Phase I/II Study of Umbralisib (TGR-1202) in Combination with Ublituximab (TG-1101) and Pembrolizumab in Patients with Relapsed/Refractory CLL and Richter’s Transformation

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Background / Rationale: PD-1/PD-L1 axis

- **Pre-clinical data supports a major role for the PD-1 and PD-L1/PD-L2 axis in mediating immune evasion in CLL:**
  - **T-cells:** PD-1 expression is significantly higher in CLL patients with increased memory and terminally differentiated cells
  - **CLL:** Higher levels of PD-L1 / PD-L2 and can inhibit T-cell proliferation and induce T-regs
  - **Microenvironment:** Within lymph node proliferation centers, PD-1+ T-cells are in close contact with PD-L1+ CLL cells
  - **TCL-1 mouse model:** Anti-PD-L1 treatment prevents aberrant T-cell subset distributions, PD-1 expression, and restores T-cell effector functions

- **Disconnect between promising preclinical data and clinical data with anti-PD-1 monotherapy:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL (Mayo), n=16</td>
<td>ORR 0%, PFS 2.4 months, OS 11.2 months</td>
</tr>
<tr>
<td>RT (Mayo), n=9</td>
<td>ORR 44%, PFS 5.4 months, OS 10.7 months</td>
</tr>
<tr>
<td>Real world data (OSU) n=10</td>
<td>90% failure rate in RT, OS 2 months</td>
</tr>
</tbody>
</table>

Grzywnowicz et al., PLOS 2012
Brusa et al., Haem 2012
Palma et al., Haem 2017
Ding et al., Blood 2017
Rogers et al., BJH 2018
Background / Rationale: PI3K inhibition

- **PI3Kδ inhibition is hypothesized to increase innate / adaptive cell-mediated immune responses**

- **PI3Kδ inhibition + PD-1 blockade:**
  - A key interaction exists between PI3K signaling and immune checkpoint surveillance by which **inhibition of PI3Kδ decreases PD-L1 tumor expression**, suggesting potential synergistic activity between agents that block PD-L1/PD-1 and PI3Kδ

- **Striking a balance between dampening immune evasion and increasing immune mediated AEs:**
  - AEs observed with all PI3Kδ inhibitors may be caused by inhibition of T-regs and T-cell mediated immune effects
  - Selection of a PI3Kδ inhibitor to pair with a PD-1 inhibitor should consider its clinical activity, immune mediated toxicity profile, and effect on T-cell subsets
Umbralisib + Ublituximab ("U2")

- **Umbralisib**: Next generation PI3Kδ inhibitor, with a unique structure and improved tolerability¹
  - Improved selectivity to PI3Kδ isoform
  - Not metabolized through CYP3A4: limited medication interactions
  - **Preclinical**: Greater retention of T-reg suppressive capacity compared to idelalisib & duvelisib²
  - **Clinical**: Integrated analysis of long-term safety: demonstrates low rates of immune-mediated toxicity³
  - Oral – once daily administration
  - Phase 3 dose: 800 mg QD

- **Ublituximab**: glycoengineered anti-CD20 monoclonal antibody
  - Enhanced ADCC compared to rituximab

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¹Burris et al., Lancet Oncology 2018; ²Maharaj et al., AACR 2016; ³Davids et al., EHA 2018
Umbralisib was selected due to **preclinical data** showing minimal effect on T-regs and **clinical experience** showing favorable toxicity profile with minimal (but not absent) autoimmune toxicities

**Study design:** Phase I/II dose-escalation (3+3 design), multicenter study to assess the safety & efficacy of U2 + pembro in patients with R/R CLL and RT (NCT02535286)

- **Cohort 1:** Pembro 100 mg
- **Cohort 2:** Pembro 200 mg

**Correlative studies:** Peripheral blood and/or bone marrow samples were collected at screening, month 2, and month 6

**First reported combination of a PD-1 inhibitor + PI3Kδ inhibitor in this population**
Study Design: Treatment Schedule for CLL

- **Induction** (28 day cycle)
  - Cycle 1: Day 1, Day 8, Day 15
  - Cycle 2: Day 1, Day 8, Day 15

- **Consolidation** (21 day cycle)
  - DLT Period
  - Cycle 3
  - Cycle 4
  - Cycle 5
  - Cycle 6

- **Maintenance** (28 day cycle)
  - UMBRALISIB DAILY
  - Starting on C1D1

- Efficacy assessed at the end of Cycles 2, 6 & 12. After Month 12, efficacy is assessed per investigator discretion.
Study Design: Treatment Schedule for RT

- Induction (28 day cycle)
  - Cycle 1
    - DLT Period
      - Day 1, Day 8, Day 15
  - Cycle 2
  - Cycle 3
  - Cycle 4
  - UMBRALISIB DAILY (Starting on C1D1)
  - UBLITUXIMAB
    - (D1, 8, 15 of C1, D1 of C2-4, D1 of C7, C10, & Q3 mos)

- Maintenance (28 day cycle)
  - Cycle 7
  - Cycle 10
  - UMBRALISIB DAILY
    - (Starting on C1D1)

- Efficacy assessed at the end of Cycles 2 & 4 and Q3 cycles thereafter until Month 12. After Month 12, efficacy assessed per investigator discretion.
Study Objectives and Key Eligibility

- **Primary Objective**
  - To determine the safety of U2 + pembro in CLL and RT patients

- **Secondary Objectives**
  - To describe the immunophenotypic profiles of B and T cells

- **Key Eligibility**
  - CLL: progressed on at least one prior therapy
    - Mid-study amendment required CLL pts to be BTK refractory (PD within 6 mos of prior BTK)
  - RT: chemo-immunotherapy refractory or not eligible for high-dose chemo
  - No limit on # of prior therapy treatment regimens
  - ANC > 750/μL, platelet count > 40,000/μL
  - Prior exposure to PD-1 or PI3K inhibitor was NOT an exclusion
## Demographics

### Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Evaluable for Safety &amp; Efficacy, n</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>70 (60 - 81)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>6 / 4</td>
</tr>
<tr>
<td>ECOG, 0/1/2</td>
<td>4 / 6 / 0</td>
</tr>
<tr>
<td>Prior Therapy Regimens, median (range)</td>
<td>2 (1 – 4)</td>
</tr>
<tr>
<td>Prior BTK (ibrutinib or acalabrutinib), n (%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Refractory to prior BTK</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>Refractory to immediate prior therapy, n (%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>At least 1 high risk feature (del17p, del11q, TP53mut, NOTCH1mut or Complex karyotype)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>≥2 high risk features</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>17p del/TP53 mutated, n (%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Complex Karyotype, n (%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>NOTCH1/ATM/SF3B1mut, n (%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>IGHV Unmutated, n (%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Bulky Disease, n (%)</td>
<td>6 (60%)</td>
</tr>
</tbody>
</table>

### Richter’s Transformation

<table>
<thead>
<tr>
<th>Evaluable for Safety, n</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable for Efficacy†, n</td>
<td>4</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>70 (53 - 73)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>4 / 1</td>
</tr>
<tr>
<td>ECOG, 0/1/2</td>
<td>3 / 1 / 1</td>
</tr>
<tr>
<td>Prior Therapy Regimens, median (range)</td>
<td>7 (2 – 9)</td>
</tr>
<tr>
<td>Prior ibrutinib</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Refractory to prior ibrutinib</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Prior idelalisib + rituximab</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Prior venetoclax</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Prior CAR-T / Allo Transplant</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Refractory to immediate prior therapy</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Bulky Disease, n (%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

†1 RT patient is too early to evaluate.
Disposition and Safety

- 1 DLT at 200 mg pembro dose (transient elevated LFT - resolved); MTD not reached
- Grade 3/4 LFT elevations occurred in 3 patients (20%)
- No Grade 3/4 diarrhea and no events of colitis observed
- No Grade 3/4 pembro associated autoimmune events
- Median follow-up: 15.6+ mos

### Enrollment by Cohort

<table>
<thead>
<tr>
<th>Pembro Dose</th>
<th>CLL</th>
<th>RT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>200 mg</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

### Adverse Events for (All Causality) >20% (N=15)

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>67%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8</td>
<td>53%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
<td>47%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>47%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>47%</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>7</td>
<td>47%</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>Blood alk phos increased</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>Cough</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>40%</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>33%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>5</td>
<td>33%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>5</td>
<td>33%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>27%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>4</td>
<td>27%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>27%</td>
</tr>
</tbody>
</table>

### Dose Modifications

<table>
<thead>
<tr>
<th></th>
<th>Delay</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Umbralisib</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>
Correlatives: T-reg population

Circulating FoxP3+ CD4+ T cell levels do not change significantly in CLL study patients

FoxP3+ CD4 T cells vs. time

FoxP3 Column analysis
(CD3+CD4+FoxP3+ Lymphs, PB)

N.S.
Efficacy & Tolerability: Duration of Exposure

- **CLL**
  - Refractory
  - Relapsed
  - Refractory
  - Refractory
  - Relapsed
  - Refractory
  - Refractory
  - Relapsed
  - Refractory
  - Refractory
  - Refractory

- **Richter’s**
  - Refractory
  - Refractory
  - Refractory

**U2 Induction**
- 0 to 4 months

**U2 + Pembro**
- 5 to 9 months

**U2 Maintenance**
- 10 to 20 months

**Follow-up Off Therapy**
- 21 to 39 months

- **PD:** Progression Disease
### Efficacy: ORR

#### BTK Refractory CLL
- **ORR: 80% (4/5)**
- 3/4 BTK Refractory responders achieved response after U2 Induction, prior to pembrolizumab.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>CR N (%)</th>
<th>PR N (%)</th>
<th>ORR N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>10</td>
<td>1 (10%)</td>
<td>8 (80%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>RT</td>
<td>4</td>
<td>2 (50%)</td>
<td>0</td>
<td>2 (50%)</td>
</tr>
</tbody>
</table>

**Percent Change from Baseline**

- **After U2 Induction**
- **After U2 + Pembro Consolidation**
Efficacy: PFS

Progression-Free Survival for CLL (N=10)

12 Month PFS: 89%
Median PFS: NR (95% CI; 5.4 – NR)
Median follow-up: 15.6 mos
73 yo Male
Cytogenetics: 17p/11q del
Prior Treatment History for CLL:
- **2010**: FCR
- **2014**: BR
- **2014**: Ibrutinib
- **2015**: Idelalisib + rituximab
- **2015**: CD19 - CAR-T
- **2017**: Ibrutinib again for 4 mos... progressed with Richter’s
Prior Treatment for RT:
- **Oct 2017**: CD19 CAR-T → ibrutinib
- Not eligible for HD chemotherapy

**Started U2 + Pembro**
Cohort 1 - 100 mg

- **End of Cycle 2**: 76%↓ - PR
- **End of Cycle 5**: Complete Response
  - **PET-negative** by Lugano Criteria (Cheson 2014)
- Tolerated U2 + Pembro well
  - 1 G3/4 AE: neutropenia
  - Umbralisib held for 4 days, G-CSF initiated and recovered. Resumed full dose umbralisib

Subject remains on study in CR 10+ months
RT Patient 2: Case Study

- **62 yo Male**
- **Prior Treatment History for CLL:**
  - **2008:** PCR
  - **2011:** BR
  - **2013:** FCR
  - **2013:** Ofatumumab + Fludara + Cyclophosphamide
  - **2014:** Alemtuzumab
  - **2014:** Allo Transplant
- **Prior Treatment for RT:**
  - **Nov 2014:** R-CHOP + Ibrutinib
    - PD while on Ibrutinib in 2017

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**Started U2 + Pembro**
**Cohort 1 - 100 mg**

- **End of Cycle 2:** 76%↓ - PR
- **End of Cycle 5:** 78%↓ - PR
- **End of Cycle 8:** Complete Response
  - **PET-negative** by Lugano Criteria (Cheson 2014)
- Tolerated U2 + Pembro well
  - 1 G3 event of Hypophosphatemia (possible related)
  - 1 G3 event of Hyperglycemia (not related)
  - No umbralisib dose modifications required

**Subject remains on study in CR**
Subject remains in Complete Response now 16+ mos on trial
Conclusions

- Triplet combination of umbralisib + ublituximab (“U2”) + pembrolizumab was well tolerated
  - Immune mediated toxicities were not increased above what would be expected with either umbralisib or pembrolizumab alone
- Responses were durable in BTK refractory, high-risk pts, including two durable CRs in RT pts
  - Data suggest that CLL pts who achieve less than CR with a checkpoint inhibitor-containing regimen can achieve durable remissions and that time-limited schedules should be explored
- Maintenance of T-regs throughout therapy may explain limited autoimmune sequelae
- Enrollment is ongoing in both the CLL (BTK refractory only) and RT cohorts
  - Protocol amendment underway to replace pembro with novel anti-PD-L1 (TG-1501)
Acknowledgements

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

- Participating Centers:
  - University of Pennsylvania Abramson Cancer Center
  - Memorial Sloan-Kettering Cancer Center
  - Fred Hutch

- Referring Center:
  - Duke Cancer Institute

- Sponsor:
  - TG Therapeutics