The Selective Bruton's Tyrosine Kinase (BTK) Inhibitor TG-1701 as Monotherapy and in Combination with Ublituximab and Umbralisib (U2) in Patients with B-cell Malignancies

Chan Y. Cheah MBBS, DMSc[1], Wojciech Jurczak MD[2], Masa Lasica MBBS[3], Tomasz Wróbel MD[4], Stanley Cheung MBBS[5], Jan Walewski MD[6], Krzysztof Giannopoulos MD; PhD[7], Costas K. Yannakou MBBS[8], Katharine L. Lewis MBBS1, Monika Długosz-Danecka MD, PhD[2], Hari P. Miskin MSc[9], Alejandro D. Ricart MD[9], Owen A. O'Connor, MD, PhD[9], Constantine S. Tam MBBS, MD[3].

[1]Linear Clinical Research, and Department of Haematology, Sir Charles Gairdner Hospital, Nedlands Western Australia, Medical School, University of Western Australia, Crawley, Western Australia; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [3]St. Vincent Hospital and University of Melbourne, Melbourne, Victoria; [4]Wroclaw Medical University, Poland; [5]Ashford Cancer Centre Research, Adelaide, South Australia; [6]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [7]Hematology Department, St John's Cancer Centre, Lublin, Poland; [8]Department of Molecular Oncology and Cancer Immunology, Epworth HealthCare, East Melbourne, Victoria; [9]TG Therapeutics, Inc., New York, NY.

BACKGROUND

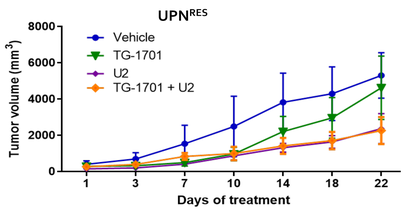
- Deep remissions with BTK monotherapy in CLL are rare
- TG-1701 is a covalently bound BTK inhibitor with superior selectivity compared with ibrutinib[1]
- The triple combination of TG-1701 with umbralisib and ublituximab (U2) inhibited tumor growth in BTK-resistant xenograft models[2]
- Here we present updated results from patients enrolled in an ongoing Phase 1 study of TG-1701 alone and in combination with U2

Kinase Selectivity Profiling at 1μM[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

[1]Normant E, et al., EHA 2018 (absPF638); [2]Ribeiro M, et al. AACR 2020 (abs 2205) .
BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukemia

TG-1701+U2 Inhibits Growth in BTK-resistant Cell Lines[2]



METHODS

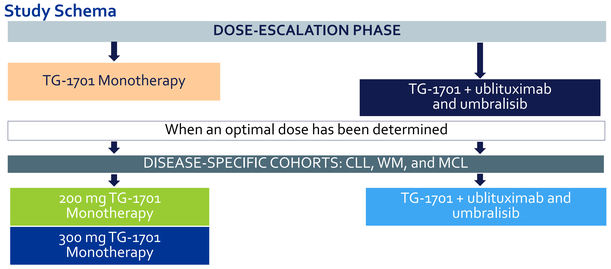
Key Inclusion Criteria

- 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 anticoagulants are allowed)
- Combination cohorts excluded prior PI3K exposure

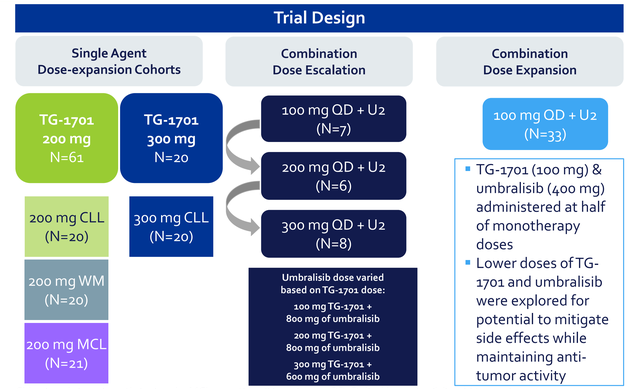
Study Schema



- 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.

BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukemia; IV: intravenous; MCL: mantle cell lymphoma; PI3K: phosphatidylinositol 3-kinase; PK: pharmacokinetics; QD: daily; R/R: relapsed or refractor; U2: umbralisib+ublituximab; WM: Waldenstrom's macroglobulinemia

Trial Design



CLL: chronic lymphocytic leukemia; MCL: mantle cell lymphoma; QD: Daily; U2: umbralisib+ublituximab; WM: Waldenstrom's macroglobulinemia

RESULTS

Patient Demographics and Disease Characteristics

Characteristic	TG-1701 200 mg Pooled N=61	TG-1701 300 mg CLL N=20	TG-1701 + U2 100 – 300 mg[b] N=21	TG-1701 + U2 100 mg[a] N=33
Male, n (%)	32 (52)	10 (50)	10(48)	24 (73)
Age, years, median (range) *≥75 years, n (%)*	71 (53 - 92) *16 (26)*	71 (49 - 80) *6 (30)*	69 (47 - 81) *5 (24)*	68 (38 - 75) *1 (3)*
ECOG 0 / 1 / 2, (%)	43 / 54 / 3	30 / 70 / -	76 / 24 / -	30 / 61 / 9
Treatment-naïve, n (%)	17 (28)	4 (20)	-	9 (27)
Previously treated, n (%)	44 (72)	16 (80)	21 (100)	24 (73)
Prior therapies, median (range)*	2 (1 - 10)	2 (1 - 7)	2 (1 - 8)	1 (1 - 5)
Refractory to last prior therapy, n (%)	14 (23)	2 (10)	4 (19)	6 (18)

*Calculation excludes treatment-naïve patients; a= 400mg of umbralisib was in combination with 100mg of TG-1701; b= Umbralisib dose varied based on TG-1701 dose; 600mg of umbralisib was in combination with 300mg of TG-1701; 800mg of umbralisib was in combination with 200mg of TG-1701; 800mg of umbralisib was in combination with 100mg of TG-1701. CLL: chronic lymphocytic leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; n: number, U2: umbralisib+ublituximab

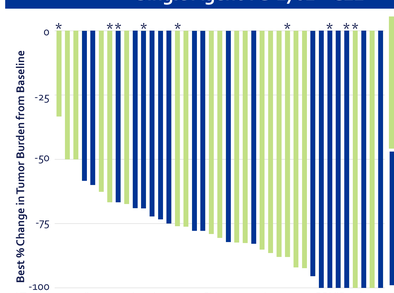
Patient Disposition

Cutoff: October 2021	TG-1701 200 mg Pooled N=61	TG-1701 300 mg CLL N=20	TG-1701 + U2 100 – 300 mg N=21	TG-1701 +U2 100 mg N=33
Median (range) Follow-up, mos	18 (12 - 24)	14 (10 - 16)	20 (3 - 30)	3 (0.2 - 6)
Pts continuing treatment, n (%)	42 (69)	18 (90)	18 (86)	33 (100)
Dose reduction (any agent), n (%)	2 (3)	-	1 (5)	-
Pts discontinued treatment, n (%)	19 (31)	2 (10)	3 (14)	-
Reason for treatment discontinuation, n(%)				
Clinical progression	11 MCL | 3 WM | 1 CLL	-	2	-
Due to treatment-related AE	-	-	-	-
Pt/physician decision	1	-	-	-
Death	1‡	2‡	-	-
Other	2*	-	1*	-

*Non-treatment-related adverse event. (1 Glioblastoma, 1 Melanoma, 1 unknown); ‡Death due to SARS-CoV-2 infection. AE: adverse event; CLL: chronic lymphocytic leukemia; MCL: mantle cell lymphoma; Mos: months; Pts: patients; U2: umbralisib+ublituximab; WM: Waldenstrom's macroglobulinemia

Efficacy

Single Agent TG-1701 – CLL

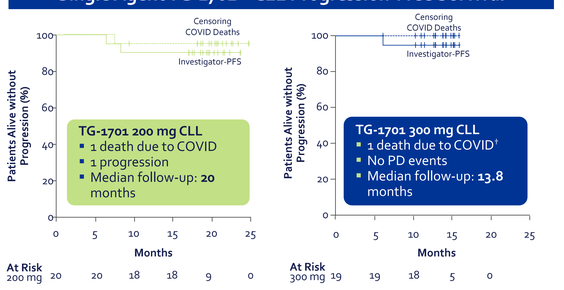


TG-1701 200 mg CLL (n=20)
- ORR – 95% (19/20)
- Median follow-up: 20 (17-23.7) months

TG-1701 300 mg CLL (n=19)†
- ORR – 100% (19/19)
- Median follow-up: 13.8 (10.3-15.9) months

*Treatment naïve. †1 patient in 300 mg CLL cohort died due to COVID prior to 1st assessment and is excluded from efficacy assessments. CLL: chronic lymphocytic leukemia; ORR: overall response rate

Single Agent TG-1701 – CLL Progression-Free Survival

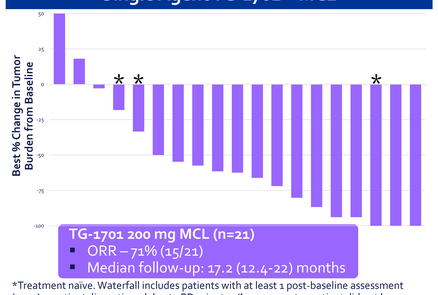


TG-1701 200 mg CLL
- 1 death due to COVID
- 1 progression
- Median follow-up: **20** months

TG-1701 300 mg CLL
- 1 death due to COVID†
- No PD events
- Median follow-up: **13.8** months

†1 additional patient in 300 mg CLL cohort died due to COVID prior to 1st assessment and is excluded from efficacy assessments. CLL: chronic lymphocytic leukemia; PD: progressive disease; PFS: progression-free survival

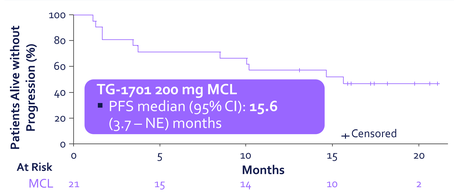
Single Agent TG-1701 – MCL



TG-1701 200 mg MCL (n=21)
- ORR – 71% (15/21)
- Median follow-up: 17.2 (12.4-22) months

*Treatment naïve. Waterfall includes patients with at least 1 post-baseline assessment (n=19). 1 patient discontinued due to PD prior to 1st assessment. 1 patient did not have nodal disease at baseline; however, was considered a responder by investigator due to reduction in splenomegaly. MCL: mantle cell lymphoma; ORR: overall response rate; PD: progressive disease

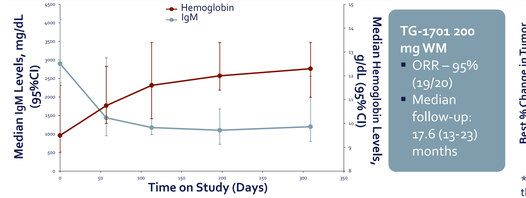
Single Agent TG-1701 – MCL Progression-free Survival



TG-1701 200 mg MCL
- PFS median (95% CI): **15.6** (3.7 – NE) months

CI: confidence interval; MCL: mantle cell lymphoma; NE: not estimable; ORR: overall response rate; PD: progressive disease; PFS: progression-free survival

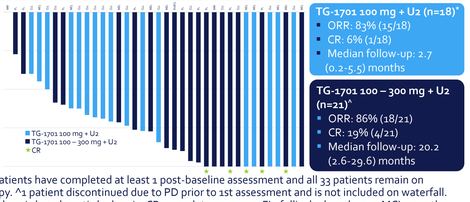
Single Agent TG-1701 – WM IgM & Hemoglobin Over Time



TG-1701 200 mg WM
- ORR – 95% (19/20)
- Median follow-up: 17.6 (13-23) months

CI: confidence interval; ORR: overall response rate; WM: Waldenstrom's macroglobulinemia. ORR included MR, VGPR, PR, and CR

Efficacy in Triplet Cohorts Dose Escalation & Dose Expansion



TG-1701 100 mg + U2 (n=18)^
- ORR: 83% (15/18)
- CR: 6% (1/18)
- Median follow-up: 2.7 (0.2-5.5) months

TG-1701 100 – 300 mg + U2 (n=21)^
- ORR: 86% (18/21)
- CR: 19% (4/21)
- Median follow-up: 20.2 (2.6-29.6) months

*18 patients have completed at least 1 post-baseline assessment and all 33 patients remain on therapy. ^1 patient discontinued due to PD prior to 1st assessment and is not included on waterfall. CLL: chronic lymphocytic leukemia; CR: complete response; FL: follicular lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; ORR: overall response rate; U2: umbralisib+ublituximab; WM: Waldenstrom's macroglobulinemia

Safety

All-causality AEs of Interest Any Cohort

AEs ≥5% TG-1701 200mg Pooled cohort or ≥20% in Triplet cohorts, n (%)§	TG-1701 200 mg Pooled N=61		TG-1701 300 mg CLL N=20		TG-1701 + U2 100 – 300 mg N=21		TG-1701 +U2 100 mg N=19[X]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	11 (18)	-	2 (10)	-	10 (48)	2 (10)	2 (11)	-
URTI	7 (11)	-	3 (15)	-	-	-	-	-
Headache	7 (11)	-	1 (5)	-	2 (10)	-	-	-
Contusion	6 (10)	-	1 (5)	-	9 (43)	-	1 (5)	-
Abdominal pain upper	5 (8)	-	-	-	1 (5)	-	-	-
Fatigue	4 (7)	-	2 (10)	-	8 (38)	-	2 (11)	-
Nausea	1 (2)	-	3 (15)	-	8 (38)	1 (5)	-	-
Infusion related reaction	-	-	-	-	6 (29)	1 (5)	1 (5)	-
Hematologic & Lab Abnormalities								
Neutropenia‡	7 (11)	5 (8)	4 (20)	4 (20)	7 (33)	4 (19)	4 (21)	3 (16)
ALT increased	8 (13)	2 (3)	3 (15)	1 (5)	6 (29)	4 (19)	1 (5)	1 (5)
AST increased	5 (8)	1 (2)	3 (15)	1 (5)	6 (29)	3 (14)	1 (5)	1 (5)
Anemia	6 (10)	3 (5)	-	-	2 (10)	-	-	-

§Excludes AEs of special interest. [X]Only including patients that has been in the study for ≥2months (n/N= 19/33).
‡Includes neutropenia & neutrophil count decreased MedDRA preferred terms
AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CLL: chronic lymphocytic leukemia; U2: umbralisib+ublituximab; URTI: upper respiratory tract infection

BTKi AEs of Special Interest

BTKi AEs of Special Interest, n (%)	TG-1701 200 mg Pooled N=61		TG-1701 300 mg CLL N=20		TG-1701 + U2 100 – 300 mg N=21		TG-1701 + U2 100mg N=19[X]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Arthralgia	4 (7)	1 (2)	1 (5)	-	2 (10)	-	-	-
Atrial fibrillation	1 (2)	1 (2)	-	-	1 (5)	-	-	-
COVID-19	4 (7)	1 (2)	3 (15)	2 (10)‡	-	-	-	-
Hemorrhage*	6 (10)	1 (2)	2 (10)	1 (5)	2 (10)	-	-	-
Hypertension^	5 (8)	3 (5)	2 (10)	1 (5)	6 (29)	1 (5)	-	-
Pneumonia	2 (3)	-	-	-	1 (5)	-	-	-

‡Death due to SARS-CoV-2 infection. ^Pooled term to Include blood pressure increase and hypertension. *Pooled term to Include blood blister, conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemorrhage, intracranial hemorrhage, mouth hemorrhage, skin hemorrhage, subdural hematoma evacuation. [X]Only including patients that has been in the study for ≥2months (n/N= 19/33); AE: adverse event; BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukemia; U2: umbralisib+ublituximab

SUMMARY AND CONCLUSIONS

- TG-1701 exhibits an encouraging safety profile with manageable adverse events
- TG-1701 shows promising antitumor activity in patients across B-Cell malignancies
  - Only 1 PD event among CLL patients treated at the 200 & 300 mg dose levels
  - TG-1701 200mg exhibits an ORR of 71% in the MCL cohort
  - TG-1701 200mg exhibits ORR of 95% in the WM cohort
- The combination of TG-1701 + U2 has been well tolerated with limited occurrences of AEs of special interest. Combination therapy is associated with encouraging clinical activity, including early CR rates
- This study (NCT03671590) is ongoing and future registration trials are being planned
- **Acknowledgements:** Thank you to the patients and their families for their participation.

Disclosures

CYC - AbbVie Inc., Ascentage Pharma, AstraZeneca, BeiGene, Celgene, Gilead Sciences, Inc., Janssen, Loxo/Lilly, MSD, Roche, and TG Therapeutics, Inc. **WJ** - AbbVie Inc., AstraZeneca, Bayer, BeiGene, Celgene, Celltrion Healthcare, Debbiopharm, Epizyme, Incyte, Janssen, Loxo Oncology, Mei Pharma, Merck, MorphoSys, Novo Nordisk, Roche, Sandoz, Takeda, and TG Therapeutics, Inc. **ML** - AbbVie Inc. and Celgene. **TW** - BeiGene, Bristol Meyers Squibb, Janssen, Novartis, Roche, and Takeda. **SC, CKY, and KLL** have nothing to disclose. **JW** - AbbVie Inc., Amgen, Gilead Sciences, Inc., GSK, Novartis, Roche, Servier, and Takeda. **KG** - AbbVie Inc., Amgen, AstraZeneca, BeiGene, Gilead Sciences, Inc., GSK, Janssen, Karyopharm Therapeutics, Novartis, Pfizer, Polish Myeloma Consortium, Next Generation Hematology Association, Roche, Sandoz, Sanofi -Genzyme, Takeda, Teva, and TG Therapeutics, Inc. **MDD** - AbbVie Inc., Acerta Pharma, BeiGene, Incyte, Janssen, MacroGenics, MEI Pharma, Roche, Servier, and Takeda. **HPM** - TG Therapeutics, Inc. **ADR** - Gilead Sciences, Inc., Merck, Pfizer, Seagen Inc., and TG Therapeutics, Inc. **OAO** - Dren, Kymera, Mundipharma, Myeloid Therapeutics, Nomocan, and TG Therapeutics, Inc. **CST** - AbbVie Inc., BeiGene, Janssen, Loxo Oncology, Novartis, Pharmacyclics LLC, an AbbVie Company, and Roche.

American Society of Hematology 63rd Congress December 11, 2021.