TGR-1202 in Combination with Ibrutinib in Patients with Relapsed or Refractory CLL or MCL: Preliminary Results of a Multicenter Phase I/Ib Study

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The durability of response with ibrutinib monotherapy is limited in high risk R/R CLL and in R/R MCL.

**Del (17p) CLL**  
(median PFS 28 mo.)

**MCL**  
(median PFS 13.9 mo.)

Byrd et al., *Blood*, 2015

Background

Resistance mutations have already been observed in patients on ibrutinib monotherapy.
Inhibiting multiple BCR pathway kinases may deepen and prolong response and overcome resistance mutations.

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

Barr et al., *Blood*, 2016
**Background**

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><img src="image" alt="TGR-1202 structure" /></td>
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<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>1Idelalisib</td>
<td>&gt;300</td>
<td>&gt;200</td>
<td>&gt;40</td>
<td>1</td>
</tr>
<tr>
<td>2IPI-145</td>
<td>&gt;640</td>
<td>&gt;34</td>
<td>&gt;11</td>
<td>1</td>
</tr>
</tbody>
</table>

In 165 patients treated with TGR-1202 alone or in combination 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)
- 5% had Grade 3 pneumonia
- Diarrhea in 47%, mainly grade 1, with 5 patients (3%) with Grade 3/4
- 8% of patients have come off study due to an adverse event

**Fold-selectivity**


Burris et al, ASCO 2016
TGR-1202 is active in R/R CLL and MCL, and preclinical data suggest that the combination with ibrutinib is promising.

**TGR-1202 Monotherapy in Patients**

**TGR-1202 + Ibrutinib in vitro**

*Thymidine incorporation assay (BCWM.1)*

*MTT (BCWM.1)*

O’Connor et al, ASH 2015

Unpublished data, Ghobrial Lab
Methods

A phase I/II investigator-initiated multicenter trial of TGR-1202 + ibrutinib in R/R CLL and MCL

Endpoints

Primary:
• MTD, safety, and DLTs of TGR-1202 when used in combination with ibrutinib

Secondary:
• Clinical response: ORR, CR, PR, PR-L, PFS, and remission duration
• Association of CLL prognostic factors (e.g. FISH, IGHV, etc.) with response

Exploratory:
• Association of novel prognostic factors such as BH3 profiling and somatic mutations (e.g. TP53, NOTCH1, SF3B1, BTK, PLCγ-2 etc.) with response
Inclusion
• ≥1 prior standard therapy, an indication for therapy, and ≥1 measurable disease site
• ANC ≥ 0.5 K/uL, platelets ≥ 30 K/uL (except pts w/ >50% CLL in marrow)
• Total bilirubin ≤1.5X ULN, unless due to Gilbert’s or hemolysis, ALT/AST ≤ 2.0X ULN or ≤ 4X ULN if known liver involvement
• Creatinine ≤ 2.5 mg/dL OR calculated creatinine clearance ≥ 50 mL/min
• In Ph I portion, patients with prior BTK or PI3Ki therapy were eligible

Exclusion
• AutoSCT within 3 mo. or alloHCT within 12 mo. of study entry
• Post-allo patients must not have active GVHD and be off immune suppression
• Active hepatitis, HIV infection, or central nervous system involvement
• Patients who require warfarin for anticoagulation

Key Eligibility Criteria
A 3+3 design was utilized with escalation of TGR-1202

- Parallel arms for CLL and MCL which 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

- Standard toxicity assessments by CTCAE v4.03, efficacy by 2008 IW-CLL or 2014 Lugano criteria (MCL)

- Phase Ib expansion cohorts of 12 pts each in CLL and MCL

### Dose escalation scheme

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<th>Dose Level</th>
<th>TGR-1202 Dose</th>
<th>Ibrutinib Dose CLL</th>
<th>Ibrutinib Dose MCL</th>
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<tr>
<td>1</td>
<td>400 mg</td>
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</tr>
<tr>
<td>2</td>
<td>600 mg</td>
<td>420 mg</td>
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</tr>
<tr>
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*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*

### Response evaluations

Methods

A 3+3 design was utilized with escalation of TGR-1202

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## Patient Characteristics (n=31)

<table>
<thead>
<tr>
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<th>All (n=31)</th>
<th>MCL (n=13)</th>
<th>CLL (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>67 (48-83)</td>
<td>67 (50-83)</td>
<td>67 (48-76)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>20 (64.5%)</td>
<td>10 (77%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>Prior therapy, median (range)</td>
<td>2 (1-6)</td>
<td>3 (2-5)</td>
<td>1.5 (1-6)</td>
</tr>
<tr>
<td>Prior autoSCT</td>
<td>4/31 (13%)</td>
<td>4/13 (31%)</td>
<td>0</td>
</tr>
<tr>
<td>Prior ibrutinib</td>
<td>4/31 (13%)</td>
<td>2/13 (15%)</td>
<td>2/18 (11%)</td>
</tr>
<tr>
<td>Prior PI3K inhibitor</td>
<td>4/31 (13%)</td>
<td>0%</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>WBC (K/uL), median (range)</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>Hgb (g/dL), median (range)</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>Platelets (K/uL), median (range)</td>
<td>179 (45-316)</td>
<td>146 (75-290)</td>
<td>194 (45-316)</td>
</tr>
<tr>
<td>Beta-2M (mg/L), median (range)</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>4/17 (24%)</td>
</tr>
<tr>
<td>Del(11q)</td>
<td></td>
<td></td>
<td>7/17 (41%)</td>
</tr>
<tr>
<td>Unmutated IGHV</td>
<td></td>
<td></td>
<td>6/17 (35%)</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.
Results

Safety Analysis

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
- The maximum administered dose of TGR-1202 of 800 mg daily was determined to be the RP2D for both CLL and MCL

Hematologic Toxicity (n=31)

<table>
<thead>
<tr>
<th>CLL (n=18)</th>
<th>MCL (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (38%, 17% Gr 3-4)</td>
<td>Neutropenia (38%; 7.7% Gr 3/4)</td>
</tr>
<tr>
<td>Thrombocytopenia (11%, all Gr 1)</td>
<td>Thrombocytopenia (38%; 7.7% Gr 3)</td>
</tr>
<tr>
<td>Anemia (15%, all Gr 1/2)</td>
<td>Anemia (31%, 7.7% Gr 3)</td>
</tr>
</tbody>
</table>
Results

Safety Analysis (cont., n=31)

**CLL (n=18)**

All grade non-heme toxicities in ≥ 20%*:
- Nausea: 39%, (33% Gr 1, 6% Gr2)
- Diarrhea: 28% (17% Gr 1, 11% Gr 2)
- Dizziness: 22% (all Gr 1)
- Fatigue: 22% (all Gr 1)

SAEs (in 1 patient each):
- Lipase elevation (Gr 3)
- Atrial fibrillation (Gr 3)
- Adrenal insufficiency (Gr 3)
- CNS aspergillus infection (Gr 3)
- Sudden death, uncertain cause (Gr 5)

Dose reduction:
- 3 patients (atrial fibrillation, palpitations, vitreous hemorrhage)

**MCL (n=13)**

All grade non-heme toxicities in ≥ 20%*:
- Fatigue: 54% (31% Gr 1, 23% Gr 2)
- Diarrhea: 46% (all Gr 1)
- Nausea: 38% (31% Gr 1, 7% Gr 2)
- Dizziness: 31% (all Gr 1)
- Anorexia: 31% (all Gr 1)
- Bruising: 23% (all Gr 1)
- Headache: 23% (all Gr 1)

SAEs:
- Hypophosphatemia (n=2, both Gr 3)
- Lipase elevation (n=1, Gr 4)
- Atrial fibrillation (n=1, Gr 3)
- C. difficile infection (n=1, Gr 3)
- Influenza A infection (n=1, Gr 4)

Dose reduction:
- 1 patient (dizziness)

* Excludes asymptomatic, low-grade laboratory abnormalities
Toxicities of Special Interest

- **Diarrhea**: 11/31 (35%) pts (29% Gr 1, 6% Gr 2, with no inflammatory colitis)
- **Transaminitis**: 7/31 (23%) pts, all Gr 1 and self-limited without the need for treatment interruption
- **Pneumonitis**: 1/31 (3%) pts, Gr 1
- **Bleeding events**: Gr 1 epistaxis, hematuria, vitreous hemorrhage in 1 CLL pt each
- **Atrial fibrillation**: 2/31 (6%) pts (both Gr 3)
- **Infection**: 7/31 (23%) pts (4 Gr 1/2, 2 Gr 3 (CNS aspergillus, C. diff, 1 Gr 4 influenza)
• Lymphocyte redistribution was observed in CLL but not MCL
• Resolution of the lymphocytosis was somewhat more rapid than is typically observed with ibrutinib monotherapy
Results

Preliminary Efficacy Analysis (n=28)

• ORR: 15/17 (88%)
  - PR or PR-L: 14/17 (82%)
  - CR: 1/17 (6%)
• 5 PR patients with >80% SPD decrease, nearing radiographic CR
• 3 pts with prior PI3Ki and 1 pt with prior ibrutinib responded

• ORR: 8/11 (73%), all PRs
• Clinical benefit observed in 2 additional patients

CLL (n=17)

MCL (n=11)
Results

Preliminary Efficacy Analysis (n=28)

- Median follow-up time among survivors: 11 mo. (range 0.1-23.5)
- 1-year PFS and OS for CLL is 94% (n=17)
- 1-year PFS and OS for MCL is 37% and 52%, respectively (n=11)
- 6 MCL patients have died (5 due to PD, 1 due to toxicity from subsequent therapy)
- 1 CLL patient had sudden death deemed unlikely due to study drugs
We report to our knowledge the first clinical data on a PI3K plus BTK inhibitor doublet in B cell malignancies

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

The toxicities of TGR-1202 + ibrutinib are manageable and comparable to the additive toxicity profiles of the two agents given individually

The preliminary efficacy results show a high response rate in both diseases
  • CLL patient achieved CR at 1 yr, several others approaching CR

Correlative studies in progress

The CLL arm has now completed accrual, MCL patients continue to accrue to this ongoing study (NCT02268851)
Acknowledgments

Patients and their families

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