Activity of TGR-1202, a Novel Once-Daily PI3Kδ Inhibitor, in Patients with Relapsed or Refractory Hematologic Malignancies

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Background

- PI3Kδ is highly expressed in cells of hematopoietic origin and is often upregulated in lymphoid malignancies
- TGR-1202 is a novel, next generation PI3Kδ inhibitor, with a unique structure which contributes to:
  - Extended half-life and accumulation that enables once-daily dosing
  - Differrentiated safety profile from other PI3Kδ inhibitors in development, notably absent of hepatotoxicity

3+3 Dose Escalation Schema:

Micronized TGR-1202 Dose Escalation Schema:

- Study TGR-1202 101 (NCT01767766) is an ongoing first-in-human, Phase 1 study of TGR-1202 in patients with relapsed or refractory hematologic malignancies
- TGR-1202 dosed orally once-daily (QD) in continuous 28 Day Cycles
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation
- Intra-patient dose escalation allowed for patients in previous cohorts following establishment of safety at higher doses

Study Design

Fold-selectivity

<table>
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<tr>
<th>Fold</th>
<th>PI3Kα</th>
<th>PI3Kβ</th>
<th>PI3Kγ</th>
<th>PI3Kδ</th>
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Key Eligibility Criteria

- Histologically confirmed B-cell non-Hodgkin lymphoma (NHL), CLL/small lymphocytic lymphoma (SLL), Hodgkin’s lymphoma (HL), and select other B-cell lymphoproliferative disorders
- Relapsed after or refractory to, at least 1 prior treatment regimen with no or limited prior therapies
- ECOG performance status ≤ 2
- Adequate organ system function: ANC ≥ 750/L; platelets ≥ 50 × 10^9/L
- Patients with prior therapy with any drug that specifically inhibits PI3Kδ and/or mTOR are excluded

Pharmacokinetics in Patients

- Pharmacokinetics of TGR-1202
- Pharmacokinetics of Micronized TGR-1202
- Pharmacokinetics of Standardized Meals

Pharmacokinetics of Micronized TGR-1202

- Fold Effect in Patients with Standardized Meals

Safety

- Adverse Events Possibly/Probable/Related to TGR-1202 (n=40)
- Select Adverse Events At Doses > 800 mg Possibly/Probable/Related

Select Adverse Events At Doses > 800 mg Possibly/Probable/Related

Fed State (n=14) vs. Fasting State (n=13)

Conclusions

- TGR-1202 is a once-daily PI3Kδ inhibitor with single agent activity observed in patients with a variety of relapsed/refractory hematologic malignancies
- Marked activity has been observed in patients with relapsed refractory CLL, with a 89% nodal response rate at doses ≥ 800 mg (median time on study of 6 months)
- TGR-1202 has been well tolerated, with no drug related transaminase elevations and no events of colitis reported, with 38% (10/26) of evaluable patients treated at ≥ 800 mg on study over 6 months and some on daily TGR-1202 for over a year, demonstrating an adverse event profile which supports combination therapy
- No MTD has been achieved and dose escalation continues with micronized formulation and fed state dosing which is projected to provide a 3-4× increase in exposure over dosing to date, with better GI tolerability demonstrated
- Additional studies are ongoing evaluating TGR-1202 in combination with approved and novel agents, with Phase III studies in development

Efficacy in Chronic Lymphocytic Leukemia

- Best Percent Change from Baseline in Nodal Size

Gantt Chart

- RPR (9%) of CLL patients treated at 800 mg or higher achieved a nodal PR (median nodal reduction of 71%)
- One patient achieved >40% nodal reduction at first response assessment and remains on study awaiting next scan
- Nodal reductions shown to improve with time on TGR-1202

Overall Efficacy

- Best Percent Change from Baseline in Nodal Size

Gantt Chart

- 2 patients at 1800 mg QD were removed due to non-compliance

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