TGR-1202 in Combination with Ibrutinib in Patients with Relapsed or Refractory CLL: Updated Results of a Multicenter Phase I/Ib Study

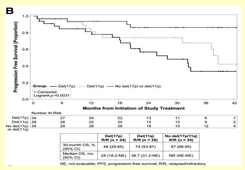
Matthew S. Davids, MD, MMSc[1], Haesook T. Kim, PhD[1], Alyssa Nicotra[1], Alexandra Savell[1], Karen Francoeur, RN[1], Jeffrey M. Hellman, PA-C[1], Hari Miskin[2], Peter Sportelli[2], Asad Bashey, MD, PhD[3], Laura Stampleman, MD[4], Jens Rueter, MD[5], Adam Boruchov, MD[6], Jon E. Arnason, MD[7], Caron A. Jacobson, MD[1], David C. Fisher, MD[1], and Jennifer R. Brown, MD, PhD[1]

[1] Dept. of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA, [2]TG Therapeutics, New York, USA, [3]Bone Marrow Transplantation Group of Georgia, Atlanta, USA, [4]Pacific Cancer Care, Salinas, CA, USA, [5]Eastern Maine Medical Center, Bangor, ME, USA, [6]St. Francis Medical Center, Hartford, CT, USA, and [7]Dept. of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, USA

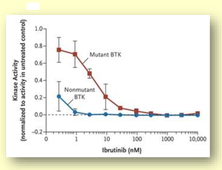
Leukemia & Lymphoma Society | Blood Cancer Research Partnership (LLS/BCRP)

Background

1. High risk CLL patients have less durable response to ibrutinib and are at risk for resistance mutations

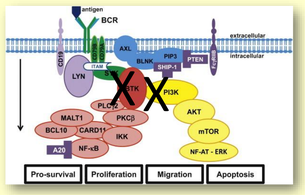


Byrd et al., *Blood*, 2015



Woyach et al., *N Engl J Med*, 2014

2. Targeting multiple BCR pathway kinases may help overcome resistance



Niemann et al., *Seminars in Cancer Biology*, 2013

3. TGR-1202 is a potent and well-tolerated next-generation PI3K-delta inhibitor

TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
Delta QD	Delta BID	Delta/Gamma BID

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

In 165 patients treated with TGR-1202 alone or in combination with anti-CD20:

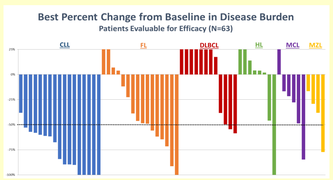
- 80 patients on study >6 cycles, and 43 patients on study >12 cycles
- Grade 3/4 AST/ALT increase was 3% (8% all grades)
- 5% had Grade 3 pneumonia
- Diarrhea in 47%, mainly grade 1, with 5 patients (3%) with Grade 3/4
- 8% of patients have come off study due to an adverse event

Burris et al, ASCO 2016

[1]Flinn et al., 2009
[2]Porter et al., 2012

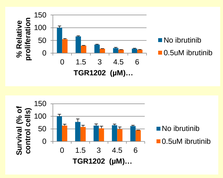
4. TGR-1202 is active in R/R CLL, and preclinical combination data with ibrutinib are promising

TGR-1202 monotherapy in CLL patients



O'Connor et al, ASH 2015

TGR-1202 + ibrutinib *in vitro*



I. Ghobrial Lab, unpublished data

Aims/Methods

Endpoints

Primary

- Maximum tolerated dose (MTD)/Recommended Phase 2 Dose (RP2D) of TGR-1202 plus ibrutinib in patients with relapsed or refractory CLL or MCL
- Safety and dose limiting toxicities (DLTs) of TGR-1202 plus ibrutinib in patients with relapsed or refractory CLL or MCL

Secondary

- Clinical response: ORR, CR, PR, PR-L, PFS, and remission duration
- Association of CLL prognostic factors (e.g. FISH, *IGHV*, etc.) with response

Exploratory

- Association of novel prognostic factors such as BH3 profiling and somatic mutations in *SF3B1, NOTCH1, MYD88* and *BCR/NFKB* with response

Key Eligibility Criteria

Inclusion

- At least 1 prior standard therapy, an indication for therapy, and at least 1 measurable site of disease
- ANC ≥ 0.500 K/uL, platelets ≥ 30 K/uL (except pts w/ >50% CLL in marrow)
- Total bilirubin ≤1.5X ULN, unless due to Gilbert's or hemolysis, then ≤3.0X ULN, ALT/AST ≤ 2.0X ULN or ≤ 4X ULN if known liver involvement
- Creatinine ≤ 2.5 mg/dL OR calculated creatinine clearance ≥ 50 mL/min
- In Ph I portion, patients with prior BTK or PI3Ki therapy were eligible

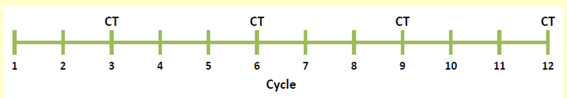
Exclusion

- AlloHCT within 12 mo. of study entry
- Post-allo patients must not have active GVHD and be off IS
- Active hepatitis, HIV infection, or central nervous system involvement
- Patients who require warfarin for anticoagulation

Study Design

Dose Level	TGR-1202 Dose	Ibrutinib Dose
1	400 mg	420 mg
2	600 mg	420 mg
3	800 mg	420 mg
If > 2 DLTs in Cohort 1, 3- 6 pts will enroll in Cohort -1 as follows:		
-1	200 mg	420 mg
If > 2 DLTs in Cohort –1, study will be terminated		

- Parallel arms for CLL and MCL which escalated independently
- TGR-1202: oral, once daily in the morning
- Ibrutinib: oral, 420 mg daily in the evening for CLL
- Both agents continued until time of progression or unacceptable toxicity
- Standard toxicity assessments by CTCAE v4.03, efficacy by 2008 IW-CLL
- Response evaluations: after cycles 2, 5, 8, 12, and q6 mo. thereafter



Statistical Design

- Phase I with a standard 3 + 3 design with up to 4 dose levels of TGR-1202
- 91% probability of dose escalation if the true rate of DLT is 10% and 17% probability of escalation if the true DLT rate is 50%
- Phase Ib expansion cohorts of 12 pts each in CLL and MCL
- Estimation of toxicity rates in 12 pt cohorts: 90%CI will be within +/- 25%
- Efficacy analyses: 2008 IW-CLL criteria

Results

Patient Characteristics (n=18)

- Median age at enrollment: 67 years (range 48-76)
- Median # prior therapies: 2 (range 1-6, with 2 prior ibrutinib, 4 prior PI3Ki)
- CLL prognostic markers:
  - -FISH: 6/18 (33%) with del(11q), 4/18 (22%) with del(17p),
  - -*IGHV*: 11/16 (69%) unmutated
  - -2 patients each with *TP53* or *NOTCH1* mutation

Safety Analysis (n=18)

- No DLTs were observed
- RP2D of TGR-1202 when given with ibrutinib is 800 mg daily

Hematologic toxicity :

- Neutropenia (38%, 17% Gr 3-4)
- Thrombocytopenia (11%, all Gr 1)
- Anemia (15%, all Gr 1/2)

All grade non-heme toxicities in ≥ 20% of pts:

- Nausea (39%, 33% Gr 1, 6% Gr 2)
- Diarrhea (28%, 17% Gr 1, 11% Gr 2)
- Fatigue, dizziness (22%, both Gr 1)

SAEs (in 1 patient each):

- Amylase/Lipase elevation (Gr 3, required study drug discontinuation)
- Atrial fibrillation (Gr 3)
- CNS aspergillus (Gr 3)
- Adrenal insufficiency (Gr 3)
- Sudden death, uncertain cause (Gr 5)

Efficacy Analysis (n=18)

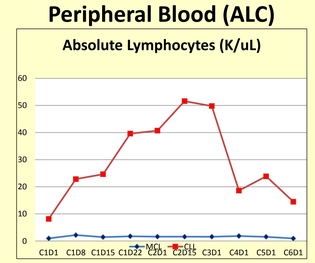
- ORR: 16/18 (89%)
  - -PR or PR-L: 15/18 (83%), including 1 pt. with radiographic CR but residual low level lymphocytosis
  - -CR: 1/18 (6%) (confirmed with neg. BM, MRD positive)
- Although none of the pts were refractory to prior BCR kinase inhibitors, 3 pts with prior PI3Ki exposure responded, as did 1 of the 2 pts with prior ibrutinib exposure.
- The median time on study is 11 mo. (range 0.1-23.5 mo.).
- One responder has progressed to date, and 1 year PFS and OS are 94%

Efficacy Analysis (n=18)

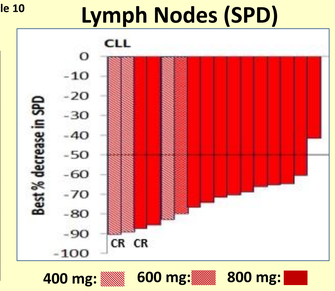
	Pt	TGR-1202 Dose	Best Response	FISH	*IGHV* status
Dose level 1	01	400 mg	PR	13q + tri 12, *NOTCH1* mut	Unmut
	02	400 mg	CR (BM MRD+)	14q32 + 13q	Unmut
Dose level 2	03	400 mg	PR	13q, *TP53* mut, VH3-21	Mut
	04#^	600 mg	SD	17p + 11q + 13q	Unmut
	05	600 mg	PR	17p + 13q	N/A
Dose level 3	06#	600 mg	PR	14q, tri12, complex	Unmut
	07*	800 mg	SD	13q	Mut
	08	800 mg	PR	14q, 13q, 11q, complex	Unmut
Dose expansion	09	800 mg	PR	Normal	Mut
	10	800 mg	PR	13q	Mut
	11	800 mg	PR	17p + 13q	Unmut
	12	800 mg	PR-L	11q + 13q	Unmut
	13	800 mg	PR	Tri12, *NOTCH1* mut	Unmut
	14	800 mg	PR	13q	Unmut
	15=	800 mg	PR	11q + *TP53* mut	N/A
	16	800 mg	PR-L	17p + 11q	Mut
	17	800 mg	PR-L	Tri12	Unmut
	18	800 mg	PR-L	11q	Unmut

Already on ibrutinib at time of study enrolment: 4 months (Pt 04) and 3 weeks (Pt 06))
* Came off study after 2 cycles due to vertigo, possibly related
^ Only on treatment intermittently, came off study due to CNS aspergillus
= Progressive disease at cycle 10

Peripheral Blood (ALC)



Lymph Nodes (SPD)



400 mg: 600 mg: 800 mg:

Conclusions

- We report to our knowledge the first clinical data on a PI3K plus BTK inhibitor doublet tested in CLL
- TGR-1202 + ibrutinib is well-tolerated in R/R CLL, with no DLTs observed in phase I, and an RP2D of TGR-1202 in combination with ibrutinib of 800 mg daily
- Immune-mediated toxicities seen with other PI3Kδi were minimal
- The toxicities of TGR-1202 + ibrutinib are manageable and comparable to the additive toxicity profiles of the two agents given individually
- The preliminary efficacy results suggest a high response rate in CLL, including those with high risk disease, with one patient achieving CR at 1 yr and several others approaching CR over time
- Accrual continues to this ongoing study

Acknowledgements/Disclosures

- The authors thank the patients and their families for participating
- This investigator-sponsored trial (NCT02268851) is supported by TG Therapeutics (New York, USA) and a Leukemia & Lymphoma Society BCRP/TAP grant
- COI: Drs. Davids and Brown: SAB/consulting fees from Pharmacyclics, Inc. and Janssen, Dr. Davids: SAB for TG Therapeutics
- Sportelli and Miskin: Employees of TG Therapeutics. All other authors have no relevant disclosures
- Dr. Davids has an ASCO Career Development Award, and is a graduate of the ASH CRTI and ASCO/AACR Vail Workshop

Corresponding Author:
matthew_davids@dfci.harvard.edu