Sierra Oncology
Delivering Transformative Therapies for Rare Cancers
March 2022
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Sierra Oncology Overview

Momelotinib (MMB) met all pre-specified primary and key secondary endpoints with statistical significance in the Phase 3 pivotal MOMENTUM study

- Symptomatic, anemic, myelofibrosis (MF) patients previously treated with a JAK inhibitor

MOMENTUM data confirm momelotinib as a potential treatment option for certain myelofibrosis patients with anemia

- Topline data have demonstrated clinically significant benefit in anemia improvement, symptom and spleen control, with stable platelet counts

~$3B potential addressable market\(^{(1)}\) in anemic MF patients in the US

- ~15K prevalent MF patients with anemia in the US

Planned clinical trials to evaluate MMB as a potential cornerstone in future combination therapies in MF

- Momelotinib + SRA515 combination clinical trial designed to provide proof-of-concept
- Combination trial expected to begin in 2022

Pro-forma cash of ~$296M \(^{(2)}\)

\(^{(1)}\) Sierra estimates ~15k U.S. prevalent patients at $200k/patient/year

\(^{(2)}\) Includes $104.7M cash as of 12/31/21, $5M cash from Oxford loan drawdown in Q1 2022, $145.6M net proceeds from 1/25/22 follow-on offering and ~$40.3M proceeds from exercise of Series A and B warrants through 3/7/22. Excludes cash used from operations from 1/1/22 through 3/7/22.
Financial Overview

Cash at 12/31/21 $105M
Cash drawn on Oxford Loan Facility(1) $5M
Cash raised in 2022 financing (net) $146M
Proceeds from exercise of Series A and B warrants through 3/7/22 $40M

Shares outstanding
Common shares as of 3/7/22 23.7M
Pre-funded warrants issued in 2022 follow-on offering 0.9M

(1) Up to $120M available on Oxford Loan Facility
Myelofibrosis (MF): a bone marrow cancer
• Caused by constitutive activation of JAK-STAT signaling
• Inflammation and fibrosis impair red blood cell production

Common manifestations of disease include constitutional symptoms, enlarged spleen and progressive anemia

Current treatments: JAK inhibitors are the mainstay option for intermediate and high-risk patients
Anemia and Hepcidin Predict Poor Survival in Myelofibrosis

Anemia of inflammation driven by elevated hepcidin

Elevated hepcidin inhibits iron transport and iron homeostasis

Anemia and elevated hepcidin are negative prognostic indicators

New therapies should aim to provide anemia benefits in addition to symptom, spleen benefits

Anemia Predicts Poor Survival in MF

Transfusion Dependency Predicts Poor Survival in MF

Elevated Hepcidin Predicts Poor Survival in MF

Nicolosi et al. Leukemia. 2018

Elena et al. Haematologica. 2011

Momelotinib Inhibits JAK1, JAK2 and ACVR1/ALK2

Hyperactive JAK-STAT signaling is driving the disease in myelofibrosis

Preclinical studies and clinical trials suggest that the clinical anemia benefits of momelotinib result from suppression of ACVR1/ALK2-mediated hepcidin production

Momelotinib Inhibits all Three Disease Drivers, Potentially Improving Splenomegaly and Symptoms of Myelofibrosis While Maintaining or Improving Hemoglobin

**Pivotal Phase 3 ‘MOMENTUM’ Trial Overview**

*Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.*

**Subjects**
- N=195
- 2:1 randomization
- JAKi taper/washout ≥ 21 day

**Double-Blind Treatment**
- Momelotinib 200 mg daily (n=130) + Placebo

**Open Label/Crossover**
- Danazol*(DAN) 600 mg daily (n=65) + Placebo

**Long Term Follow-up**
- Early crossover to open label in the event of confirmed symptomatic splenic progression

**Primary Endpoint**
- Day 1
- Week 24

- Total symptom score (TSS) response rate at Week 24

**Secondary Endpoints**
- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24

*Previously Treated with JAK inhibitor
Symptomatic (TSS ≥ 10)
Anemic (Hgb < 10 g/dL)
And PLT ≥ 25 × 10⁹/L

*(Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.*
**MMB Showed Strong Activity Across Key Endpoints**

<table>
<thead>
<tr>
<th>Endpoint at Week 24</th>
<th>Test Order</th>
<th>Criterion for Significance</th>
<th>MMB (n=130)</th>
<th>DAN (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFSAF TSS 24 response (primary endpoint) (^{(1)})</td>
<td>1</td>
<td>Superiority (p≤0.05)</td>
<td>25%</td>
<td>9%</td>
<td>p=0.0095 (superior)</td>
</tr>
<tr>
<td>TI 24 Status (^{(2)})</td>
<td>2</td>
<td>Non-inferiority Boundary 0.8</td>
<td>31%</td>
<td>20%</td>
<td>p=0.0064 (non-inferior) (^{(3)})</td>
</tr>
<tr>
<td>SRR 24 (25% reduction)</td>
<td>3</td>
<td>Superiority (p≤0.05)</td>
<td>40%</td>
<td>6%</td>
<td>p&lt;0.0001 (superior)</td>
</tr>
<tr>
<td>MFSAF TSS change from baseline</td>
<td>4</td>
<td>Superiority (p≤0.05)</td>
<td>-11.5(^{(4)})</td>
<td>-3.9(^{(4)})</td>
<td>p=0.0014 (superior) (^{(4)})</td>
</tr>
<tr>
<td>SRR 24 (35% reduction)</td>
<td>5</td>
<td>Superiority (p≤0.05)</td>
<td>23%</td>
<td>3%</td>
<td>p=0.0006 (superior)</td>
</tr>
<tr>
<td>Rate of no transfusion to week 24</td>
<td>6</td>
<td>Superiority (p≤0.05)</td>
<td>35%</td>
<td>17%</td>
<td>p=0.0012 (superior)</td>
</tr>
</tbody>
</table>

\(^{(1)}\) TSS response is defined as a ≥ 50% reduction in mean TSS over the 28 days immediately prior to the end of Week 24 compared to baseline.

\(^{(2)}\) Proportion of subjects with TI status defined as not requiring RBC transfusion for ≥ 12 weeks, with all Hgb levels during the ≥ 12-week interval of ≥ 8 g/dL.

\(^{(3)}\) TI tested for superiority with a p-value (2-sided) of 0.0861.

\(^{(4)}\) Mean change from baseline for subjects with week 24 data available. P-value is from mixed model for repeated measures.
**MFSAF* Total Symptom Score (TSS) Response Rate at Week 24**

<table>
<thead>
<tr>
<th></th>
<th>MMB (N=130)</th>
<th>DAN (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSS response rate of 50% at W24, n (%)</strong></td>
<td>32 (24.6%)</td>
<td>6 (9.2%)</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(17.49, 32.94)</td>
<td>(3.46, 19.02)</td>
</tr>
<tr>
<td><strong>p-value (superiority)</strong></td>
<td></td>
<td>0.0095</td>
</tr>
<tr>
<td><strong>Mean TSS at Baseline (SD)</strong></td>
<td>28.0 (13.8)</td>
<td>25.7 (12.8)</td>
</tr>
<tr>
<td><strong>TSS Mean Change from baseline (SD)</strong>(1)</td>
<td>-11.5 (12.9)</td>
<td>-3.9 (11.9)</td>
</tr>
<tr>
<td><strong>p-value (superiority)</strong>(1)</td>
<td></td>
<td>0.0014</td>
</tr>
</tbody>
</table>

(1) Mean change from baseline for subjects with week 24 data available. P-value is from mixed model for repeated measures.

**Total Symptom Score (TSS) Response Rate**

- Proportion of subjects who achieve ≥ 50% reduction in TSS over the 28 days immediately prior to the end of Week 24 compared to baseline

**Myelofibrosis Symptom Assessment Form (MFSAF) v4.0**

- 7-item MFSAF v4.0 (scale 0-70) is a validated MF patient reported outcome (PRO) measure tool
- 7 symptoms measured: Fatigue, Night Sweats, Itching, Abdominal discomfort, Rib pain, Fullness, Bone Pain
  - Each scored on a 10-point scale from 0, Absent, to 10, Worst Imaginable
- Daily assessment completed electronically by the patient on an ePRO device
# Transfusion Independence (TI) Rate at Week 24

<table>
<thead>
<tr>
<th></th>
<th>MMB (N=130)</th>
<th>DAN (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TI at Baseline, n (%)</strong></td>
<td>17 (13.1%)</td>
<td>10 (15.4%)</td>
</tr>
<tr>
<td><strong>TI Rate at W24, n (%)</strong></td>
<td>40 (30.8%)</td>
<td>13 (20.0%)</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(22.98, 39.46)</td>
<td>(11.10, 31.77)</td>
</tr>
<tr>
<td><strong>Non-inferiority difference (95% CI), One sided p-value</strong></td>
<td>14.77 (3.13, 26.41), ( p=0.0064 )</td>
<td></td>
</tr>
<tr>
<td><strong>Superiority difference (95% CI), p-value</strong></td>
<td>10.99 (-0.80, 22.77), ( p=0.0861 )</td>
<td></td>
</tr>
<tr>
<td><strong>Zero RBC Transfusions to W24, n (%)</strong></td>
<td>46 (35.4%)</td>
<td>11 (16.9%)</td>
</tr>
<tr>
<td><strong>p-value (superiority)</strong></td>
<td>( 0.0012 )</td>
<td></td>
</tr>
</tbody>
</table>

The bar chart shows the rate of transfusion independence at baseline and week 24, with MMB and DAN groups compared.
Safety Summary (through Week 24)

<table>
<thead>
<tr>
<th>Subjects with at least one, n (%)</th>
<th>MMB (N=130)</th>
<th>DAN (N=65)</th>
<th>Total (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Emergent Adverse Events (TEAEs)</td>
<td>122 (93.8%)</td>
<td>62 (95.4%)</td>
<td>184 (94.4%)</td>
</tr>
<tr>
<td>Grade ≥3 TEAEs</td>
<td>70 (53.8%)</td>
<td>42 (64.6%)</td>
<td>112 (57.4%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>45 (34.6%)</td>
<td>26 (40.0%)</td>
<td>71 (36.4%)</td>
</tr>
</tbody>
</table>

Favorable trend for overall survival observed at Week 24
- HR 0.506 and p value = 0.072, favoring MMB
MOMENTUM Confirms and Reinforces the Potential Effect Observed in SIMPLIFY-2 in a More Symptomatic and Anemic Population

### MOMENTUM

**Primary Endpoint**
- **Randomization**: 2:1
- **Day 1**
  - RUX-exposed: Double-blind, N=195
  - Hgb < 10 g/dL
  - TSS of ≥ 10
- **Week 24**
  - Open label

**JAKi taper/washout**
- ≥ 21 day

<table>
<thead>
<tr>
<th>Mean BL Scores</th>
<th>Hgb - 8g/dL</th>
<th>TSS - 27</th>
</tr>
</thead>
</table>

**Endpoints**
- **Week 24 Response Rate**
  - **MMB**
    - N: 130
    - SRR ≥35%: 23%
    - TSS ≥50%: 25%
    - TI for ≥ 12weeks at W24: 31%
  - **DAN**
    - N: 65
    - SRR ≥35%: 3%
    - TSS ≥50%: 9%
    - TI for ≥ 12weeks at W24: 20%

### SIMPLIFY-2

**Primary Endpoint**
- **Randomized treatment**
- **Extension**
- **Day 1**
  - RUX-exposed: Open label
  - No min Hgb
  - No min TSS
- **Week 24**
  - Best available therapy

**RUX-exposed**
- Open label
- No JAKi taper/washout

**Mean BL Scores**
- Hgb - 8g/dL
- TSS - 27

**Primary Endpoint**
- **Randomized treatment**
- **Extension**
- **Day 1**
  - RUX-exposed: Open label
  - No min Hgb
  - No min TSS
- **Week 24**
  - Best available therapy
- **2:1 randomization**
- **No JAKi taper/washout**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Week 24 Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>104</td>
</tr>
<tr>
<td>SRR ≥35%</td>
<td>7%</td>
</tr>
<tr>
<td>TSS ≥50%</td>
<td>26%</td>
</tr>
<tr>
<td>TI for ≥ 12weeks at W24</td>
<td>43%</td>
</tr>
<tr>
<td>TI for ≥ 12weeks at W24 in patients with baseline Hgb&lt;10*</td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Week 24 Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>52</td>
</tr>
<tr>
<td>SRR ≥35%</td>
<td>6%</td>
</tr>
<tr>
<td>TSS ≥50%</td>
<td>6%</td>
</tr>
<tr>
<td>TI for ≥ 12weeks at W24</td>
<td>21%</td>
</tr>
<tr>
<td>TI for ≥ 12weeks at W24 in patients with baseline Hgb&lt;10*</td>
<td>13%</td>
</tr>
</tbody>
</table>

* Retrospective analysis not pre-specified

**Harrison, et al, The Lancet Haematology, 2018**
MMB Demonstrated Impact on Hemoglobin in SIMPLIFY-1 and MOMENTUM

**SIMPLIFY-1**

**Hemoglobin Levels**


**MOMENTUM**

**Hemoglobin Levels**

Source: Preliminary data from MOMENTUM.

Momelotinib Demonstrated an Increase in Hemoglobin in both JAKi Naïve and Previously JAKi-Treated Patients
MOMENTUM Data Confirm Momelotinib can be a Potential Option for Certain Myelofibrosis Patients with Anemia

Positive pivotal Phase 3 MOMENTUM topline results for momelotinib in symptomatic anemic MF patients previously treated with a JAK inhibitor

• Met all pre-specified primary and key secondary endpoints with statistical significance in a difficult to treat patient population
  – Symptomatic, anemic, MF patients previously treated with a JAK inhibitor
• Topline data have demonstrated clinically significant benefit in anemia improvement, symptom and spleen control, with stable platelet counts
• Replicated strong impact on anemia as observed in SIMPLIFY-2 in a more difficult to treat patient population

Data support planned clinical trials to evaluate MMB as a potential cornerstone in future combination therapies in MF
Momelotinib Phase 3 Topline findings

Momelotinib met all pre-specified primary and key secondary endpoints with statistical significance in the pivotal MOMENTUM Study

- Symptomatic, anemic, MF patients previously treated with a JAK inhibitor

SIMPLIFY-1 and SIMPLIFY-2 Phase 3 trial data expected to be included in NDA submission to FDA in Q2 2022

- SIMPLIFY-1 met primary endpoint in first-line setting in comparison to ruxolitinib*
- Post-hoc analyses from SIMPLIFY-1
  - Demonstrated improvement in Hgb and transfusion status over course of treatment
  - Transfusion independence (TI) was achieved for anemic patients and all patients, irrespective of baseline platelets or transfusion status
  - TI was associated with improved overall survival

Safety profile has enabled long duration of dosing

- Several patients from early trials have now received >10 years of continuous momelotinib therapy
- Many patients from SIMPLIFY-1 and -2 continue to receive momelotinib

* (215 patients in the MMB arm, 217 patients in the ruxolitinib arm)
Anemia Could Become the Primary Driver of JAKi Choice

- Momelotinib, if approved, could offer unique benefits for anemic myelofibrosis patients
  - In S-1 at baseline, ~75% of anemic with 30% requiring transfusions
  - In Rux-experienced patients, 90% are anemic with more than two thirds require transfusions
- A differentiated JAKi could allow hem/oncs to transition patients early in their treatment journey
- Upside potential with a potential future indication that allows for use in JAKi-naïve patients

~30% Require Transfusions

JAKi Naïve Patients (S-1) – at Baseline

- Hgb ≥12g/dL: 25%
- Mild anemia Hgb 10-<12g/dL: 31%
- Moderate Anemia Hgb 8-<10g/dL: 32%
- Severe anemia Hgb <8 g/dL: 12%

~75% mild/moderate/severe anemia

RUX Experienced Patients (S-2) – at Baseline

- Hgb ≥12g/dL: 11%
- Mild anemia Hgb 10-<12g/dL: 22%
- Moderate Anemia Hgb 8-<10g/dL: 46%
- Severe anemia Hgb <8 g/dL: 21%

~70% Require Transfusions

~90% mild/moderate/severe anemia

Source: SIMPLIFY-1, -2 analysis
Momelotinib + SRA515 Combinations Could Expand the Myelofibrosis Opportunity

Myelofibrosis landscape is evolving with multiple combination studies ongoing

- BET inhibition has shown initial proof-of-concept with disease-modifying potential
- Unlike other BET inhibitors, SRA515 has a novel bivalent binding bode
  - A stronger connection on the cellular level leads to improved potency
- SRA515 has favorable PK, PD and safety profile when dosed as monotherapy and in combination

Clinical validation plans for MMB + BET combination

- SRA515 has synergistic preclinical activity in combination with diverse agents
  - Best-in-class potential
- As a non-myelosuppressive inhibitor of JAK1, JAK2, and ACVR1, MMB is an ideal combination partner for novel agents
- SRA515+MMB has the potential to improve outcomes in patients with MF

Momelotinib + SRA515 may provide the opportunity for longer and more durable responses for myelofibrosis patients
Sierra Oncology Clinical Program

Sierra’s pipeline affords numerous combination opportunities, with SOC and with other investigational agents.

<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib monotherapy</td>
<td>Myelofibrosis</td>
<td>Positive results announced Jan 2022. NDA planned to be filed Q2 2022.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Momelotinib + SRA515*</td>
<td>Myelofibrosis</td>
<td>Planned for H1 2022</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRA515 monotherapy and/or</td>
<td>Heme malignancies**</td>
<td>Finalizing Design</td>
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<td></td>
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</tr>
<tr>
<td>SRA515 + SRA737</td>
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<tr>
<td>SRA515 monotherapy and/or</td>
<td>Solid tumor in combo with</td>
<td>Finalizing Design</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRA515 + SRA737</td>
<td>SOC**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRA737 + IO/gemcitabine</td>
<td>Solid tumors</td>
<td>Finalizing Design</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Formerly AZD5153

**Opportunities currently under consideration include co-operative trials
Recent and Upcoming Milestones

**January 2022**
- **Positive MOMENTUM Topline Data**

**Q2 2022**
- **Field Medical Team Deployed**
  - Continue to educate medical community on the unmet need in anemia
- **Planned NDA Submission***

**Q2 2022**
- **MMB + 515 Combo Study Initiation**

**H1 2022**
- **MMB + 515 Combo Study Initiation**

**June 2022**
- **ASCO and EHA Planned MOMENTUM data presentations**

**H1 2023**
- **Potential NDA Acceptance & PDUFA Date Determined**

**H1 2023**
- **Potential Momelotinib US Approval & Launch**

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* Expected additional regulatory filings for EMA, MHRA and other jurisdictions approximately 6 months after NDA.
Appendix
**Completed Phase 3 Studies SIMPLIFY-1 and 2**

### SIMPLIFY-1

**1st-Line Population**
JAK inhibitor naïve

- **Goal:** Non-Inferiority
- **Endpoints at Week 24:**
  - MMB: 27%
  - RUX: 29%
  - Symptom score reduction ≥50%
  - 28% vs. 42%
  - TI for ≥ 12weeks
  - 67% vs. 49%

- **Primary Endpoint**
  - MMB vs. RUX
  - ≥35% (primary)*

- **Randomization**
  - 1:1

### SIMPLIFY-2

**2nd-Line Population**
Prior ruxolitinib complicated by hematologic toxicity

- **Goal:** Superiority
- **Endpoints at Week 24:**
  - MMB: 7%
  - RUX/BAT: 6%
  - Symptom score reduction ≥50%
  - 26% vs. 6%
  - TI for ≥ 12weeks
  - 43% vs. 21%

- **Primary Endpoint**
  - MMB vs. RUX/BAT
  - ≥35% (primary)*

- **Randomization**
  - 2:1

---

*Met endpoint
*Journal of Clinical Oncology, 2017 35(34):3844
*The Lancet Haematology, 2018 5(2): 7
Transfusion Independence (TI) with Momelotinib is Associated with Improved Overall Survival

**SIMPLIFY-1**

Week 24 TI response = no RBC transfusion for ≥ 12 weeks immediately prior to Week 24, Hgb level ≥ 8 g/dL.


**Achieving or Maintaining TI Predicted Better Survival in Patients Treated with Momelotinib – The Goal of Achieving TI Should Become an Important Driver of Treatment Decisions**

Week 24 TI response = no RBC transfusion for ≥ 12 weeks immediately prior to Week 24, Hgb level ≥ 8 g/dL.

OS Benefit Seen in Both JAKi-naïve and JAKi-exposed Patients

SIMPLIFY-1

JAKi-naïve Patients

- Week 24 Crossover to open-label MMB
- Median OS 53.1 months in RUX→MMB patients
- Median not reached in originally MMB-randomized patients

Durable survival reflects momelotinib benefit on extended treatment or crossover to momelotinib, regardless of starting therapy

SIMPLIFY-2

JAKi-exposed Patients

- Week 24 Crossover to open-label MMB
- Median OS 37.5 months for BAT/RUX→MMB patients
- Median OS 34.3 months for originally MMB-randomized patients

The OS results are amongst the best survival reported in patients who have been previously treated with ruxolitinib
Momelotinib Increased Hemoglobin Levels and Maintained Platelet Counts