

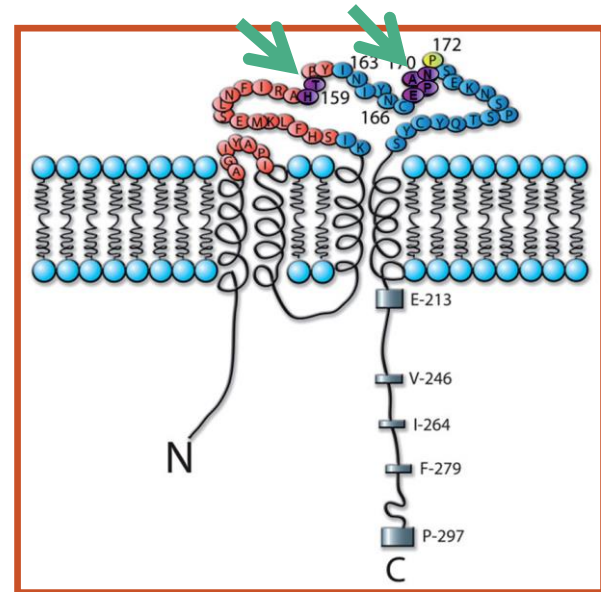
Safety and Activity of the Chemotherapy-free Triplet of Ublituximab, TGR-1202, and Ibrutinib in Relapsed B-cell Malignancies

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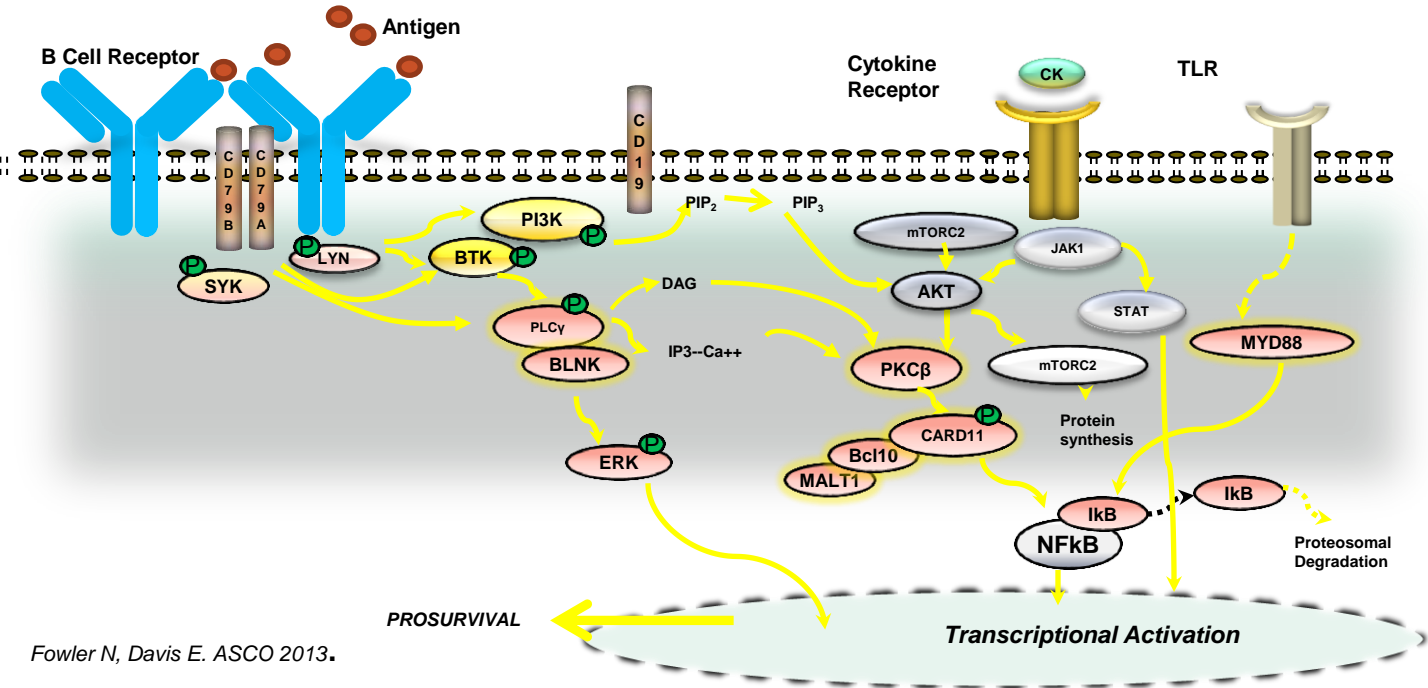
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Ublituximab: Glycoengineered Anti-CD20 mAb

- 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 patients¹

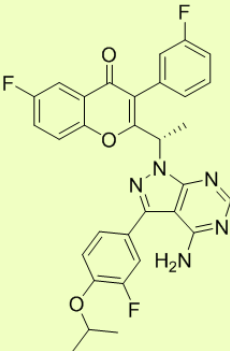
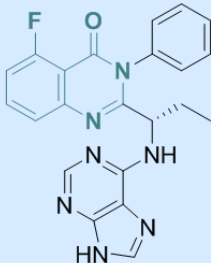
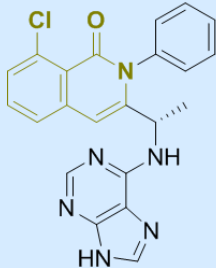


B-Cell Receptor Signaling in Lymphoma



Fowler N, Davis E. ASCO 2013.

TGR-1202: Novel PI3K delta Inhibitor

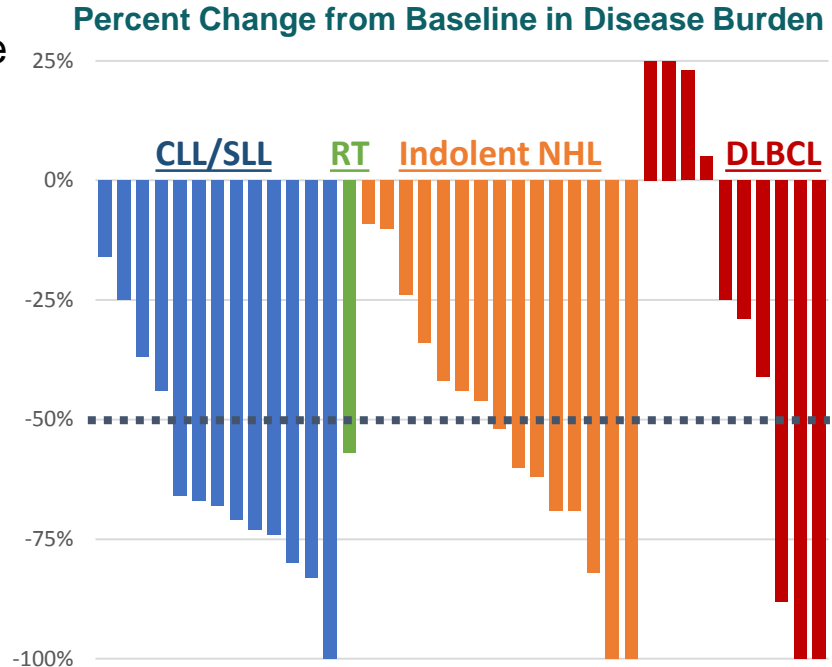
TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
 <p>The chemical structure of TGR-1202 features a central pyrazole ring. One nitrogen of the pyrazole is substituted with a 4-fluorophenyl group. The other nitrogen is substituted with a 4-(2-fluoro-4-isopropoxyphenyl)phenyl group. A methyl group is attached to the 5-position of the pyrazole ring.</p>	 <p>The chemical structure of Idelalisib (GS-1101) consists of a pyrazolo[1,5-a]pyridine core. It has a 4-fluorophenyl group at the 2-position, a phenyl group at the 3-position, and a 4-amino-1H-imidazole-2-ylmethyl group at the 4-position. A methyl group is attached to the 5-position of the pyridine ring.</p>	 <p>The chemical structure of Duvelisib (IPI-145) is a pyrazolo[1,5-a]pyridine derivative. It features a 4-chlorophenyl group at the 2-position, a phenyl group at the 3-position, and a 4-amino-1H-imidazole-2-ylmethyl group at the 4-position. A methyl group is attached to the 5-position of the pyridine ring.</p>
Delta	Delta	Delta/Gamma
QD	BID	BID

- PK profile that allows once-daily oral dosing
- 93% nodal PR rate in patients with rel/ref CLL¹

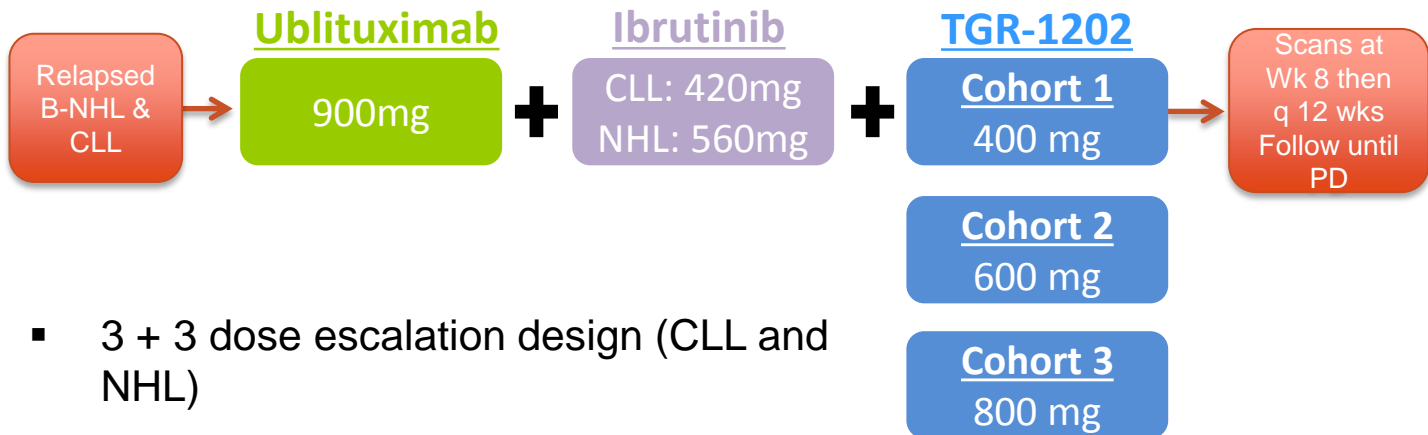
¹Burris et al, ASCO 2015, Abstract # 7069

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



Trial Design: TGR-1202 + Ublituximab + Ibrutinib

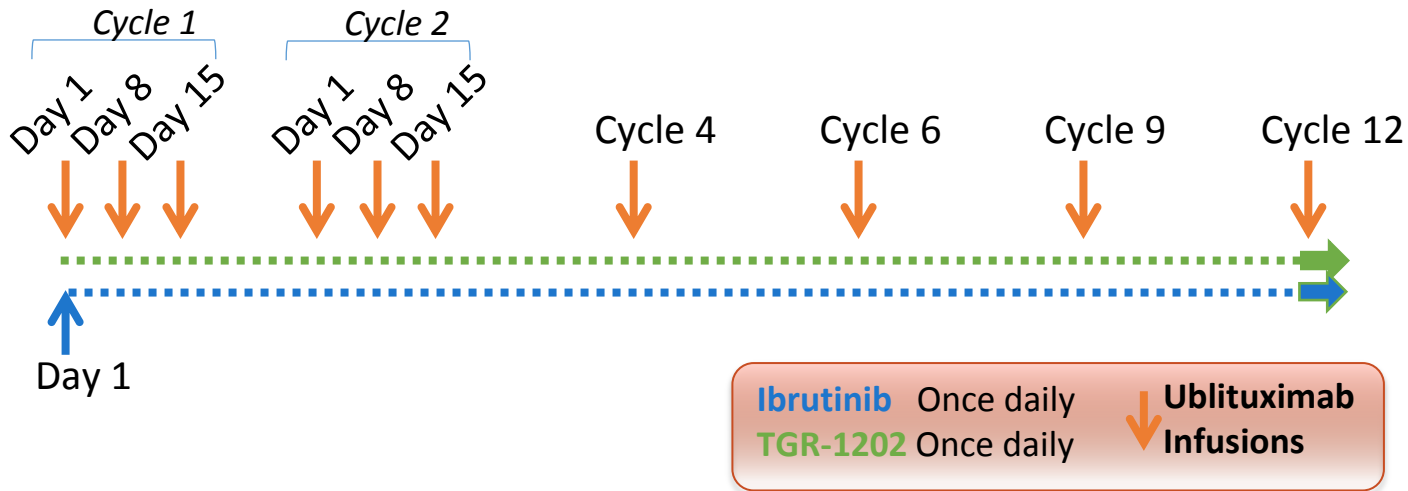


- 3 + 3 dose escalation design (CLL and NHL)
- No limit on prior # of therapies
- ECOG Performance Status ≤ 2
- ANC > 500 / Plts > 30,000
- Patients with Richter's Transformation, or refractory to prior PI3K δ inhibitors or prior BTK inhibitors are eligible

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%)	

- 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

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

Safety:

TGR-1202 + Ublituximab + Ibrutinib

Cohort Summary

- CLL and NHL cohorts evaluated separately

				<u>NHL</u> <u>Pts</u>	<u>#</u> <u>DLT</u>	<u>CLL</u> <u>Pts</u>	<u>#</u> <u>DLT</u>
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:

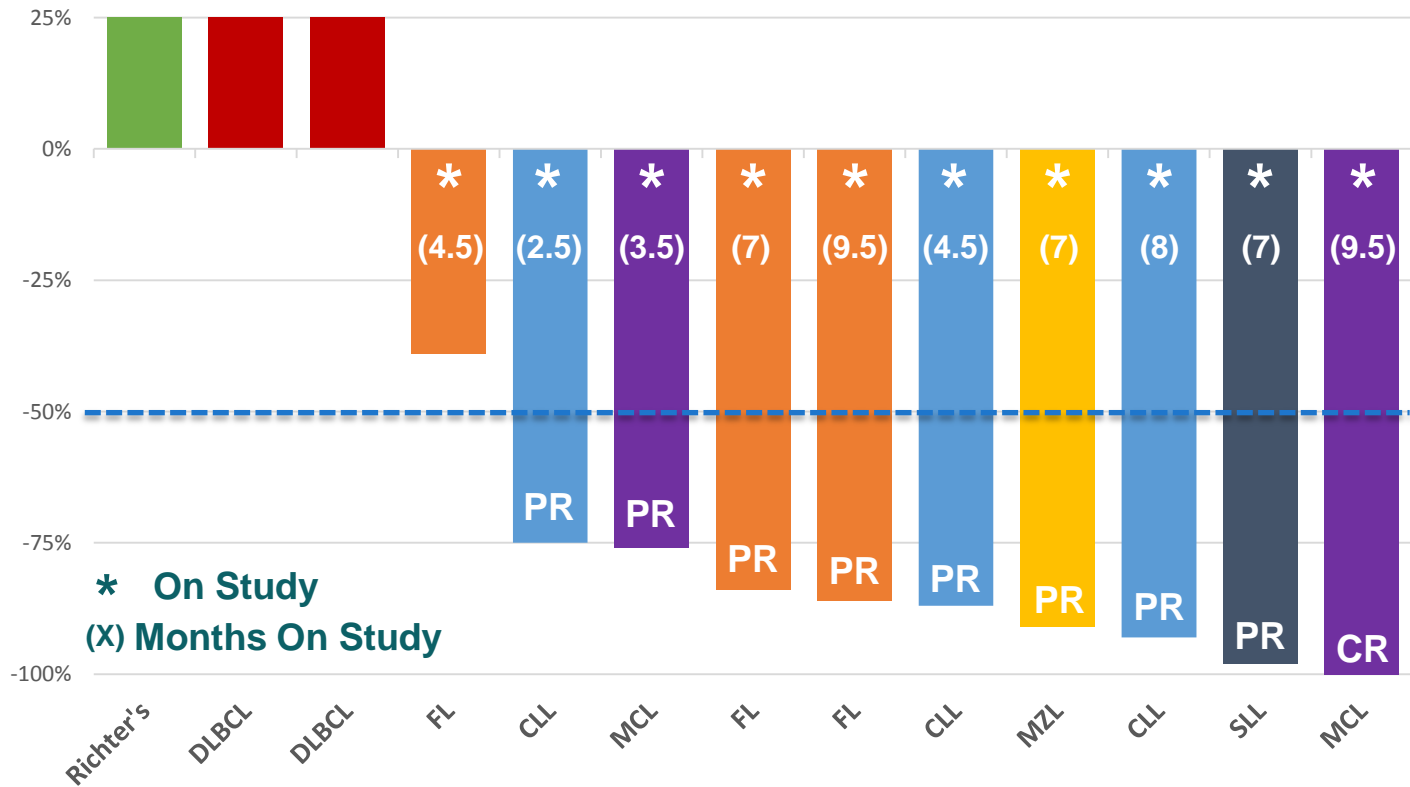
TGR-1202 + Ublituximab + Ibrutinib

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

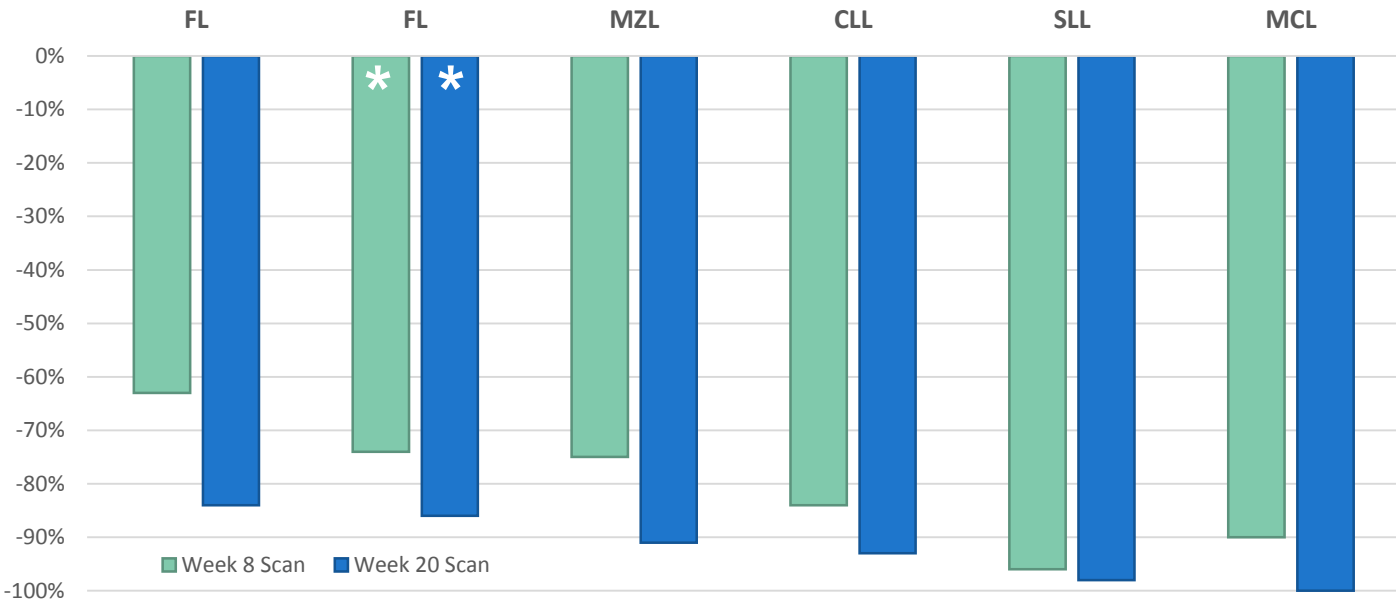
BEST PERCENT CHANGE FROM BASELINE IN DISEASE BURDEN



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](https://clinicaltrials.gov/ct2/show/study/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