A Phase I Trial of TGR-1202, a Next Generation Once Daily PI3K-Delta Inhibitor in Combination with Obinutuzumab Plus Chlorambucil, in Patients with Chronic Lymphocytic Leukemia

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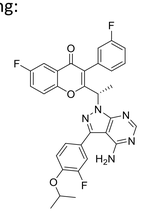
Background

- TGR-1202 is a next generation PI3Kδ inhibitor with a unique structure and activity profile distinct from other PI3Kδ inhibitors in development including:
  - A prolonged half-life (T1/2 = xx) and accumulation that enables once-daily dosing
  - A differentiated safety profile from other PI3Kδ inhibitors in development, notably with respect to hepatic toxicity and colitis to date



Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>10000	>50	>48	1
idelalisib[1]	>300	>200	>40	1
duvelisib[2]	>640	>34	>11	1

[1]Flinn et al. 2009, [2]Porter et al. 2012

- Single agent activity for TGR-1202 has been observed in a variety of hematologic malignancies, including a 94% nodal response rate in relapsed/refractory CLL (Burris et al, ASH 2015)
- An ongoing study is evaluating TGR-1202 in combination with a glycoengineered anti-CD20 mAb, ublituximab, in patients with NHL and CLL

Study Design

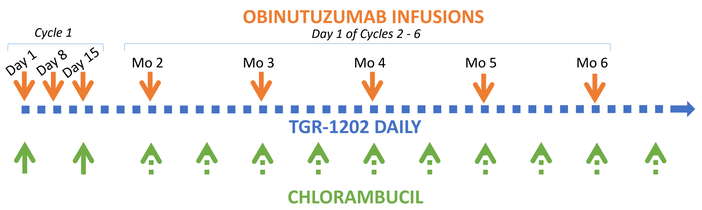
Study TGR-GA-106 (NCT02100852) is a Phase I study of TGR-1202 in combination with the glycoengineered anti-CD20 mAb, obinutuzumab, and chlorambucil in patients with treatment naïve and previously treated CLL:

- 3+3 design evaluating escalating doses of TGR-1202 dosed orally once-daily (QD) in continuous 28 Day Cycles
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation

3+3 Dose Escalation Schema:

Cohort	TGR-1202	Obinutuzumab	Chlorambucil
1	800 mg	1000 mg	0.5 mg/kg
2	400 mg *(micronized)*	1000 mg	0.5 mg/kg
3	800 mg *(micronized)*	1000 mg	0.5 mg/kg

- **TGR-1202: Once Daily starting Day 1 of Cycle 1**
- **Obinutuzumab IV: Days 1, 8 and 15 in Cycle 1 followed by Day 1 of Cycles 2 – 6**
- **Chlorambucil: Days 1 & 15 of Cycles 1, Optional in Cycles 2-6**



Study Objectives & Eligibility

- **Primary Objective:** Safety and Maximum Tolerated Dose (MTD)
- **Secondary Objective:** Efficacy (overall response rate and MRD^{Neg})

Key Eligibility Criteria:

- Histologically confirmed CLL/SLL
- Treatment Naïve or Relapsed after, or refractory to prior treatment with no limit on prior therapies
- ECOG performance status ≤ 2

Results

Demographics

Evaluable for Safety (n)	18
Evaluable for Efficacy† (n)	18
Median Age, years (range)	66 (51– 85)
Male/Female	5/12
ECOG 0/1/2	7/11/0
Treatment Naïve/Previously Treated	15/3
del17p and/or del11q, n (%)	7 (39%)

- Of the 3 previously treated patients, all were refractory to a prior BTK inhibitor (CC-292) and all had high-risk cytogenetics (del 17p and/or 11q)

Safety

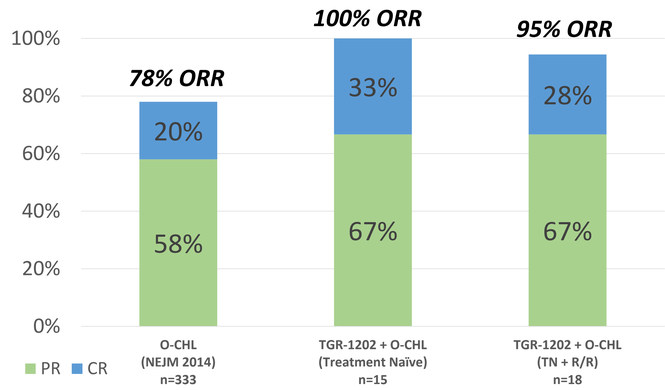
Adverse Events in TGR-1202 + O-CHL Treated Patients

All Events in >20% of Pts (N=18)				
AE	**All Grades**		**Gr. 3/4**	
	N	**%**	**N**	**%**
Neutropenia	14	78%	11	61%
Thrombocytopenia	14	78%	7	39%
Diarrhea	10	56%	2	11%
Nausea	9	50%	-	-
Anemia	8	44%	1	6%
Infusion related reaction	8	44%	-	-
Insomnia	8	44%	-	-
AST increased	7	39%	5	28%
Headache	7	39%	-	-
ALT increased	6	33%	5	28%
Constipation	6	33%	-	-
Fatigue	6	33%	-	-
Vomiting	6	33%	-	-
Cough	5	28%	-	-
Dizziness	5	28%	-	-
Pyrexia	5	28%	-	-
Alk phosph increased	4	22%	-	-
Dysgeusia	4	22%	-	-
Hypokalemia	4	22%	1	6%
Hypophosphatemia	4	22%	-	-
Sinusitis	4	22%	-	-
Stomatitis	4	22%	-	-

- Chlorambucil was mandatory in Cycle 1 and optional in Cycles 2-6
- 5/18 (28%) completed 6 cycles of chlorambucil
- 11/18 (61%) discontinued chlorambucil upon completion of Cycle 1

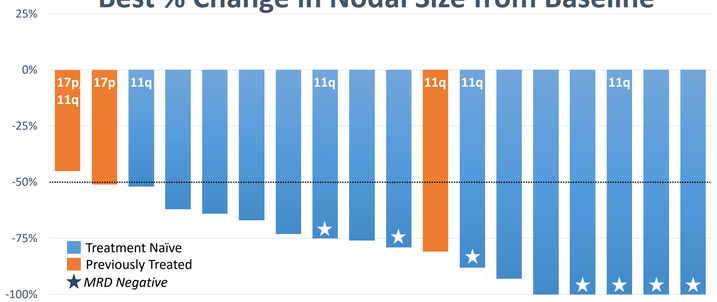
Efficacy

Overall Response Rate and CR rate

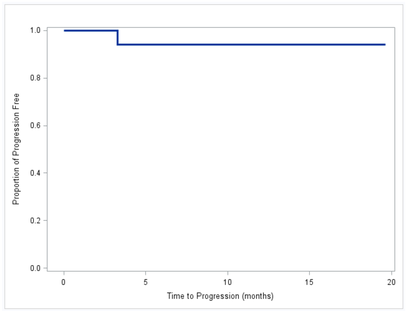


- 7/15 (47%) of treatment naïve patients achieved MRD-negative status with TGR-1202 + O-CHL

Best % Change in Nodal Size from Baseline



Progression-Free Survival

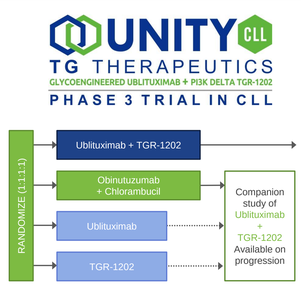


- To date, 17/18 (94%) have not had a PFS event on study
- Median PFS has not been reached, with longest patient on study now 20+ months on single agent TGR-1202
- All patients on study remain on single agent TGR-1202 oral daily maintenance

Phase 3 UNITY-CLL Study

A Phase 3 Study of Ublituximab + TGR-1202

- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA)
- Enrolling patients with treatment naïve and previously treated CLL
- Study Chair: John Gribben, MD, PhD
- Clinical trials.gov #: NCT02612311



Conclusions

- Data from this ongoing Phase 1 study suggests the triple combination of TGR-1202 + obinutuzumab + chlorambucil demonstrates acceptable tolerability and high activity in patients with treatment naïve and relapsed/refractory CLL
- In treatment naïve patients, combination therapy resulted in a 100% ORR, with 33% of patients achieving a CR, and 47% of patients achieving MRD negativity
- Notably, the AE profile observed with TGR-1202 + O-CHL differed from that observed when TGR-1202 was combined with the other glycoengineered anti-CD20 mAb, ublituximab, specifically regarding neutropenia (78% vs. 30%), thrombocytopenia (78% vs. <10%), and transaminase elevations (39% vs. 8%) (Lunning et al, ASH 2015, Abstract#1538)
- TGR-1202 is currently in Phase 3 testing in combination with the glycoengineered anti-CD20 mAb, ublituximab, in patients with previously untreated and relapsed/refractory CLL in a randomized trial compared to obinutuzumab + chlorambucil

COI: **Mahadevan:** *Pharmacyclics*; *Alexion*. **Pauli:** *Clearview Cancer Institute*; *TG Therapeutics, Inc.* **Cutter:** *Clearview Cancer Center*. **Sportelli & Miskin:** *TG Therapeutics, Inc.:* Employment , Equity Ownership. **Schreeder:** *TG Therapeutics, Inc.*

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