Unmet Medical Needs in Myelofibrosis
October 17, 2018
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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 (06/30/18):
74.3M outstanding
84.9M fully diluted
Cash and cash equivalents:
$125.4M (06/30/18)
Structured debt facility:
$5M used
### Sierra Oncology: Our Updated Pipeline of Targeted Therapeutics

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeting</strong></td>
<td></td>
<td><strong>Additional Registration Study TBD (Myelofibrosis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK1/2 ACVR1</td>
<td></td>
<td>Two Phase 3 trials completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Targeting</strong></td>
<td></td>
<td><strong>Monotherapy (Six Indications; Prioritized for HGSOC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chk1</td>
<td></td>
<td><strong>Target N=145 (N=65 for HGSOC)</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Low Dose Gemcitabine Combination (Four Indications; incl HGSOC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Target N=80 (20x4)</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Targeting</strong></td>
<td></td>
<td><strong>PARPi Combination (Prostate)</strong></td>
<td></td>
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</tr>
<tr>
<td>Chk1</td>
<td></td>
<td>Study expected to be initiated Q4 2018</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>I/O Combination</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Preclinical ongoing</td>
<td></td>
<td></td>
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<tr>
<td><strong>Targeting</strong></td>
<td></td>
<td><strong>Monotherapy (Colorectal)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cdc7</td>
<td></td>
<td>IND expected to be submitted H2 2018</td>
<td></td>
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</tr>
</tbody>
</table>
Momelotinib (MMB) is a potent, selective and orally-bioavailable JAK1, JAK2 & ACVR1 inhibitor with a differentiated therapeutic profile in myelofibrosis.

- Experienced JAKi development team with unique insight into momelotinib.

- Momelotinib – a dual JAK1/2 & ACVR1 inhibitor – addresses unmet medical needs in myelofibrosis.

- Unique and pronounced clinical benefit for anemia & transfusion dependency.

- Robust body of existing clinical data to guide and support registration strategy.

- Broad development opportunities.
• Full asset acquisition.
• Sierra to assume all ongoing clinical studies following transition period.
• $3M upfront.
• $195M in additional milestones; heavily weighted to commercial success.
• Royalties from mid-teens to high-twenties; tiered by commercial success.
• Long patent life remaining: U.S. exclusivity projected to 2035*, EU exclusivity projected to 2033.*
  *assumes anticipated 5 years PTE and SPC extensions.
Momelotinib’s Development History: An Experienced JAKi Team with Unique Insights

1997 - 2011
- Dr. Andrew Wilks founded Cytopia based on his seminal discovery of JAK1 and JAK2 at the Ludwig Institute for Cancer Research.
- Cytopia discovered and advanced momelotinib into Phase 1/2 clinical trials.
- Major collaboration with Novartis for JAK3.

2011 - 2013
- Dr. Nick Glover, CEO.
- Acquired Cytopia in 2011.
- Completed Phase 1/2 studies demonstrating competitive JAKi profile.
- First delineation of momelotinib’s anemia benefit.
- Preliminary elucidation of biological basis for anemia benefit.

2013 - 2018
- Acquired YM in 2013 for $510M.
- Key operational YM team joined Gilead to continue working on momelotinib.
- Completed two momelotinib Phase 3 studies (SIMPLIFY-1 and SIMPLIFY-2).
- Also completed several ancillary studies, including Phase 2 translational biology study.
- Identified ACVR1 as driver of anemia benefit.

2018 -
- Dr. Nick Glover, CEO.
- Key members of the Cytopia, YM and Gilead momelotinib teams join Sierra.
- Acquired momelotinib in August 2018.
- Experienced JAKi drug developers will lead Sierra’s momelotinib development program.
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.
- The only JAKi that has been tested H2H vs. RUX and demonstrated clinically comparable efficacy.

<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>
</tr>
<tr>
<td><strong>Targets</strong></td>
<td>JAK1, JAK2, ACVR1</td>
<td>JAK1, JAK2</td>
<td>JAK2, FLT3</td>
<td>JAK2, FLT3</td>
</tr>
<tr>
<td><strong>Splenic Response</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Symptom Benefit</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<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 Registration Strategy: MMB Potentially Addresses the Key Needs in MF

Active in thrombocytopenic patients:
- Spleen and symptom benefits in low platelet patients.
- Maintains platelet levels in 1L & 2L; platelets rebound after RUX crossover to momelotinib in 1L.

Symptomatic benefit:
Clinically comparable to RUX in 1L; Superior benefit in 2L.

Spleen benefit:
- Equivalent to RUX in 1L.
- Maintains and decreases spleen volume in 2L.

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

Gilead sponsored physician survey (2016):
60 Qualitative Interviews (15 US; 45 EU)
240 Quantitative Surveys (100 US; 140 EU)
*percentages indicate physician responses of key needs.
Wealth of Gilead data supports Sierra’s re-oriented approach:

- More than 1,200 subjects have received momelotinib across its entire development history across all indications and sub-studies.
- Well defined, predictable safety and efficacy profile.
- More than 180 MF patients still remain on active long-term extended therapy.
- Several patients have been benefitting from momelotinib for >7 years (longest >8 years), reinforcing long-term durable efficacy and tolerability.

**MMB Benefit**

- **Anemia**
  - Maintain Ti; reduce rate/number transfusions; convert TD patients to Ti; increase Hgb.

- **Symptoms**
  - Improve relevant constitutional symptoms in patients with pronounced symptom burden.

- **Splenomegaly**
  - Maintain spleen volume in patients with maximal/stable spleen response.
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 likely additional Phase 3 study in 2L setting.

- Registration plan clarity projected for H1 2019.

- Considering potential development opportunities in unmet 1L settings, such as patients not eligible for RUX due to thrombocytopenia, or those presenting with substantive anemia at diagnosis.

- Considering rational combination clinical trial strategies to further leverage momelotinib’s unique positioning in MF via synergistic mechanisms to build upon its activity profile.
Dr. Verstovsek’s clinical and translational research is focused on understanding the biology of and developing new therapies for myeloproliferative neoplasms (MPNs).

Principal investigator for more than 50 clinical trials testing novel therapies for patients with MPNs; published more than 400 peer-reviewed manuscripts.

Recipient of numerous awards including: Celgene 2010 Young Investigator Award, 7th Annual Irwin H. Krakoff Award for Excellence in Clinical and the Distinguished Lecturer Award from the Society of Hematologic Oncology and the Otis W. and Pearl L. Walters Faculty Achievement Award in Clinical Research by MD Anderson Cancer Center.

Member of The American Society for Clinical Investigation in recognition of his contributions as a physician-scientist.
Unmet Medical Needs in Myelofibrosis

Srdan Verstovsek, MD, PhD
Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson
Cancer Center
Houston, Texas
2016 WHO classification of myeloid malignancies

CLASSIC:
- Primary Myelofibrosis (PMF)
  - PMF, prefibrotic/early stage
  - PMF, overt fibrotic stage
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)

NON CLASSIC:
- Mastocytosis
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; WHO, World Health Organization.
Disease Evolution in PMF

Evolution → Manifestation → Transformation (blastic crisis)

Initial stage:
- reticulin
- collagen fibrosis
- osteosclerosis

(years after diagnosis)

Clinical presentation:
- pronounced thrombocytosis
- no blasts
- no / borderline anemia
- no / borderline splenomegaly
- normal / borderline increased LDH

Grade of myelofibrosis:
- MF-0
- MF-1
- MF-2
- MF-3

Relative Survival:

<table>
<thead>
<tr>
<th>Grade</th>
<th>5 yrs.</th>
<th>10 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF-0</td>
<td>91 %</td>
<td>78 %</td>
</tr>
<tr>
<td>MF-1</td>
<td>85 %</td>
<td>71 %</td>
</tr>
<tr>
<td>MF-2</td>
<td>81 %</td>
<td>67 %</td>
</tr>
<tr>
<td>MF-3</td>
<td>60 %</td>
<td>35 %</td>
</tr>
</tbody>
</table>

Prefibrotic/early PMF

Advanced PMF (MMM)
Mechanisms of Disease in MF

Hyperactive JAK-STAT Pathway

JAK1

Aberrant Cytokine Production and Immune Dysregulation

Ineffective Hematopoiesis
- Cytopenia

Extramedullary Hematopoiesis
- Splenomegaly

JAK2

JAK-STAT-Driven Clonal Myeloproliferation

Alteration of Microenvironment
- Bone Marrow Fibrosis

Leukocytosis Thrombocytosis
- Blastic Transformation
Phenotypic Driver Mutations (Activate JAK-STAT Pathway) in MPNs

PV
- JAK2 V617F: 96%
- JAK2 Exon12: 3%
- Others (SH2B3): 1%

ET
- MPL (W515x): 20-25%
- CALR mut: 10-15%
- JAK2 Exon12: 3-5%
- Unknown (Triple Negative): 5-8%

MF
- MPL (W515x): 5-8%
- CALR mut: 20-25%
- Unknown (Triple Negative): 10-15%

Disease Course and Complications

Early PMF

Short term problem: vascular events

Overt PMF Post-ET/PV MF

Progressive constitutional symptoms

Progressive organomegaly/EMH

Progressive cytopenias

Leukemic transformation

MF-related complications

Premature death

Lead time: typically more than a decade

Time: variable (3-7 years common)

Abbreviations: EMH, extramedullary hematopoiesis; ET, essential thrombocythemia; PMF, primary myelofibrosis; PS, performance status; PV, polycythemia vera; QOL, quality of life.
MF is a Progressive Disease

After 1 year of diagnosis, significantly more patients have anemia, thrombocytopenia, circulating blasts, transfusion requirements, constitutional symptoms, splenomegaly, and unfavorable karyotype.

<table>
<thead>
<tr>
<th></th>
<th>At Diagnosis (n = 340)</th>
<th>After 1 Year of Diagnosis (n = 386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin &lt; 10 g/dL</td>
<td>38%</td>
<td>64%</td>
</tr>
<tr>
<td>Platelet count &lt; 100 × 10⁹/L</td>
<td>18%</td>
<td>31%</td>
</tr>
<tr>
<td>Circulating blasts ≥ 1%</td>
<td>45%</td>
<td>66%</td>
</tr>
<tr>
<td>Requires transfusions</td>
<td>24%</td>
<td>45%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>29%</td>
<td>34%</td>
</tr>
<tr>
<td>Splenomegaly &gt; 10 cm</td>
<td>21%</td>
<td>46%</td>
</tr>
<tr>
<td>Unfavorable karyotype</td>
<td>10%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Why do we Prognosticate?

International Prognostic Scoring System (IPSS) in Primary Myelofibrosis

**Prognostic Factors**

- Age > 65 years
- Constitutional symptoms
- Hb < 10 g/Dl
- Leukocytes > 25 x 10⁹ /L
- Blood blasts > 1%

**Risk Groups**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>#Factors</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>0 --- 11 y</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>1</td>
<td>1 --- 8 y</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>2</td>
<td>2 --- 4 y</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3</td>
<td>≥ 3 --- 2 y</td>
</tr>
</tbody>
</table>

**Survival by PMF-PS**

- PMF-PS = 0
- PMF-PS = 1
- PMF-PS = 2
- PMF-PS = 3

[Graph showing survival by PMF-PS with different risk groups and their survival rates over months]
MF Symptom Burden Clusters

Difference in each symptom between clusters all $p<0.001$

Cluster 4 (N=21)

Cluster 1 (N=150)

Cluster 2 (N=105)

Cluster 3 (N=53)

NCCN Guideline for Treatment of MF Based on Risk & Symptoms/Signs

Low Risk: Observation or ruxolitinib (if symptomatic) or clinical trial

Intermediate-1: Observation or ruxolitinib (if symptomatic) or clinical trial or allogeneic HSCT (selected pts)

Intermediate-2: Transplant candidate ➔ Allogeneic HSCT

Or

High Risk: Transplant ineligible/symptomatic ➔ ruxolitinib or clinical trial

AND/or

Transplant ineligible/anemia ➔ anemia rx or clinical trial

Low risk = 0 on IPSS, DIPSS-Plus, or DIPSS
INT-1 risk = IPSS = 1, DIPSS-Plus = 1, DIPSS = 1 or 2
INT-2 risk = IPSS = 2, DIPSS-Plus = 2 or 3, DIPSS = 3 or 4
High risk = IPSS = 3, DIPSS-Plus = 4 to 6, DIPSS = 5 or 6

Anemia
An Important Clinical Feature of MF

- Anemia in myelofibrosis occurs from a reduction in bone marrow function and impaired hematopoiesis.
- Anemia is present at the time of diagnosis and the rate increases over time in patients with myelofibrosis.
  - One-third of patients with MF experience anemia at the time of diagnosis.
- Anemia can increase the symptom burden of myelofibrosis associated symptoms such as fatigue.
- There is a lack of adequate therapeutic options for patients with treatment emergent cytopenias.
The pathogenesis of anemia in myelofibrosis is the result of a multifactorial process, which is only partially understood.

The relative contributions of each of the above etiologies vary from patient to patient, and this variability in pathogenesis may explain the variability in responses to different therapeutic modalities.
MF and Cytopenias (N=364)
Scope of a Problem

Hb - Normal
25%

Hb 10g/dL - Normal
33%

Hb <10g/dL - not Tx Dep
18%

PLT > 150
70%

PLT  = 100-149
10%

PLT  = 50-99
11%

PLT < 50
9%

WBC ≥ Normal
90%

WBC < Normal
10%

N.B.
- Varying times
- Normal Hg
  - Men 13.5 g/dL
  - Women 12 g/dL

Emanuel et. al. JCO 2012

Hb - Normal
25%

Hb 10g/dL - Normal
33%

Hb <10g/dL - not Tx Dep
18%

PLT > 150
70%

PLT  = 100-149
10%

PLT  = 50-99
11%

PLT < 50
9%

WBC ≥ Normal
90%

WBC < Normal
10%
Anemia
Most Important Prognostic in MF

- Severe anemia (Hgb level of <8 g/dL or transfusion dependence) associated with >1.5-fold increase in risk of death, compared to moderate anemia.
- DIPSS-plus prognostic tool places extra emphasis on transfusion requirement (2 points) and non-TD anemia (Hgb < 10g/dL; 1 point).

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
Anemia Management Options

Anemia is multifactorial (hypersplenism, ineffective erythropoiesis, hemolysis, iron deficiency, etc...)

Multiple options for therapy, none approved or very effective:
- Danazol
- ESAs
- Steroids
- IMiD
- Etc.
Ruxolitinib for MF Patients
Key Efficacy Results from COMFORT-I

Spleen volume reduction
Primary Analysis at week 24\(^1\)
(median follow-up ~7 months)*

Ruxolitinib (n=154)  Placebo (n=153)

Individual Patients

<table>
<thead>
<tr>
<th>Change From Baseline (%)</th>
<th>Ruxolitinib (n=154)</th>
<th>Placebo (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>35% Decrease</td>
<td></td>
</tr>
<tr>
<td>-80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-60</td>
<td></td>
<td></td>
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<tr>
<td>-40</td>
<td></td>
<td></td>
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<tr>
<td>-20</td>
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<tr>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>20</td>
<td></td>
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<tr>
<td>40</td>
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<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
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</table>

Total Symptom Score

<table>
<thead>
<tr>
<th>Mean % Change From Baseline ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Placebo</td>
</tr>
<tr>
<td>Improvement</td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>&lt;10%</td>
</tr>
<tr>
<td>10–&lt;35%</td>
</tr>
<tr>
<td>≥35%</td>
</tr>
</tbody>
</table>

\(n=99\)

\(n=20\)  \(P=.0004\)
\(n=46\)  \(P<.0001\)
\(n=60\)  \(P<.0001\)
### Key Safety Issue

**Myelosuppression of Ruxolitinib in COMFORT-I**

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib Randomized (n = 155)</th>
<th>Placebo (n = 151)</th>
<th>Ruxolitinib Crossover (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-years of study drug exposure</td>
<td>460.4</td>
<td>98.9</td>
<td>254.9</td>
</tr>
<tr>
<td><strong>Hematologic abnormality, a %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 3 or 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>98.7</td>
<td>88.1</td>
<td>95.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>83.9</td>
<td>33.1</td>
<td>90.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26.5</td>
<td>4.6</td>
<td>18.9</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>All Grades</td>
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<td></td>
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</tr>
<tr>
<td>Grades 3 or 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>54.2</td>
<td>20.5</td>
<td>54.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22.6</td>
<td>2.6</td>
<td>28.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14.2</td>
<td>3.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*aThe data shown are for events of the worst grade during the study, regardless of whether this grade was a change from the baseline grade.*

COMFORT-I
Discontinuation Over Time

Discontinuation rates:
- At year 1: 21%
- At year 2: 35%
- At year 3: 51%

No. of patients at risk
Ruxolitinib 155 139 122 107 101 87 27 0
Outcomes in MF after Ruxolitinib Discontinuation - Survival is 14 months

Newberry at al, Blood 130(9):1125-1131
Medical Needs in MF

• Spectrum of MF encompasses spleen, symptoms and anemia
• Only one agent approved for MF (ruxolitinib)
• Physicians need more choices to treat MF
• While ruxolitinib and other JAKi in development have shown variable spleen and symptom benefit, treating anemia remains an unmet need
• Optimally, an MF therapeutic would address all three components of disease – anemia, spleen and symptoms
Momelotinib Addresses All Three Components of the Disease

**Anemia**

- Progressive bone marrow fibrosis due to inflammation.
- Degraded marrow function.
- Decreased erythropoiesis, leading to anemia.
- Often necessitates transfusion.

**Splenomegaly**

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

**Constitutional Symptoms**

- Fatigue
- Bone pain
- Early satiety
- Night sweats
- Pruritis
- Cachexia
- Fever

Momelotinib is uniquely positioned to provide a spectrum of robust benefits in MF - anemia, spleen and symptoms.
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.
Momelotinib’s Development

Momelotinib has been studied in a comprehensive clinical development program:

- >20 Phase 1, 2 and 3 clinical studies are ongoing or have been completed in the momelotinib program.
- In aggregate, >1,220 subjects dosed with momelotinib.
- In MF, 7 clinical studies completed/ongoing (~550 MF patients treated with momelotinib).
- Key studies include:

  Phase 3, double blind, 1:1 study comparing the efficacy of momelotinib to RUX in 1L MF. (N=430).

  Phase 3, 2:1 randomized 2L study comparing momelotinib vs. BAT (~90% RUX) in anemic or thrombocytopenic MF patients previously treated with RUX. (N=156).

In totality, these studies reinforce that momelotinib is well tolerated, and has unequivocal clinical activity on spleen, symptoms and anemia-related outcomes in MF.
Momelotinib’s Benefit on Splenomegaly

- Only JAKi shown equivalent to RUX for splenic response in 1L.
- Momelotinib statistically non-inferior to RUX on spleen \((p=0.011)\).
• Patients remaining on momelotinib after crossover continue to show deepened spleen responses (spleen response at any timepoint in open label phase = 46.2%).

• Data show a further increase in spleen response rate when subjects switched from RUX to momelotinib; an additional 16.5% of subjects who did not achieve a 35% spleen response on RUX did so after 24 weeks of additional momelotinib treatment.
Momelotinib’s Benefit on Symptoms

- Data demonstrate a pronounced and continued symptomatic improvement for momelotinib vs. BAT (~90% RUX) in 2L setting
- Momelotinib TSS = 26.2% vs. BAT 5.9% (nominally significant (p<0.001))
- All individual symptom scores markedly improved from baseline vs BAT

- Momelotinib marginally missed Total Symptom Score (TSS) non-inferiority to RUX in 1L: momelotinib = 28.4% vs. RUX 42.2% (Noninferior Proportion Difference 0.00 (-0.08, 0.08))

- Both momelotinib and RUX substantially improved all symptoms relative to baseline in a clinically comparable manner
Momelotinib’s Benefits on Anemia

- 73.5% of momelotinib patients remained transfusion free through W24 (vs. 46.5% RUX)
- Median rate of red blood cell (RBC) transfusions on momelotinib = 0 units/month (p<0.001 vs. RUX; 0.4 units/month)
- Median total number of RBC transfusions/ over 24 weeks on momelotinib was zero (vs. RUX = 2 transfusions)
Momelotinib’s Benefits on Anemia

Statistically significant effect on transfusion independence (TI) vs. RUX in 1L

- 66.5% momelotinib Transfusion Independence (TI) rate @ W24 (vs. 49.3%; p <0.001 vs. RUX)
- 81% of TI patients at baseline remained TI on momelotinib
- More RUX patients were transfusion dependent (TD) @ W24 (40% vs. 30%; p=0.019)
- 30.2% of TD momelotinib patients at baseline became TI @ W24 (vs. 17% RUX)

Statistically significant effect on transfusion independence vs. BAT (~90% RUX) in 2L

- 43.3% momelotinib Transfusion Independence (TI) rate @ W24 (vs. 21.2%; p = 0.001 vs. BAT)
- 62% of TI patients at baseline remained TI on momelotinib
- More BAT patients were transfusion dependent (TD) @ W24 (63.5% vs. 50%)
- 32.8% of TD momelotinib patients at baseline became TI @ W24 (vs. 3.7% BAT)
Evidence for Momelotinib’s Anemia MOA

- Transfusion independence benefit in transfusion dependent patients validated in translational biology TD study (N=41; GS-US-352-1672).
- **34% 12 Week TI response rate; 39% TI for ≥8 Weeks.**
- PD analysis demonstrates consistent effects on hepcidin, hematocrit, Hgb and serum iron consistent with increased momelotinib-driven erythropoiesis.
- Reinforces ACVR1i MOA.

**Hepcidin Levels**

At every study visit, median blood hepcidin decreased 6 hours after dosing with momelotinib.

Overall trend to reduced hepcidin over time.
Momelotinib’s Effect on Platelets

- Mean hemoglobin, platelet and neutrophil levels were consistently higher in the momelotinib group vs. RUX/BAT in SIMPLIFY studies.

RUX induces rapid and sustained drop in platelets; not observed for momelotinib.

Momelotinib demonstrates generally sustained level of platelets over extended dosing.

Momelotinib better than RUX in subset of thrombocytopenic patients (<100k/μL):
  - SRR: MMB=39% vs. RUX=0%
  - TSS: MMB=35% vs. RUX=21%

RUX patients that crossover to momelotinib experience a pronounced and sustained improvement in platelets.
Momelotinib’s Tolerability

Safety and Durability:

• Momelotinib is well tolerated.

• Across SIMPLIFY-1 & SIMPLIFY-2 momelotinib’s safety profile remained consistent with previous studies and no new safety concerns emerged.

• Momelotinib has a comparable overall safety profile to RUX in SIMPLIFY-1, and demonstrates significantly lower rates of thrombocytopenia and anemia.

• Patients experienced fewer AEs on momelotinib vs. RUX in 1L, and experienced lower rates of Grade 3 or 4 AEs.

• Grade 3/4 anemia rate is 4x higher on RUX vs. momelotinib in 1L.

• In 1L, LFS and mOS appear comparable to RUX (mLFS/mOS NR) following crossover.
Almost every MF patient develops anemia; anemia becomes worse over time, often leading to transfusion dependency.

There are no approved therapies to treat this facet of the disease.

Optimal drug therapy in myelofibrosis would address anemia and transfusion dependency, while also improving splenomegaly and constitutional symptoms.

Momelotinib has unequivocal clinical benefit on spleen, symptoms and anemia-related outcomes in MF.
Thank You

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