Phase 1 Study of TG-1701, a Selective Irreversible Inhibitor of Bruton's Tyrosine Kinase (BTK), in Patients with Relapsed/Refractory B-Cell Malignancies

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Abstract # 4001

Background

Study Rationale

- Agents targeting BTK have demonstrated activity in a variety of B-cell malignancies, however not all patients respond to therapy, and amongst those that do respond, complete remissions are rare
- BTK based combination regimens have the potential to increase depth of response and permit time-limited therapy
- TG-1701 is a novel, orally available and covalently-bound BTK inhibitor that exhibits superior selectivity for BTK compared with ibrutinib in an *in vitro* whole kinome screening (Abstr 3973, EHA 2018)
- Herein we report interim results of the dose-escalation cohorts of TG-1701 monotherapy and of TG-1701 in combination with umbralisib, a novel PI3K-δ and casein kinase-1ε dual inhibitor, and ublituximab, a glycoengineered anti-CD20 mAb (1701 + U2).

TG-1701 Selectivity

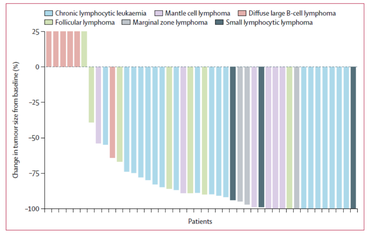
Kinase Selectivity Profiling at 1uM

Drug	Kinase inhibition IC50 (nM)						
	BTK	TEC	TXK	HER2	EGFR	ITK	JAK3
Acalabrutinib	5.1	93	368	1000	> 1000	> 1000	> 1000
TG-1701	3	4	136	3000	270	> 3000	> 3000
Ibrutinib	1.5	7	2	6.4	5.3	4.9	32

Umbralisib and Ublituximab (U2) + Ibrutinib

- A Phase 1 study to evaluate the combination of umbralisib + ublituximab (U2) + ibrutinib was undertaken in patients with advanced CLL and NHL
- The combination of U2 and ibrutinib was well tolerated and is associated with encouraging activity across various lymphoid malignancies (Nastoupil et al., Lancet Haematol 2019)

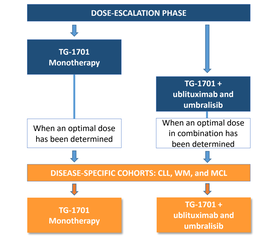
Best Change from Baseline in Tumor Burden



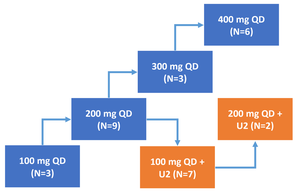
Study Design

Methods

- Primary objective: to characterize the safety profile and to determine the recommended Phase 2 dose (RP2D) of TG-1701 as a single agent and in combination with U2.
- Other objectives: pharmacokinetics (PK), preliminary antitumor activity, and pharmacodynamics (PD [BTK occupancy])
- Treatment consists of escalating doses of oral TG-1701 once daily (QD), continuously administered in 28-day (D) cycles (C). Intra-patient dose escalations are permitted in the TG-1701 monotherapy arm.
- Patients in the 1701 + U2 arm receive escalating TG-1701 oral QD + umbralisib 800 mg oral QD + ublituximab 900 mg IV on D1, 8, 15 of C1, and D1 of C2 through C6, and D1 every 3 cycles thereafter.
- All patients are treated until disease progression, unacceptable toxicity, or investigator/patient decision to withdraw study consent.



Disposition



Key Eligibility Criteria

- B-cell lymphoma or CLL that is relapsed or refractory to prior standard therapy and warrants systemic therapy
- For the new specific cohorts (CLL, WM, and MCL), patients who are previously-untreated could be enrolled, if they are considered to be unsuitable for standard front-line chemoimmunotherapy by the treating physician based on the patient's documented comorbidities and risk factors (e.g. 17p deletion or TP53 mutation)
- No prior therapy with a BTK inhibitor
- Any severe or uncontrolled illness or other conditions that could affect their participation in the study
- No concomitant warfarin therapy, other anticoagulation therapy is allowed

Disclosures
Cheah: Roche, Janssen, MSD, Gilead, Loxo Oncology, Acerta, BMS, Celgene, Abbvie. Wickham: Roche, Celgene. Miskin, Turpuseema, Ricart, Tang & Normant: TG Therapeutics Inc. Tam: Abbvie, Janssen, Beigene, Roche, Novartis.

Results

Demographics

	TG-1701 Monotherapy (N = 21)	TG-1701 + U2 (N = 9)
Male sex, n (%)	12 (57)	2 (22)
Age, years median (min / max)	61 (49 / 86)	70 (64 / 79)
≥75 years, n (%)	5 (24)	3 (33)
ECOG PS 0 or 1, n (%)	21 (100)	9 (100)
Prior therapies, median (range)	1 (1 - 5)	1 (1 - 5)
Refractory, n (%)	5 (24)	1 (11)
Previous anti-CD20 therapy	21 (100)	9 (100)
Bulky disease (≥ 5 cm)	7 (33)	4 (44)
Extranodal disease	6 (29)	3 (33)

Safety

TG-1701 Monotherapy: Treatment-related AEs (Incidence >5% or any ≥ G3)

Adverse Event	Patients (N = 21)		
	Any Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	6 (29)	2 (10)	-
Respiratory tract infection	4 (19)	1 (5)	-
Bruising	4 (19)	-	-
ALT increased	4 (19)	1 (5)	-
AST increased	3 (14)	1 (5)	-
Rash	2 (10)	1 (5)	-
Diarrhea	2 (10)	-	-
Skin infection / cellulitis	2 (10)	-	-
Nausea	2 (10)	-	-
Lipase increased	2 (10)	1 (5)	-

*All ALT/AST events were brief in asymptomatic patients with normal liver function (total bilirubin within normal range)

- Median cycles (range) monotherapy = 8 (1-16), combination = 5 (1-8). Two patients (10%) had a dose reduction on monotherapy
- One dose limiting toxicity (DLT), G3 ALT elevation at 400 mg QD dose level
  - Dose reduced to 300 mg QD and continues on study
- No significant changes between pre- and on-treatment diastolic blood pressure nor QTc. No treatment-related death. No treatment discontinuations due to AEs

TG-1701 + U2: Treatment-related AEs (Incidence >5% or any ≥ G3)

Adverse Event	Patients (N = 9)		
	Any Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
IRR	3 (33)	-	-
Neutropenia	1 (11)	-	1 (11)
ALT increased	2 (22)	2 (22)	-
AST increased	2 (22)	1 (11)	-
Hypertension	1 (11)	-	-
Diarrhea	1 (11)	-	-
Rash	1 (11)	-	-
Nausea	1 (11)	1 (11)	-
Vomiting	1 (11)	-	-
Bilirubin increased	1 (11)	-	-
Abdominal pain	1 (11)	-	-
Headache	1 (11)	-	-

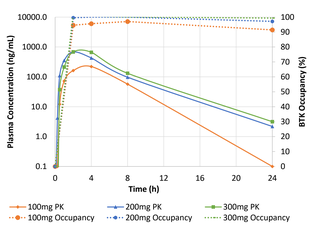
Note: IRR: Infusion-related reaction includes the terms "chest tightness", and "facial flushing". Both cases of elevated ALT/AST were episodes in asymptomatic patients with normal liver function (total bilirubin within normal range). Both patients continue therapy at a reduced dose of umbralisib (600 mg QD).

Efficacy

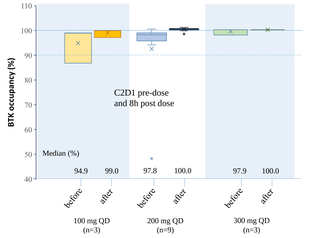
Pharmacokinetics and Pharmacodynamics

- Linear kinetics are apparent, evidenced by an approximately dose proportional increase in AUC over the dose range of 100 to 200 mg on C1D1 and C1D8 of monotherapy group.
- High systemic clearance has been observed with a mean CL/F of 55.4 L/hr and half-life of 2.24 hours. Tmax is observed between 1 to 4 hrs post dose.
- Near complete BTK occupancy was achieved in patients at doses ≥ 100 mg QD and sustained for 24 hours

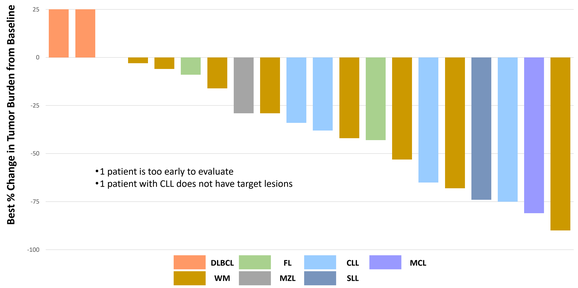
PK/PD Relationship on C1D1



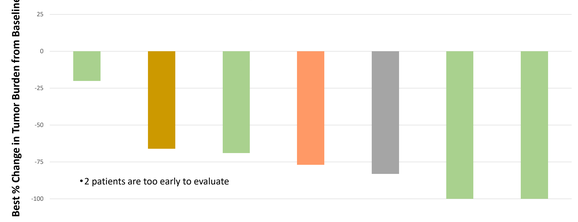
BTK Occupancy on C2D1 Pre-Dose and 8h Post-Dose



TG-1701 Monotherapy: Best Change from Baseline in Tumor Burden



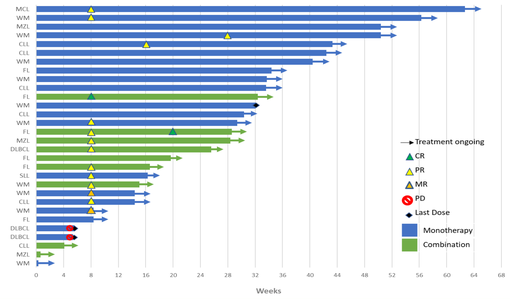
TG-1701 + U2: Best Change from Baseline in Tumor Burden



Responses by Cohort & Dose Level

Disease Type	Cohort / Dose Level (Response)					
	I 100 mg QD	II 200 mg QD	III 300 mg QD	IV 400 mg QD	Combo I 100 mg QD + U2	Combo II 200 mg QD + U2
WM	1 (PR)	4 (PR, PR, SD, SD)	1 (SD)	3 (MR, MR, 1 pending)	1 (PR)	-
CLL	-	3 (PR, SD, SD)	1 (SD)	1 (PR)	-	1 (pending)
SLL	-	-	-	1 (PR)	-	-
FL	-	-	1 (SD)	1 (SD)	4 (CR, CR,PR, SD)	-
MZL	-	1 (SD)	-	-	1 (PR)	1 (pending)
MCL	1 (PR)	-	-	-	-	-
DLBCL	1 (PD)	1 (PD)	-	-	1 (PR)	-

Treatment Exposure and Response Duration



Summary and Conclusions

- We report the first results of a Phase 1 study of TG-1701 monotherapy and TG-1701 in combination with umbralisib and ublituximab (U2)
- TG-1701 has an encouraging preliminary safety profile, with clinical and pharmacodynamic activity at all dose levels evaluated that supports QD dosing
- TG-1701 + U2 has been well tolerated at the first dose level and dose escalation continues. Combination treatment is associated with encouraging clinical activity, including early complete responses. This study (NCT03671590) continues enrollment.

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