Safety and Activity of the Chemotherapy-free Triplet of Ublituximab, TGR-1202, and Ibrutinib in Relapsed B-cell Malignancies

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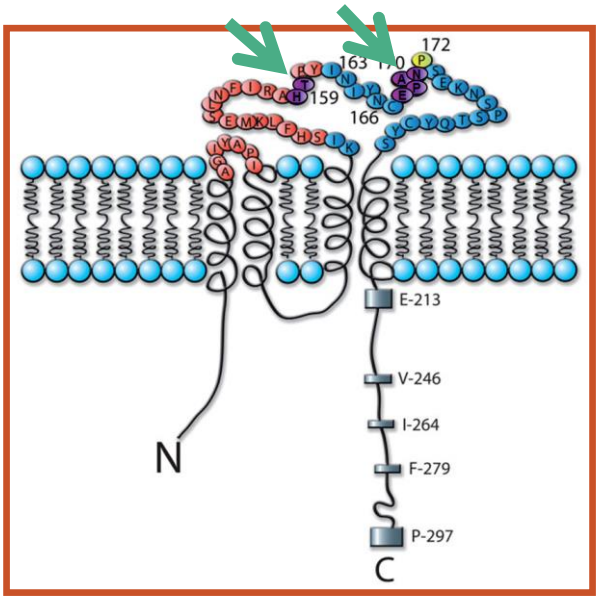
Ublituximab: Glycoengineered Anti-CD20 mAb

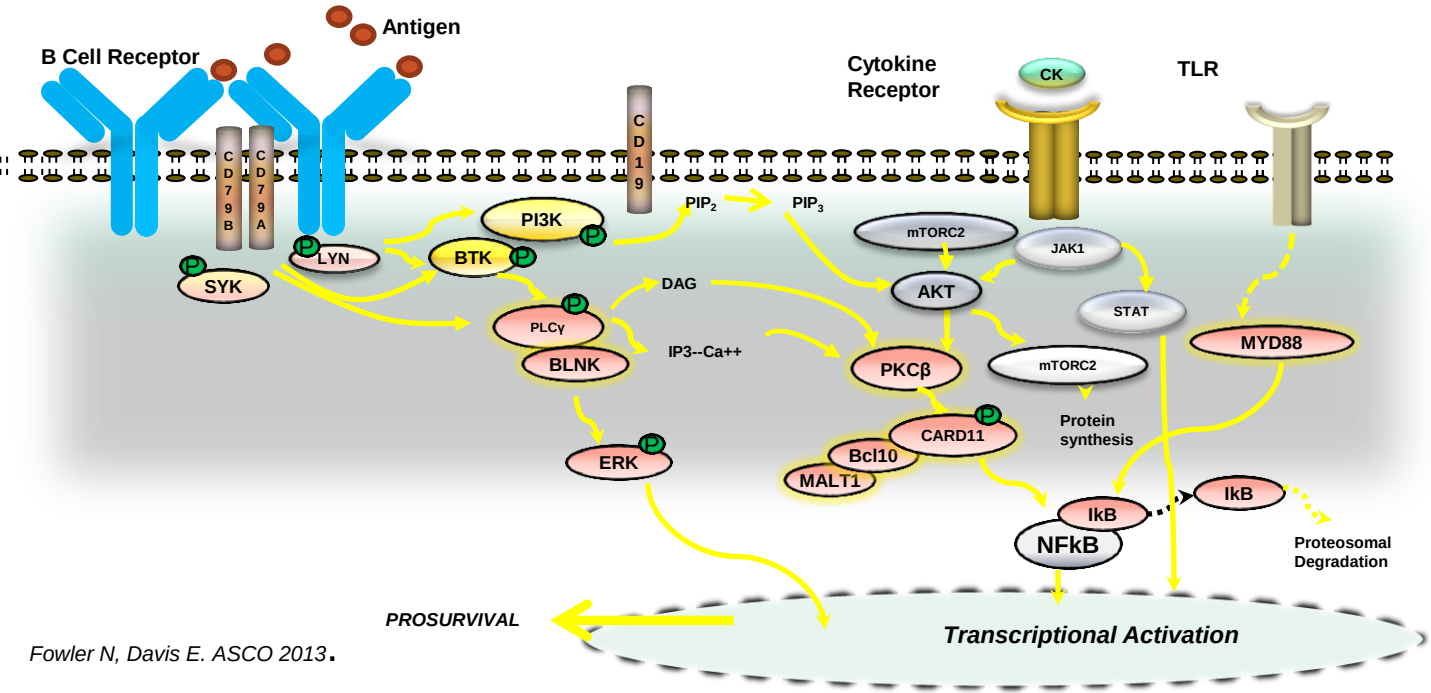
- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20 (**Green** arrows in figure)
- Potential advantages over current standards of care:
  - Glycoengineered for enhanced ADCC
  - Activity in “low” CD20 expressing cell lines
- Single agent responses observed in rituximab refractory patients[1]



(1) O’Connor et al, ASCO 2014

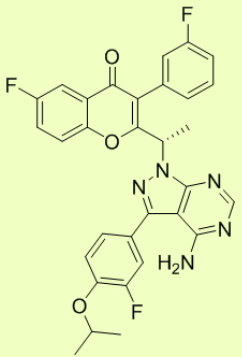
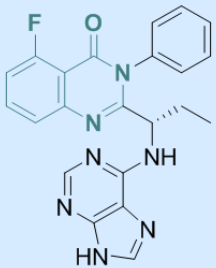
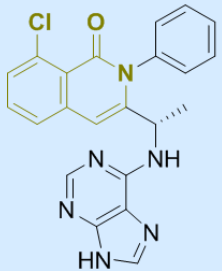
Source: Adapted from Ruuls et al 2008

B-Cell Receptor Signaling in Lymphoma



Fowler N, Davis E. ASCO 2013.

TGR-1202: Novel PI3K delta Inhibitor

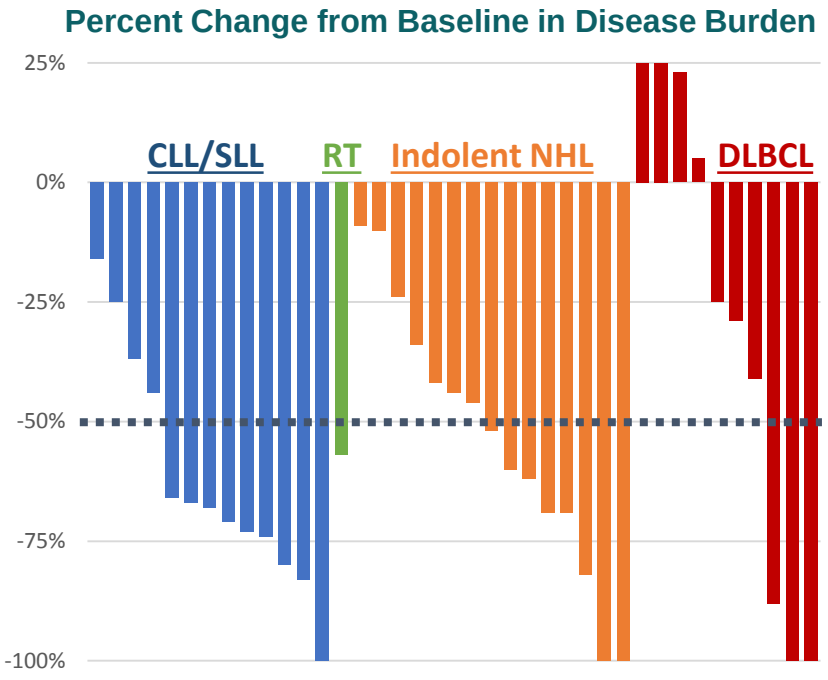
TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

- PK profile that allows once-daily oral dosing
- 93% nodal PR rate in patients with rel/ref CLL[1]

[1]Burris et al, ASCO 2015, Abstract # 7069

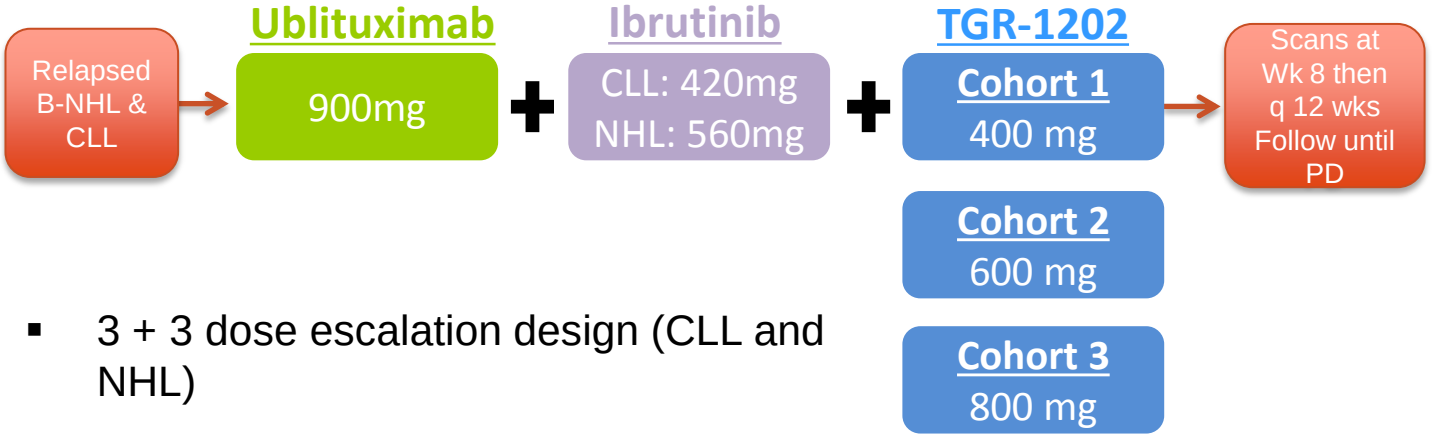
TGR-1202 + Ublituximab Doublet

- 55 patients treated to date
  - 60% ≥3 prior therapies
  - 51% refractory to prior therapy
- Combination well tolerated
  - Minimal Gr. 3/4 AE's
- Clinical activity demonstrated in CLL, indolent NHL, and aggressive NHL



Lunning et al, ASCO 2015

Trial Design:
TGR-1202 + Ublituximab + Ibrutinib

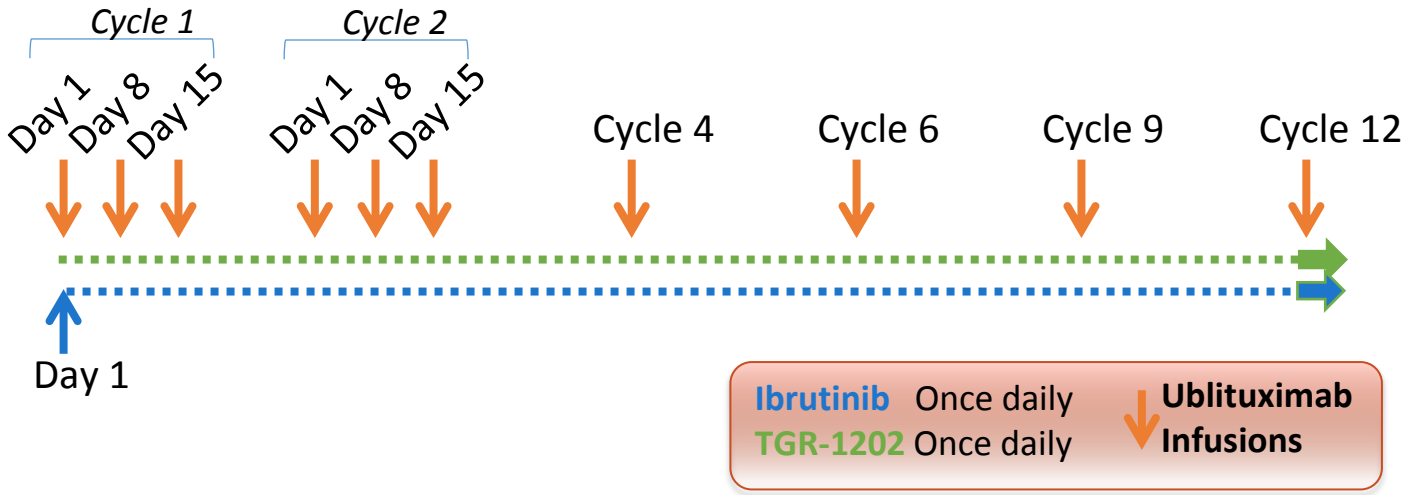


- 3 + 3 dose escalation design (CLL and NHL)
- No limit on prior # of therapies
- ECOG Performance Status ≤ 2
- ANC > 500 / Plts > 30,000
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible

Endpoints:

- Primary: Safety
- Secondary: ORR, DOR, PFS

Schema:
TGR-1202 + Ublituximab + Ibrutinib



- Both ibrutinib and TGR-1202 were administered once-daily starting on Day 1
- Ublituximab given on Day 1,8,15 of cycles 1 and 2, and day 1 of cycles 4, 6, 9, and 12.

Demographics: TGR-1202 + Ublituximab + Ibrutinib

Evaluable for Safety (n)		16
Evaluable for Efficacy† (n)		13
Median Age, years (range)		63 (51 – 85)
Male/Female		12/4
ECOG, 0/1/2		5/8/3
Prior Treatment Regimens, median (range)		4 (1 – 5)
Histologies	4 CLL	1 SLL
	4 Follicular	1 MZL
	3 DLBCL	2 MCL
	1 Richter's Transformation	
≥ 2 Prior R–Chemo Regimens, n		13 (81%)
Refractory to Prior Therapy, n		8 (50%)

†1 removed per investigator discretion and 2 too early to evaluate

- 100% of CLL had 17p and/or 11q del
- 4/5 FL/MZL pts had ≥ 4 prior lines of treatment
  - 1 ibrutinib refractory
  - 1 duvelisib refractory
- 2/3 DLBCL were ABC subtype and had ≥ 4 prior lines of treatment

Safety:
TGR-1202 + Ublituximab + Ibrutinib

Cohort Summary

- CLL and NHL cohorts evaluated separately

						NHL Pts	# DLT	CLL Pts	# DLT
1:	Ublituximab 900mg	Ibrutinib 420/560mg	+	TGR-1202 400 mg	⇨	3	0	5	1*
2:	Ublituximab 900mg	Ibrutinib 420/560mg	+	TGR-1202 600 mg	⇨	4	0	0	0
3:	Ublituximab 900mg	Ibrutinib 420/560mg	+	TGR-1202 800 mg	⇨	4	0	0	0

**DLT of reactivated varicella zoster – no additional DLT's to date in CLL cohort*

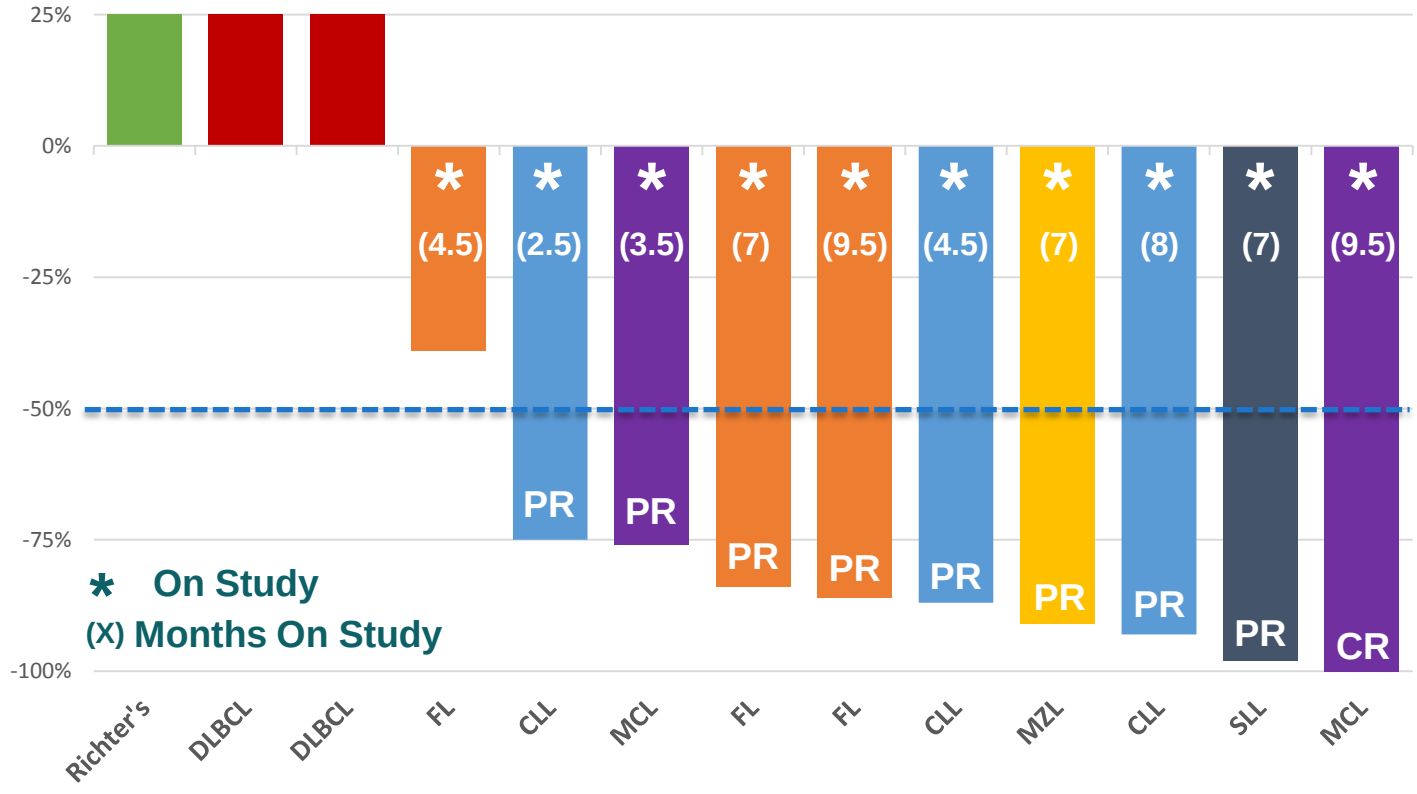
- Median time on study = 4 mos (range 1 – 9 mos)
- DLT in CLL 400 mg cohort
- 800 mg TGR-1202 cohort cleared in NHL

Safety:
TGR-1202 + Ublituximab + Ibrutinib

AE's (at least possibly related) in > 1 Patient N=16		
Adverse Event	**All Grades** n (%)	**Grade 3/4** n (%)
Infusion reaction	4 (25%)	-
Diarrhea	3 (19%)	-
Nausea	3 (19%)	-
Fatigue	3 (19%)	-
Rash	3 (19%)	-
Anemia	2 (13%)	-
Neutropenia	2 (13%)	1 (6%)
Leukopenia	2 (13%)	1 (6%)
Insomnia	2 (13%)	-

Activity in NHL:
TGR-1202 + Ublituximab + Ibrutinib

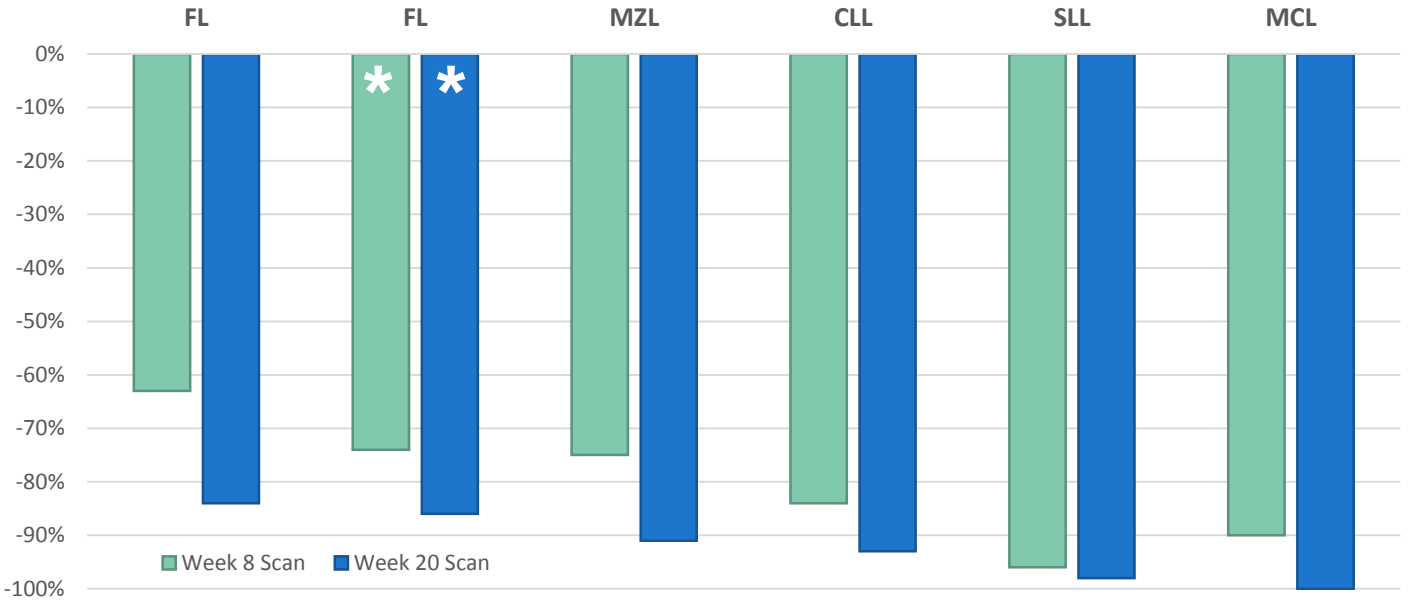
Best Percent Change from Baseline in Disease Burden



Activity in NHL:
TGR-1202 + Ublituximab + Ibrutinib

Clinical Response at First (8 week) and Second (20 week) Assessment

(All patients who had second assessment shown)



* Durable PR (9+ months) in an ibrutinib refractory Follicular patient

Conclusions

- The biologic combination of Ublituximab, TGR-1202 + Ibrutinib is safe in patients with relapsed B cell malignancies.
  - 800 mg cohort of TGR-1202 in NHL enrolled
  - 400mg cohort of TGR-1202 in CLL continues to enroll
    - One DLT was observed in a CLL for re-activated varicella
      - patient resumed treatment
  - The majority of patients remain on study

- The combination appears highly active in B-cell malignancies
  - CLL/SLL: ORR 100% in all patients with high risk features (n=4)
  - Responses were rapid in the majority of patients
    - 76% reduction in nodal disease noted at first assessment in responders.

- Triplet combination continues to accrue, with dose expansion planned at 800mg.
  - Clinicaltrials.gov: NCT02006485

- Phase II studies are planned in multiple histologies.

Acknowledgements

- **Thank you to the patients and families for their participation.**

- **Participating Centers**

- **MD Anderson Cancer Center**
  - Nathan Fowler, MD
  - Jan Burger, MD, PhD
- **UNMC**
  - Julie Vose, MD
  - James Armitage, MD
  - Matthew Lunning, DO
- **Clearview Cancer Institute**
  - Marshall Schreeder, MD
- **City of Hope**
  - Tanya Siddiqi, MD
  - Robert Chen, MD
- **Emory**
  - Christopher Flowers, MD
  - Jonathon Cohen, MD
- **UC Irvine**
  - Susan O'Brien, MD