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Sierra Oncology’s Broad Pipeline: Addressing Unmet Medical Needs

**momelotinib**
TARGETING JAK1/2 AND ACVR1

**sRA737**
TARGETING Chk1

**sRA141**
TARGETING Cdc7

**THERAPEUTIC FOCUS**
Myelofibrosis

**THERAPEUTIC FOCUS**
High Grade Serous Ovarian Cancer
Squamous & Other Solid Tumors

**THERAPEUTIC FOCUS**
Colorectal Cancer

**DDR Network Programs**
## Sierra Oncology: Our Pipeline of Targeted Therapeutics

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<th>Product</th>
<th>Preclinical</th>
<th>Phase 1</th>
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<td>Myelofibrosis</td>
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<tr>
<td>JAK1/2 AND ACVR1</td>
<td>Simplify 1</td>
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<td>Simplify 2</td>
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<td>Additional registration study</td>
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<td>SRA737</td>
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<td>I/O Combination</td>
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</table>

**SRA737**

- Monotherapy; prioritized for HGSOC
- Low Dose Gemcitabine Combination; prioritized for HGSOC
- PARPi Combination; Prostate Cancer
- I/O Combination
- Monotherapy; Colorectal Cancer
Momelotinib: Targeting JAK1, JAK2 and ACVR1
Myelofibrosis: A Chronic Myeloproliferative Neoplasm (MPN)

- Inflammation
- Constitutional symptoms
- Inefficient hematopoiesis
- Anemia & transfusion dependency
- Extramedullary hematopoiesis
- Splenomegaly

CONSTITUTIONAL SYMPTOMS
ANEMIA
SPLENOMEGALY
Myelofibrosis: The Three Hallmarks of a Progressive Disease

>1 Year After Diagnosis:

- **64%** anemia
  - Extramedullary hematopoiesis (EMH) in the spleen and other organs.
  - Enlarged spleen due to EMH, inflammation and/or RBC sequestration.

- **45%** transfusion dependent
  - Progressive bone marrow fibrosis due to inflammation.
  - Degraded marrow function.
  - Decreased erythropoiesis (often necessitating transfusion).

- **46%** splenomegaly
  - Extra-medullary hematopoiesis (EMH) in the spleen and other organs.
  - Enlarged spleen due to EMH, inflammation and/or RBC sequestration.

- **34%** constitutional symptoms
  - Anemia, chronic inflammation, and splenomegaly lead to constitutional symptoms:
    - Fatigue
    - Bone pain
    - Early satiety
    - Night sweats
    - Pruritis
    - Cachexia
    - Fever

Myelofibrosis: Myelofibrosis By The Numbers

- 40-50k patients living with MF
- 70-80% of patients categorized as intermediate - high risk
- >70% of INT-2/HIGH MF patients have anemia
- ~245 days average time on 1L treatment
Myelofibrosis: Unmet Medical Needs

Initial Treatment:

- Ruxolitinib (Jakafi®) addresses ~70% 1L patients; not labeled for patients with severe thrombocytopenia.
- No approved treatments for ruxolitinib ineligible patients.
- Ruxolitinib only addresses spleen and symptom issues.
- Projected global market for ruxolitinib ~$2B.

Unmet Medical Needs:

- Physicians need more choices to treat myelofibrosis.
- Only one agent approved – ruxolitinib for 1L MF.
- Most patients need additional treatment after ruxolitinib.
- Optimally, an MF therapeutic would address all three components of disease: anemia, spleen and symptoms.
- Treating anemia and transfusion dependency remain significant unmet medical needs.
“Ruxolitinib may control the signs and symptoms of the disease for some time… but it doesn’t prevent progression.”

“Three quarters of the patients would be candidates… for a second line therapy.”

“The majority of patients… need another agent to salvage their quality of life, to control spleen, symptoms, and to improve the anemia, if possible.”

“Momelotinib… unlike any other JAK inhibitor, can benefit patients to a great extent on all three aspects.”
“Anemia is major area of unmet need. That’s one of the major problems… a quarter of the patients at the beginning may require transfusions, and after one year of therapy almost half of the patients already require transfusion. Anemia and transfusion dependency are important prognostic factors.”

Srdan Verstovsek, MD, PhD
Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, Houston.

Unmet Medical Needs In Myelofibrosis - KOL Presentation, October 17, 2018
Myelofibrosis: Anemia – Most Important Prognostic Factor in MF

Baseline Anemia:
Mild = Hgb ≥ 10 g/dl but below lower limit of normal
Moderate = Hgb between 8 g/dl and <10 g/dl;
Severe = Hgb <8 g/dl or transfusion dependent.

Nicolosi et al; Leukemia 2018.
Myelofibrosis: Pathways To Anemia in Myelofibrosis

- **BONE MARROW FIBROSIS**
  - Displacement of marrow erythropoietic tissue by fibrosis
  - Extramedullary hematopoiesis & splenomegaly
  - Inadequate extramedullary erythropoiesis & RBC sequestration

- **INFLAMMATION**
  - Alterations in bone marrow cytokine expression
  - Pro-inflammatory cytokine profile
  - Impaired erythroid differentiation

- **HEPCIDIN**
  - Activated ACVR1
  - Increased hepcidin
  - Impairment of iron metabolism

- **JAK THERAPY**
  - JAK inhibitor therapy induced myelosuppression

ANEMIA
Momelotinib: Biological Basis for Momelotinib’s Anemia Benefit

Acvr1 and hepcidin

- The iron metabolism pathway involves TGFβ superfamily receptors such as Acvr1.
- Acvr1 signals through Smads activating the transcription of hepcidin.
- Elevated hepcidin leads to decreased erythropoiesis.
- Other therapeutics targeting the TGFβ superfamily include luspatercept and sotatercept.

Hepcidin correlates with poor prognosis in MF. Increased hepcidin levels are predictive of inferior survival in MF.

Activated Acvr1

Hepcidin increased

Blockage of ferroportin

Iron unable to leave cells

Decreased free iron

Decreased hemoglobin

High hepcidin

Low hepcidin

Cumulative survival

Time (months)
Momelotinib: Improves All Three Facets of Disease

- Impaired Erythropoiesis
- Aberrant Cytokine Production and Immune Dysregulation
- JAK-STAT-Driven Clonal Myeloproliferation

CONSTITUTIONAL SYMPTOMS

SPLENOMEMEGALY

MMB INHIBITS JAK1

MMB INHIBITS JAK2

MMB INHIBITS ACVR1

Hepcidin Impaired Erythropoiesis

ANEMIA

MMB INHIBITS MMB INHIBITS MMB INHIBITS
Momelotinib: Differentiated JAKi Tested H2H vs. RUX

- No other JAKi has consistently demonstrated a broader ability to address the needs of MF patients: Only momelotinib has robust spleen, symptom and anemia benefits.

<table>
<thead>
<tr>
<th></th>
<th>Momelotinib (MMB)</th>
<th>Ruxolitinib (RUX)</th>
<th>Fedratinib (FED)</th>
<th>Pacritinib (PAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Status in Myelofibrosis</strong></td>
<td>Phase 3 (2x completed P3s; P2 translational biology)</td>
<td>Approved (intermediate / high-risk; platelets ≥50 × 10³/dL)</td>
<td>Post-Phase 3 (NDA filing 2018 TBD)</td>
<td>Phase 2 (P3 trial requested by FDA; EU MAA refiled)</td>
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<tr>
<td><strong>Targets</strong></td>
<td>JAK1, JAK2, ACVR1</td>
<td>JAK1, JAK2</td>
<td>JAK2, FLT3</td>
<td>JAK2, FLT3</td>
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<td><strong>Splenic Response</strong></td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
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<td><strong>Symptom Benefit</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td><strong>Anemia Benefit</strong></td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td><strong>Toxicity: Anemia &amp; Thrombocytopenia</strong></td>
<td>LOW</td>
<td>HIGH</td>
<td>HIGH</td>
<td>HIGH</td>
</tr>
</tbody>
</table>
Momelotinib: Key Facts & Figures

>20 Phase 1, 2 & 3 studies

>1,200 subjects dosed with momelotinib

>550 MF patients treated

>7 years on treatment for several patients

Momelotinib is uniquely positioned to provide a spectrum of robust benefits in MF – spleen, symptoms & anemia.
**Completed Phase 3 Studies with Momelotinib: SIMPLIFY-1 & SIMPLIFY-2**

**Simplify 1**

**1L Population:** previously untreated with JAKi.

- **Goal:** Non-Inferiority
  - **MMB:** N=215
  - **RUX:** N=217

**Primary endpoint:**
- Splenic response rate

**Secondary endpoints:**
- Total symptom score
- Effects on RBC transfusion requirements

**Simplify 2**

**2L Population:** anemic or thrombocytopenic subjects previously treated with RUX.

- **Goal:** Superiority
  - **MMB:** N=104
  - **BAT:** N=52

**Primary endpoint:**
- Splenic response rate

**Secondary endpoints:**
- Total symptom score
- Effects on RBC transfusion requirements

- **RBC transfusions on RUX = 64%**
- **RUX dose adjustment for:**
  - thrombocytopenia = 21%
  - anemia/hematoma = 35%

**90% = RUX/RUX+**
Momelotinib: Non-Inferior H2H Activity on Splenomegaly

Momelotinib statistically non-inferior to RUX on spleen ($p=0.011$).

Only JAKi shown equivalent to ruxolitinib for splenic response in 1L.

26.5% SRR vs. 29% RUX

SRR: Splenic Response Rate
Momelotinib: Deepened Spleen Response After RUX Crossover

**Deepening Response Post-RUX Benefit**

46.2% SRR on momelotinib at anytime in open label phase. (momelotinib arm)

16.5% SRR percentage of subjects who did not achieve a spleen response on ruxolitinib but did so after 24 weeks of additional momelotinib treatment. (crossover arm)
Momelotinib: Pronounced Activity on Symptoms

Statistically significant symptom response \((p < 0.001)\).

26.2% TSS vs. 5.9% Best Available Treatment (BAT)

momelotinib compared to BAT (~90% ruxolitinib) in second line patients.

TSS: Total Symptom Score
Both momelotinib and ruxolitinib substantially improved all symptoms relative to baseline in a clinically comparable manner*.

*Marginal missed Total Symptom Score (TSS) non-inferiority to RUX in SIMPLIFY-1: 28.4% vs. 42.2% (Noninferior Proportion Difference 0.00 (-0.08, 0.08)).
Momelotinib: Differentiated Activity on Anemia & Transfusions

Simplify 1
PREVENTS TRANSFUSIONS
66%
vs. 49% RUX
Statistically significant TI rate ($p < 0.001$).

Simplify 2
ELIMINATES TRANSFUSIONS
32.8%
vs. 3.7% BAT
of TD patients at baseline were TI at week 24 on momelotinib.

TD: Transfusion Dependent
TI: Transfusion Independent
Myelofibrosis: Hemoglobin Improvement After MMB Crossover

Simplify 1

Double-Blind Phase vs. Open-Label Phase

- Momelotinib
- Ruxolitinib

Crossover: All patients on MMB
Momelotinib: Consistently Decreased Hepcidin Post-MMB

CLINICALLY EFFECTIVE MECHANISM

34%

12 Week TI response rate

Abstract #4282
ASH Annual Meeting 2018

Translational biology Phase 2 study (N=41; GS-US-352-1672).
Momelotinib:
Noteworthy Survival Post-RUX vs. Historical Control

28 months mOS
vs. 14 months*

momelotinib compared to historical control in post-ruxolitinib treated patients.

*Snewberry at al, 2017 Blood 130(9):1125-1131
Momelotinib: Potentially Addresses the Key Unmet Needs in MF

- Convert Transfusion Dependence into Independence.
- Maintain Transfusion Independence.
- Eliminate or decrease transfusion frequency and overall burden.
- Increase Hgb levels.

- Clinically comparable to ruxolitinib in 1L.
- Superior benefit in 2L.

MF Physician Survey (2016):
60 Qualitative Interviews (15 US; 45 EU); 240 Quantitative Surveys (100 US; 140 EU)
*percentages indicate physician survey responses of key needs
Myelofibrosis: Momelotinib is Well Tolerated

- Momelotinib has a comparable overall safety profile to ruxolitinib in SIMPLIFY-1 and demonstrates substantially lower rates of thrombocytopenia and anemia.

- While AE rates were generally comparable, fewer patients experienced AEs on momelotinib vs. ruxolitinib in 1L, and with fewer G3 or 4 AEs in 1L and 2L.

- In 1L, LFS and mOS appear comparable to ruxolitinib (mLFS/mOS NR) following crossover. LFS and OS trends favor momelotinib over ruxolitinib in both the 1L and 2L settings (mLFS/mOS NR in 1L).
Momelotinib Registration Strategy: Planned Next Steps

- Sierra is currently reviewing and mining the robust body of existing clinical data generated by Gilead.

- Planning for near-term regulatory interactions to determine registration path and requirements for a likely additional Phase 3 study in 2L setting.

- Focus on 2L anemic & transfusion dependent patients, major unmet need in MF.

- Registration plan clarity projected for H1 2019.
IN MYELOFIBROSIS, GREAT STRIDES HAVE BEEN MADE WITH SPLENOMEGALY AND CONSTITUTIONAL SYMPTOMS, BUT THE MAJORITY OF PATIENTS STILL CARRY THE BURDEN OF ANEMIA.
Targeting the DNA Damage Response
SRA737: Chk1i Program Focused on Ovarian Cancer

- SRA737 has significant anti-tumor activity and a profound survival benefit in CCNE1 HGSOC preclinical models.
- PARPi inactive in this population.
- Supports our ovarian cancer development focus.

- Phase 2 study of Lilly's Chk1i prexasertib in BRCA wild type (PARPi insensitive) high-grade serous ovarian cancer demonstrates clinical efficacy in CCNE1 genetic background.

Orthotopic PDX (CCNE1 amplified + TP53 mutated)

Prexasertib Efficacy
- 33% ORR (8/24) Evaluable
- 42% ORR (8/19) CCNE1 (All)
- 33% ORR (4/12) CCNE1 amplification

Hong et al. Lancet Oncology 2018
SRA737-01 Monotherapy: Program Expansion & Prioritized Design

- Focus on genetically-defined replication stress driven patient populations.
- Continuous daily oral administration.

Prospective patient selection using NGS technology

Phase 2 cohorts

Dose optimization (non-selected)

Dose escalation (non-selected)

Target enrollment N=80 (20x4)

Target enrollment N=65

Ovarian (CCNE1)

Ovarian (non-CCNE1)

Prioritizing for Ovarian Cancer

Prostate

Non-Small Cell Lung

Head & Neck + Anus

Colorectal

Tumor Suppressor
TP53, RAD50...

Oncogenic Drivers
CCNE1, MYC...

Replicative Stress
ATR, CHEK1...

DNA Repair Machinery
BRCA1, FANCA...
SRA737-02 LDG Combination: Program Expansion & Amended Design

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

*One or more mutations required for eligibility.
SRA141: Cdc7i Program Focused on Colorectal Cancer

- 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.

- Phase 1/2 clinical trial focused on colorectal cancer.
- Takeda Cdc7i clinical data demonstrate preliminary monotherapy responses; P2 ongoing in colorectal.

COLO205 model: TP53 & MSS - relevant genetics for Cdc7i. Tumor growth inhibition (TGI) = 99%; CRs in 4/7 (57%) animals.
Sierra Oncology: Targeted Hematology & Oncology Therapeutics

A clinical-stage drug development company advancing targeted therapeutics for patients with significant unmet needs in hematology and oncology.

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

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

**Nasdaq: SRRA**
**Headquarters: Vancouver, BC**
**Shares (09/30/18):**
- 74.4M outstanding
- 85.2M fully diluted
**Cash and cash equivalents:**
- $116.1M (09/30/18)
**Structured debt facility:**
- $5M borrowed
Sierra’s Management Team:
Proven Leadership In Drug 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
## Sierra Oncology: Our Pipeline of Targeted Therapeutics

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<th>Product</th>
<th>Q1 18</th>
<th>Q2 18</th>
<th>Q3 18</th>
<th>Q4 18</th>
<th>H1 19</th>
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</thead>
</table>
| **momelotinib**  
JAK1/2 AND ACVR1 |  | Asset acquisition ✓ | ASH Poster | Registration plan clarity |  |
| **SRA737**  
TARGETING Chk1 |  | Program Update Feb 2018 ✓ | CCNE1 HGSOC Cohort Initiated ✓ | Trial prioritized for HGSOC ✓ | Preliminary data |
| SRA737-01 |  |  |  |  |  |
| SRA737-02 |  |  |  |  | Preliminary data |
| SRA737-03 |  |  |  |  | Initiate Phase 1b/2 |
| SRA737-04 |  |  |  |  | Preclinical data |
| **SRA141**  
TARGETING Cdc7 |  |  |  |  |  |
|  |  |  |  | Submit IND ✓ |  |