TG-1701, a Selective Bruton Tyrosine Kinase (BTK) Inhibitor, as Monotherapy and in Combination with Ublituximab and Umbralisib (U2) in Patients with Chronic Lymphocytic Leukemia

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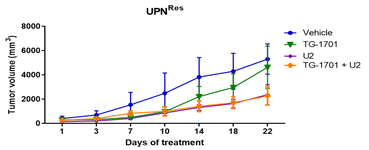
BACKGROUND AND METHODS

- Deep remissions with BTK monotherapy in CLL are rare
- TG-1701 is a covalently bound BTK inhibitor with superior selectivity compared with ibrutinib1
- The triple combination of TG-1701 with umbralisib and ublituximab (U2) inhibited tumor growth in BTK-resistant xenograft models2
- Here we present results from CLL patients enrolled in an ongoing Phase 1 study of TG-1701 alone and in combination with U2

Kinase Selectivity Profiling at 1uM[1]

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

TG-1701+U2 inhibits growth in BTK resistant cell lines[2]



[1]*Normant E, et al., EHA 2018 (absPF638);*
[2]*Ribeiro M, et al. AACR 2020 (abs 2205); BTK: Bruton's tyrosine kinase, CK-1:casein kinase-1; PI3K: phosphatidylinositol 3-kinase*

Methods

OBJECTIVES

- Characterize the safety profile of TG-1701
- Determine the RP2D of TG-1701 as monotherapy and in combination with U2
- PK, preliminary antitumor activity, BTK occupancy

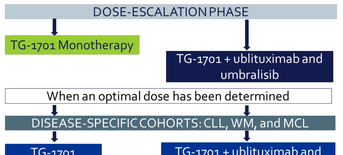
KEY INCLUSION CRITERIA

- R/R disease to prior standard therapy, histologically confirmed B-cell lymphoma or CLL that warrants systemic therapy
  - For the disease-specific cohorts, previously untreated pts could be enrolled if unsuitable for standard front-line chemoimmunotherapy
- Adequate organ system function

KEY EXCLUSION CRITERIA

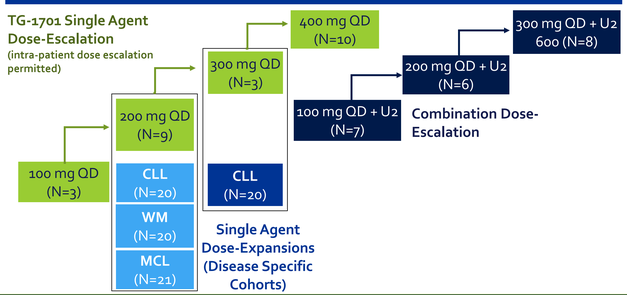
- Prior therapy with a BTK inhibitor; any severe or uncontrolled illness or condition; concomitant warfarin therapy (other anticoagulation is allowed)

STUDY SCHEMA



- Oral TG-1701 QD, continuously administered in 28-day (D) cycles (C). Intra-patient dose escalations are permitted in monotherapy arm.
- 1701 + U2 arm: escalating TG-1701 QD + umbralisib 800 mg oral QD (or 600 mg QD) + ublituximab 900 mg IV on D1, 8, 15 of C1, and D1 of C2 through C6, and D1 every 3 C up to 24 cycles.

Trial Design



RESULTS

Patient Demographics and Disease Characteristics – CLL Patients

	Dose-Escalation Phase		Dose-Expansion Cohorts	
Characteristic	TG-1701 100 – 400 mg N=6	TG-1701 + U2 100 – 300 mg N=4	TG-1701 200 mg N=20	TG-1701 300 mg N=20
Male sex, N(%)	4 (67)	3 (75)	7 (35)	10 (50)
Age, years, median (min/max)	63 (57 / 83)	60 (47 / 70)	70 (53 – 86)	71 (49 – 80)
≥75 years, N(%)	*2 (33)*	-	*3 (15)*	*6 (30)*
ECOG 0 / 1 / 2 (%)	50 / 50 / 0	75 / 25 / 0	35 / 65 / 0	30 / 70 / 0
Prior therapies, median (range)*	1 (1 - 2)	1 (1 - 2)	1 (0 – 4)	1 (0 – 7)
Refractory to last prior therapy, N(%)	-	1 (25)	3 (15)	2 (10)
Treatment-naïve, N(%)	-	-	5 (25)	4 (20)
High Risk features				
Unmutated IGHV status % (n/N)	80% (4/5)	100% (4/4)	41% (7/17)	72% (13/18)
Del 17p or TP53 mutation % (n/N)	50% (3/6)	50% (2/4)	5% (1/19)	20% (4/20)
Del 17P & TP 53 mutation % (n/N)	50% (2/4)	50% (2/4)	6% (1/17)	23% (3/13)

*Calculation excludes treatment-naïve patients

Patient Disposition - CLL

	Dose-Escalation Phase		Dose-Expansion Cohorts	
Cutoff: Aug 20, 2021	TG-1701 100 – 400 mg N=6	TG-1701 + U2 100 – 300 mg N=4	TG-1701 200 mg N=20	TG-1701 300 mg N=20
Pts continuing treatment, N(%)	4 (67)	4 (100)	18 (90)	18 (90)
Dose reduction (any agent), N(%)	3	-	1 (5)	-
Pts discontinued treatment, N(%)	2 (33)	-	2 (10)	2 (10)
Reason for treatment discontinuation, N(%)				
Progression by iwCLL criteria	1	-	-	-
Clinical progression	-	-	-	-
Due to AE	-	-	-	-
Pt/physician decision	-	-	1	-
Death	-	-	1‡	2‡
Other	1*	-	-	-

*Intercurrent illness developed which compromises further participation in the study. ‡Death due to SARS-CoV-2 infection

Safety

All-Causality AEs ≥15% in Either of the Dose-Expansion Cohorts

	Dose-Escalation Phase				Dose-Expansion Cohorts			
	TG-1701 100 – 400 mg N=6		TG-1701 + U2 100 – 300 mg N=4		TG-1701 200 mg N=20		TG-1701 300 mg N=20	
Adverse event, N (%)§	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Contusion	4	-	-	-	4 (20)	-	1 (5)	-
Diarrhea	-	-	1	-	4 (20)	-	2 (10)	-
URTI	3	-	-	-	2 (10)	-	3 (15)	-
Nausea	1	-	1	-	-	-	3 (15)	-
COVID-19	-	-	-	-	1 (5)	-	3 (15)	1 (5)
Hematologic & Lab Abnormalities								
Neutropenia	1	1	-	-	2 (10)	2 (10)	4 (20)	4 (20)
ALT increased	2	1	-	-	4 (20)	-	3 (15)	1 (5)
AST increased	1	1	-	-	2 (10)	-	3 (15)	1 (5)
Anemia	-	-	1	-	3 (15)	1 (5)	-	-
BTKi AEs of Special Interest								
Arthralgia	1	-	-	-	1 (5)	1 (5)	1 (5)	-
Atrial fibrillation	1	1	-	-	-	-	-	-
Hypertension	-	-	-	-	1 (5)	-	1 (5)	-

§Dose-escalation data reported as n patients with respective AEs

Efficacy

Efficacy Dose-Escalation Phase: Monotherapy and Combination Therapy

One patient in monotherapy did not have measurable adenopathy, but achieved PR by >50% reduction in lymphocytosis
One patient in combination therapy recently enrolled and is too early to evaluate

TG-1701 monotherapy
- ORR – 83% (5/6)
- Median follow up:
- 28 (18 – 31) months

TG-1701 + U2
- ORR – 100% (3/3)
- Median follow up:
- 19 (2 - 22) months

Efficacy Dose-Expansion Cohorts: Monotherapy 200 mg & 300 mg Dose Levels

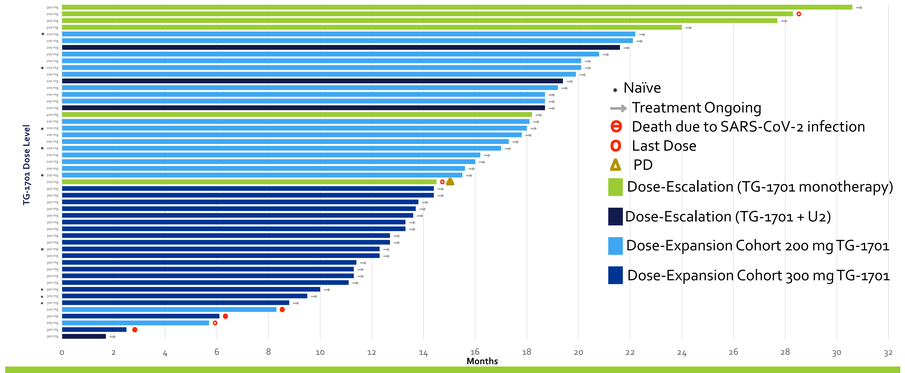
* Treatment naïve

TG-1701: 200 mg QD
- ORR – 95% (19/20)
- Median follow up:
- 19 (16– 22) months

TG-1701: 300 mg QD
- ORR – 100% (19/19)§
- Median follow up:
- 12 (9 – 14) months

§One patient in 300 mg dose cohort died due to SARS-CoV-2 infection before the first assessment and was not evaluable for efficacy

Treatment Exposure in CLL Patients



SUMMARY

- TG-1701 exhibits an encouraging safety and efficacy profile in patients with CLL
- TG-1701 shows promising activity and a manageable tolerability profile as monotherapy and in combination with U2
- The MTD has not been achieved in the monotherapy arm (up to 400mg QD)
- This study (NCT03671590) continues enrollment and future registration trials are being planned

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