Ublituximab (TG-1101), a Novel Glycoengineered Anti-CD20 Monoclonal Antibody, in Combination with Ibrutinib Is Highly Active in Patients with Relapsed or Refractory CLL and MCL: Results of a Phase II Trial

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Abstract # 6678

Background

Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen, and is glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab, particularly against tumor cells that express low CD20 levels.

Glycoengineered anti-CD20 mAbs have recently demonstrated greater efficacy (ORR, PFS) than rituximab in CLL (NEJM, 2014). Two Phase I trials of single agent ublituximab in patients with relapsed/refractory CLL reported response rates of 67% (ASCO 2014) and 45% (EHA 2015), with rapid and sustained lymphocyte depletion. Herein we report data from an ongoing Phase 2 study evaluating the combination of ublituximab with ibrutinib in patients with relapsed/refractory CLL and MCL.

Results

Demographics

<table>
<thead>
<tr>
<th></th>
<th>CLL</th>
<th>MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available for Safety (n)</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Evaluable for Efficacy (n)</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>71 (39–86)</td>
<td>72 (55–80)</td>
</tr>
<tr>
<td>1st ECOG performance status</td>
<td>22/22</td>
<td>7/1</td>
</tr>
</tbody>
</table>

CD20 Antigen Binding Epitope of Ublituximab

- Black
- White
- Purple: Core amino acids of CD20 epitope
- Cyan: Glycoengineered amino acids

Overall Best Percent Change from Baseline in Nodal Size

- Addition of ublituximab appears to control ibrutinib-related lymphocytosis in patients with CLL, with a median 75% decrease in ALC from baseline by the end of Cycle 3
- More than 50% of CLL patients had lymphocyte counts in normal range (<4000/µL) within 6 cycles of therapy

Study Design

Dose Escalation Schema:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>UTE Dose (Days 1, 15)</th>
<th>Ibrutinib (Daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500 mg</td>
<td>420 mg</td>
</tr>
<tr>
<td>2</td>
<td>500 mg</td>
<td>420 mg</td>
</tr>
</tbody>
</table>

A safety run-in (Part 1) of the design is studied to enroll 6 patients per cohort. Efficacy is assessed at 3 and 6 months. After month 6, all patients can stay on ibrutinib single agent, off protocol:

- All rash and Grade 3/4 diarrea events were deemed related to ibrutinib per investigator assessment. All IRR events related to ublituximab.
- Dose Reductions & Treatment Discontinuations:
  - Ibrutinib was dose reduced in 4 patients (diarrea, rash, cough, fatigue)
  - No patient had their ublituximab dose reduced
  - 2 patients discontinued due to ibrutinib related AEs (rash, diarrea)
  - 2 patients discontinued due to non-related AEs (pre-existing AEs)

Future Steps

The GENUINE Trial: A Phase 3 Study of Ibrutinib vs. Ublituximab + Ibrutinib

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling 330 patients with High-Risk CLL (17p del, 11q del, and/or p53 mutation)
- Study Chair: Jeff Sharman, MD
- Clinical trial.gov #: NCT02301556

Conclusions

- Data from this ongoing study suggests ublituximab, a glycoengineered anti-CD20 mAb, in combination with ibrutinib is both a well tolerated and highly active regimen for patients with relapsed or refractory CLL and MCL
- Contrary to non-clinical data describing antagonism between BTK inhibition and ADDC, the addition of ublituximab appears to improve ORR in patients with CLL and MCL over that published historically with single agent ibrutinib in these patient populations
- A 95% ORR in patients with high-risk CLL (17p del, 11q del, and/or p53 mutation) suggests the combination may be an effective treatment regimen in this patient population; supporting a planned randomized Phase 3 clinical trial (the GENUINE trial)

Additional studies are ongoing evaluating ublituximab in combination with other novel, targeted agents, with Phase III studies in development

Presented at the 56th American Society of Hematology (ASH) Annual Meeting and Exposition, December 6 – 9, 2014, San Francisco, CA