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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.

Transforming Promise into Patient Impact
Sierra Oncology Highlights

Momelotinib
a potential cornerstone MF therapy

JAK1
JAK2
ACVR1

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 Overview**

**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. Symptoms(^1)</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be managed with frequent RBC transfusions, but no curative treatments are available</td>
<td>Patients experience early satiety leading to weight loss and severe left upper quadrant pain</td>
<td>Common symptoms include; fatigue, bone pain, pruritus, night sweats, and fever</td>
<td>May cause significant bleeding, bruising, headaches, and pain in the joints or muscles</td>
</tr>
</tbody>
</table>

70 – 90% of patients at diagnosis

50 – 70% of patients at diagnosis

40 – 60% of patients at diagnosis

10 – 30% of patients at diagnosis

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

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

Most Patients Will Experience Anemia Progression Over Time

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

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

Anemia predicts poor survival in myelofibrosis

Hepcidin predicts poor survival in myelofibrosis

P<0.0001

Nikolić 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

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>Endpoint</th>
<th>SIMPLIFY-1</th>
<th></th>
<th>SIMPLIFY-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMB</td>
<td>RUX</td>
<td>MMB</td>
<td>BAT</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic reduction ≥35% @w24</td>
<td>27%</td>
<td>29%</td>
<td>7%*</td>
<td>6%*</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom score reduction ≥50% @w24</td>
<td>28%</td>
<td>42%</td>
<td>26%</td>
<td>6%</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion independence for ≥12weeks @w24</td>
<td>67%</td>
<td>49%</td>
<td>43%</td>
<td>21%</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></th>
<th>ITT Population</th>
<th>Symptomatic Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline TSS, mean</td>
<td>MMB 19.4</td>
<td>RUX 17.9</td>
</tr>
<tr>
<td></td>
<td>MMB 25.3</td>
<td>RUX 23.3</td>
</tr>
<tr>
<td>Change in Mean TSS at W24, vs Baseline</td>
<td>-6.2</td>
<td>-7.3</td>
</tr>
<tr>
<td></td>
<td>-8.9</td>
<td>-10.0</td>
</tr>
<tr>
<td>Delta on a 70-point scale</td>
<td>1.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>
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
**The Pivotal Phase 3 ‘MOMENTUM’ Trial is Underway**

Global Study, currently enrolling patients
Topline Data Expected H1 2022

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**Subjects**

- **N=180**
- 2:1 randomization
- JAKi taper/washout ≥ 21 day

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

**Double-Blind Treatment**

1. **Momelotinib 200 mg daily**
   + Placebo

2. **Danazol* 600 mg daily**
   + Placebo

**Primary Endpoint**

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

**Open Label/Crossover**

- **Momelotinib 200 mg daily**

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

**SIMPLIFY-1**

*1st-Line Population*

JAK inhibitor naïve

- **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

- **Primary Endpoint**
  - Day 1
  - Week 24
  - Year 7
  - Randomized treatment
  - Extension
  - LTFU
  - Best available therapy

- **Goal:** Superiority
- **MMB**
  - N=104
- **BAT**
  - N=52
- **Primary Endpoint:** Splenic Response Rate
- **Secondary Endpoints**
  - Total Symptom Score
  - Transfusion Independence Rate
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

- 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>50-150</th>
<th>&gt;150-300</th>
<th>&gt;300</th>
</tr>
</thead>
<tbody>
<tr>
<td># in stratum</td>
<td>n=47</td>
<td>n=89</td>
<td>n=79</td>
</tr>
<tr>
<td>% Response</td>
<td>62%</td>
<td>72%</td>
<td>63%</td>
</tr>
</tbody>
</table>

**MMB Overall (87%)**

**RUX Overall (49%)**

- 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

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

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

SIMPLIFY-2

JAKi-exposed Patients

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

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

## 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

#### 24-Week RT Period

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

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