Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies

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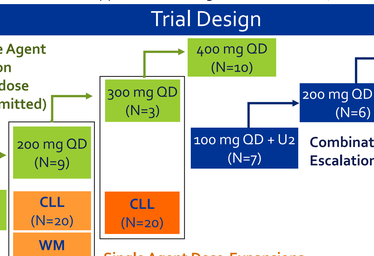
BACKGROUND AND METHODS

- Deep remissions with BTK monotherapy in CLL are rare
- TG-1701 is a covalently bound BTK inhibitor with superior selectivity compared with ibrutinib[1]
- The triple combination of TG-1701 with umbralisib and ublituximab (U2) inhibited tumor growth in BTK-resistant xenograft models[2]

Kinase Selectivity Profiling at 1uM in an *in vitro* whole kinome screening[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

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 Eligibility Criteria

- R/R pts with histologically confirmed B-cell lymphoma or CLL warranting systemic therapy were included. Previously untreated pts could be enrolled if unsuitable for standard front-line chemoimmunotherapy, in the disease-specific cohorts
- Pts with prior therapy with a BTK inhibitor; any severe or uncontrolled illness or condition; concomitant warfarin therapy (other anticoagulation is allowed), were excluded

Trial Design

- 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 thereafter.

RESULTS

Patient Demographics and Disease Characteristics

Characteristic	Dose-escalation Phase		Disease-specific Cohorts			
	TG-1701 (N = 25)	TG-1701 + U2 (N = 19)	200 mg QD CLL (N = 20)	200 mg QD WM (N = 20)	200 mg QD MCL (N = 21)	300 mg QD CLL (N = 20)
Male sex N(%)	14 (56)	8 (42)	7 (35)	12 (60)	13 (62)	10 (50)
Age, years, median (min/max)	68 (49 / 86)	69 (47/81)	71 (53 /87)	73 (57/92)	70 (57 /85)	71 (49/ 78)
≥75 years N(%)	7 (28)	5 (26)	4 (20)	8(40)	5(24)	6(30)
ECOG 0 / 1 / 2 (%)	56 / 44 / 0	79 / 21 / 0	35 / 65 / 0	45 / 50 / 5	48 / 48 /4	35 / 65 / 0
Prior therapies, median (range)	1 (1 - 5)	2 (1 - 5)	1 (0 – 5)	1 (0 – 4)	3 (0 – 10)	1 (0 – 5)
Refractory to last prior therapy N(%)	7 (28)	3 (16)	2 (10)	3 (15)	4 (19)	1 (5)
Prev. anti-CD20 therapy N(%)	25 (100)	19 (100)	14 (93)*	12 (100)*	18 (100)*	14 (93)*
Treatment-naïve N(%)	-	-	5 (25)	8 (40)	3 (14)	4 (20)

*Calculation excludes treatment-naïve patients

RESULTS

Patient Disposition

Cutoff: Apr 30, 2021	Dose-escalation Phase		Disease-specific Cohorts	
	TG-1701 (N=25)	TG-1701 + U2 (N=19)	200 mg (N=61)	300 mg (N=20)
Ongoing treatment N(%)	18 (72)	16 (84)	45 (74)	18 (90)
Intra-pt dose escalation N(%)	7 (28)	-	-	-
Dose redn. (any agent) N(%)	4 (16)	5 (31)	2 (3)	1 (5)
Pts off study N(%)	7 (28)	3 (16)	16 (26)	2 (10)
Reason for tx d/c N(%)				
Progression by criteria	5 (20)	2 (11)	10 (16)	-
Clinical progression	-	-	1 (2)	-
Treatment-related AE	-	-	1 (2)	-
Non-treatment related AE	-	1 (5)	2 (3)	2 (10)
Pt / physician decision - Other	2 (8)	-	2 (3)	-

Safety

All Causality AEs (≥10%) TG-1701 Monotherapy

Adverse event, N (%)	Dose escalation (100 to 400 mg) N=25		Disease-specific cohorts (200 mg) N=61		CLL cohort (300 mg) N=20	
	Any Grade	Grade 3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Respiratory tract infection	9 (36)	2 (8)	6 (10)	-	2 (10)	-
Constipation	8 (32)	-	3 (5)	-	-	-
Bruising	7 (28)	-	5 (8)	-	-	-
Fatigue	5 (20)	-	2 (3)	-	1 (5)	-
Rash	4 (20)	1 (4)	3 (5)	-	1 (5)	-
Nausea	4 (16)	-	1 (2)	-	2 (10)	-
Dizziness	4 (16)	-	1 (2)	-	-	-
Headache	3 (12)	-	6 (10)	-	1 (5)	-
Diarrhea	3 (12)	-	7 (11)	-	2 (10)	-
Epistaxis	3 (12)	-	2 (3)	-	-	-
COVID-19	-	-	4 (7)	1 (2)	3 (15)	2 (10)
Hematologic and lab abnormalities	**Any Grade**	**Grade 3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Neutropenia	6 (24)	2 (8)	8 (13)	5 (8)	2 (10)	2 (10)
ALT increased	6 (24)	3 (12)[a]	5 (8)	1 (2)	3 (15)	1 (5)
AST increased	5 (20)	1 (4)	3 (5)	-	3 (15)	1 (5)
Anemia	4 (16)	-	7 (11)	3 (5)	-	-

- **There have been no G4 AEs in the dose escalation of monotherapy**
- **At 200mg and 300 mg QD (n=81), AE's of special interest were G3 hypertension 4.9% and atrial fibrillation 1.2%. There have been no instances of major bleeding**

[a]All at 400 mg QD. 2 cases were brief episodes in asymptomatic pts with normal liver function (total bilirubin within normal range).
1 case was in the context of significant progression of disease in the liver.

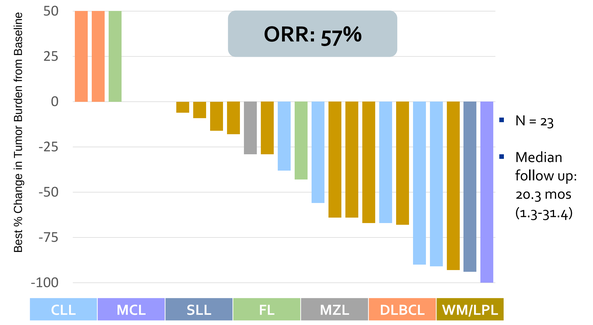
All Causality AEs (≥15%) TG-1701+U2 Combo

Adverse event, N(%)	Patients (N = 19)		
	Any Grade	Grade 3	Grade 4
Diarrhea	9 (47)	2 (11)	-
IRR[a]	9 (47)	1 (5)	-
Bruising	9 (47)	-	-
Nausea	6 (32)	1 (5)	-
Hypertension	6 (32)	1 (5)	-
Fatigue	4 (21)	-	-
Rash	3 (16)	-	-
Vomiting	3 (16)	-	-
Hematologic and laboratory abnormalities	**Any Grade**	**Grade 3**	**Grade 4**
Neutropenia	7 (37)	2 (11)	2 (11)
ALT increased	6 (32)	3 (16)[b]	1 (5)[c]
AST increased	6 (32)	3 (16)	-

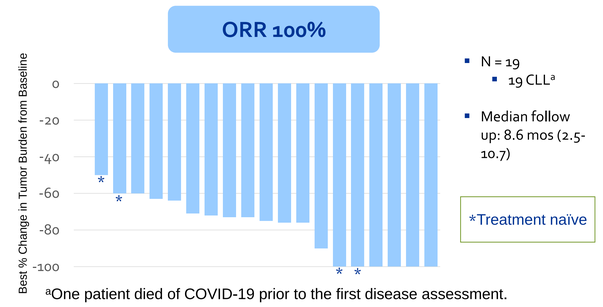
[a]IRR: includes the terms "chest tightness", and "facial flushing".
[b]All cases of G3 ALT increased were in patients with normal liver function (total bilirubin within normal range). Two patients continue therapy at a reduced dose of umbralisib (600 mg and 400 mg). The third patient discontinued ublituximab due to serum sickness.
[c]The G4 ALT increased was symptomatic (vomiting) and with abnormal liver function, the patient has recovered with complete response and remains on study therapy.

Efficacy

Dose-escalation (100 to 400 mg QD) Monotherapy

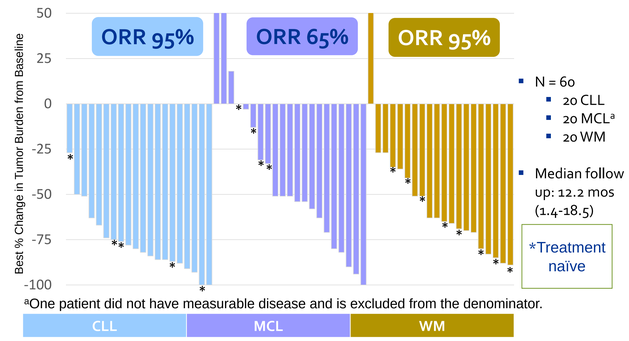


CLL Cohort Monotherapy (300mg)



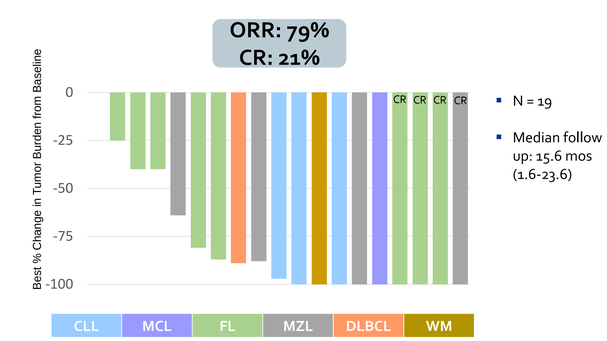
[a]One patient died of COVID-19 prior to the first disease assessment.

Disease-Specific Cohorts Monotherapy (200mg)



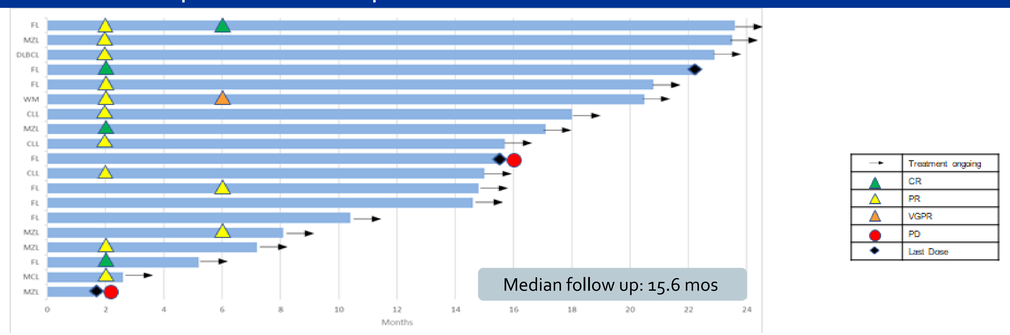
[a]One patient did not have measurable disease and is excluded from the denominator.

TG-1701 + U2 (100 to 300 mg QD)



Note: Waterfall plots include all patients with measurable disease at baseline and at least one evaluable post-baseline scan

Treatment Exposure and Response Duration Dose Escalation Combination Therapy



SUMMARY

- TG-1701 exhibits an encouraging safety profile, with clinical and pharmacodynamic activity at all dose levels evaluated that support QD dosing
- The MTD has not been achieved in the monotherapy arm (up to 400mg QD)
- 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 and future registration trials are being planned

Acknowledgements

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