**PHASE I/II STUDY OF UMBRALISIB, UBLITUXIMAB, AND PEMBROLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND RICHTER’S TRANSFORMATION: 5-YEAR FOLLOW-UP**

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

- Pre-clinical data support a major role for the PD-1 and PD-1/PD-L1 PD-1axis in mediating immune evasion in CLL. However, there is a discerned between protruding preclinical data and clinical data with preclinical data and clinical data with preclinical data with PD-1+ monoclonal antibody.
- A key intersection exists between PD-1 signaling and immune checkpoint surveillance by which inhibition of PD-1 decreases PD-1 tumor expression, enabling potential activity with PD-1+ blockade.

**Umbralisib + Ublituximab (U2)**

- Umbralisib: an oral, once-daily, novel, inhibitor of PI3Kδ and co-activator kinase 16 (GSK638)
- Phase 2/3 dose: 800 mg OD

**Disposition and Safety**

<table>
<thead>
<tr>
<th>Pembrolizumab Dose</th>
<th>CLL</th>
<th>RT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
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<td>400 mg</td>
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**Adverse Events (For All Causality) >20% (N=20)**

- Grade 1-2: Pembrolizumab related: 8/20 (40%)
- Grade 3-4: Pembrolizumab related: 0/20 (0%)

**Rationale**

Umbralisib was selected due to preclinical data showing minimal effect on T-rep and clinical data showing favorable toxicity profile.

**Study Design**

- PHASE I/II dose-escalation (0.3-3 dose), multicenter study to assess the safety & efficacy of U2 + pembrolizumab in patients with R/R CLL and RT.
- **Primary Objective**
  - To determine the safety of U2 + pembrolizumab in CLL and RT patients (NCT:02233586)
  - **U2**: umbralisib 100 mg

### Correlative studies:

- Peripheral blood and/or bone marrow samples were collected at screening, during cycle 2 and cycle 6

**Study Objectives**

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

**Key Secondary Objectives**

- To describe the immunophenotypic profiles of B and T cells

**Study Treatment**

- **Treatment Schedule**
  - Cycle 1: cycle 15
  - Cycle 2: cycle 1
  - Cycle 3: cycle 2
  - Cycle 4: cycle 3
  - Cycle 5: cycle 4
  - Cycle 6: cycle 5

<table>
<thead>
<tr>
<th>CLL Patients</th>
<th>Induction (28 day cycle)</th>
<th>Consolidation (21 day cycle)</th>
<th>Maintenance (28 day cycle)</th>
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<td>(CLL, 16, L1, 14, D2, 13, D4, 14, D1, 13, CLC, 6, GCL, OD)</td>
<td>Cycle 1: cycle 1 2 3 4 5</td>
<td>Cycle 2: cycle 1 2 3 4 5</td>
<td>Cycle 7: cycle 1 2 3 4 5</td>
</tr>
</tbody>
</table>

- **RT Patients**
  - Cycle 1: cycle 1
  - Cycle 2: cycle 1
  - Cycle 3: cycle 2
  - Cycle 4: cycle 3
  - Cycle 5: cycle 4
  - Cycle 6: cycle 5

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<th>RT Patients</th>
<th>Induction (28 day cycle)</th>
<th>Maintenance (28 day cycle)</th>
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<td>(CLL, 16, L1, 14, D2, 13, D4, 14, D1, 13, CLC, 6, GCL, OD)</td>
<td>Cycle 2: cycle 1 2 3 4 5</td>
<td>Cycle 10: cycle 1 2 3 4 5</td>
</tr>
</tbody>
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**Results**

- **Demographics**
  - Chronic Lymphocytic Leukemia
    - Evaluable for Safety & Efficacy, n = 20
    - Median Age, years (range): 68 (21-82)
    - Male/Female: 12/8
    - BTK refractory: 18/2
    - Cycle 1D1 dose split between D1 and D2
  - Richter’s Transformation
    - Evaluable for Safety, n = 11
    - Median Age, years (range): 73 (70-80)
    - Male/Female: 8/3

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**Oral Presentation**

At American Society of Hematology (ASH) November 2018

**Study Outline**

- Phase 1D1 dose split between D1 and D2
- Cycle 2D1 dose split between D1 and D2
- Cycle 10D1 dose split between D1 and D2
- Dose reductions
- Treatment Schedule
- Cycle 1D1 dose split between D1 and D2
- Cycle 2D1 dose split between D1 and D2
- Cycle 3D1 dose split between D1 and D2
- Cycle 4D1 dose split between D1 and D2
- Cycle 5D1 dose split between D1 and D2

**Efficacy: ORR in CLL**

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

**Efficacy & Tolerability: Duration of Exposure**

- **Key Secondary Objectives**

**Conclusions**

- Triplet combination of umbralisib + pembrolizumab (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 both PD-1/PD-L1 positive and negative patients, including two durable CRs in RT patients.
- Final efficacy analysis suggests triplet combination who achieve less than CR with umbralisib and pembrolizumab alone.
- Maintenance of Traps throughout therapy may explain limited antitumor seqequence

**Acknowledgements**

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

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