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

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Disclosures

- Consulting and research support from TG Therapeutics
Background / Rationale

- Inhibition of BCR signaling and BCL2 is 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
  - Goal is to 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 an oral, once-daily, novel, inhibitor of PI3Kδ and CK1ε
  - Preclinical: Greater retention of T-reg suppressive capacity compared to idelalisib & duvelisib
  - Clinical: Integrated analysis of long-term safety demonstrates low rates of immune-mediated toxicity

- **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: Binding Affinities**

<table>
<thead>
<tr>
<th>Isoform</th>
<th>K_d (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3Kα</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>PI3Kβ</td>
<td>&gt;10000</td>
</tr>
<tr>
<td>PI3Kγ</td>
<td>1400</td>
</tr>
<tr>
<td>PI3Kδ</td>
<td>6.2</td>
</tr>
<tr>
<td>CK1ε</td>
<td>180</td>
</tr>
</tbody>
</table>

1Burris et al., Lancet Oncology 2018; 2Maharaj et al., Blood Advances, 2020; 3Davids et al. (PF444), EHA 2018
Study Design and Objectives

- **Study Design**
  - Multi-center Phase 1/2 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

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CR: complete response; PFS: progression-free survival; uMRD: undetectable minimal residual disease.
Study Design: Treatment Schedule

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

End of Cycle 3
- Response Assessment
  - TLS Restaging

Consolidation
- Cycle 4 - 12
  - VENETOCLAX

End of Cycle 7
- Response Assessment

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

Extended Therapy
- (Detectable MRD Only)

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

Cycle = 28 Days
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 1 and >30 mL/min for Phase 2
- Prior exposure to BCL2 or PI3K inhibitor was NOT an exclusion
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for Safety, n</td>
<td>47</td>
</tr>
<tr>
<td>Evaluable for Efficacy, n</td>
<td>46(^\d)</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>64 (43 - 85)</td>
</tr>
<tr>
<td>Male/Female, n</td>
<td>33 / 14</td>
</tr>
<tr>
<td>ECOG, 0/1/2, n</td>
<td>6 / 39 / 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>18 (38%)</td>
</tr>
<tr>
<td>Prior anti-CD20, n (%)</td>
<td>40 (85%)</td>
</tr>
<tr>
<td>Prior chemoimmunotherapy, n (%)</td>
<td>34 (72%)</td>
</tr>
<tr>
<td>Prior BTKi (ibrutinib / acalabrutinib), n (%)</td>
<td>27 (57%)</td>
</tr>
<tr>
<td>Refractory to prior BTKi, % (n/N)</td>
<td>48% (13/27)</td>
</tr>
<tr>
<td>BTK or PLCγ mutation detected, % (n/N)</td>
<td>73% (11/15)*</td>
</tr>
<tr>
<td>Prior PI3Ki, n (%)</td>
<td>3 (6%)</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>10/46 (22%)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>10/46 (22%)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>10/33 (30%)</td>
</tr>
<tr>
<td>NOTCH1 mutation</td>
<td>8/27 (30%)</td>
</tr>
<tr>
<td>SF3B1 mutation</td>
<td>5/27 (19%)</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>29/39 (74%)</td>
</tr>
<tr>
<td>At least 1 high risk feature</td>
<td>34/47 (72%)</td>
</tr>
</tbody>
</table>

\(^\d\) 1 patient not evaluable
- discontinued prior to first response assessment and did not receive venetoclax
*15 patients tested for mutations
### Adverse Events (All Causality) >20% (N=47)

<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>30</td>
<td>64%</td>
<td>4</td>
<td>9%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25</td>
<td>53%</td>
<td>13</td>
<td>28%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26</td>
<td>53%</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24</td>
<td>51%</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>Anemia</td>
<td>23</td>
<td>49%</td>
<td>3</td>
<td>6%</td>
</tr>
<tr>
<td>Creatinine increase</td>
<td>22</td>
<td>47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>20</td>
<td>43%</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>38%</td>
<td>4</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST Increase</td>
<td>14</td>
<td>30%</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phos increase</td>
<td>12</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT Increase</td>
<td>10</td>
<td>21%</td>
<td>1</td>
<td>2%</td>
</tr>
</tbody>
</table>

- **G3/4 AEs of Special Interest:**
  - Pneumonia: 3 (6%)
  - Colitis: 2 (4%) – 1 of whom had c-diff
  - TLS: 1 (2%) - umbralisib related, prior to ven 
  - Rash: 1 (2%)
  - Pneumonitis: 0
  - LFT elevations: 1 (2%)

- **Dose of umbralisib was reduced in 3 (6%) patients**

- Two (4%) patients discontinued all therapy due to AEs related to therapy:
  - Diarrhea (Grade 3)
    - Patient off all therapy at Cycle 9 but still achieved uMRD in PB and BM at Cycle 12
  - Rash (Grade 1)

uMRD: undetectable minimal residual disease; BM: bone marrow; PB: peripheral blood.
3 Cycles of U2 Induction Reduces Venetoclax TLS risk

- After 3 cycles of ublituximab and umbralisib debulking:
  - 79% 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

**Best Response**
- 100% ORR
  - 63%
  - N=46

**Cycle 12**
- 91% PB uMRD
  - 6%
  - N=34

- 72% BM uMRD
  - 25%
  - N=32

**Post Cycle 12 Follow Up**

**Cycle 18**
- 76% PB uMRD
  - 12%
  - N=17

**Cycle 24**
- 71% PB uMRD
  - 14%
  - N=7

BM: bone marrow; ORR: Overall response rate; PB: peripheral blood; uMRD: undetectable minimal residual disease.

At Cycle 12
- 90% (9/10*) uMRD in PB
- 78% (7/9) uMRD in BM in BTK-refractory pts

*3 BTK Ref pts too early to evaluate
Efficacy: Progression-free survival (n=46)

Median Follow up: 24.5 months
(range 9.3 – 40.4 months)

1 death due to COVID, occurring 4 mos after Cycle 12 uMRD in BM, and discontinuation of all therapy
Conclusions

- Combination of umbralisib, ublituximab and venetoclax is well tolerated
  - U2 induction mitigates TLS risk
- Encouraging efficacy in relapsed/refractory CLL patients including those refractory to prior BTKi
  - 100% ORR, 37% CR rate
  - Undetectable MRD of 91% and 72% in peripheral blood and bone marrow, respectively, at Cycle 12
  - Over 70% of patients remain undetectable following completion of venetoclax
  - Re-treatment strategies are being investigated for patients that have progressed
- Expansion cohorts for Richter's transformation and mantle cell lymphoma are currently open for enrollment
- ULTRA-V: Phase 2/3 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