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On a Quest to Deliver Targeted Therapies for Rare Cancers

Our team takes an evidence-based approach to understand the limitations of current treatments and explore new ways to change the cancer treatment paradigm.
Sierra Oncology Highlights

Momelotinib
a potential cornerstone MF therapy

JAK inhibitor that may improve anemia

- Approximately 1 year from pivotal Phase 3 data
- Robust data set on >820 myelofibrosis patients, some of whom have been treated for >10 years
- Global commercial opportunity; JAK inhibitors approved for MF generate > $2 Billion annually

- Experienced management team across Development, Regulatory & Commercial
- $104 million in cash/equivalents as of 12/31/2020
- Focused on commercializing in North America
Myelofibrosis (MF): a bone marrow cancer
- Caused by constitutive activation of JAK-STAT signaling; can progress through polycythemia vera
- Inflammation and fibrosis impair red blood cell production

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

Current treatments: Allogeneic stem-cell transplantation, hydroxyurea and JAK inhibitors (JAKi)
- Intermediate and high-risk patients primarily receive JAKi
Myelofibrosis: Global Market Overview

Rare oncology condition with ~40k diagnosed patients worldwide
- Median Age at Diagnosis: 60–67 years
- Median Survival for Intermediate / High-risk Patients: 2–7 years

Hematologist-oncologists (Hem/Oncs) are the primary disease manager
- 60–70% of patients treated by community physicians
- Referrals to academic centers driven by availability of SCT and clinical trials

FDA approved JAK inhibitors for myelofibrosis—ruxolitinib and fedratinib—with ruxolitinib reaching >$2.0 Billion in annual revenues globally

Approved JAK inhibitors address spleen and symptoms, but not anemia
- JAKi treatment leads to myelosuppression
- Dose reductions are common
- Some patients never receive JAKi due to hemoglobin and platelet count
Four Factors Figure into Treatment Decisions

<table>
<thead>
<tr>
<th>Anemia</th>
<th>Splenomegaly</th>
<th>Const. Symptoms¹</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Blood Bag]</td>
<td>![Spleen]</td>
<td>![Person]</td>
<td>![Blood Cells]</td>
</tr>
<tr>
<td>70 – 90% of patients at diagnosis</td>
<td>50 – 70% of patients at diagnosis</td>
<td>40 – 60% of patients at diagnosis</td>
<td>10 – 30% of patients at diagnosis</td>
</tr>
</tbody>
</table>

- May be managed with frequent RBC transfusions, but no curative treatments are available
- Patients experience early satiety leading to weight loss and severe left upper quadrant pain
- Common symptoms include: fatigue, bone pain, pruritus, night sweats, and fever
- May cause significant bleeding, bruising, headaches, and pain in the joints or muscles

While Factors Can Overlap, the Most Burdensome Factor in Terms of Clinical Severity and Quality of Life (QoL) Impact Guides the Treatment Choice

¹ Constitutional or non-specific symptoms. Source: Sierra Qualitative Market Research
The Majority of MF Patients Exhibit Anemia

- **Normal (~10–30% of patients)**
  - Hemoglobin (Hb) ≥13 g/dL

- **Anemic (~50–60% of patients)**
  - Hemoglobin (Hb) 8-12 g/dL

- **Severe Anemia (~20–30% of pts)**
  - Hemoglobin (Hb) <8 g/dL
  - Transfusion Dependence

Most Patients Will Experience Anemia Progression Over Time

Transfusion Dependence and Low Hb Have a Significant Impact on Quality of Life (QoL)

Sources: Sierra Market Research, Simplify 1 and 2 studies, https://doi.org/10.1182/blood.V114.22.2500.2500
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 provide anemia benefits in addition to symptom, spleen benefits

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**Anemia predicts poor survival in myelofibrosis**

- **No anemia (Hb ≥12 g/dL)**
  - Median survival 7.9 years
- Mild anemia (Hb 10-12 g/dL)
  - Median survival 4.9 years
- Moderate anemia (Hb 8-10 g/dL)
  - Median survival 3.4 years
- Severe anemia (Hb <8 g/dL)
  - Median survival 2.1 years

---

**Hepcidin predicts poor survival in myelofibrosis**

- Low hepcidin
- High hepcidin

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*P<0.0001*

Nicolosi M et al, Leukemia 2018
Pardanani et al, American Journal of Hematology 2013
Momelotinib
A JAK1, JAK2 and ACVR1 inhibitor
Mechanism of Action: Momelotinib Inhibits Drivers of All Three Disease Hallmarks

Inflammation and aberrant cytokine signaling producing debilitating constitutional symptoms

Clonal proliferation leading to extra medullary hematopoiesis and burdensome splenomegaly

Aberrant activation of hepcidin transcription via hyperactivated ACVR1 signaling resulting in profound functional iron deficiency anemia
Momelotinib: SIMPLIFY Phase 3 Trials Informed MOMENTUM Trial Design

<table>
<thead>
<tr>
<th>COMPLETED</th>
<th>COMPLETED</th>
<th>Ongoing Data</th>
<th>Ongoing &gt;10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIMPLIFY-1</td>
<td>SIMPLIFY-2</td>
<td>Expected H1 2022</td>
<td></td>
</tr>
</tbody>
</table>

**Phase 3 Clinical Trial**

- **Patient Population**
  - JAKi-naïve patients (n=432)
  - Prior ruxolitinib-treated patients (n=156)
  - Ongoing pivotal study for JAK-exposed patients (n=180)
  - Ongoing with some patients receiving momelotinib for >10 years

- **Comparator**
  - Ruxolitinib
  - Best available therapy (88.5% RUX/RUX+)
  - Danazol

- **Primary Endpoint**
  - Splenic reduction >35% @ Week 24
  - Splenic reduction >35% @ Week 24
  - Difference in TSS response rate @ Week 24

- **Key Notes**
  - Met primary endpoint
  - No washout period
  - Ongoing; 21-day taper & washout period
  - First patients reached 10+ years

More Than 1,000 Myelofibrosis Patients Will Have Received Momelotinib When the Registration-enabling MOMENTUM Study is Complete
SIMPLIFY-1 and SIMPLIFY-2
Clinical Results from Key Endpoints

<table>
<thead>
<tr>
<th></th>
<th>SIMPLIFY-1</th>
<th>SIMPLIFY-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMB</td>
<td>RUX</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Splenic reduction ≥35% @w24</td>
<td>27%</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td>Symptom score reduction ≥50% @w24</td>
<td>28%</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td>Transfusion independence for ≥12weeks @w24</td>
<td>67%</td>
</tr>
</tbody>
</table>

* Mean change in both arms was zero

- Study design elements played a role in outcome
- Data set provided a roadmap for registration-enabling MOMENTUM study
Prior Clinical Results
SIMPLIFY-1: JAK Inhibitor-naïve Patients

Potential for MMB to improve outcomes in JAK-naïve patients:

- **Splenic control with MMB equivalent** to that achieved with RUX (27% vs. 29%)
- **Symptom benefit clinically comparable** when measured longitudinally and as individual scores
- **Higher rates of transfusion independence** for MMB-treated patients
- **Long overall survival**: Medians of 53 months and not reached

### Absolute Change in Mean TSS at Week 24, From Baseline

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>Symptomatic Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMB</td>
</tr>
<tr>
<td>Baseline TSS, mean</td>
<td>19.4</td>
</tr>
<tr>
<td>Change in Mean TSS at W24, vs Baseline</td>
<td>- 6.2</td>
</tr>
</tbody>
</table>

Delta on a 70-point scale | 1.1 | 1.1 |
Prior Clinical Results
SIMPLIFY-2: JAK Inhibitor-exposed Patients

In patients previously treated with a JAK inhibitor:

- MMB maintains **splenic control**
  - MMB provides some measure of **splenic shrinkage** in 35% of MMB treated patients at Week 24
  - The mean percent change in spleen volume at Week 24 was 0.2% in the MMB group
- **Higher rates of symptom response and transfusion independence** achieved for MMB-treated patients
- **Long overall survival observed** in this JAK inhibitor-exposed setting
  - Median of 37.5 and 34.3 months

SIMPLIFY Findings Contribute to the Totality of Evidence Supporting a Momelotinib New Drug Application
The Pivotal Phase 3 ‘MOMENTUM’ Trial is Underway

Global Study, currently enrolling patients
Topline Data Expected H1 2022

Subjects
N=180

- Previously Treated with JAK inhibitor
- Symptomatic (TSS ≥ 10) and Anemic (Hgb < 10 g/dL)

2:1 randomization
JAKi taper/washout ≥ 21 day

Primary Endpoint
- 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

Danazol* 600 mg daily + Placebo

Momelotinib 200 mg daily + Placebo

Early crossover to open label in the event of confirmed symptomatic splenic progression

Momelotinib 200 mg daily

Long Term Follow-up

Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.
SIMPLIFY Trials: Previously Reported Outcomes
Background: Completed Phase 3 Studies SIMPLIFY-1 and 2

**SIMPLIFY-1**

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

<table>
<thead>
<tr>
<th>Double-blind, N=432</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib 200 mg QD</td>
</tr>
<tr>
<td>Ruxolitinib 20 mg BID</td>
</tr>
</tbody>
</table>

1:1 randomization

**Primary Endpoint**

Day 1

Week 24

Year 7

Double-blind treatment

Open label

LTFU

**Goal**
Non-Inferiority

**MMB**
N=215

**RUX**
N=217

**Primary Endpoint**
Splenic Response Rate

**Secondary Endpoints**
- Total Symptom Score
- Transfusion Independence Rate

**SIMPLIFY-2**

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

<table>
<thead>
<tr>
<th>Open label, N=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib 200 mg QD</td>
</tr>
</tbody>
</table>

2:1 randomization

**Primary Endpoint**

Day 1

Week 24

Year 7

Randomized treatment

Extension

LTFU

**Goal**
Superiority

**MMB**
N=104

**BAT**
N=52

**Primary Endpoint**
Splenic Response Rate

**Secondary Endpoints**
- Total Symptom Score
- Transfusion Independence Rate

*Journal of Clinical Oncology, 2017 35(34):3844*
Momelotinib Data: Hemoglobin and Platelet Levels Over Time

SIMPLIFY-1

Momelotinib increased hemoglobin levels and maintained platelet counts

Momelotinib Data: SRR & TSS Compared by Baseline PLT Strata

SIMPLIFY-1

In S1, SRR was maintained with MMB across the continuum of baseline platelet counts. MMB achieves good SRR in patients whose baseline count was less than 150 and less than 300 x 10^9.

In contrast, a marked reduction in SRR was observed with RUX as the baseline platelet count declined.

In S1, the TSS response rate was maintained with MMB across the continuum of baseline platelet counts, including in patients whose platelet count was less than 150 and less than 300 x 10^9 at baseline.

In comparison, in the RUX arm of S1, TSS response rates declined as patient’s baseline platelet counts declined.

Source: Kiladjian, J. et al. ASH 2020. PLT = platelets
**Momelotinib Data: Anemia Response & Transfusion Dependency**

**SIMPLIFY-1**

### W24 TI (Anemia) Response

<table>
<thead>
<tr>
<th>PLTs (×10^9/L)</th>
<th># in stratum</th>
<th>% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-150</td>
<td>n=47</td>
<td>62%</td>
</tr>
<tr>
<td>&gt;150-300</td>
<td>n=89</td>
<td>72%</td>
</tr>
<tr>
<td>&gt;300</td>
<td>n=79</td>
<td>63%</td>
</tr>
</tbody>
</table>

- MMB treatment elicited a TI response rate greater than 60% in each baseline PLT stratum, higher in each stratum in comparison to rates of 42%-54% for RUX

### Transfusion Requirement

- In SI, the transfusion burden for MMB treatment was approximately one half that of RUX patients

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

SIMPLIFY-1

JAKi-naïve Patients

- Median OS 53.1 months in RUX→MMB patients
- Median not reached in originally MMB-randomized patients

Week 24 Crossover to open-label MMB

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


SIMPLIFY-2

JAKi-exposed Patients

- Median OS 37.5 months for BAT/RUX→MMB patients
- Median OS 34.3 months for originally MMB-randomized patients

Week 24 Crossover to open-label MMB

The OS results are amongst the best survival reported in patients who have been previously treated with ruxolitinib

SIMPLIFY-1 Trial: Safety Results

Safety Generally Similar for Momelotinib, Ruxolitinib in the 24-week Double-blind Period

- Grade 3 or 4 hematological AEs were very low for momelotinib
- Anemia and thrombocytopenia were more common in the ruxolitinib arm
- Nausea was more common with momelotinib
- No evidence of long-term toxicity observed during extended momelotinib dosing up to 10 years

SIMPLIFY-1

<table>
<thead>
<tr>
<th>Select TEAEs, by PT</th>
<th>MMB (N=214)</th>
<th>RUX (N=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3/4 TEAEs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with any Gr3/4 TEAE, n (%)</td>
<td>74 (34.6%)</td>
<td>94 (43.5%)</td>
</tr>
<tr>
<td>Gr3/4 Thrombocytopenia</td>
<td>15 (7.0%)</td>
<td>10 (4.6%)</td>
</tr>
<tr>
<td>Gr3/4 Anemia</td>
<td>13 (6.1%)</td>
<td>49 (22.7%)</td>
</tr>
<tr>
<td>Gr3/4 Pneumonia</td>
<td>5 (2.3%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td><strong>Any Grade TEAEs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with Any Grade TEAE, n (%)</td>
<td>198 (92.5%)</td>
<td>206 (95.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 (18.2%)</td>
<td>43 (19.9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>31 (14.5%)</td>
<td>81 (37.5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40 (18.7%)</td>
<td>63 (29.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (15.9%)</td>
<td>8 (3.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (14.5%)</td>
<td>26 (12.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>38 (17.8%)</td>
<td>43 (19.9%)</td>
</tr>
</tbody>
</table>

1 RT = Randomized Treatment
Executive Leadership: Purpose-Built Team for the Next Phase

Stephen G. Dilly, MBBS, PhD
President & Chief Executive Officer
Former CEO and Board Member of Aimmune Therapeutics

Sukhi Jagpal, CPA, CA, CBV, MBA
Chief Financial Officer
Former CFO of QLT Inc

Barbara Klencke, MD
Chief Development Officer
Former SVP of Onyx Pharmaceuticals
Former Group Medical Director, Genentech

Mark Kowalski, MD, PhD
Chief Medical Officer
Former CMO and SVP of Arbutus Biopharma, Former CMO of YM BioSciences Inc

Kevin Norrett, MS, MBA
Chief Business Officer
Former Chief Commercial Officer of Angion Biomedica

Christina Thomson, MS, JD
General Counsel and Corporate Secretary
Former General Counsel of Athira Pharma, APT Pharmaceuticals and Avigen

William Turner
Chief Regulatory & Technical Operations Officer
Former SVP of Technical Operations and Regulatory Science at Aimmune Therapeutics
The Long-term Vision of Sierra

Sierra Oncology has the Vision, the Leadership and the Execution Ability to Deliver Extraordinary Therapeutic Outcomes for Patients with Rare Oncology Diseases

- Successful Completion of MOMENTUM Clinical Trial
- Regulatory and Commercial Execution for Momelotinib
- Expand with Combination Studies and Pipeline Additions
Upcoming Milestones

- **Mid-2021:** MOMENTUM Enrollment Completion
- **Dec 2021:** ASH (Virtual & Atlanta)
- **June 2021:** EHA (Virtual)
- **H1 2022:** Topline Data
- **H2 2022:** File New Drug Application with FDA
- **2023:** Expected US Approval & Commercialization
Thank You