Updated Results of a Multicenter Phase I/IB Study of Umbralisib (TGR-1202) in Combination with Ibrutinib in Patients with Relapsed or Refractory MCL or CLL

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for the Leukemia & Lymphoma Society Blood Cancer Research Partnership (LLS/BCRP)

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Background

Inhibiting multiple BCR pathway kinases may deepen and prolong response and overcome resistance mutations

Niemann et al., Seminars in Cancer Biology, 2013
**Background**

Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor with a differentiated safety profile from other PI3Kδ inhibitors.

<table>
<thead>
<tr>
<th>TGR-1202</th>
<th>Idelalisib (GS-1101)</th>
<th>Duvelisib (IPI-145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Chemical Structure]</td>
<td>[Chemical Structure]</td>
<td>[Chemical Structure]</td>
</tr>
<tr>
<td>Delta</td>
<td>Delta</td>
<td>Delta/Gamma</td>
</tr>
<tr>
<td>QD</td>
<td>BID</td>
<td>BID</td>
</tr>
</tbody>
</table>

**Fold-selectivity**

<table>
<thead>
<tr>
<th>Isoform</th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGR-1202</td>
<td>&gt;1000</td>
<td>&gt;50</td>
<td>&gt;48</td>
<td>1</td>
</tr>
<tr>
<td>(^1)Idelalisib</td>
<td>&gt;300</td>
<td>&gt;200</td>
<td>&gt;40</td>
<td>1</td>
</tr>
<tr>
<td>(^2)IPI-145</td>
<td>&gt;640</td>
<td>&gt;34</td>
<td>&gt;11</td>
<td>1</td>
</tr>
</tbody>
</table>

**Safety**

In 165 patients treated with umbralisib (TGR-1202) alone or with anti-CD20:

- 80 patients on study over 6 cycles, and 43 patients have been on study over 12 cycles
- Grade 3/4 AST/ALT increase was 3% (8% all grades)
- Diarrhea in 47%, mainly grade 1, with 5 patients (3%) with Grade 3/4
- 8% of patients off study due to an AE

**Efficacy**

![Graph showing best percent change from baseline in disease burden](image)

O'Conner et al, ASH 2015

\(^1\)Flinn et al. 2009, \(^2\)Porter et al. 2012

Burriss et al, ASCO 2016
A phase I/Ib investigator-initiated multicenter trial of umbralisib (TGR-1202) + ibrutinib in R/R CLL and MCL

Endpoints

Primary:
- MTD, safety, and DLTs of TGR-1202 + ibrutinib

Secondary:
- Clinical response: ORR, CR, PR, PR-L, PFS, and remission duration
- Association of CLL prognostic factors with response

Exploratory:
- Association of novel prognostic factors such as BH3 profiling and somatic mutations with response

Key Eligibility Criteria

Inclusion:
- ≥1 prior standard therapy
- ANC ≥ 0.5 K/uL, platelets ≥ 30 K/uL
- Intact renal/hepatic function
- Ph I: pts with prior BTK/PI3Ki therapy were eligible

Exclusion:
- AutoSCT < 3 mo. or alloHCT < 12 mo. of study entry
- Active GVHD, immune suppression
- Active hepatitis, HIV, CNS involvement
- Require warfarin

Treatment Plan

- Parallel MCL/CLL arms, escalated independently
- TGR-1202: oral, daily (qam) and ibrutinib: oral, 420 mg daily for CLL, 560 mg daily for MCL (qpm)
- Both agents continued until time of progression or unacceptable toxicity
- Toxicity assessments by CTCAE v4.03, efficacy by 2008 IW-CLL or 2014 Lugano criteria (MCL)
- Phase Ib exp cohorts of 12 pts each in MCL/CLL

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>TGR-1202 Dose</th>
<th>Ibrutinib Dose CLL</th>
<th>Ibrutinib Dose MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400 mg</td>
<td>420 mg</td>
<td>560 mg</td>
</tr>
<tr>
<td>2</td>
<td>600 mg</td>
<td>420 mg</td>
<td>560 mg</td>
</tr>
<tr>
<td>3</td>
<td>800 mg</td>
<td>420 mg</td>
<td>560 mg</td>
</tr>
</tbody>
</table>

If > 2 DLTs in Cohort 1, 3-6 pts will enroll in Cohort -1 as follows:

| -1         | 200 mg | 420 mg | 560 mg |

If > 2 DLTs in Cohort -1, study will be terminated
## Results

### Patient Characteristics (n=32)

<table>
<thead>
<tr>
<th></th>
<th>All (n=32)</th>
<th>MCL (n=14)</th>
<th>CLL (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range)</strong></td>
<td>67 (48-83)</td>
<td>67 (50-83)</td>
<td>67 (48-76)</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td>20 (64.5%)</td>
<td>10 (77%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td><strong>Prior therapy, median (range)</strong></td>
<td>2 (1-6)</td>
<td>3 (2-5)</td>
<td>1.5 (1-6)</td>
</tr>
<tr>
<td><strong>Prior autoSCT</strong></td>
<td>4/32 (13%)</td>
<td>4/14 (29%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Prior ibrutinib</strong></td>
<td>4/32 (13%)</td>
<td>2/14 (14%)</td>
<td>2/18 (11%)</td>
</tr>
<tr>
<td><strong>Prior PI3K inhibitor</strong></td>
<td>4/32 (13%)</td>
<td>0%</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td><strong>WBC (K/uL), median (range)</strong></td>
<td>11.2 (3.9-338)</td>
<td>8.1 (4-338)</td>
<td>16.7 (3.9-116.8)</td>
</tr>
<tr>
<td><strong>Hgb (g/dL), median (range)</strong></td>
<td>11.7 (7.7-15.9)</td>
<td>12.4 (7.8-15.9)</td>
<td>11.2 (7.7-15.1)</td>
</tr>
<tr>
<td><strong>Platelets (K/uL), median (range)</strong></td>
<td>179 (45-316)</td>
<td>146 (75-290)</td>
<td>194 (45-316)</td>
</tr>
<tr>
<td><strong>Beta-2M (mg/L), median (range)</strong></td>
<td>4.1 (2.2-19.7)</td>
<td>4.2 (2.6-19.7)</td>
<td>4.1 (2.2-9.2)</td>
</tr>
<tr>
<td>Del(17p)</td>
<td></td>
<td></td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>Del(11q)</td>
<td></td>
<td></td>
<td>7/18 (39%)</td>
</tr>
<tr>
<td>Unmutated IGHV</td>
<td></td>
<td></td>
<td>12/18 (67%)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td></td>
<td></td>
<td>3/18 (17%)</td>
</tr>
<tr>
<td>NOTCH1 mutation</td>
<td></td>
<td></td>
<td>2 pts (limited testing)</td>
</tr>
</tbody>
</table>

*Note: Three pts signed consent but never received study treatment due to not meeting eligibility criteria on C1D1, and are not included above or in subsequent analyses.*
## Summary of Phase I portion (n=18 patients)
- 3 CLL and 3 MCL patients each treated at TGR-1202 400 mg, 600 mg, 800 mg qd
- There were no DLTs, and an MTD was not identified
- TGR-1202 maximum administered dose/RP2D: 800 mg qd for both CLL and MCL

## Results

### Safety Analysis

#### Hematologic Toxicity (n=32)

**CLL (n=18)**
- Neutropenia (38%, 17% Gr 3-4)
- Thrombocytopenia (11%, all Gr 1)
- Anemia (15%, all Gr 1/2)

**MCL (n=14)**
- Neutropenia (36%; 7.1% Gr 3/4)
- Thrombocytopenia (36%; 7.1% Gr 3)
- Anemia (29%, 7.1% Gr 3)

#### Toxicities of Special Interest
- **Diarrhea:** 11/32 (34%) pts (28% Gr 1, 6% Gr 2, with no inflammatory colitis)
- **Transaminitis:** 7/32 (22%) pts, all Gr 1 and self-limited, no treatment interruption
- **Pneumonitis:** 1/32 (3%) pts, Gr 1
- **Bleeding events:** Gr 1 epistaxis, hematuria, vitreous hemorrhage in 1 CLL pt each
- **Atrial fibrillation:** 2/32 (6%) pts (both Gr 3)
- **Infection:** 8/32 (25%) pts (4 Gr 1/2, 2 Gr 3 aspergillus, 1 C. diff, 1 Gr 4 influenza)
### Results

#### Additional Safety Analysis

<table>
<thead>
<tr>
<th>CLL (n=18)</th>
<th>MCL (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All grade non-heme toxicities in ≥20%*:</strong></td>
<td><strong>All grade non-heme toxicities in ≥20%*:</strong></td>
</tr>
<tr>
<td>• Nausea: 39%, (33% Gr 1, 6% Gr 2)</td>
<td>• Fatigue: 43% (29% Gr 1, 14% Gr 2)</td>
</tr>
<tr>
<td>• Diarrhea: 28% (17% Gr 1, 11% Gr 2)</td>
<td>• Diarrhea: 36% (all Gr 1)</td>
</tr>
<tr>
<td>• Dizziness: 22% (all Gr 1)</td>
<td>• Nausea: 36% (29% Gr 1, 7% Gr 2)</td>
</tr>
<tr>
<td>• Fatigue: 22% (all Gr 1)</td>
<td>• Dizziness: 29% (all Gr 1)</td>
</tr>
<tr>
<td><strong>SAEs (in 1 patient each):</strong></td>
<td><strong>SAEs:</strong></td>
</tr>
<tr>
<td>• Lipase elevation (Gr 3)</td>
<td>• Hypophosphatemia (n=2, both Gr 3)</td>
</tr>
<tr>
<td>• Atrial fibrillation (Gr 3)</td>
<td>• Lipase elevation (n=1, Gr 4)</td>
</tr>
<tr>
<td>• Adrenal insufficiency (Gr 3)</td>
<td>• Atrial fibrillation (n=1, Gr 3)</td>
</tr>
<tr>
<td>• CNS aspergillus infection (Gr 3)</td>
<td>• C. difficile infection (n=1, Gr 3)</td>
</tr>
<tr>
<td>• Sudden death, uncertain cause (Gr 5)</td>
<td>• Influenza A infection (n=1, Gr 4)</td>
</tr>
<tr>
<td><strong>Dose reduction:</strong></td>
<td><strong>Dose reduction:</strong></td>
</tr>
<tr>
<td>• Ibrutinib: 3 patients (atrial fib, palpitations, vitreous hemorrhage)</td>
<td>• TGR-1202: 1 patient (dizziness)</td>
</tr>
<tr>
<td>• TGR-1202: 1 patient (diarrhea)</td>
<td></td>
</tr>
</tbody>
</table>

* Excludes asymptomatic, low-grade laboratory abnormalities
Results

Updated Efficacy Analysis (n=31)

**CLL (n=17)**
- ORR: 16/17 (94%)
- PR or PR-L: 15/17 (88%)
- CR: 1/17 (6%), 3 other pts with radiographic CR
- All 3 pts with prior PI3Ki and 1 of the 2 pts with prior ibrutinib responded

**MCL (n=14)**
- ORR: 11/14 (79%)
- PR: 10/11 (71%)
- CR: 1/11 (9%), 1 other pt with radiographic CR
- Marked clinical benefit observed in 2 additional pts

*meets formal disease-specific criteria for CR*
Results

Updated Efficacy Analysis (n=31)

• Median follow-up time among survivors: 14 mo. (range 0.8-29.5)
• 1-year PFS for CLL is 88%, 1-year OS is 94%
• Median PFS and OS for MCL is 8.4 and 11.6 mo.
• 1 CLL pt has died due to progressive disease
• 6 MCL pts have died (5 due to PD, 1 due to tox from next therapy)
Conclusions

• We report updated clinical data on the first study of PI3K plus BTK inhibitor doublet therapy in B cell malignancies

• Umbralisib (TGR-1202) + ibrutinib is well-tolerated in R/R CLL and MCL, with no DLTs observed and an RP2D of umbralisib of 800 mg daily

• Toxicities of umbralisib (TGR-1202) + ibrutinib are manageable and comparable to the additive toxicity profiles of the 2 drugs individually

• Preliminary efficacy results show a high response rate in both diseases
  • CLL patient achieved CR at 1 yr, several others with radiographic CR
  • MCL patient achieved CR at 6 mo, another with radiographic CR

• Correlative studies in progress

• Patients continue to accrue to the MCL arm (NCT02268851)
Acknowledgments

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