Safety and Activity of the Chemotherapy-free Triplet of Ublituximab, TGR-1202, and Ibrutinib in Relapsed B-cell Malignancies

Loretta Nastoupil, MD¹, Nathan Fowler, MD¹, Matthew Lunning, DO², Julie Vose, MD², Tanya Siddiqi, MD³, Christopher Flowers, MD⁴, Jonathon Cohen, MD⁴, Jan Burger, MD, PhD¹, Marshall T. Schreeder, MD⁵, Myra Miguel, RN¹, Susan Blumel, RN, BSN², Brianna Phye, BS³, Emily K. Pauli, PharmD⁵, Kathy Cutter, RN⁵, Peter Sportelli⁶, Hari P. Miskin, MS⁶, Michael S. Weiss⁶, Swaroop Vakkalanka, PhD⁷, Srikant Viswanadha, PhD⁸ and Susan O’Brien, MD⁹

¹MD Anderson Cancer Center, Houston, TX; ²University of Nebraska Medical Center, Omaha, NE; ³City of Hope National Medical Center, Duarte, CA; ⁴Emory University/Winship Cancer Institute, Atlanta, GA; ⁵Clearview Cancer Institute, Huntsville, AL; ⁶TG Therapeutics, Inc., New York, NY; ⁷Rhizen Pharmaceuticals S.A, La Chaux-de-Fonds, Switzerland; ⁸Incozen Therapeutics, Hyderabad, India; ⁹University of California Irvine Cancer Center, Orange, CA.
Ublituximab: Glycoengineered Anti-CD20 mAb

- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20 (Green arrows in figure)
- Potential advantages over current standards of care:
  - Glycoengineered for enhanced ADCC
  - Activity in “low” CD20 expressing cell lines
- Single agent responses observed in rituximab refractory patients¹

¹ O’Connor et al, ASCO 2014

Source: Adapted from Ruuls et al 2008
B-Cell Receptor Signaling in Lymphoma

Fowler N, Davis E. ASCO 2013.
**TGR-1202: Novel PI3K delta Inhibitor**

<table>
<thead>
<tr>
<th>TGR-1202</th>
<th>Idelalisib (GS-1101)</th>
<th>Duvelisib (IPI-145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Delta</td>
<td>Delta</td>
<td>Delta/Gamma</td>
</tr>
<tr>
<td>QD</td>
<td>BID</td>
<td>BID</td>
</tr>
</tbody>
</table>

- PK profile that allows **once-daily oral** dosing
- 93% nodal PR rate in patients with rel/ref CLL\(^1\)

\(^1\)Burris et al, ASCO 2015, Abstract # 7069
TGR-1202 + Ublituximab Doublet

- 55 patients treated to date
  - 60% ≥3 prior therapies
  - 51% refractory to prior therapy
- Combination well tolerated
  - Minimal Gr. 3/4 AE’s
- Clinical activity demonstrated in CLL, indolent NHL, and aggressive NHL

Percent Change from Baseline in Disease Burden

<table>
<thead>
<tr>
<th>Disease</th>
<th>CLL/SLL</th>
<th>RT</th>
<th>Indolent NHL</th>
<th>DLBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>-25%</td>
<td>-50%</td>
<td>-75%</td>
<td>-100%</td>
</tr>
</tbody>
</table>

Lunning et al, ASCO 2015
**Trial Design:**

**TGR-1202 + Ublituximab + Ibrutinib**

- **Ublituximab**
  - 900mg

- **Ibrutinib**
  - CLL: 420mg
  - NHL: 560mg

- **TGR-1202**
  - Cohort 1: 400 mg
  - Cohort 2: 600 mg
  - Cohort 3: 800 mg

**Endpoints:**

- **Primary:** Safety
- **Secondary:** ORR, DOR, PFS

- **3 + 3 dose escalation design (CLL and NHL)**
- **No limit on prior # of therapies**
- **ECOG Performance Status ≤ 2**
- **ANC > 500 / Plts > 30,000**
- **Patients with Richter’s Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible**

**Scans at Wk 8 then q 12 wks Follow until PD**
- Both ibrutinib and TGR-1202 were administered once-daily starting on Day 1

- Ublituximab given on Day 1, 8, 15 of cycles 1 and 2, and day 1 of cycles 4, 6, 9, and 12.
### Demographics:

**TGR-1202 + Ublituximab + Ibrutinib**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for Safety (n)</td>
<td>16</td>
</tr>
<tr>
<td>Evaluable for Efficacy* (n)</td>
<td>13</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>63 (51 – 85)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>12/4</td>
</tr>
<tr>
<td>ECOG, 0/1/2</td>
<td>5/8/3</td>
</tr>
<tr>
<td>Prior Treatment Regimens, median (range)</td>
<td>4 (1 – 5)</td>
</tr>
</tbody>
</table>

- **Histologies**
  - 4 CLL
  - 4 Follicular
  - 3 DLBCL
  - 1 Richter’s Transformation
  - 1 SLL
  - 1 MZL
  - 2 MCL

- **≥ 2 Prior R–Chemo Regimens, n** | 13 (81%) |
- **Refractory to Prior Therapy, n** | 8 (50%) |

- 100% of CLL had 17p and/or 11q del
- 4/5 FL/MZL pts had ≥ 4 prior lines of treatment
  - 1 ibrutinib refractory
  - 1 duvelisib refractory
- 2/3 DLBCL were ABC subtype and had ≥ 4 prior lines of treatment

*1 removed per investigator discretion and 2 too early to evaluate
Safety: TGR-1202 + Ublituximab + Ibrutinib

Cohort Summary

- CLL and NHL cohorts evaluated separately

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Ublituximab</th>
<th>Ibrutinib</th>
<th>TGR-1202</th>
<th>NHL Pts</th>
<th># DLT</th>
<th>CLL Pts</th>
<th># DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>900mg</td>
<td>420/560mg</td>
<td>400 mg</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>1*</td>
</tr>
<tr>
<td>2</td>
<td>900mg</td>
<td>420/560mg</td>
<td>600 mg</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>900mg</td>
<td>420/560mg</td>
<td>800 mg</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*DLT of reactivated varicella zoster – no additional DLT’s to date in CLL cohort

- Median time on study = 4 mos (range 1 – 9 mos)
- DLT in CLL 400 mg cohort
- 800 mg TGR-1202 cohort cleared in NHL
Safety:
TGR-1202 + Ublituximab + Ibrutinib

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>4 (25%)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (19%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (19%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (19%)</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (19%)</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (13%)</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (13%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (13%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (13%)</td>
<td>-</td>
</tr>
</tbody>
</table>
Activity in NHL:
TGR-1202 + Ublituximab + Ibrutinib

**BEST PERCENT CHANGE FROM BASELINE IN DISEASE BURDEN**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Months On Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richter's</td>
<td>(4.5)</td>
</tr>
<tr>
<td>DLBCL</td>
<td>(2.5)</td>
</tr>
<tr>
<td>FL</td>
<td>(3.5)</td>
</tr>
<tr>
<td>CLL</td>
<td>(7)</td>
</tr>
<tr>
<td>MCL</td>
<td>(7)</td>
</tr>
<tr>
<td>FL</td>
<td>(9.5)</td>
</tr>
<tr>
<td>CLL</td>
<td>(4.5)</td>
</tr>
<tr>
<td>MZL</td>
<td>(7)</td>
</tr>
<tr>
<td>CLL</td>
<td>(8)</td>
</tr>
<tr>
<td>SLL</td>
<td>(7)</td>
</tr>
<tr>
<td>MCL</td>
<td>(9.5)</td>
</tr>
</tbody>
</table>

* On Study
(X) Months On Study
Activity in NHL: TGR-1202 + Ublituximab + Ibrutinib

Clinical Response at First (8 week) and Second (20 week) Assessment
(All patients who had second assessment shown)

* Durable PR (9+ months) in an ibrutinib refractory Follicular patient
Conclusions

- The biologic combination of Ublituximab, TGR-1202 + Ibrutinib is safe in patients with relapsed B cell malignancies.
  - 800 mg cohort of TGR-1202 in NHL enrolled
  - 400mg cohort of TGR-1202 in CLL continues to enroll
    - One DLT was observed in a CLL for re-activated varicella patient resumed treatment
  - The majority of patients remain on study

- The combination appears highly active in B-cell malignancies
  - CLL/SLL: ORR 100% in all patients with high risk features (n=4)
  - Responses were rapid in the majority of patients
    - 76% reduction in nodal disease noted at first assessment in responders.

- Triplet combination continues to accrue, with dose expansion planned at 800mg.
  - Clinicaltrials.gov: NCT02006485

- Phase II studies are planned in multiple histologies.
Acknowledgements

- Thank you to the patients and families for their participation.

- Participating Centers
  - MD Anderson Cancer Center
    - Nathan Fowler, MD
    - Jan Burger, MD, PhD
  - UNMC
    - Julie Vose, MD
    - James Armitage, MD
    - Matthew Lunning, DO
  - Clearview Cancer Institute
    - Marshall Schreeder, MD
  - City of Hope
    - Tanya Siddiqi, MD
    - Robert Chen, MD
  - Emory
    - Christopher Flowers, MD
    - Jonathon Cohen, MD
  - UC Irvine
    - Susan O’Brien, MD