Background

Antibody therapies such as the CD20 monoclonal antibodies rituximab and obinutuzumab are commonly used in CLL alone and in combination with chemotherapy, however, CD20 density is low on CLL cells, suggesting this may not be the ideal target. CD19 is an attractive target in lymphoid malignancies as it is highly expressed in nearly all CLL and non-Hodgkin’s lymphomas. MOR208 is an Fc-engineered CD19 monoclonal antibody which has been shown in a Phase I trial in patients with relapsed and refractory CLL to be generally well tolerated and have preliminary efficacy, with an overall response rate (ORR) of 30% by IWCLL 2008 guidelines (Woyach et al, Blood 2014). Compared to non-engineered CD19 monoclonal antibodies, MOR208 has significantly enhanced antibody dependent cellular cytotoxicity (ADCC), which can be further augmented in vitro with the addition of lenalidomide. Given the in vitro synergy of these agents, acceptable individual safety profiles, and efficacy of each as a single agent, we chose to combine MOR208 and lenalidomide in patients with CLL and Richter’s Transformation. We also included a cohort of patients with progressive acquisition of the brutinib-resistant C481S BTK mutation where MOR208 was added to ibritinib.

Study Design

**COHORT 1:**
- No previous treatment
- Rituximab or one ineligible for standard therapy

**COHORT 2:**
- Relapsed or refractory disease

**COHORT 3:**
- Richter’s Transformation

**COHORT 4:**
- Ibrutinib resistance
- Activity in all patient cohorts

**Study Demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previously Untreated Number (%)</th>
<th>Relapsed Refractory Number (%)</th>
<th>Richter’s Number (%)</th>
<th>Brutinib Progressing Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>11 (44.7)</td>
<td>11 (44.7)</td>
<td>5 (71)</td>
<td>7 (28.6)</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>62 (44-75)</td>
<td>70 (62-75)</td>
<td>60 (55-77)</td>
<td>62 (45-77)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (64)</td>
<td>10 (91)</td>
<td>3 (60)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (36)</td>
<td>1 (9)</td>
<td>2 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Rai Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (9)</td>
<td>0</td>
<td>NA</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4 (36)</td>
<td>4 (36)</td>
<td>NA</td>
<td>3 (43)</td>
</tr>
<tr>
<td>High</td>
<td>6 (55)</td>
<td>7 (64)</td>
<td>NA</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Complex Stimulated Karyotype</td>
<td>3 (27)</td>
<td>9 (82)</td>
<td>4 (85)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Interphase Cytogenetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(1p)</td>
<td>4 (36)</td>
<td>7 (64)</td>
<td>3 (60)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>9 (45)</td>
<td>5 (9)</td>
<td>1 (20)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>del(11q22,3)</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>2 (40)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>1 (14)</td>
<td>2 (18)</td>
<td>4 (85)</td>
<td>5 (71)</td>
</tr>
</tbody>
</table>

Toxicities Without Regard to Attribution

**COHORT 1:**
- Nausea
- Diarrhea
- Anorexia
- Hypokalemia
- Hypocalcemia
- Tinnitus
- Pustular Rash

**COHORT 2:**
- Hypothyroidism
- Hypothyroidism
- Hypertension
- Neutropenia

**COHORT 3:**
- Neuropathy
- Hypothyroidism
- Hypothyroidism
- Hypothyroidism

**COHORT 4:**
- Neuropathy
- Hypothyroidism
- Hypothyroidism
- Hypothyroidism

BTK C481S in Cohort 4

**Conclusions**

- The combinations of MOR208 and lenalidomide and MOR208 and ibritinib have been well tolerated in all patient cohorts
- Preliminary efficacy has been seen in all cohorts, but particularly interesting is activity in ibritinib-resistant CLL