Preliminary Results From a Phase I Dose Escalation Trial of Ruxolitinib and the PI3Kδ Inhibitor TGR-1202 in Myelofibrosis

Tamara K. Moyo, Andrew Sochacki, Gregory D. Ayers, Michael T. Byrne, Stephen A. Strickland, Sanjay R. Mohan, Jill Harrison, Lynne D. Berry, Channing V. Dudley, Rachel Severs, Hari P. Miskin, Amy Cavers, Peter Sportelli, Laura C. Michaelis, Ruben A. Mesa, and Michael R. Savona
Background

• The JAK1/2 inhibitor ruxolitinib improves symptoms, reduces spleen size, and improves overall survival in Intermediate-2/High risk myelofibrosis.
• Response is variable, but few patients achieve complete remission.
• Loss of response remains a major problem.

Verstovsek S, et al. NEJM 2012
Harrison CN, et al. NEJM 2012
Harrison CN, et al. Leukemia 2016
PI3 Kinase and Myelofibrosis

- PI3Kδ is overexpressed in MF patient samples, independent of ruxolitinib pre-exposure.
- Inhibition of PI3K/AKT signaling reduced proliferation and clonogenic potential of hematopoietic progenitors of MF patients.

TGR-1202 is a potent PI3Kδ Inhibitor

- Highly selective for PI3Kδ isoform

<table>
<thead>
<tr>
<th>Isoform</th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGR-1202</td>
<td>&gt;1000</td>
<td>&gt;50</td>
<td>&gt;48</td>
<td>1</td>
</tr>
<tr>
<td>¹Idelalisib</td>
<td>&gt;300</td>
<td>&gt;200</td>
<td>&gt;40</td>
<td>1</td>
</tr>
<tr>
<td>²IPI-145</td>
<td>&gt;640</td>
<td>&gt;34</td>
<td>&gt;11</td>
<td>1</td>
</tr>
</tbody>
</table>
TGR-1202 is a potent PI3Kδ Inhibitor

• Highly selective for PI3Kδ isoform
• Led to apoptosis in leukemia and lymphoma cell lines
• Was well-tolerated, with a toxicity profile distinct from that of ruxolitinib and other PI3Kδ inhibitors

Definite, Probable, or Possibly Related AEs (N=22)

<table>
<thead>
<tr>
<th>Adverse Event, n</th>
<th>Grade 1 &amp; 2 (&gt;5% of patients)</th>
<th>Grade ≥ 3 (all events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Hypothesis

Addition of TGR-1202 to ruxolitinib could resensitize or augment the response of MF patients with suboptimal response to single-agent ruxolitinib.
Phase I Study Design

- Two escalation stages based on a 3+3 (Up and Down) design:
  - Stage I: Any stable dose of ruxolitinib + escalating dose of TGR-1202
  - Stage II: Escalating doses of ruxolitinib + maximum tolerated dose of TGR-1202
Study Objectives

• **Primary Objectives:**
  – To evaluate safety of TGR-1202 in combination with ruxolitinib
  – To evaluate pharmacokinetics of TGR-1202 administered with ruxolitinib

• **Secondary Objectives:**
  – To evaluate efficacy of the drug combination
    • Marrow response
    • Hematologic parameters
    • Symptom burden
Study population

- Adult patients with PPV-MF, PET-MF, or PMF
- ≥ Grade 1 marrow fibrosis
- Intermediate -1 risk or higher disease by the DIPSS
- Lost, suboptimal or no response to a stable dose of ruxolitinib for at least 8 weeks
- No prior PI3K or mTOR inhibition
- ECOG PS 0-2
- Adequate organ function
- Life expectancy ≥ 6 months
### Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N=12 (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>66.5 (52-81)</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td><strong>MF Subtype</strong></td>
<td></td>
</tr>
<tr>
<td>Primary MF</td>
<td>5</td>
</tr>
<tr>
<td>PET MF</td>
<td>4</td>
</tr>
<tr>
<td>PPV MF</td>
<td>3</td>
</tr>
<tr>
<td><strong>DIPSS Plus</strong></td>
<td></td>
</tr>
<tr>
<td>Int-1</td>
<td>4</td>
</tr>
<tr>
<td>Int-2</td>
<td>6</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
</tr>
<tr>
<td>Median Plt x10^{-9}/L</td>
<td>252 (108-1139)</td>
</tr>
<tr>
<td>Median Hgb g/dL</td>
<td>10.0 (8.5-12.9)</td>
</tr>
<tr>
<td>Median ANC x10^{-9}/L</td>
<td>5.3 (1.8-10.4)</td>
</tr>
<tr>
<td>Leukoerythroblastosis</td>
<td>9</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>7</td>
</tr>
<tr>
<td>JAK2 V617F</td>
<td>5</td>
</tr>
<tr>
<td>CALR</td>
<td>4</td>
</tr>
<tr>
<td>MPL</td>
<td>3</td>
</tr>
</tbody>
</table>
Patient Characteristics

Frequency

- Blood Counts: 8
- Blasts: 3
- Splenomegaly: 6
- Symptoms: 6
- >1 Indication: 9
Baseline Mutation Status

- Next Generation Sequencing of 37 genes commonly mutated in myeloid disease
Baseline Mutation Status

- Next Generation Sequencing of 37 genes commonly mutated in myeloid disease
400mg TGR-1202, 20mg ruxolitinib (n=3)

800mg TGR-1202, 5mg ruxolitinib (n=1)

800mg TGR-1202, 10mg ruxolitinib (n=3)

800mg TGR-1202, 15mg ruxolitinib (n=2)

Asymptomatic Grade 3 elevation in amylase/lipase (n=1)

600mg TGR-1202, 10mg ruxolitinib (n=1)

600mg TGR-1202, 15mg ruxolitinib (n=1)

600mg TGR-1202, 20mg ruxolitinib (n=1)
## Adverse Events (any cause)

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia*</td>
<td>1 (8.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (25%)</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (8.3%)</td>
<td>3</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>5 (41.7%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Amylase/lipase elevation</td>
<td>1 (8.3%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Neck pain</td>
<td></td>
<td>4 (16.7%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td></td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td></td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td></td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Sepsis*</td>
<td></td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

*Unrelated events in one patient
# Adverse Events (any cause)
At least possibly related to TGR-1202

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia*</td>
<td>2 (16.7%)</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (25%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (8.3%)</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>2 (16.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase/lipase elevation</td>
<td>1 (8.3%)</td>
<td></td>
<td></td>
<td>2</td>
<td>16.7%</td>
</tr>
<tr>
<td>Neck pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>8.3%</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unrelated events in one patient
Safety/Pharmacokinetics

**Amylase (units/L)**

- **Time (Days):** 0, 20, 40, 60, 80
- **Levels:** NL, I, II, III

**Lipase (units/L)**

- **Time (Days):** 0, 20, 40, 60, 80
- **Levels:** NL, I, II, III

**TGR-1202 (ng/mL)**

- **Time (Hours):** 0, 0.5, 1, 2, 4, 6, 8
- **Time (Days):** 2, 8, 15, 29

**AE Grade**

- **AE Grade**
  - I
  - II
  - III

VANDERBILT UNIVERSITY MEDICAL CENTER
NCI Integrated Comprehensive Cancer Center
National Clinical Trials Network
VANDERBILT-INGRAM CANCER CENTER
Treatment Outcomes

- Complete response
- Dose-limiting toxicity (DLT)
- Off study
- Continues on study

Best Marrow Response:
- Unevaluable
- Stable disease
- Complete response

Time on Treatment (Weeks):

0 10 20 30 40 50 60 70

Patients:
- Week 6: 11 (DLT)
- Week 8: 13 (DLT)
- Week 16: 22
- Week 29: 44 (DLT)
- Week 56: 68 (DLT)
- Week 72: 72
Best Hemoglobin Response

![Graph showing the best hemoglobin response for TGR-1202 and Ruxolitinib with different doses and platelet reduction percentages. The x-axis represents the platelet reduction percentage, and the y-axis represents the hemoglobin change (g/dL). The graph shows the effectiveness of different dosages on increasing hemoglobin levels in patients with baseline platelet counts above 375 x 10^9/L.]
Symptom Reduction

Percent Change in TSS

TGR-1202  Ruxolitinib

- 400mg QD, 20mg BID
- 600mg QD, 15mg BID
- 800mg QD, 5mg BID
- 800mg QD, 10mg BID
- 800mg QD, 15mg BID
Conclusions

• TGR-1202 + ruxolitinib was well-tolerated.
• Ruxolitinib does not alter absorption or metabolism of TGR-1202.
• Maximum tolerated dose of TGR-1202 was 600 mg by mouth daily.
• 83% of study participants experienced clinical benefit (hematologic improvement, reduced spleen size and/or improvement in symptoms).
• Further exploration of the drug combination in myelofibrosis is warranted.
Ongoing Research

• Stage 2 of the Dose Escalation Study of TGR-1202 + Ruxolitinib in Myelofibrosis

• Does combination therapy reduce pro-inflammatory cytokine production in a predictable and meaningful way?

• Does treatment reduce mutation burden in the bone marrow? Is there clonal evolution?

• Do intracellular signaling patterns correlate with disease response?
Acknowledgements

- **Savona lab**
  Michael Savona
  Andrew Sochacki

- **Vanderbilt CTSR**

- **Division of Hematology/Oncology**

- **Collaborators**
  Dan Ayers
  Lynne Berry
  Laura Michaelis
  Ruben Mesa

- **Funding**
  TG Therapeutics

The patients and their families