First-in-Human (FIH) Study of the Fully-Human Kappa-Lambda CD19/CD47 Bispecific Antibody TG-1801 in Patients (pts) with B-Cell Lymphoma

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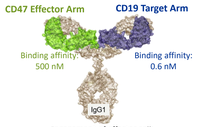
BACKGROUND

- TG-1801 is a bispecific IgG1 antibody that combines the selective, high affinity targeting to CD19+ cells with the blockade of the CD47-SIRPα axis[1]
- Since CD47 is ubiquitously expressed, a major limitation of CD47 targeted therapies is target-mediated drug disposition ("sink effect") resulting in potential safety concerns which include anemia or thrombocytopenia[2]
- TG-1801 has a thousand-fold difference between the binding affinity to CD19 and CD47 which allows it to selectively block CD47 on CD19+ B cells but not on red blood cells or platelets
- Ublituximab is a novel glycoengineered anti-CD20 monoclonal antibody

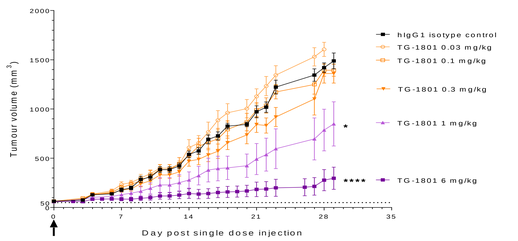


Engagement of effector cell: macrophages (ADCP), NK cells (ADCC)

1. Buatois, V., 2018, Mol. Cancer. Ther.
2. Sikic B.I., 2020, J. Clin. Onc

Preclinical Efficacy in Lymphoma Xenograft Study

- Dose-dependent anti-tumor activity of TG-1801 after a single dose was assessed in CB17 SCID subcutaneously implanted with Raji cells (Burkitt's Lymphoma)
- Mice received a single IV injection of TG-1801 at 0.03, 0.1, 0.3, 1, or 6 mg/kg or hIgG1 control Ab at 6 mg/kg. Tumor volume was measured 3 times a week.
- Dose levels of ≥1 mg/kg TG-1801 significantly reduced tumor growth.



Graph represents the mean ± SEM of tumor volumes for each treatment group (n=8/group). Statistics are performed using one-way ANOVA Tukey's multiple comparison test. * p<0.05, **p<0.01, ****p<0.0001.

METHODS

Key Study Outline

- Single patient dose escalation until Dose Limiting Toxicity (DLT)
- Intra patient dose escalation was allowed

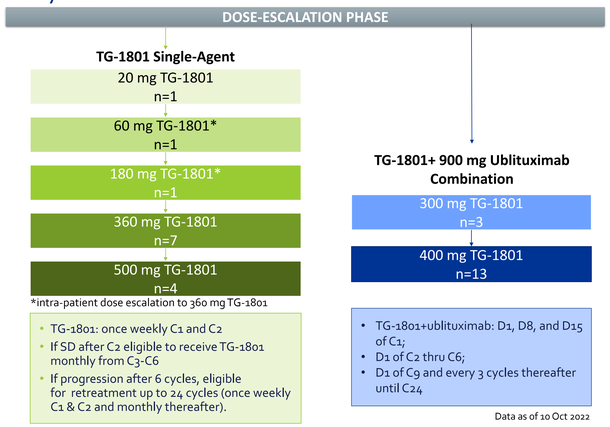
Key Inclusion Criteria

- Histologically confirmed B-cell lymphoma or CLL that warrants systemic therapy
  - R/R disease to prior standard therapy with no limit on the number of prior lines
- Absolute neutrophil count (ANC) ≥ 1,000/μL and platelet count ≥ 75,000/μL
- Adequate organ system function

Key Exclusion Criteria

- Prior CD47/SIRPα pathway or CD19-directed therapies
- Prior autologous stem cell transplant within 6 months; prior allogeneic hematologic stem cell transplant within 1 year; any active graft versus host disease
- Any severe or uncontrolled illness or condition; concomitant warfarin therapy (other anticoagulants allowed)

Study Schema



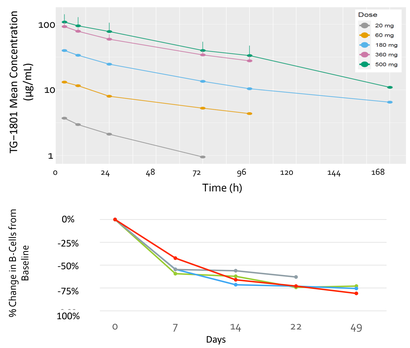
Data as of 10 Oct 2022

Baseline Characteristics

Demographics	TG-1801 n=14	TG-1801 + ublituximab n=16	Overall N=30
Age, median (min, max)	69 (51, 82)	71 (50,87)	**70 (50, 87)**
Males / Females	8/6	11/5	**19 / 11**
NHL Subtype			
Diffuse Large B Cell Lymphoma (DLBCL)	4	9	**13**
Follicular Lymphoma (FL)	4	4	**8**
Marginal Zone Lymphoma (MZL)	5	2	**7**
Mantle Cell Lymphoma (MCL)	0	1	**1**
Richter's Transformation (RT)	1	0	**1**
Prior Lines of Treatment, median (min, max)	4 (1,8)	3 (1,5)	**3 (1, 8)**
Stem Cell Transplant	2 (14%)	3 (19%)	5 (17%)
Anti-CD20 Treatment	14 (100%)	16 (100%)	**30 (100%)**
Refractory to last line of therapy	8 (57%)	8 (50%)	**16 (53%)**

Pharmacokinetics - Pharmacodynamics

- Preliminary evaluation shows approximate dose linearity over the dose range studied (N= 1 to 3). A rapid pharmacodynamic effect (B-cell depletion) was observed at all dose levels.



RESULTS

Safety

TG-1801 Single-Agent

- 2 patients discontinued the study due to a TEAE
  - 1 patient due to IRR
  - 1 patient due to rash
- No fatal TEAEs
- At 500 mg, one patient experienced a DLT of Grade 4 thrombocytopenia

Table 1. TEAEs occurring in >10% of pts treated with TG-1801 up to 360 mg (n=10)

Preferred Term	All Grades, n(%)	Grades ≥3, n(%)
Fatigue	3 (30%)	-
Thrombocytopenia	3 (30%)	1 (10%)
Infusion related reaction	3 (30%)	-
Dyspepsia	2 (20%)	-
Blood creatinine increased	2 (20%)	-
Anemia	2 (20%)	2 (20%)
Pulmonary embolism	2 (20%)	1 (10%)
Cancer pain	2 (20%)	1 (10%)
Rash	2 (20%)	1 (10%)
Constipation	2 (20%)	-
Diarrhea	2 (20%)	-
Headache	2 (20%)	-

Serious adverse events: pulmonary embolism, pleural effusion, rash, atrial flutter, pneumonitis, cardiac failure, pyrexia, infusion related reaction, anemia, musculoskeletal chest pain

Table 2. TEAEs occurring in at least 2 pts treated with TG-1801 at 500 mg (n=4)

Preferred Term	Any Grade (%)	Grade ≥3 (%)
Thrombocytopenia	3 (75%)	3 (75%)
Anaemia	2 (50%)	1 (25%)
Abdominal pain upper	2 (50%)	-

TG-1801+Ublituximab

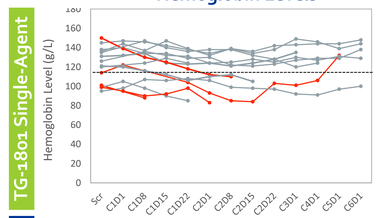
- No discontinuations due to a TEAE
- No fatal TEAEs
- No DLTs

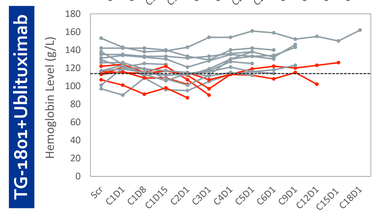
Table 3. TEAEs occurring in >10% of pts treated with TG-1801+Ublituximab (n=16)

Preferred Term	All Grades, n(%)	Grades ≥3, n(%)
Anemia	5 (31%)	1 (6%)
Headache	5 (31%)	
Fatigue	5 (31%)	
Abdominal pain	4 (25%)	
COVID-19	4 (25%)	
Dizziness	3 (19%)	
Neutropenia	3 (19%)	3 (19%)
Thrombocytopenia	3 (19%)	2 (13%)
Back pain	2 (13%)	
Upper respiratory tract infection	2 (13%)	
Night sweats	2 (13%)	
Constipation	2 (13%)	
Anxiety	2 (13%)	
Fall	2 (13%)	1 (6%)
Hypomagnesaemia	2 (13%)	
Hypotension	2 (13%)	
Diarrhea	2 (13%)	
Nausea	2 (13%)	
Tinnitus	2 (13%)	

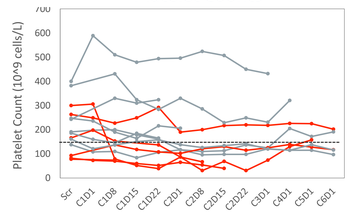
Serious adverse events: squamous cell carcinoma, papillary thyroid cancer, transient ischemic attack, dizziness, partial seizures, dysphagia, tibia fracture, fall, atrial fibrillation, lower respiratory tract infection

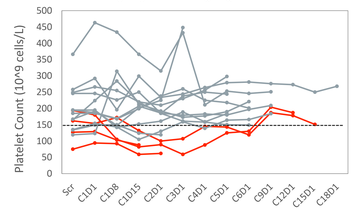
Hemoglobin Levels





Platelet Counts



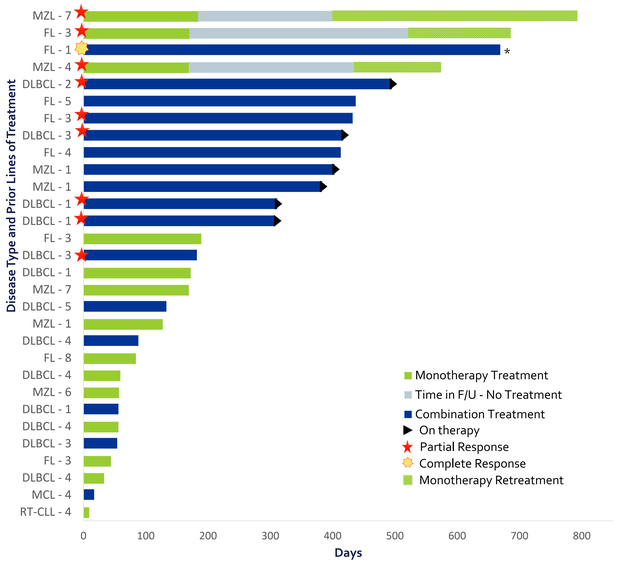


*Lower Limit of Normal (LLN) ranged from 115-130 (g/L) for hemoglobin levels; black dotted line represents the LLN; red lines represent patients with anemia (hemoglobin graphs) or thrombocytopenia (platelet graphs)

- Time course analysis of hemoglobin levels and platelet counts do not indicate a "sink effect", consistent with the bispecific nature of TG-1801 with specificity for CD19+ cells
- There was no apparent difference in the rates of anemia and thrombocytopenia with the addition of ublituximab
- Generally, reductions in hemoglobin levels or platelet counts occurred in patients with low baseline values and events of anemia and thrombocytopenia were manageable and did not lead to discontinuation at doses ≤400 mg

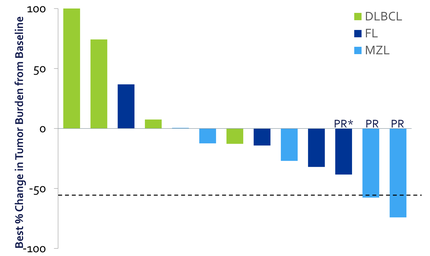
Efficacy

Disposition of Patients



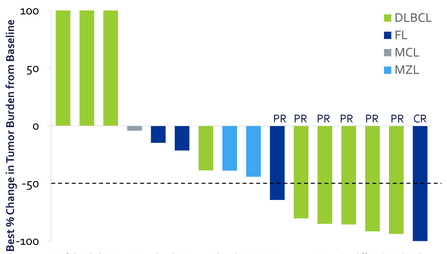
*Subject completed the treatment course with 24 cycles of TG-1801+ublituximab treatment;
DLBCL, diffuse large b cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma

TG-1801 Single Agent



Waterfall includes patients with at least 1 post-baseline assessment (n=13), 1 patient discontinued due to PD prior to 1st assessment (clinical progression). *1 patient was considered a PR by metabolic response. DLBCL, diffuse large b cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; PR, partial response by Lugano criteria

TG-1801 + Ublituximab Combination



Waterfall includes patients with at least 1 post-baseline assessment (n=16). DLBCL, diffuse large b cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PR, partial response; CR, complete response

CONCLUSIONS

- Herein, we report the results of a first-in-human Phase 1 study of the first-in-class CD47/CD19 bispecific antibody, TG-1801, as a monotherapy and TG-1801 in combination with the anti-CD20 monoclonal antibody ublituximab.
- TG-1801 had a tolerable preliminary safety profile, with limited hematologic toxicities previously observed with other CD47 targeted therapies. No additive toxicities were observed with combination treatment.
- Pharmacokinetics were approximately dose-proportional and pharmacodynamic B-cell depletion of more than 50% was detected in all patients.
- Preliminary efficacy was observed in a heavily pre-treated patient population, with partial responses in 3 patients (23%) treated with single-agent TG-1801 including one patient with 7 prior lines of therapy. One (1) complete response and 6 partial responses (44%) were observed on TG-1801+ublituximab combination treatment in DLBCL and FL patients.
- Further exploration of TG-1801 single-agent and combination treatment is warranted.
- This study (NCT03804996) has completed enrollment.
- **Acknowledgements:** Thank you to the patients and their families for their participation.

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