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

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Background

1. High risk CLL patients have less durable response to ibrutinib and are at risk for resistance mutations

Aims/Methods

Endpoints

Primary

• Maximum tolerated dose (MTD)/Recommended Phase 2 Dose (RP2D) of TGR-1202 plus ibrutinib in patients with relapsed or refractory CLL or MCL
• Safety and dose limiting toxicities (DLTs) of TGR-1202 plus ibrutinib in patients with relapsed or refractory CLL or MCL

Secondary

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

Key Eligibility Criteria

Inclusion

• At least 1 prior standard therapy, an indication for therapy, and at least 1 measurable site of disease
• ANC ≥ 0.500 x10^9/L, platelets ≥ 30 x10^9/L (except pts with >50% CLL in marrow)
• Total bilirubin ≤ 1.5x ULN, unless due to Gilbert’s or hemolysis, then ≤3x ULN, ALT/AST ≤ 2x ULN or ≤ 4x ULN if known liver involvement
• Creatinine ≤ 2.5 mg/dL OR calculated creatinine clearance ≥ 50 mL/min
• In Ph1 portion, patients with prior BTK or PI3K inhibition were eligible

Exclusion

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

Study Design

In 165 patients treated with TGR-1202 alone or in combination with anti CD20:
80 patients on study ≥5 cycles, and 43 patients on study ≥12 cycles
Grade 3/4 AST/ALT increase was 3% (8% all grades)
5% had Grade 3 thrombocytopenia
Diabetes 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

4. TGR-1202 is active in R/R CLL, and preclinical combination data with ibrutinib are promising

Results

Patient Characteristics (n=18)

- Median age at enrollment: 67 years (range 48-76)
- Median # prior therapies: 2 (range 1-6, with 2 prior ibrutinib, 4 prior PI3K)

- CLL prognostic markers:
  - FISH: 6/18 (33%) with del(11q), 4/18 (22%) with del(17p)
  - IGHV: 11/16 (69%) unmutated

- 2 patients each with 17p31 and NOTCH1 mutation

Safety Analysis (n=18)

- No DLTs were observed
- RP2D of TGR-1202 when given with ibrutinib is 800 mg daily

Efficacy Analysis (n=18)

- Hematologic toxicity:
  - Neutropenia (38%, 17% Gr 3-4)
  - Thrombocytopenia (11%, all Gr 1-3)
  - Anemia (15%, all Gr 1-2)

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

Conclusions

- We report to our knowledge the first clinical data on a PI3K plus BTK inhibitor doublet tested in CLL
- TGR-1202 + ibrutinib is well-tolerated in R/R CLL, with no DLTs observed in phase I, and an RP2D of TGR-1202 in combination with ibrutinib of 800 mg daily
- Immune-mediated toxicities seen with other PI3Kδi were minimal

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