-Tumor Activity**

Excessive DNA damage → Replication / mitotic catastrophe

- SRA737 demonstrates robust efficacy either as monotherapy or LDG combination in immunodeficient mouse tumor models, further supporting its potent intrinsic anti-tumor activity even in the absence of cytotoxic T cells.
Immune-Mediated Anti-Tumor Activity

Genetically-driven RS +/- LDG

Genomic Instability

Intrinsic RS-mediated anti-tumor activity

- Excessive DNA damage
- Replication / mitotic catastrophe

Immune-mediated anti-tumor activity

- Moderate DNA damage
- Micronuclei formation
- STING activation
- IFN signaling / chemokine release
- T cell, APC recruitment

Chk1 regulates RS

Tumor Cell Death

IFN: Interferon
APC: Antigen-presenting cell
RS: Replication Stress
AACR 2019 Late-Breaking Oral Presentation:

Combination treatment of the CHK1 inhibitor, SRA737, and low dose gemcitabine demonstrates profound synergy with anti-PD-L1, inducing durable tumor regressions and modulating the immune microenvironment in small cell lung cancer.
Dr. Byers’ research goal is to identify changes in cancer cells at the molecular level that contribute to their growth and drug resistance and apply this knowledge to develop more effective, personalized therapy for patients. Dr. Byers’ laboratory research led to the discovery of several novel drug targets for lung cancer and important ways in which cancer cells can become resistant to existing therapies, including immunotherapy. The results obtained by her team have led directly to clinical trials with new combinations of drugs that will impact patient care. Currently, Dr. Byers’ work includes examining the inhibitory effects of different drugs targeting the protein Chk1 to treat small cell lung cancer.

Dr. Byers is an Associate Professor in the Department of Thoracic/Head and Neck Medical Oncology. She has an impressive list of funded grants and awards, including Women Leading the Way and NCI Cancer Clinical Investigator Team Leadership Award (both in 2013), R. Lee Clark Fellow Award and President’s Recognition for Faculty Excellence (both in 2014), ASCO Top Ten Clinical Research Achievement Award (2015), and an NIH R01 (2016).

Dr. Byers completed her BA degree in Molecular Biology at Princeton University in 1998, her M.D. degree at Baylor College of Medicine in 2003, her clinical fellowship in Medical Oncology at the University of Texas MD Anderson Cancer Center and M.S. degree in Patient-Based Research at the University of Texas Graduate School of Biomedical Sciences both in 2009.
Combination treatment of the CHK1 inhibitor, SRA737, and low dose gemcitabine demonstrates profound synergy with anti-PD-L1 inducing durable tumor regressions and modulating the immune microenvironment in small cell lung cancer

Triparna Sen, PhD
Thoracic Head and Neck Medical Oncology
MD Anderson Cancer Center

Abstract Co-authors:
MD Anderson: Lauren A Byers, MD; Carmen M. Delta Corte, MD; Luxia Ciao, PhD; Robert J Carroll, PhD; Jing Wang, PhD
Sierra Oncology: snezana Milutinovic, PhD; Ryan J. Hansen, PhD; Bryan Strouse, PhD; Michael P. Hedrick, BS;GA; Christian A. Hassig, PhD

AACR Annual Meeting
April 1, 2019
Atlanta, Georgia, USA.
SRA737 Induces Micronuclei, Activates STING and Interferon Immune Signaling \textit{In Vitro}

- SRA737-induced DNA damage may lead to dose-dependent micronuclei formation in a range of cell lines
- Micronuclei are a source of ssDNA that activates innate immune signaling through STING and IFN

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Representative image of micronuclei}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart}
\caption{SCLC (H1694, H847) STING pathway activation}
\end{figure}
SRA737 and the ICB Combination Activates STING and Induces IFN Signaling In Vivo

**Immune-Mediated Anti-Tumor Activity**

- Moderate DNA damage → Micronuclei formation → STING activation → IFN signaling / chemokine release → T cell, APC recruitment

- SRA737 treatment (5d out of 7d) in mice stimulates STING activation and expression of immune-cell recruiting chemokines and cytokines in mTmG SCLC tumors

**STING activation in tumors at day 7**

**Immune-cell recruiting chemokine and cytokine genes in tumors at day 7**

- **mRNA expression**
  - IFNβ: Vehicle < SRA737 (5/7), p<0.001
  - CXCL10: Vehicle < SRA737 (5/7), p<0.001
  - CCL5: Vehicle < SRA737 (5/7), p<0.001
SRA737+LDG Induced Expression of IFN Response Genes is Further Enhanced by Anti-PD-L1 *In Vivo*

**Immune-Mediated Anti-Tumor Activity**
- Moderate DNA damage → Micronuclei formation → STING activation → IFN signaling / chemokine release → T cell, APC recruitment

- SRA737+LDG in combination with anti-PD-L1 shows superior induction of IFN response genes such as IFNβ and inflammatory chemokines CXCL10 and CCL5 in tumors after 3 weeks of treatment.

**Dosing Schedule x 3 weeks**

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<tr>
<th>Day</th>
<th>1</th>
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<th>4</th>
<th>5</th>
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<tr>
<td>PD-L1</td>
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**Graphical Representation:**
- mRNA expression of IFNβ, CXCL10, and CCL5 under different treatment conditions.

- **Vehicle**: Black
- **LDG**: Orange
- **SRA737+LDG**: Green
- **SRA737+anti-PD-L1**: Blue
- **Anti-PD-L1**: Pink
- **LDG+anti-PD-L1**: Red
- **SRA737+LDG+anti-PD-L1**: Purple

- **Significance Levels**:
  - ***p < 0.001
  - **p < 0.01
  - *p < 0.05
SRA737+LDG Promotes Favorable Anti-Tumor Immune Microenvironment That is Further Augmented by ICB

- SRA737/LDG promotes an optimal anti-tumor lymphocyte profile by increasing CD8+ CTLs while reducing Exhausted and Regulatory T-cells in tumors, which is further augmented by ICB agent treatment.
SRA737+LDG Promotes Favorable Anti-Tumor Immune Microenvironment That is Further Augmented by ICB

• SRA737/LDG induces favorable macrophage polarization by promoting the anti-tumor M1 type and suppressing the tumor-promoting M2 type

Immune-Mediated Anti-Tumor Activity

Moderate DNA damage → Micronuclei formation → STING activation → IFN signaling / chemokine release → T cell, APC recruitment

M1 macrophages (pro-inflammatory)

M2 macrophages (immunosuppressive)
SRA737+LDG Promotes Favorable Anti-Tumor Immune Microenvironment That is Further Augmented by ICB

**Immune-Mediated Anti-Tumor Activity**

- Moderate DNA damage
- Micronuclei formation
- STING activation
- IFN signaling / chemokine release
- T cell, APC recruitment

- Antigen presenting dendritic cells that support CTL activation are also increased while the immunosuppressive MDSC are significantly suppressed

**Dendritic cells (antigen presenting)**

**Immunosuppressive MDSCs**
SRA737+LDG with ICB Demonstrates Profound In Vivo Synergy

- Single agent ICB and low dose "Gem" inactive
- SRA737 synergizes with either LDG or ICB alone
- SRA737/LDG + ICB is the most effective regimen
  - 10/10 (100%) regressions at the end of treatment (day 21)
  - 8/10 (80%) sustained CRs / cures at day 60
- Well tolerated, no weight loss

Byers Collaboration (MDACC) – mTmG SCLC model
• Recent approvals of chemotherapy and ICB combinations in lung cancer demonstrate proof-of-concept for the enhancement of immunotherapy in cancers with inadequate response to immunotherapy alone

• Our data demonstrates that SRA737+LDG induces direct tumor cell death and activates innate immune signaling, resulting in synergistic anti-tumor activity in combination with ICB

• The unique replication stress-inducing mechanism of SRA737+LDG results in micronuclei formation, STING activation and an IFN response signature including the induction of CTL-recruiting proinflammatory chemokines (e.g. CXCL10, CCL5)

• SRA737+LDG in combination with ICB demonstrated profound anti-tumor activity with complete durable regressions accompanied by a highly favorable tumor immune microenvironment as evidenced by infiltration of CTLs and dendritic cells and a concurrent inhibition of suppressive immune cells (Tregs, M2 macrophages and MDSCs) in tumors

• Additional studies are planned/underway to further validate the combination of ICB with SRA737+LDG in immunocompetent models beyond SCLC
SRA737+LDG with ICB : Strategic Opportunity
Opportunity for Clinical Combinations of SRA737+LDG with ICB Therapy

• **SRA737+LDG with ICB** represents a tractable potential clinical opportunity

• There is a strong biological rationale and preclinical support for combining SRA737+LDG with ICB therapies

• Sierra has shown SRA737+LDG in combination with ICB results in superior immune profile and profound efficacy in preclinical models

• SRA737+LDG activates innate immune signaling and establishes an anti-tumor immune microenvironment that synergizes with immune checkpoint inhibitors

• These preclinical data suggest SRA737+LDG combined with ICB may be effective in SCLC, and potentially also in other clinical settings where monotherapy IO efficacy is modest

• A Phase 2 study of SRA737+LDG with ICB could readily determine the magnitude of combination clinical benefit
We are a clinical stage drug development company advancing targeted therapeutics for the treatment of patients with unmet medical needs in hematology and oncology.

- Bold drug development company oriented to registration and commercialization
- Lead asset, momelotinib, for the treatment of myelofibrosis with large 2nd-line market opportunity
- Two assets focused on DNA Damage Response (DDR) targeting: SRA737 and SRA141
- Highly experienced management team with proven track record in drug development
- Strong financial standing:
  - Shares (as of December 31):
    - 74.4M outstanding
    - 84.9M fully diluted
  - $106.0M in cash and cash equivalents (as of December 31)
  - $5M borrowed in structured debt