A Phase I Trial of TGR-1202, a Next Generation Once-Daily PI3Kδ Inhibitor, in Combination with Brentuximab Vedotin, in Patients with Relapsed/Refractory Hodgkin's Lymphoma

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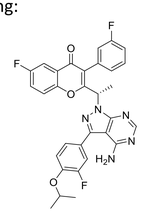
Background

- 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 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



Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>1000	>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 Chronic Lymphocytic Leukemia (Burris et al, ASH 2015)
- TGR-1202 is currently in registration directed studies for patients with CLL and Diffuse Large B-cell Lymphoma (DLBCL)

Rationale for Study TGR-BV-107

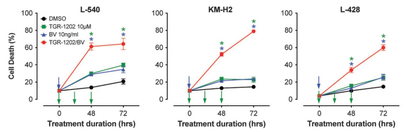
- Brentuximab vedotin (BV) monotherapy is active in pts with relapsed and refractory Hodgkin's lymphoma with a 73% ORR (32% CR), however the duration of response varies significantly between patients achieving a CR compared to those achieving a PR (*BV Prescribing Information*)

Table 1: ORR and DOR for BV Monotherapy

N=102	ORR	DOR
	Percent (95% CI)	Mos., Median (95% CI)
CR	32 (23, 42)	20.5 (12.0, NE*)
PR	40 (32, 49)	3.5 (2.2, 4.1)
ORR	73 (65, 83)	6.7 (4.0, 14.8)

- The combination of TGR-1202 and BV has demonstrated strong synergy in pre-clinical studies (Locatelli et al, *Leukemia* 2016)
- Co-administration of TGR-1202 and BV resulted in marked mitotic arrest and in increase in cell death in 3 Hodgkin's Lymphoma cell lines (Fig. 1).

Figure 1: In-vitro synergy of TGR-1202 + BV



*P ≥0.0001 compared with single agent treatments

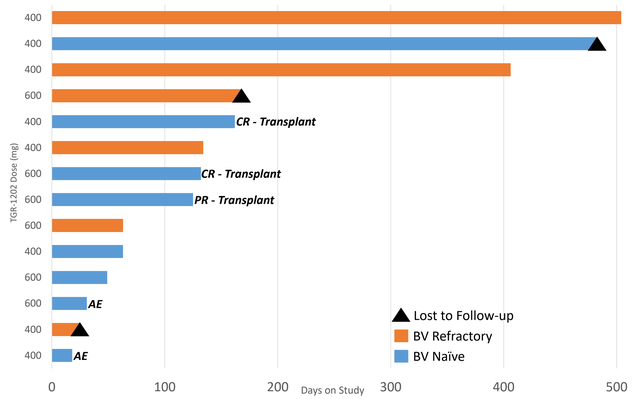
Results

Demographics

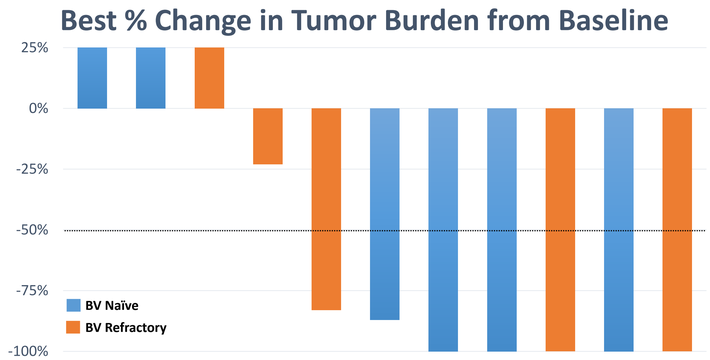
Evaluable for Safety (n)	14
Evaluable for Efficacy† (n)	11
Median Age, years (range)	34 (21– 81)
Male/Female	9/5
ECOG 0/1/2	7/7/0
Median Prior Therapies (range)	3 (2 – 6)
Prior ASCT	4 (29%)
Prior Brentuximab Vedotin	6 (43%)

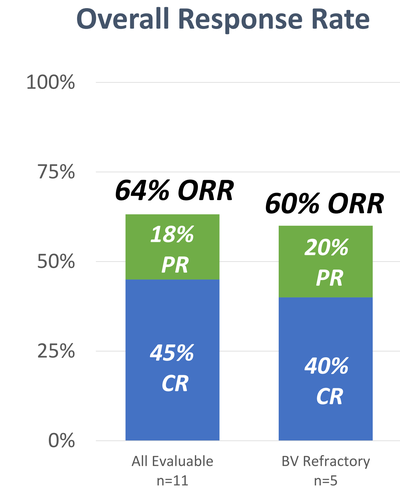
- 3 discontinued prior to disease evaluation (2 AEs, 1 withdrew consent)
- Of the 6 previously treated with BV, all were refractory to prior BV therapy (progressing on or within 6 months of a prior BV regimen)

Duration on Study



Efficacy





Safety

Adverse Events in TGR-1202 + BV Treated Patients

All Causality Events in >20% of Pts (N=14)				
Event	All Grades		Gr. 3/4	
	N	%	N	%
Nausea	10	71%	-	-
Diarrhea	9	64%	1	7%
Neutropenia	8	57%	6	43%
Cough	6	43%	-	-
Edema peripheral	6	43%	-	-
Rash	6	43%	1	7%
Vomiting	6	43%	1	7%
AST Increase	5	36%	2	14%
Dyspnea	5	36%	1	7%
Headache	5	36%	-	-
Abdominal pain	4	29%	-	-
Fatigue	4	29%	2	14%
Pruritus	4	29%	-	-
WBC count decreased	4	29%	1	7%
ALT Increase	3	21%	1	7%
Anemia	3	21%	2	14%
Back pain	3	21%	-	-
Chest pain	3	21%	1	7%
Dizziness	3	21%	-	-
Muscle spasms	3	21%	-	-
Paresthesia	3	21%	-	-
Peripheral sensory neuropathy	3	21%	-	-
Thrombocytopenia	3	21%	-	-

- 2 patients discontinued due to AEs (1 Gr. 3 pancreatitis, and 1 Gr. 3 diarrhea occurring 11 days following treatment initiation); both the event of Gr. 3 diarrhea and a separate event of Gr. 3 rash met the criteria for DLTs at the 600mg TGR dose level

Study Design

Study TGR-BV-107 (NCT02164006) is a Phase I/Ib study of TGR-1202 in combination with the anti-CD30 antibody-drug conjugate, brentuximab vedotin, in patients with previously treated Hodgkin's Lymphoma:

- 3+3 design evaluating two doses of TGR-1202 dosed orally once-daily (QD) in combination with brentuximab vedotin in continuous 21 Day Cycles
- Dose-limiting toxicities (DLTs) assessed in Cycle 1 prior to escalation
- Phase Ib expansion at optimal dose

3+3 Dose Escalation Schema:

Cohort	TGR-1202	Brentuximab Vedotin
1	400 mg	1.8 mg/kg
2	600 mg	1.8 mg/kg

BRENTUXIMAB INFUSIONS

Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6+

TGR-1202 DAILY

Study Objectives & Eligibility

- Primary Objective: Safety and Maximum Tolerated Dose (MTD)
- Secondary Objective: Efficacy (Overall Response Rate & Progression-Free Survival)

Key Eligibility Criteria:

- Histologically confirmed Hodgkin's Lymphoma (HL)
- Disease status defined as refractory or relapsed after autologous stem cell transplant (ASCT) or at least two prior multi-agent chemotherapy regimens in patients not candidates for ASCT
- Prior exposure to brentuximab vedotin is allowed provided patient did not stop therapy due to toxicity
- Patients with Grade 2 or greater peripheral neuropathy excluded
- ANC ≥ 1000/mm^2
- ECOG performance status ≤ 2

Conclusions

- The goal of this Phase 1 study was to assess combinability of TGR-1202 + brentuximab vedotin, and to assess the ability for the combination to drive complete response rate compared to that historically seen with BV monotherapy
- Data from this Phase 1 study suggests that the combination of TGR-1202 + brentuximab vedotin exhibits an acceptable tolerability profile and is clinically active
- Responses were observed in patients with advanced Hodgkin's Lymphoma, including responses in 60% of patients previously refractory to brentuximab vedotin
- 45% of patients on this study achieved a complete response, including two patients previously refractory to brentuximab vedotin monotherapy
- Further studies evaluating this combination are warranted

COI: **Ramchandren**: None; **Mulroney**: None; **Patel**: None; **Sportelli:** *TG Therapeutics, Inc.* **Miskin:** *TG Therapeutics, Inc.* **Chen:** *Genentech; Merck; Seattle Genetics; Millenium.*

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