A Phase 1/2 Study of Umbralisib Ublituximab and Venetoclax in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

Paul M. Barr, MD¹, Shuo Ma, MD, PhD², Clive S. Zent, MD¹, Andrea M. Baran, MS¹, Andrew Bui¹, Philip J. Meacham, PhD¹, Ashley Morrison, RN³, Kelsey Holkovic, RN³, Jane L. Liesveld, MD¹, Deborah A. Mulford, MD¹, Peter Sportelli, BS⁴, Hari P. Miskin, MSc⁴, Michael S. Weiss⁴, Jonathan W. Friedberg, MD, MSSc¹, and Brian T. Hill, MD, PhD³

¹Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY; Division of Hematology and Oncology, ²Northwestern University Feinberg School of Medicine; Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; ³Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; ⁴TG Therapeutics, Inc., New York, NY
**Background / Rationale: Venetoclax**

- Inhibition of BCR signaling and BCL2 has been shown to be synergistic *in vitro*
- Targeting PI3K may prevent drug resistance to BCL2 inhibition
- Phase 1/2 study evaluating U2-Ven combination in a multicenter setting
  - Umbralisib and ublituximab (U2) combination ideal to minimize TLS risk
  - Achieve undetectable MRD in relapsed refractory CLL patients

Choudhary et al. *Cell Death Dis* 2015 Jan 15;6:e1593

*Figure adapted from Riches et al., 2011*
Background / Rationale: Umbralisib + Ublituximab (U2)

- Umbralisib is a novel PI3Kδ/CK1ε dual inhibitor, with a unique structure and improved tolerability\(^1\)
  - Preclinical: Greater retention of T-reg suppressive capacity compared to idelalisib & duvelisib\(^2\)
  - Clinical: Integrated analysis of long-term safety demonstrates low rates of immune-mediated toxicity\(^3\)

- Ublituximab is a glycoengineered anti-CD20 monoclonal antibody
  - Enhanced ADCC compared to rituximab

- UNITY-CLL study with U2 in treatment-naïve and previously treated CLL recently met its primary endpoint of PFS

<table>
<thead>
<tr>
<th>Isoform</th>
<th>(K_d) (nM)</th>
<th>(K_d) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K(\alpha)</td>
<td>&gt;10000</td>
<td>600</td>
</tr>
<tr>
<td>PI3K(\beta)</td>
<td>&gt;10000</td>
<td>19</td>
</tr>
<tr>
<td>PI3K(\gamma)</td>
<td>1400</td>
<td>9.1</td>
</tr>
<tr>
<td>PI3K(\delta)</td>
<td>6.2</td>
<td>1.2</td>
</tr>
<tr>
<td>CK1(\epsilon)</td>
<td>180</td>
<td>&gt;30,000</td>
</tr>
</tbody>
</table>

\(^1\)Burris et al., Lancet Oncology 2018; \(^2\)Maharaj et al., ASH 2017; \(^3\)Davids et al., EHA 2018
Study Design and Objectives

- **Study Design**
  - Multi-center Phase I/II dose-escalation (3+3 design) study to assess the safety & efficacy of U2 + venetoclax in patients with R/R CLL
    - Fixed dose ublituximab (900 mg), escalating doses of umbralisib (600 mg and 800 mg)
    - Standard dosing of venetoclax (5-week ramp up to 400 mg)

- **Primary objective**
  - To evaluate the safety of venetoclax addition after U2 induction

- **Secondary objectives**
  - Clinical efficacy as defined by CR rate and PFS (iwCLL 2018)
  - Undetectable MRD rate after 12 cycles of therapy
    - Centrally conducted 8-color flow cytometry
Study Design and Treatment

- **Protocol amended June 11th 2019 to add ublituximab infusions (900mg) on Day 1 of Cycles 4, 5, and 6**

  - **Cycle = 28 Days**

  - End of Cycle 3
    - Response Assessment
    - TLS Restaging

  - End of Cycle 7
    - Response Assessment

  - End of Cycle 12
    - MRD (PB & BM)  

  - Induction/Debulking
    - *Cycle 1*
    - UBLITUXIMAB INFUSIONS
      - Day 1/2
      - Day 8
      - Day 15
      - Day 1
      - UMBRALISIB DAILY

  - Consolidation
    - *Cycle 4 - 12*
    - VENETOCLAX
      - Day 1 (Standard 5-Wk Ramp)

  - Extended Therapy
    - (Detectable MRD Only)
Key Eligibility Criteria

- CLL/SLL: progressed after at least one prior therapy and requiring treatment
  - Mid-study amendment required CLL pts to be BTKi intolerant or refractory (PD within 6 mos of prior BTK)
- 21 day washout from prior therapy except prior BTK inhibitor (longer of 3 days or 5 half-lives)
- ANC > 750/μL, platelet count > 40,000/μL
- CrCl > 50 mL/min for Phase I and > 30 mL/min for Phase II
- Prior exposure to BCL2 or PI3K inhibitor was NOT an exclusion
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for Safety, n</td>
<td>43</td>
</tr>
<tr>
<td>Evaluable for Efficacy, n</td>
<td>39</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>64 (43 - 83)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>31 / 12</td>
</tr>
<tr>
<td>ECOG, 0/1/2</td>
<td>5 / 36 / 2</td>
</tr>
<tr>
<td>Prior Therapy Regimens, median (range)</td>
<td>2 (1 – 6)</td>
</tr>
<tr>
<td>Refractory to immediate prior therapy, n (%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Prior anti-CD20, n (%)</td>
<td>32 (74%)</td>
</tr>
<tr>
<td>Prior chemoimmunotherapy, n (%)</td>
<td>30 (70%)</td>
</tr>
<tr>
<td>Prior BTKi (ibrutinib / acalabrutinib), n (%)</td>
<td>25 (58%)</td>
</tr>
<tr>
<td>Refractory to prior BTK</td>
<td>13/25 (52%)</td>
</tr>
<tr>
<td>BTK or PLCγ mutation detected</td>
<td>7/8 (88%)*</td>
</tr>
<tr>
<td>Prior PI3Ki, n (%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Prior venetoclax, n (%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

### Molecular Aberrations

<table>
<thead>
<tr>
<th>High Risk Features</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11q deletion</td>
<td>13/43 (30%)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>11/43 (26%)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>7/40 (18%)</td>
</tr>
<tr>
<td>NOTCH1 mutation</td>
<td>7/26 (27%)</td>
</tr>
<tr>
<td>SF3B1 mutation</td>
<td>4/26 (15%)</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>25/34 (74%)</td>
</tr>
</tbody>
</table>

At least 1 high risk feature: 34/43 (79%)

*2 patients too early to evaluate, 2 not evaluable – came off prior to first response assessment
*8 patients were tested
### All Causality AEs >20% (N=43)

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th></th>
<th>Grade 3/4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>26</td>
<td>60%</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>24</td>
<td>56%</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23</td>
<td>53%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22</td>
<td>51%</td>
<td>9</td>
<td>21%</td>
</tr>
<tr>
<td>Creatinine increase</td>
<td>21</td>
<td>49%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>20</td>
<td>47%</td>
<td>5</td>
<td>12%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>42%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>40%</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>35%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AST increase</td>
<td>13</td>
<td>30%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alkaline phos increase</td>
<td>11</td>
<td>26%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>11</td>
<td>26%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALT increase</td>
<td>9</td>
<td>21%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- **G3/4 AEs of Special Interest:**
  - Lung Infection/Pneumonia: 3 (7%)
  - Colitis: 2 (5%)
  - TLS: 1 (2%) - ublituximab related, prior to ven infusion
  - Rash: 1 (2%)
  - Pneumonitis: 0
  - No grade 3/4 LFT elevations

- Umbralisib dose reduced in 2 (4%) patients
- Umbralisib discontinued in 4 (9%) patients
- Venetoclax discontinued in 2 (4%) patients
3 Cycles of U2 Induction Reduces Venetoclax TLS risk

After 3 cycles of ublituximab and umbralisib debulking:
- 81% relative reduction in TLS risk after 3 cycles of U2
- No patients developed clinical or laboratory TLS during venetoclax ramp up
Efficacy: Response and MRD

Cycle 3
N=39
- 77% ORR
- 23% SD
- 23% PR
- 77% CR
- MRD Intermediate (0.01%-1.0%)
- Undetectable MRD (<0.01%)

Cycle 7
N=31
- 100% ORR
- 100% PB uMRD
- 59% BM uMRD
- 41% SD
- 59% PR
- 41% CR
- 59% MRD Intermediate (0.01%-1.0%)
- 59% Undetectable MRD (<0.01%)

Cycle 12
N=27
- 96% PB uMRD
- 77% BM uMRD
- 77% SD
- 77% PR
- 77% CR
- 77% MRD Intermediate (0.01%-1.0%)
- 77% Undetectable MRD (<0.01%)

U2 Induction + Venetoclax

Cycle 3 & 7 Assessments were by CT only without BM, therefore CR could not be assessed

*1 BM sample was not analyzed, N=26

At Cycle 3, 64% ORR in BTK-refractory patients, 74% for all patients with prior BTKi
Progression-free survival (n=43)

- Median Follow up: 15.6 months (range 1.3 – 30.8 months)
- 1 patient progressed 10 months after achieving uMRD in PB and BM and stopping therapy
Conclusions

- Umbralisib, ublituximab and venetoclax is well tolerated at the Phase 2 doses
  - U2 induction mitigates TLS risk
  - Only 3 out of 43 (7%) patients discontinued the U2-Ven regimen prior to cycle 12

- Encouraging efficacy in relapsed/refractory CLL patients including those refractory to prior BTKi
  - 100% ORR, 41% CR rate at cycle 12
  - Undetectable MRD of 96% (26/27) and 77% (20/26) in peripheral blood and bone marrow, respectively
  - Only 1 patient has progressed and re-treatment strategies are being investigated

- Expansion cohorts for Richter's transformation and mantle cell lymphoma

- ULTRA-V: Phase 2 Study of U2-Ven in treatment naïve and relapsed/refractory CLL is ongoing
Acknowledgments

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

- Participating Centers:
UNIVERSITY of ROCHESTER MEDICAL CENTER

Medicine of the Highest Order