Resurrecting response to ruxolitinib: A Phase I study of ruxolitinib and umbralisib (TGR-1202) in ruxolitinib-experienced myelofibrosis


June 15, 2018
23rd Congress of EHA
Background

- The JAK1/2 inhibitor ruxolitinib improves symptoms, reduces spleen size, and improves overall survival in Intermediate-2/High risk myelofibrosis.

- Depth of response is variable.

- Loss of response to ruxolitinib poses a clinical challenge
  - Alternative therapies are currently limited
  - OS after failure of ruxolitinib response is poor.

- New *adjunct* therapies may resurrect or amplify inhibition of JAK-STAT signaling, and/or improve outcomes in myelofibrosis.

Harrison CN, et al. *NEJM* 2012
• PI3Kδ is overexpressed in PMF patient samples irrespective of prior exposure to ruxolitinib.

• Inhibition of PI3K/AKT signaling reduces proliferation and clonogenic potential of hematopoietic progenitors of PMF patients.

Umbralisib (TGR-1202) is highly selective for PI3Kδ

- Chemically distinct from other inhibitors in its class.
- More selective than other PI3K inhibitors for the delta isoform.
- Led to apoptosis in AML and ALL cell lines and patient-derived AML, ALL, and CLL cells.

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Umbralisib</th>
<th>Idelalisib</th>
<th>Duvelisib</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3Kα</td>
<td>&gt;10 000</td>
<td>600</td>
<td>40</td>
</tr>
<tr>
<td>PI3Kβ</td>
<td>&gt;10 000</td>
<td>19</td>
<td>0.89</td>
</tr>
<tr>
<td>PI3Kγ</td>
<td>1400</td>
<td>9.1</td>
<td>0.21</td>
</tr>
<tr>
<td>PI3Kδ</td>
<td>6.2</td>
<td>1.2</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Burris HA, et al. Lancet Oncology 2018
Single-agent umbalisib is well-tolerated

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Umbalisib (n = 90 CLL)</th>
<th>Idelalisib (n =125 NHL)</th>
<th>Duvelisib (n=210 LEUK/LYMPH)</th>
<th>Ruxolitinib (n=155 MF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9%</td>
<td>2%</td>
<td>19%</td>
<td>45%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13%</td>
<td>27%</td>
<td>32%</td>
<td>7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6%</td>
<td>6%</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>3-6%</td>
<td>13%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>13%</td>
<td>11%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2%</td>
<td>4%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

* in combination with rituximab

- Toxicity profile is distinct from other PI3Kδ inhibitors and ruxolitinib
- Most common side effects were diarrhea, fatigue, and nausea/vomiting.
  - Majority of diarrhea was Gr 1 and resolved without intervention
  - Two cases of colitis in patients receiving dose that exceeds the RP2D (800 mg daily)

References:
- Burris HA, et al. *Lancet Oncology* 2018
- Flinn IW, et al. *Blood* 2018
Hypothesis

Addition of umbralisib to ruxolitinib could *augment* or *re-sensitize* response for patients with *suboptimal or lost response* to single-agent ruxolitinib.
Study design and patient populations

**Ruxolitinib-experienced Myelofibrosis (MF)**
- PMF, post-PV MF or post-ET MF
- Grade ≥1 fibrosis
- Lost, suboptimal or no response on a stable dose of ruxolitinib for ≥ 8 weeks

**ESCALATION STAGE 1**
- Ruxolitinib-experienced MF
- Stable ruxolitinib + Escalating umbralisib

**ESCALATION STAGE 2**
- Ruxolitinib-experienced MF
- Escalating ruxolitinib + Umbralisib MTD from ES1

**EXPANSION COHORT 1**
- Ruxolitinib-experienced MF

**EXPANSION COHORT 2**
- Treatment-naïve MF

**EXPANSION COHORT 3**
- Polycythemia vera

**EXPANSION COHORT 4**
- CMML

**EXPANSION COHORT 5**
- Other MDS/MPNs
  - Stable ruxolitinib (cleared ES2) + Umbralisib MTD from ES1
Patient characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>n = 23 (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>67 (49-83)</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Primary MF</td>
<td>7</td>
</tr>
<tr>
<td>PET MF</td>
<td>10</td>
</tr>
<tr>
<td>PPV MF</td>
<td>6</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DIPSS Plus</td>
<td></td>
</tr>
<tr>
<td>Low (Score 0)</td>
<td>0</td>
</tr>
<tr>
<td>Int-1 (Score 1-2)</td>
<td>8</td>
</tr>
<tr>
<td>Int-2 (Score 3-4)</td>
<td>8</td>
</tr>
<tr>
<td>High (Score 5-6)</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>N = 23 (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Plt x10^-9/L</td>
<td>197 (34-1420)</td>
</tr>
<tr>
<td>Median Hgb g/dL</td>
<td>9.5 (8.5-13.9)</td>
</tr>
<tr>
<td>Median ANC x10^-9/L</td>
<td>6.7 (2.1-57.1)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>&lt;5cm below LCM</td>
<td>14</td>
</tr>
<tr>
<td>5-10 cm below LCM</td>
<td>7</td>
</tr>
<tr>
<td>&gt;10 cm below LCM</td>
<td>4</td>
</tr>
<tr>
<td>Driver Mutation Status</td>
<td></td>
</tr>
<tr>
<td>JAK2 V617F</td>
<td>10</td>
</tr>
<tr>
<td>CALR</td>
<td>7*</td>
</tr>
<tr>
<td>MPL</td>
<td>4*</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>3</td>
</tr>
</tbody>
</table>

*co-occurring CALR & MPL mut in 1 patient
Safety
umbralisib / ruxolitinib
daily / BID

400mg / 20mg
(n=3)

800mg / 5mg
(n=1)

800mg / 10mg
(n=3)

800mg / 15mg
(n=2)

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

Asymptomatic Gr 3 elevation in amylase/lipase
(n=1)
umbralisib / ruxolitinib
daily / BID

ESC/AL/TION
1

ESC/AL/TION
2

EXPANSION

400mg / 20mg
(n=3)

800mg / 5mg
(n=1)

800mg / 10mg
(n=3)

800mg / 15mg
(n=2)

600mg / 10mg
(n=1)

600mg / 15mg
(n=1)

600mg / 20mg
(n=2)

600mg / 5mg
(n=3)

600mg / 10mg
(n=2)

600mg / 15mg
(n=1)
Dose limiting toxicity investigation

Amylase (units/L) vs. Time (Days)

Lipase (units/L) vs. Time (Days)

Umbralisib (ng/mL) vs. Time (Hours)

AE Grade

NL

I

II

III

Time (Days)

Time (Hours)

Time (Days)
Adverse events (all cause)

- Seventeen subjects experienced at least one adverse event (AE).
- Thirteen subjects collectively experienced 17 AEs Grade ≥ 3.

<table>
<thead>
<tr>
<th>Most Common (&gt;5%) AEs and all AEs of Special Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Grade 1 n (%)</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Neutrophil decreased</td>
</tr>
<tr>
<td>Platelet count decreased</td>
</tr>
<tr>
<td>AST increased</td>
</tr>
<tr>
<td>ALT increased</td>
</tr>
<tr>
<td>Amylase increased</td>
</tr>
<tr>
<td>Lipase increased</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Colitis</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Other infections</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
</tbody>
</table>
Efficacy
IWG-MRT & ELN responses to umbralisib + ruxolitinib

Best IWG-MRT & ELN Response*
- Not Assessed
- Stable Disease
- Clinical Benefit
- Complete Remission

Status
- Off-study
- Continues on Treatment

Off Study Reason
- DLT: Dose-limiting Toxicity (n=2)
- AE: Adverse Event (n=1)
- PD: Progressive Disease (n=3)
- MC: Physician or Patient Decision (n=6)
- SCT: Transplant (n=1)

Two subjects achieved complete remission

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th></th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow</td>
<td><img src="image1" alt="Baseline" /> <img src="image2" alt="Follow-up" /></td>
<td><img src="image3" alt="Baseline" /> <img src="image4" alt="Follow-up" /></td>
<td></td>
</tr>
<tr>
<td>Marrow</td>
<td><img src="image5" alt="Baseline" /> <img src="image6" alt="Follow-up" /></td>
<td><img src="image7" alt="Baseline" /> <img src="image8" alt="Follow-up" /></td>
<td></td>
</tr>
<tr>
<td>Reticulin</td>
<td><img src="image9" alt="Baseline" /> <img src="image10" alt="Follow-up" /></td>
<td><img src="image11" alt="Baseline" /> <img src="image12" alt="Follow-up" /></td>
<td></td>
</tr>
</tbody>
</table>
## Complete remission case comparison

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Post-ET MF</td>
<td>Post-PV MF</td>
</tr>
<tr>
<td><strong>EHA Fibrosis Score</strong></td>
<td>MF-2</td>
<td>MF-1</td>
</tr>
<tr>
<td><strong>DIPSS Risk</strong></td>
<td>Intermediate-1</td>
<td>Intermediate-1</td>
</tr>
<tr>
<td><strong>Driver Mutation</strong></td>
<td>MPL 515W</td>
<td>JAK2 V617F</td>
</tr>
<tr>
<td><strong>Stable dose of ruxolitinib</strong></td>
<td>20 mg BID</td>
<td>15 mg BID</td>
</tr>
<tr>
<td><strong>Measures of insufficient response</strong></td>
<td>Thrombocytosis, leuko-erythroblastosis, persistent MF-related symptoms</td>
<td>New MF-related symptoms, rising LDH, thrombocytosis</td>
</tr>
<tr>
<td><strong>Umbralisib dose</strong></td>
<td>400 mg QD</td>
<td>600 mg QD</td>
</tr>
<tr>
<td><strong>First notation of CR</strong></td>
<td>Cycle 15</td>
<td>Cycle 5</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Remained on study 2y → MRD HSCT and NED ~1yr</td>
<td>Remains on study, currently cycle 12</td>
</tr>
</tbody>
</table>
Umbralisib augments rux to reduce spleen volume

- Spleen volume determined from CT images using synthetic segmentation network
- Median decrease in spleen volume by 13% (mean 18%)
  - Largest absolute reductions in spleen size with baseline spleen volumes >1000 cm$^3$

$n = 17$ (incl. 2 s/p splenectomy)  
p = 0.025
Umbralisib led to increase in hemoglobin levels

- Five subjects achieved >2 g/dL increase in hemoglobin
  - Median time to >2 g/dL was 141 days (range 36-197 days)
  - Response was sustained beyond 100 days in 3/5 subjects
Umbralisib improved MF-related symptoms

- Majority of subjects had improvement in MF-related symptoms after addition of umbralisib to ruxolitinib
- Seven subjects achieved IWG-MRT and ELN Symptom Response criterion (50% reduction)
- Median response was 35% reduction in MPN-SAF total symptom score
Conclusions

• Umbralisib + ruxolitinib was well-tolerated
  – Dose-limiting toxicities of asymptomatic amylase/lipase elevations of unclear clinical consequence
  – AST/ALT elevations were mild and transient.
  – Only one event of colitis (in pt with known mesenteric ischemia) and no pneumonitis

• Increases in hemoglobin, improvements in spleen size, and reduction in symptoms meeting IWG-MRT criteria for clinical improvement were seen in 13 (57%) ruxolitinib-experienced myelofibrosis patients.

• Importantly, 2 patients (9%) achieved a durable complete remission after progressing on ruxolitinib.

• The addition of umbralisib to ruxolitinib can augment or resurrect a response in myelofibrosis patients who had suboptimal or lost response to ruxolitinib alone.

• Further exploration of this combination in a randomized study is warranted.
Acknowledgements

The Patients and their Families

Dan Ayers
Richard Abramson
Bennett Landman
Michael Savona

Brandon McMahon
Dan Pollyea

UT Health
San Antonio
Ruben Mesa
Jeanne Palmer

University of Colorado
Boulder | Colorado Springs | Denver | Anschutz Medical Campus

TG Therapeutics
Peter Sportelli
Hari Miskin
Amy Cavers
Mike Weiss

Medical College of Wisconsin