Safety and Activity of the Once Daily Selective Bruton Tyrosine Kinase (BTK) Inhibitor TG-1701 in Patients with Chronic Lymphocytic Leukemia (CLL) and Lymphoma

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BACKGROUND

- BTK inhibition is effective in the treatment of CLL and lymphoma but requires continuous treatment and complete responses (CR) are rare
- BTK based combination regimens have the potential to increase depth of response and to permit time-limited therapy
- TG-1701 is a once-daily (QD), covalently bound BTK inhibitor that exhibits superior selectivity for BTK compared with ibrutinib in an *in vitro* whole kinome screening (Abstr 3973, EHA 2018) (Table)

Kinase Selectivity Profiling at 1uM

TG-1701 Is More Selective than Ibrutinib on a Panel of Kinases

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

- **Herein we report:**
  - Complete dose-escalation of TG-1701 monotherapy
  - Interim results 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), and
  - Interim results of TG-1701 monotherapy at 200 mg QD in Disease-specific cohorts: CLL, Waldenström's macroglobulinemia (WM), and Mantle Cell Lymphoma (MCL)

METHODS

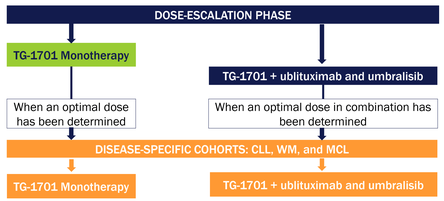
Study Objectives

- The primary objectives of the study are: 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 (BTK occupancy)

Dose Escalation

- Treatment consists of escalating doses of oral TG-1701 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 QD + umbralisib 800 mg oral QD + ublituximab 900 mg IV on D1, 8, 15 of C1, and D1
- All patients are treated until disease progression, unacceptable toxicity, or investigator/patient decision to withdraw study consent

Dose Escalation

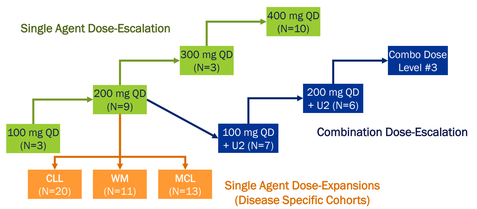


Key Eligibility Criteria

- Relapsed or refractory to prior standard therapy, histologically confirmed B-cell lymphoma or CLL, that warrants systemic therapy
- For the Disease-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)
- Usual adequate organ function criteria (e.g. ANC > 1,000/μL, platelet count ≥ 50,000/μL, total bilirubin ≤ 1.5 times the ULN, ALT / AST ≤ 2.5 x ULN if no liver involvement, calculated creatinine clearance > 30 mL/min)
- 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

RESULTS

Patient Disposition



RESULTS

Baseline Characteristics

Patient Demographics

Dose-escalation Phase	TG-1701 Monotherapy Patients (N = 25)	TG-1701 + U2 Patients (N = 13)
Male sex, n (%)	14 (56)	5 (38)
Age, years		
Median (min / max)	68 (49 / 86)	69 (47 / 79)
≥75 years, n (%)	7 (28)	3 (23)
ECOG performance status 0 or 1, n (%)	25 (100)	13 (100)
Prior systemic therapies, median (range)	1 (1 - 5)	2 (1 - 5)
Refractory to last prior therapy, n (%)	7 (28)	2 (15)
Previous anti-CD20 therapy, n (%)	25 (100)	13 (100)
Bulky disease (≥ 5 cm), n (%)	9 (36)	6 (46)
Extranodal disease	8 (32)	6 (46)

Disease Characteristics

Disease-specific Cohorts (200 mg QD)	CLL Patients (N = 20)	WM Patients (N = 11)	MCL Patients (N = 13)
Male sex, n (%)	7 (35)	9 (82)	7 (54)
Age, years			
Median (min / max)	71 (53 – 87)	73 (59 – 92)	70 (57 – 85)
≥75 years, n (%)	4 (20)	5 (45)	3 (23)
ECOG performance status 0 or 1, n (%)	20 (100)	11 (100)	13 (100)
Prior systemic therapies, median (range)	1 (0 – 5)	1 (0 – 2)	3 (0 – 10)
Previous anti-CD20 therapy, n (%)	12 (60)	7 (64)	11 (85)

Safety

Dose-escalation (N = 38):

- Median (range) cycles of exposure to monotherapy = 13 (1 - 22); combination = 10 (1 - 14)
- Two patients had a dose reduction on monotherapy due to treatment-related adverse events (AEs): grade (G) 2 abdominal pain and G3 ALT elevation
- One patient had a dose reduction for TG-1701 (100 mg to 50 mg) due to G3 nausea in the combination arm. Another 3 patients had a dose reduction of umbralisib due to G3-4 ALT elevation
- There was 1 dose limiting toxicity (DLT), G3 ALT elevation at 400 mg
- The maximum tolerated dose (MTD) has not been achieved. Dose escalation proceeded until 3 dose levels above full BTK occupancy (100 mg) by TG-1701
- No significant changes between pre- and on-treatment diastolic blood pressure nor QTc were noted. No treatment-related death. No treatment discontinuations due to treatment-related AEs

Disease-specific Cohorts (N = 44):

- Median cycles (range) monotherapy = 4 (1-8). There have been no treatment discontinuations.

TG-1701 Monotherapy: Treatment-related AEs (Incidence ≥10% or any ≥ Grade 3)

Adverse Event	Dose Escalation				Dose Expansion	
	100 - 300 mg N = 15		400 mg N = 10		200 mg N = 44 CLL-WM-MCL	
	Any G, n (%)	G3, n (%)	Any G ,n (%)	G3, n (%)	Any G, n (%)	G3, n (%)
Neutropenia	5 (33)	2 (13)	1 (10)	-	2 (5)	1 (2)
Respiratory tract infection	3 (20)	1 (7)	1 (10)	-	3 (7)	-
Bruising	4 (27)	-	1 (10)	-	4 (9)	-
ALT increased	3 (20)	-	2 (20)	2 (20)*	1 (2)	-
AST increased	2 (13)	-	2 (20)	2 (20)*	-	-
Rash	2 (13)	1 (7)	1 (10)	-	-	-
Diarrhea	2 (13)	-	-	-	3 (7)	-
Skin infection / cellulitis	2 (13)	-	-	-	-	-
Nausea	1 (7)	-	1 (10)	-	-	-
Lipase increased	2 (13)	1 (7)	-	-	2 (5)	1 (2)
Abdominal pain	2 (13)	-	-	-	1 (2)	-
Arthralgia	2 (13)	-	-	-	2 (5)	-
Amylase increased	1 (7)	-	-	-	1 (2)	1 (2)

Note: There have been no G4 AEs on TG-1701 monotherapy
*Both cases were brief episodes in asymptomatic patients with normal liver function. One case was in the context of significant PD in the liver.

TG1701 + U2: Treatment-related AEs (Incidence ≥10% or any ≥ Grade 3)

Adverse Event	Patients (N = 13)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 (%)
ALT increased#	5 (38)	2 (15)	1 (8)
AST increased#	5 (38)	2 (15)	-
Fatigue	3 (23)	-	-
Bruising	3 (23)	-	-
IRR*	3 (23)	-	-
Diarrhea	2 (15)	1 (8)	-
Hypertension	2 (15)	1 (8)	-
Neutropenia	2 (15)	1 (8)	1 (8)
Vomiting	2 (15)	-	-
Taste changes	2 (15)	-	-
Nausea	1 (8)	1 (8)	-

#Both cases of G3 elevated ALT 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 and 400 mg). The G4 was symptomatic (vomiting) and with abnormal liver function, patient has recovered with CR and remain on study.
*IRR: Infusion-related reaction includes the terms "chest tightness", and "facial flushing".

Efficacy

Dose-escalation

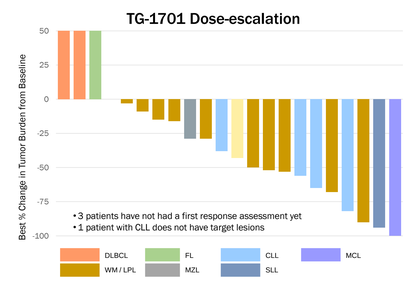
Disease Type	TG-1701 QD Dose Level (Response Category)					
	100 mg N = 3	200 mg N = 9	300 mg N = 3	400 mg N = 10	100 mg + U2 N = 7	200 mg + U2 N = 6
WM / LPL*	1 (PR)	4 (PR, PR, SD, SD)	2 (SD)*	3 (MR, PR, PR)	1 (PR)	-
CLL	-	3 (PR, SD, SD)	1 (PR)	2 (PR, pending)	-	3 (PR, PR, PR)
SLL	-	-	-	1 (PR)	-	-
FL	-	-	-	2 (SD, PD)	4 (CR, CR,PR, SD)	2 (SD, SD)
MZL	-	1 (SD)	-	2 (pending)	1 (PR)	1 (PR)
MCL	1 (PR)	-	-	-	-	-
DLBCL	1 (PD)	1 (PD)	-	-	1 (PR)	-

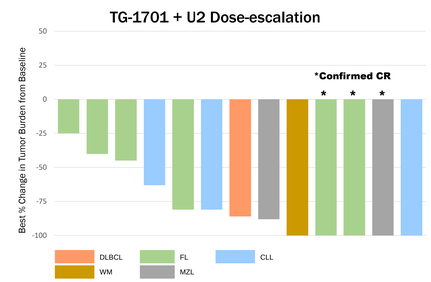
Disease-specific cohorts

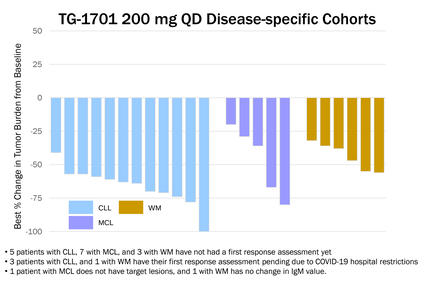
Response Category	Disease Type		
	WM (N = 7)	MCL (N = 6)	CLL (N = 12)
CR, n (%)	-	-	-
VGPR, n (%)	-	N/A	N/A
PR, n (%)	2 (29)	2 (33)	11 (92)*
MR, n (%)	4 (57)	N/A	N/A
SD, n (%)	1 (14)	3 (50)	1 (8)
PD, n (%)	-	-	-
NE, n (%)	-	1 (17)	-
ORR	86%	33%	92%

Note: Evaluable patients had at least one response assessment
*All had PR with persistent lymphocytosis (PR-L)

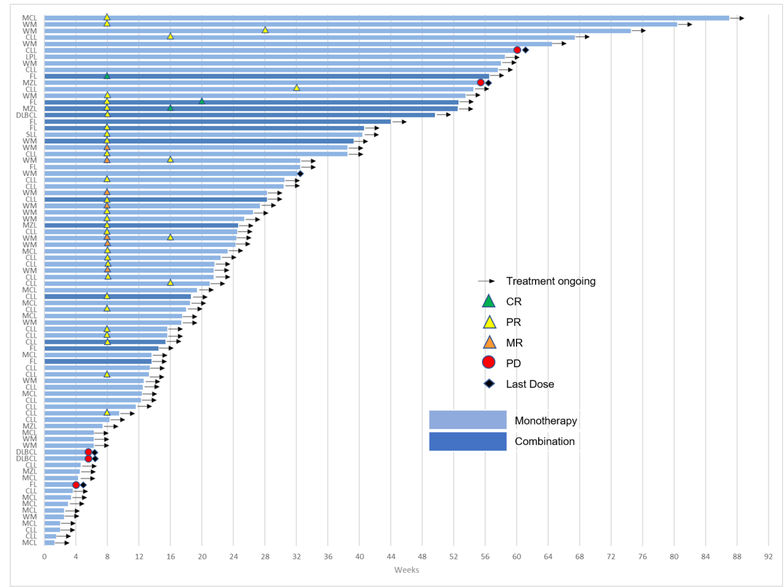
Best Change from Baseline in Tumor Burden







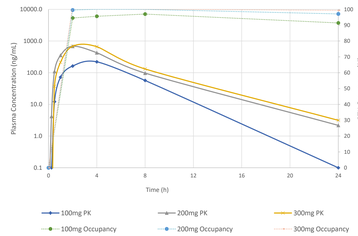
Treatment Exposure and Response Duration



Pharmacokinetics and Pharmacodynamics

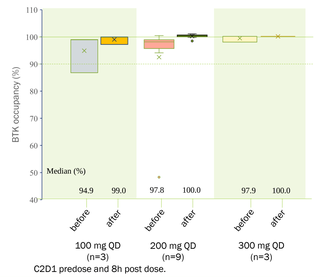
Pharmacokinetics

- Linear kinetics are apparent, evidenced by 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 (CL) has been observed with a mean CL/F of 55.4 L/hr and half-life of 2.24 hours.
- T_{max} is observed between 1 to 4 hrs post dose.



Pharmacodynamics

- Comparison of the degree of BTK occupancy by TG-1701 at 100 mg to 300 mg QD cohorts in the study.
- These data suggest that near full BTK occupancy was achieved in patients at doses ≥ 100 mg QD



SUMMARY and CONCLUSIONS

- We report results of a unique Phase 1 parallel dose-escalation study of TG-1701 monotherapy and TG-1701 in combination with umbralisib and ublituximab (1701 + U2)
- TG-1701 exhibits an encouraging preliminary safety profile, with clinical and pharmacodynamic activity at all dose levels evaluated that support QD dosing
- Linear kinetics are apparent based on approximately dose proportional increase in AUC over the dose range of 100 to 200 mg
- The MTD has not been achieved in the monotherapy arm. Dose escalation proceeded until 3 dose levels above full BTK occupancy (100 mg)
- The combination of TG-1701 with U2 has been well tolerated and dose escalation continues. Combination treatment is associated with encouraging clinical activity, including early complete responses
- This study (NCT03671590) continues enrollment.

Disclosures
Cheah: Roche, Janssen, MSD, Gilead, Loxo Oncology, Acerta, BMS: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Celgene, Roche, Abbvie: Research Funding; Roche: Other: Travel expenses. Wickham: Roche: Honoraria; Celgene: Other: Travel/Meeting Expenses . Turpuseema, Miskin, and Normant: TG Therapeutics Inc.: Employment, Equity Ownership. Tang: TG Therapeutics Inc., Roche, Alexion: Equity Ownership; TG Therapeutics Inc.: Employment. Ricart: TG Therapeutics, Pfizer, Merck: Equity Ownership; TG Therapeutics Inc.: Employment. Tam: Abbvie, Janssen, Beigene, Roche, Novartis: Honoraria; Abbvie, Janssen: Research Funding.

Presented at the 25th Congress of the European Hematology Association (EHA), 12 June 2020. Final Abstract Code: EP705.