TG Therapeutics

Introduction

Michael S. Weiss
Executive Chairman & CEO

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

Forward Looking Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements are often, but not always, made through the use of words or phrases such as "anticipates", "expects", "plans", "believes", "intends", and similar words or phrases. Such statements involve risks and uncertainties that could cause TG Therapeutics' actual results to differ materially from the anticipated results and expectations expressed in these forward-looking statements. These statements are only predictions based on current information and expectations and involve a number of risks and uncertainties. Actual events or results may differ materially from those projected in any of such statements due to various factors, including the risks and uncertainties inherent in clinical trials, drug development, and commercialization. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement and TG Therapeutics undertakes no obligation to update these statements, except as required by law.

AGENDA

Topic	Presenter
Welcome / Introductions	**Michael S. Weiss** Chief Executive Officer, TG
Umbralisib Differentiation	**Owen O'Connor, MD, PhD** Columbia University Medical Center
Current Treatment Landscape for Indolent Lymphoma Evolution of Treatment Landscape with PI3K Delta	**Loretta Nastoupil, MD** MD Anderson Medical Center
Future Combinations: • U2 plus Ibrutinib Data	**Loretta Nastoupil, MD** MD Anderson Medical Center
Future Combinations: • U2 plus Bendamustine • U2 plus Pembrolizumab	**Matthew Lunning, DO** University of Nebraska Medical Center
Question & Answer Session	**John Pagel, MD, PhD,** Swedish Cancer Institute
Closing Remarks	**Michael S. Weiss** Chief Executive Officer, TG

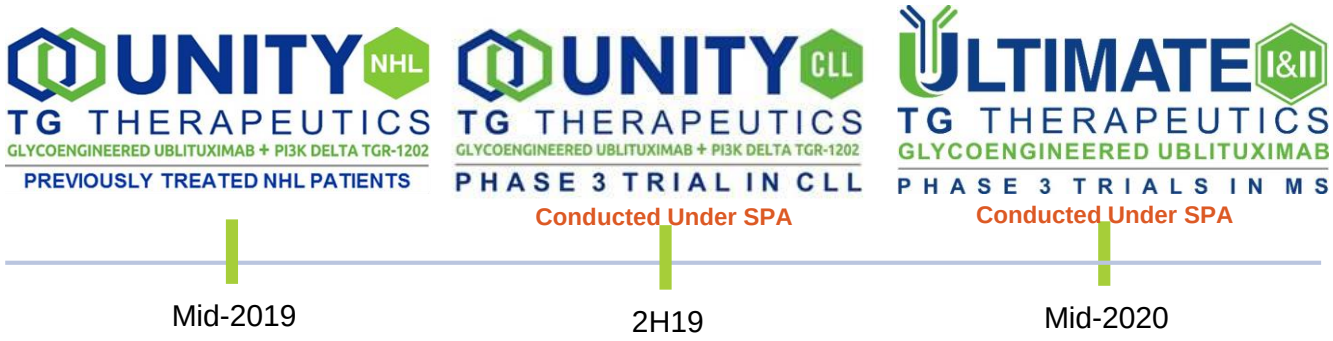
Five – Three – One

5 – Pivotal Programs

3 – Diseases (CLL, NHL and MS)

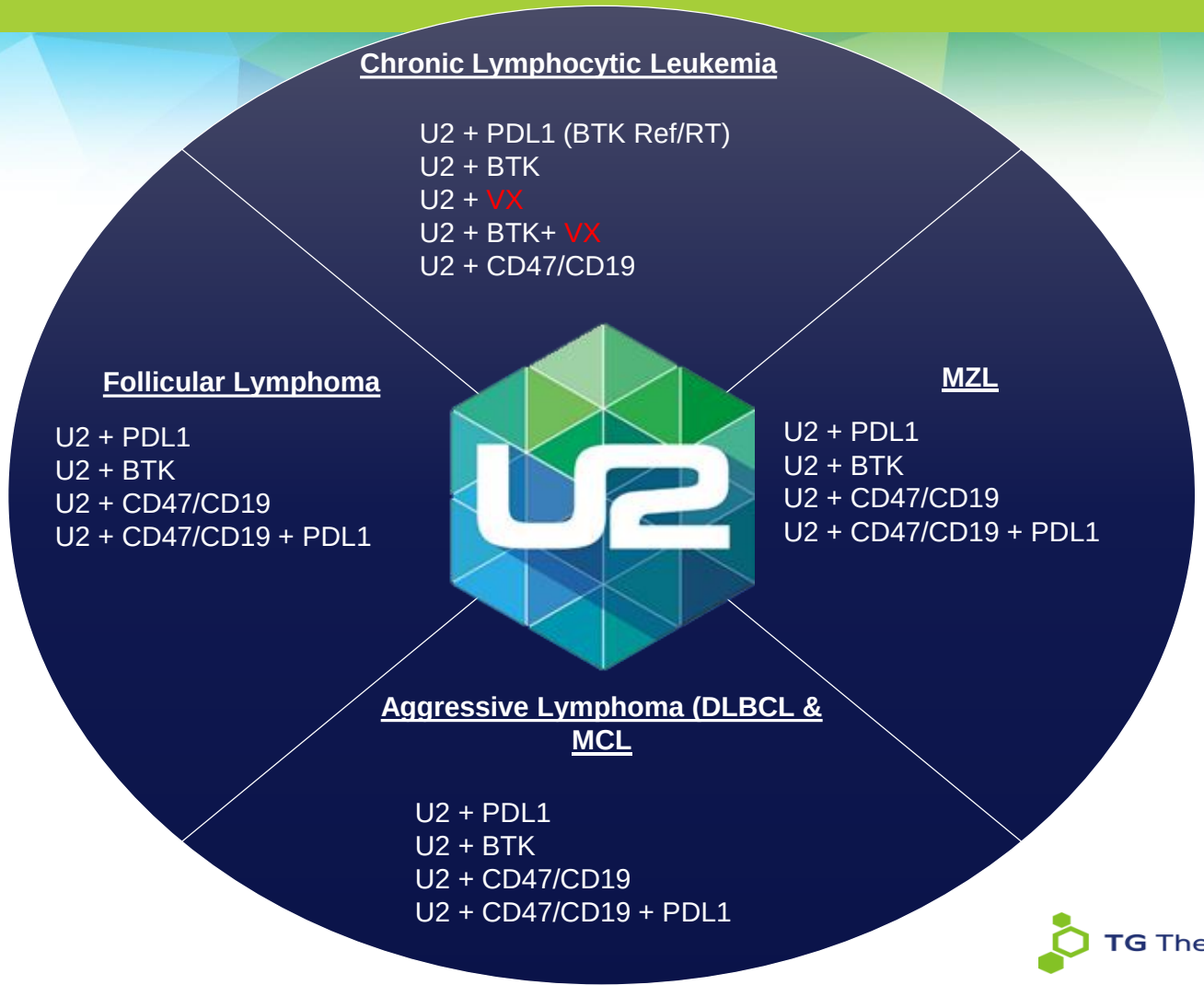
1 – Goal (Bring Novel Medicines to Patients)

All fully enrolled, waiting for data



Early Pipeline Update

- **Pipeline Update**
  - **TG-1501: Anti PD-L1 Monoclonal Antibody**
    - Phase 1 dose escalation complete
    - Commencement of heme focused cohort in 1Q 2019
  - **TG-1701: BTK Inhibitor**
    - TG sponsored Phase 1/2 trial currently enrolling in Australia
    - The first two cohorts fully enrolled
      - First patient enrolled, a rel/ref Mantle Cell Lymphoma (MCL), achieved a PR at the first assessment
  - **TG-1801: CD47-CD19 Bispecific Antibody**
    - Targeting Phase 1 to commence in 1Q 2019


Chronic Lymphocytic Leukemia
U2 + PDL1 (BTK Ref/RT)
U2 + BTK
U2 + VX
U2 + BTK+ VX
U2 + CD47/CD19
Follicular Lymphoma
U2 + PDL1
U2 + BTK
U2 + CD47/CD19
U2 + CD47/CD19 + PDL1
MZL
U2 + PDL1
U2 + BTK
U2 + CD47/CD19
U2 + CD47/CD19 + PDL1
Aggressive Lymphoma (DLBCL & MCL
U2 + PDL1
U2 + BTK
U2 + CD47/CD19
U2 + CD47/CD19 + PDL1

TG Therapeutics

Umbralisib Differentiation

Owen A. O'Connor, MD, PhD
Columbia University Medical Center

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PREVIOUSLY TREATED NHL PATIENTS

Deciphering the Mechanistic Similarities and Differences Among the PI3 Kinase Inhibitors

Owen A. O'Connor, M.D., Ph.D.
American Cancer Society Professor

Founding Director, Center for Lymphoid Malignancies
Professor of Medicine and Developmental Therapeutics
The New York Presbyterian Hospital
Columbia University College of Physicians and Surgeons
New York, N.Y.

American Society of Hematology 2018
San Diego, CA

Columbia University Medical Center

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

NewYork-Presbyterian The University Hospital of Columbia and Cornell

Deciphering the Mechanistic Similarities and Differences Among the PI3 Kinase Inhibitors

Observations and Questions

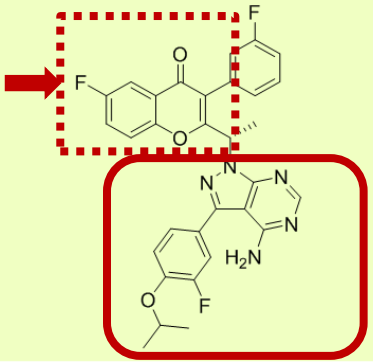
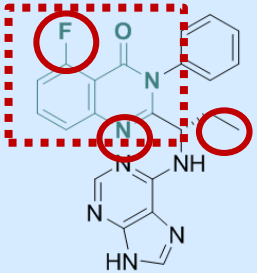
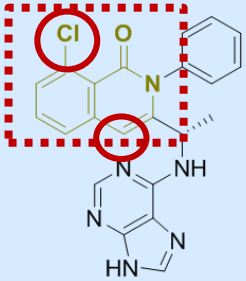
OBSERVATIONS

- **The PI3K pathway is undisputedly one of the most important 'driver' pathways across all of cancer – regulating major oncogenes like c-myc, bcl-2 and cyclin D1, among others**
- **The target is not a simple single protein/gene target. Like the proteasome and HDAC there is enormous family diversity**
- **Inhibitors of the pathway have important clinical activity in lymphoid malignancies, but that activity is not uniform across all subtypes.**
- **Some inhibitors have demonstrated unusual adverse events manifest as GVHD-like toxicity and increased infections.**

QUESTIONS

- **Are there differences in the on- or off-target affects that might account for differences in toxicity and/or clinical activity? How do we interpret the balance between potency and selectivity?**
- **Are all agents in the class 'equivalent' with regard to toxicity, efficacy and drug:drug interactions? How might differences in molecular pharmacology provide clues into the deciphering those differences?**
- **How do we deconvolute the immunologic influences among the compounds? Are they even different?**

The PI3 Kinase Inhibitors Share Similarities & Differences

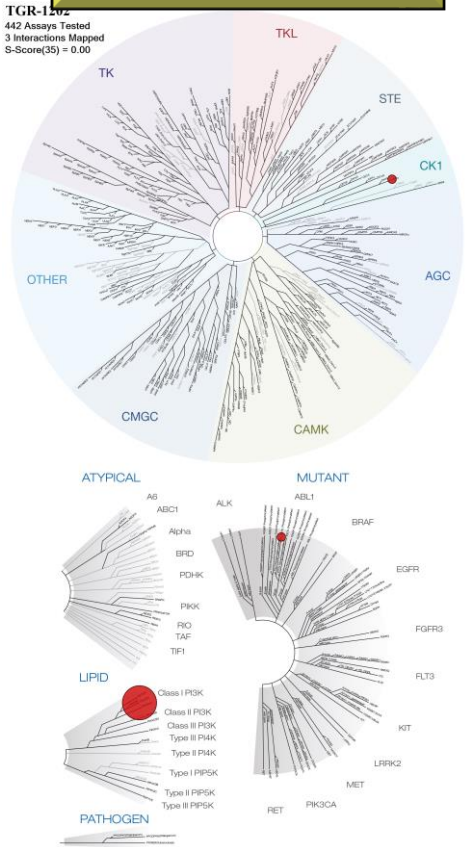
TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

- Similarities in the upper structural motif – differences in the lower structural motif
- Subtle pharmacologic and target difference

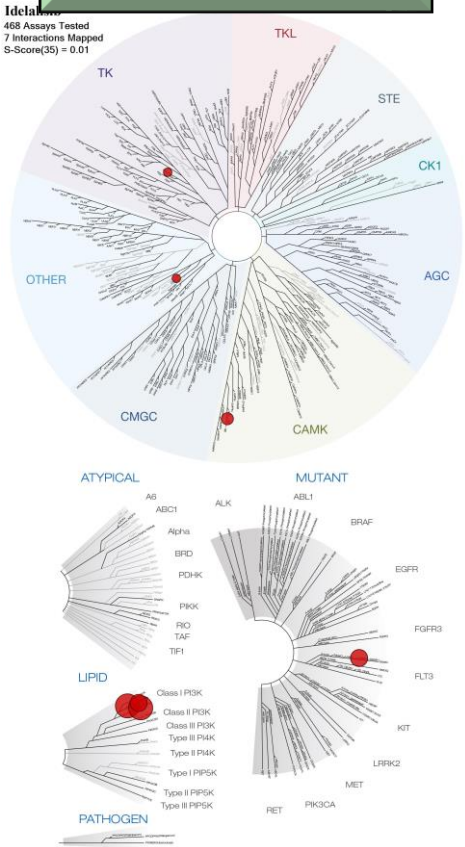
[1]O'Connor et al, ASCO 2015, Abstract # 7069

KINOME SCAN SPECIFICITY OF 3 PI3K

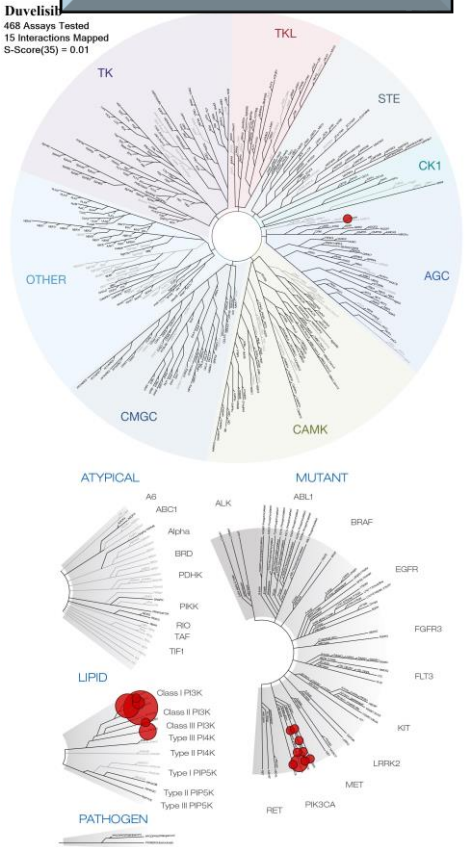
Umbralisib (TGR-1202)



Idelalisib

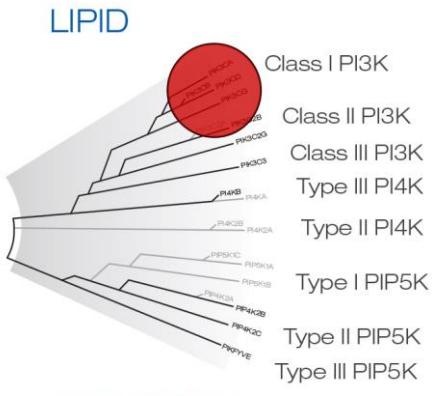
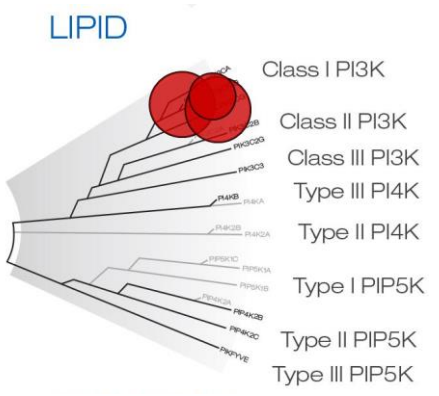
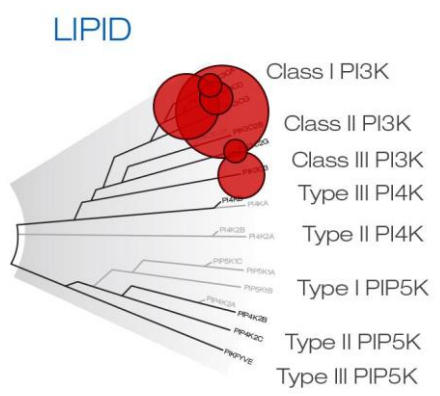


Duvelisib



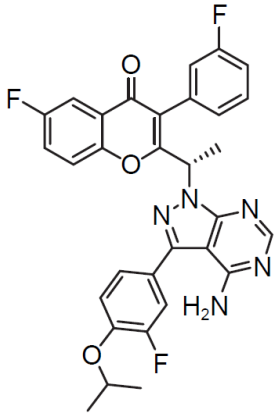
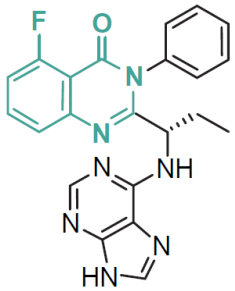
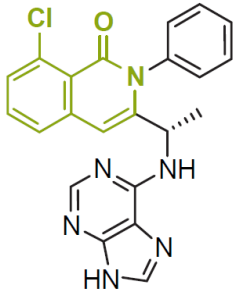
DiscoverRx Kinome Scan against a panel of 442 kinases

KINOME SCAN FOCUS ON PI3K ONLY – DIRECT COMPARISON OF SPECIFICITY

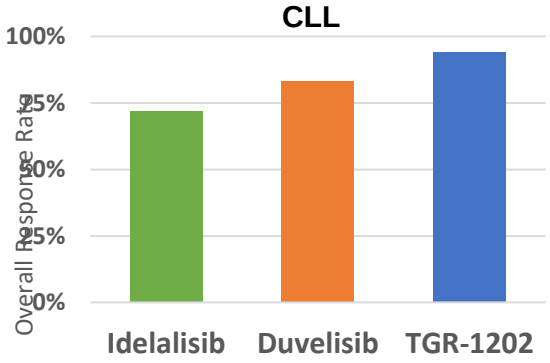
Umbralisib	Idelalisib	Duvelisib
		

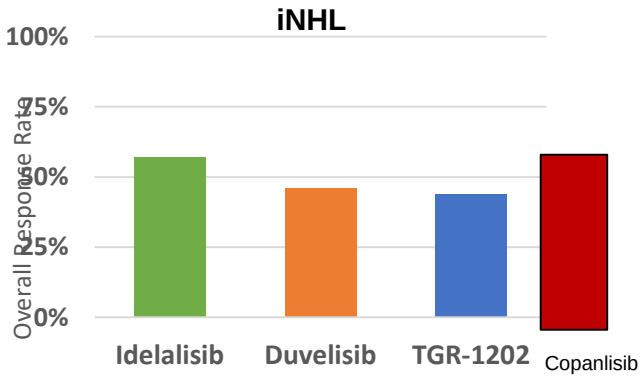
Is it possible these subtle differences explain some of the clinical observations?

Structures and Dissociation Constants (Kd) Against Class I PI3K Isoforms of Umbralisib (TGR-1202), Idelalisib, and Duvelisib

	TGR-1202	Idelalisib	Duvelisib
			
Isoform	**K_d (nM)**		
PI3Kα	>10,000	600	40
PI3Kβ	>10,000	19	0.89
PI3Kγ	1400	9.1	0.21
PI3Kδ	6.2	1.2	0.047

Clinically the PI3K Inhibitors Appear to Have Comparable Activity Across CLL and iNHL

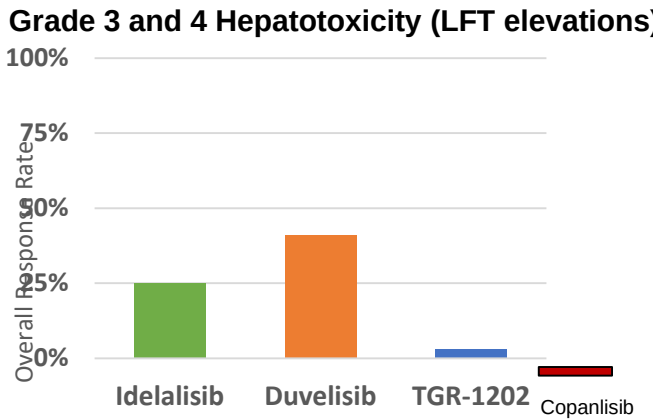


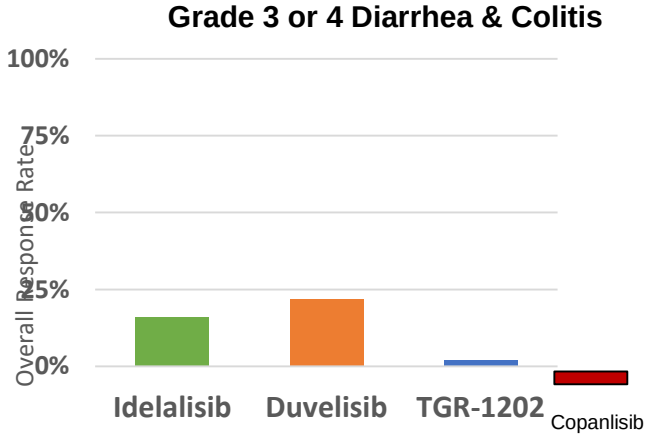


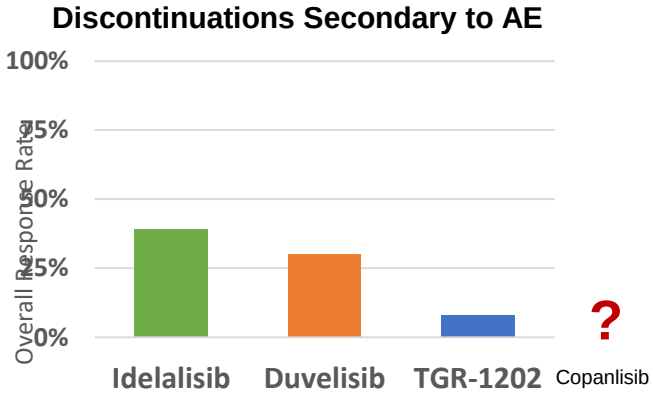
- Comparable activity across CLL and iNHL
- Small numbers across multiple studies so lots of population variability.

Brown et al, iwCLL 2013
O'Brien et al, ASH 2014
O'Connor et al, ASH 2015
Gopal et al, NEJM 2014
Infinity PR, 2016
O'Connor et al, EHA 2016
Westin et al, 2014
O'Connor et al, EHA 2016

…..Though There are Substantial Differences in Tolerability Across the PI3K Inhibitors







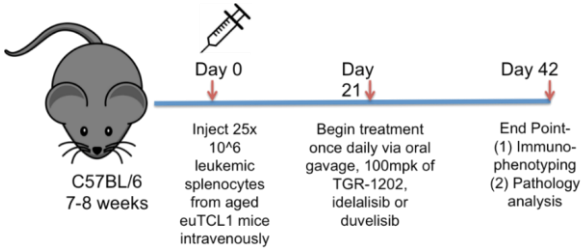
- Reduced incidence of hepatic toxicity with TGR1202 & copanlisib
- Reduced gastrointestinal toxicity with TGR1202 & copanlisib
- Fewer discontinuations due to AE with TGR1202

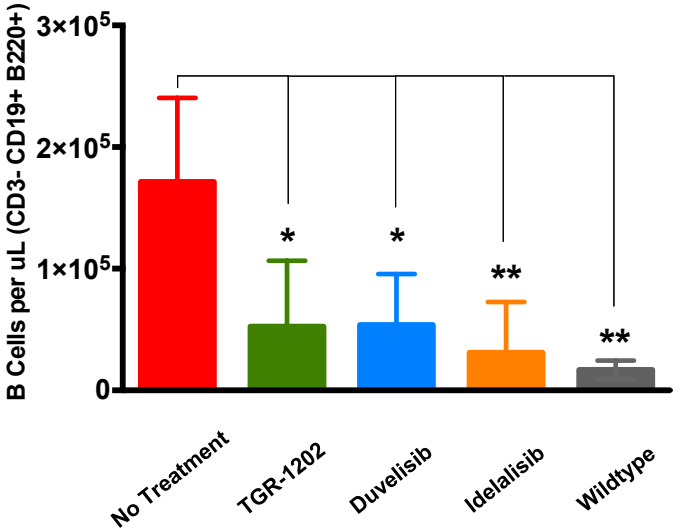
Brown et al, iwCLL 2013; O'Brien et al, ASH 2014; O'Connor et al, ASH 2015; Gopal et al, NEJM 2014; Infinity PR, 2016; O'Connor et al, EHA 2016; Jones et al, ASCO 2016; Coutre et al, 2015; Flinn et al, Blood 2014;

Copanlisib Laboratory Abnormalities (20% of patients)

Laboratory Parameter	Copanlisib Monotherapy (N = 168)		
	Any Grade N (%)	Grade 3 N (%)	Grade 4 N (%)
Anemia	130 (78%)	7 (4%)	0
Lymphopenia	126 (78%)	43 (27%)	4 (2%)
Leukopenia	118 (71%)	30 (18%)	3 (2%)
Thrombocytopenia	109 (65%)	11 (7%)	3 (2%)
Neutropenia	104 (63%)	20 (12%)	25 (15%)
Hyperglycemia	160 (95%)	72 (43%)	9 (5%)
Hypertriglyceridemia	74 (58%)	6 (5%)	0
Hypophosphatemia	72 (44%)	24 (15%)	0
Hyperuricemia	42 (25%)	40 (24%)	2 (1%)
Serum lipase increase	34 (21%)	11 (7%)	2 (1%)

Differential Regulation by PI3KΔi on T regs
No Real Difference on Efficacy

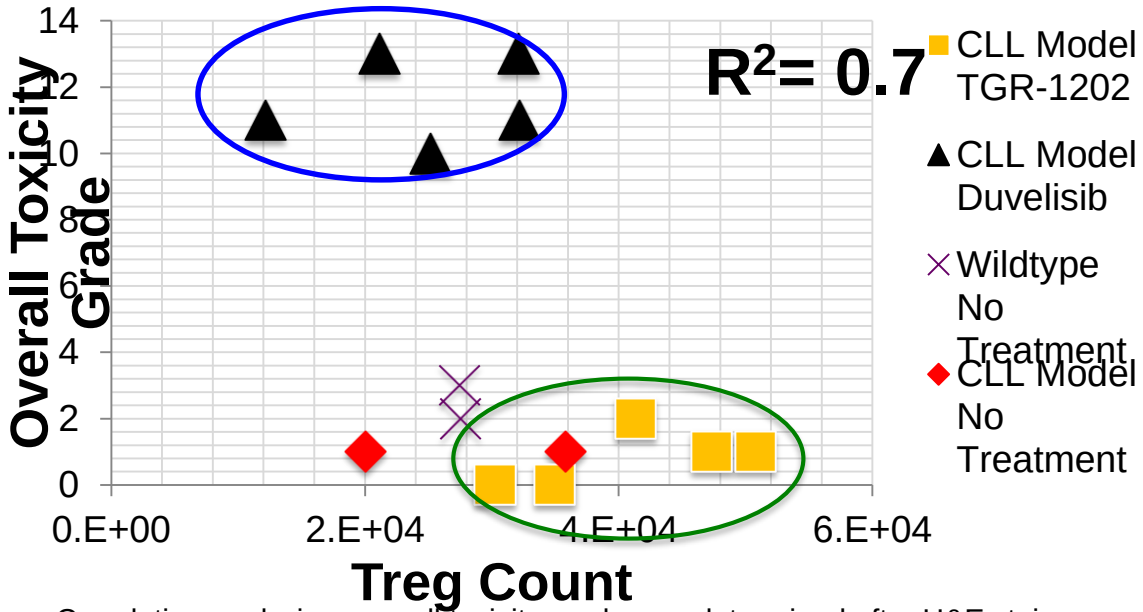




In vivo efficacy equivalent among cohorts treated with umbralisib, duvelisib and idelalisib

Maharaj, Pinilla et al iwCLL 2017

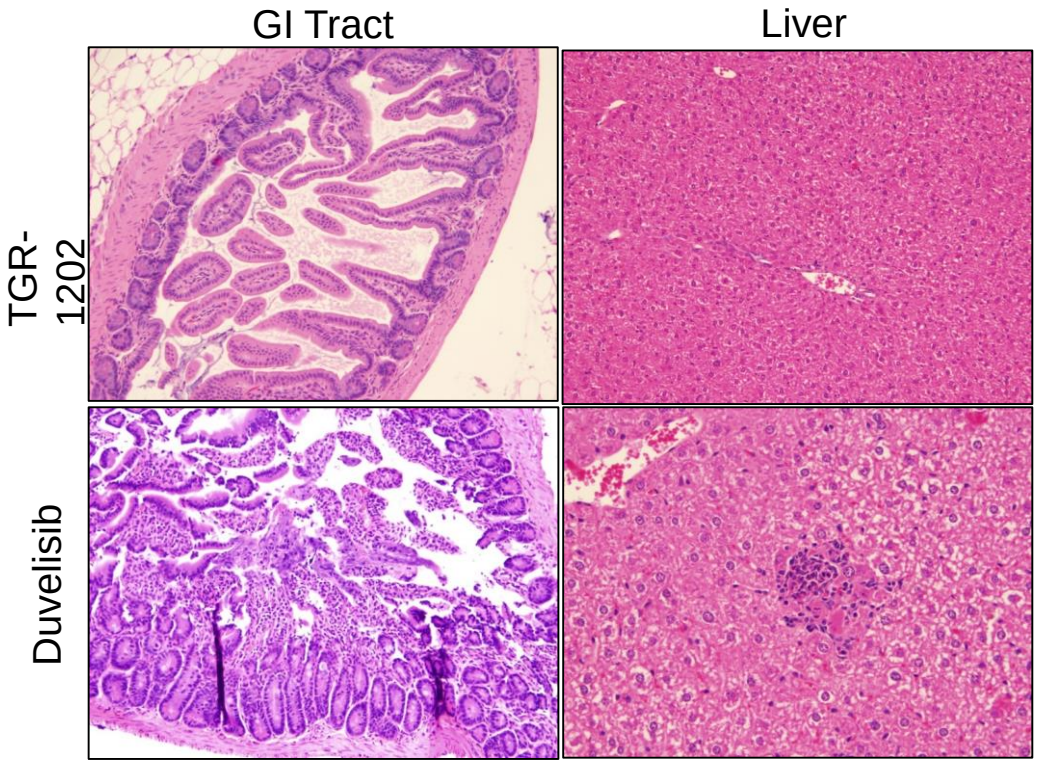
DIFFERENTIAL REGULATION BY PI3KΔI ON T REGS



Correlation analysis – overall toxicity grade was determined after H&E stain using blinded histological analysis of liver and GI tract using known indicators of immune-mediated adverse events.

Maharaj, Pinilla et al
iwCLL 2017

Differential Regulation by PI3KΔI on T regs



Representative histologic findings.

Top Left: bowel section from TGR-1202 treated mouse with normal appearance.

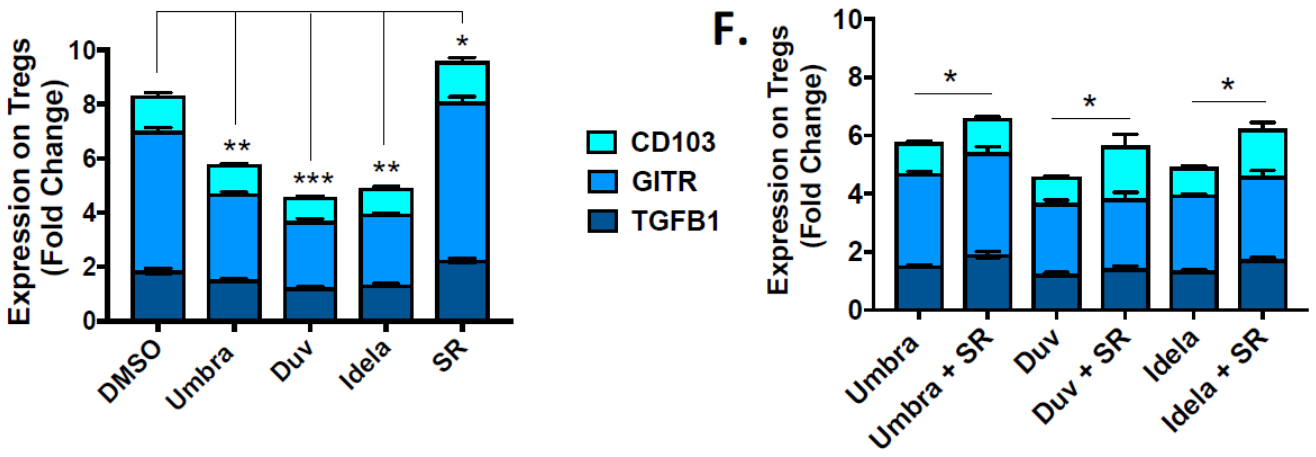
Top Right: liver section from TGR-1202 treated mouse with normal appearance.

Lower Left: Bowel section from duvelisib treated mouse with inflammation and denuded mucosa indicating GI tract toxicity.

Lower right: Liver section from duvelisib treated mouse with inflammation indicating immune-mediated hepatotoxicity

Maharaj, Pinilla et al
iwCLL 2017

Effect of CK1ε Inhibition on Murine CLL T-cells



- Umbralisib uniquely inhibited CK1ε in euTCL1 T cells dose-dependently
- CK1ε inhibition by umbralisib may offer an explanation for less anti-Treg effects

Maharaj, Pinilla et al ASH 2017

Umbralisib, A Novel PI3Kδ and Casein Kinase-1ε Inhibitor, in Relapsed or Refractory Chronic Lymphocytic Leukemia and Lymphoma: An Open-Label, Phase 1, Dose-Escalation, First-in-Human Study

Howard A Burris III, Ian W Flinn, Manish R Patel, Timothy S Fenske, Changchun Deng, Danielle M Brander, Martin Gutierrez, James H Essell, John G Kuhn, Hari P Miskin, Peter Sportelli, Michael S Weiss, Swaroop Vakkalanka, Michael R Savona, Owen A O'Connor

THE LANCET Oncology

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Patient Demographics and Baseline Characteristics

Characteristic	All patients (safety population; N=90)	MITT population (patients assessable for activity, n=73)
Age, years (range)	64 (51–72)	65 (51–71)
Sex, M:F, n (%)	57 (63) / 33 (37)	45 (62) / 28 (38)
ECOG PS (range)	1 (0 – 1)	1 (0 – 1)
Histology, n (%)		
CLL	24 (27)	20 (27)
B-cell NHL		
FL	22 (24)	17 (23)
DLBCL	16 (18)	13 (18)
MCL	6 (7)	6 (8)
MZL	5 (6)	5 (7)
Waldenström macroglobulinemia	3 (2)	2 (3)
Hodgkin lymphoma	11 (12)	9 (12)
T-cell lymphoma	2 (1)	1 (1)
HCL	1 (1)	-
Prior therapies, n (range)	3 (2 – 5)	3 (2 – 5)
Patients receiving ≥3 prior therapies, n (%)	52 (58)	41 (56)
Refractory to prior therapy, n (%)	44 (49)	36 (49)

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

Umbralisib Adverse Events Occurring >10% of Patients: Single Agent Phase 1

Adverse event, n (%)	All grades		Grades 3 or 4	
Diarrhea	39	43%	3	3%
Nausea	38	42%	1	1%
Fatigue	28	31%	3	3%
Vomiting	25	28%	-	-
Cough	19	21%	-	-
Headaches	19	21%	2	2%
Rash	17	19%	4	4%
Constipation	14	16%	1	1%
Decreased Appetite	14	16%	-	-
Hypokalemia	14	16%	4	4%
Anemia	13	14%	8	9%
Neutropenia	13	14%	12	13%
Arthralgia	12	13%	-	-
Dyspnea	12	13%	4	4%
Pyrexia	12	13%	-	-
Upper Respiratory Tract Infection	12	13%	-	-
Abdominal Pain	12	13%	-	-
Dizziness	11	12%	-	-
Insomnia	11	12%	-	-
Thrombocytopenia	10	11%	6	7%
Abdominal Distension	10	11%	-	-

- Grade 3 or 4 diarrhea 3%
- Essentially no cases of colitis
- No cases of pneumonitis
- No cases of Grade 5 toxicity
- Infections rare
- Median time on treatment now about 6 months

Burris et al. 2017. *Lancet Oncology*

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Treatment Discontinuation

- Discontinuation of umbralisib due to treatment related adverse events was uncommon, occurring in 6 (7%) of patients

Reason for Discontinuation	n (%)	Grade
Colitis*	2 (2)	Grade 3 – Both
Elevated liver function tests	2 (2)	Grade 1 – 1; Grade 4 – 1
Diarrhea	1 (1)	Grade 2
Fatigue	1 (1)	Grade 3

*Both occurred at doses higher than the micronized RP2D of 800 mg/day

- Dose delays due to adverse events (n=39)
  - Median interruption time: 2 days (IQR 1–7)
- Dose reductions to the next lower dose (n=15)
  - Fatigue (n=5), neutropenia (n=4), abnormal LFTs (n=3), and rash, worsened dysgeusia, diarrhea, neutropenic fever, anemia, arthralgia, nausea and vomiting (n=1 each†)

†Same patient had more than one reason for dose reduction.

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Clinical Efficacy

- Responses according to disease type (N=73):

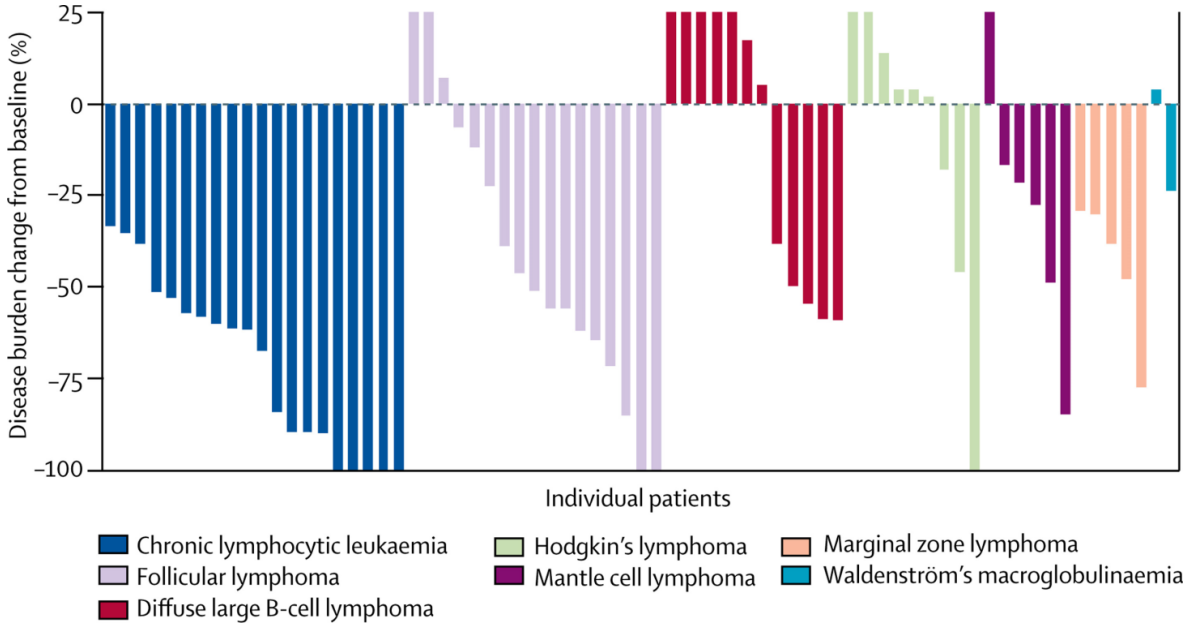
Disease	Objective response, n (%)	CR, n (%)	PR, n (%)	PR-L, n (%)	Duration of Response, mo (n)
CLL, n=20	17 (85)	-	10 (50)*	7 (35)	13.4 (16)
CLL, del 17p/del 11q,n=8	6 (75)	-	4 (50%)*	2 (25%)	-
FL, n=17	9 (53)	2 (12)	7 (41)	-	9.3 (9)
DLBCL, n=13	4 (31)	-	4 (31)	-	6.4 (4)

-HL: 1 CR, 4 SD, 4 PD; MZL: 1 PR, 4 SD; Waldenström macroglobulinemia: 2 SD; MCL: 1 PR, 4 SD, 1 PD.*iwCLL 2008

- Umbralisib was clinically active in most treated patients (N=90)
  - 56 of 90 (62%) study patients had reductions in disease burden by CT scan
  - ORR 37% (PR 33%) amongst all evaluable patients
- Responses increased over time amongst patients with CLL and iNHL

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

Umbralisib in Relapsed/Refractory Lymphoid Malignancies: Best Percentage Change from Baseline in Disease Burden



- 53% (9 of 17) Overall Response Rate in patients with Follicular Lymphoma (FL), including 2 patients, 12%, who achieved a Complete Response (CR)
  - Mean duration of response was 9.3 months (3.6 – 15.1) in FL patients

mITT, modified intention-to-treat.

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

CONCLUSIONS

- While generally selective, there are differences in the relative selectivity of agents in the class. The marked differences among the agents in the clinic are unlikely explained by differences in potency – **all are highly selective potent low nanomolar inhibitors of PI3K δ (+/– γ)**
- Is it possible other off-target (**PI3K +/– γ**) effects contribute to produce some of the GVHD like toxicities?
- **Complementary - synergistic - inhibition of other kinases (ex CK-1) may help explain some of the differences in toxicity and efficacy.**
- Drug : drug interactions (ex: with proteasome inhibitors), albeit limited, appear **markedly different** and requires further work to understand all contributing factors
- Clinically, there are differences in toxicity - in the preclinical setting there are marked differences on T-regs and cytokine effects
- A significant investment in appreciating differences at the SCIENTIFIC level is required in order to leverage the advantages of the available agents

THANK YOU!

COLUMBIA UNIVERSITY MEDICAL CENTER

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

TG Therapeutics

iNHLTreatment Landscape & Future Plans for Novel Agents

Loretta Nastoupil, MD
MD Anderson Medical Center

UNITY CLL
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GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
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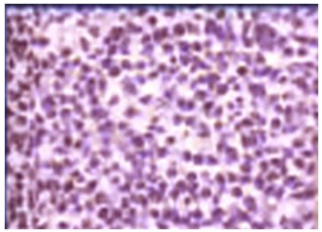
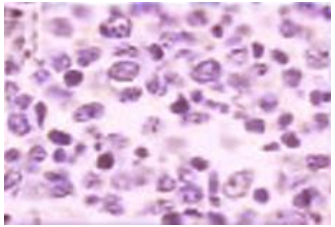
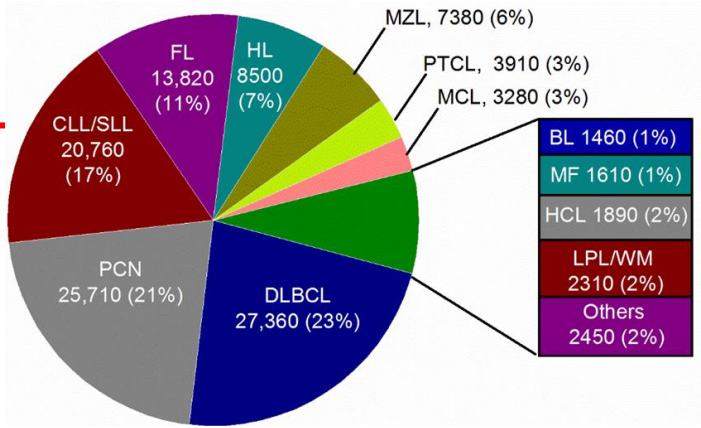
PREVIOUSLY TREATED NHL PATIENTS

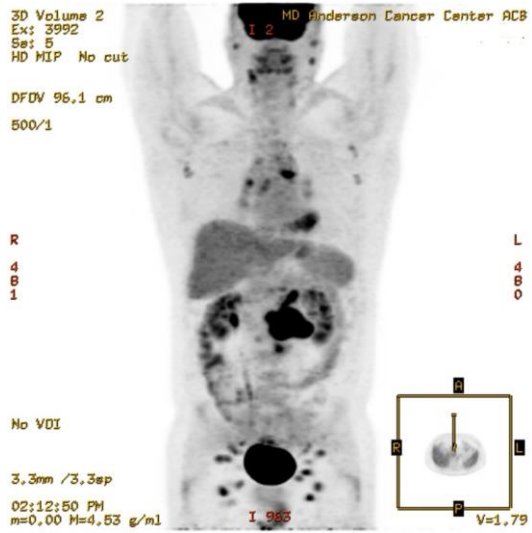
Follicular Lymphoma

- Indolent (low grade) NHL
  - Often asymptomatic
  - Prolonged natural history
  - Heterogeneous treatment options
  - Treatable, but incurable with standard therapy





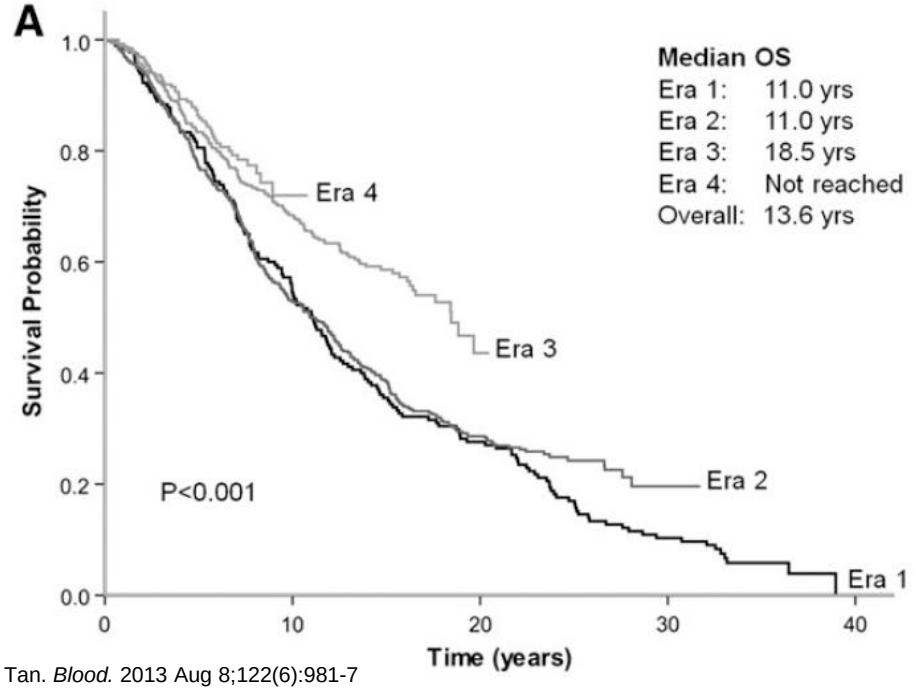




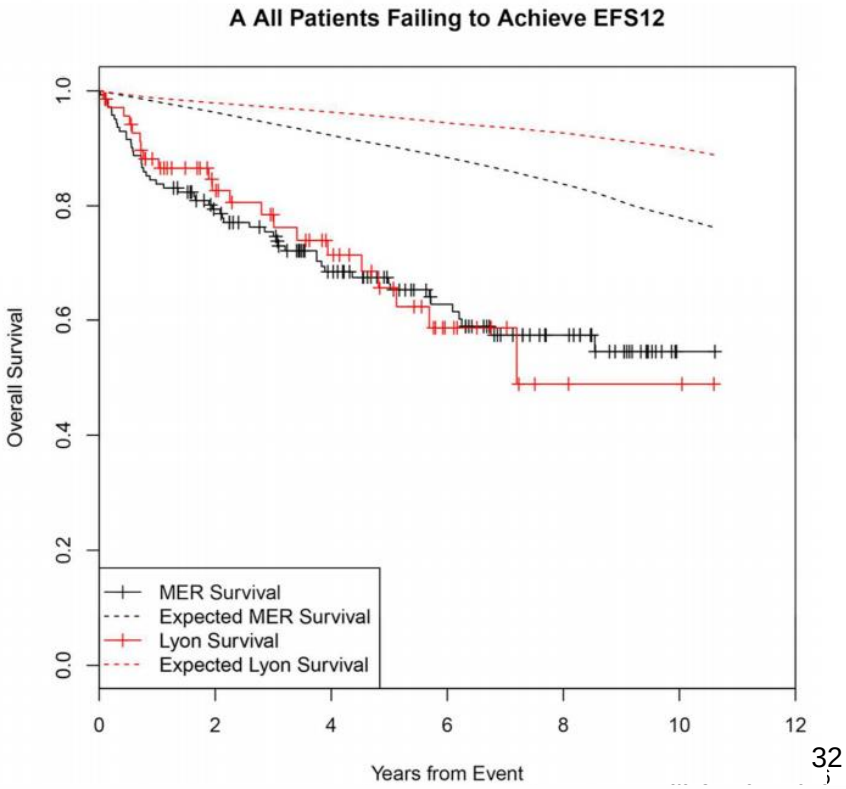
The Natural History of FL

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Stanford Experience



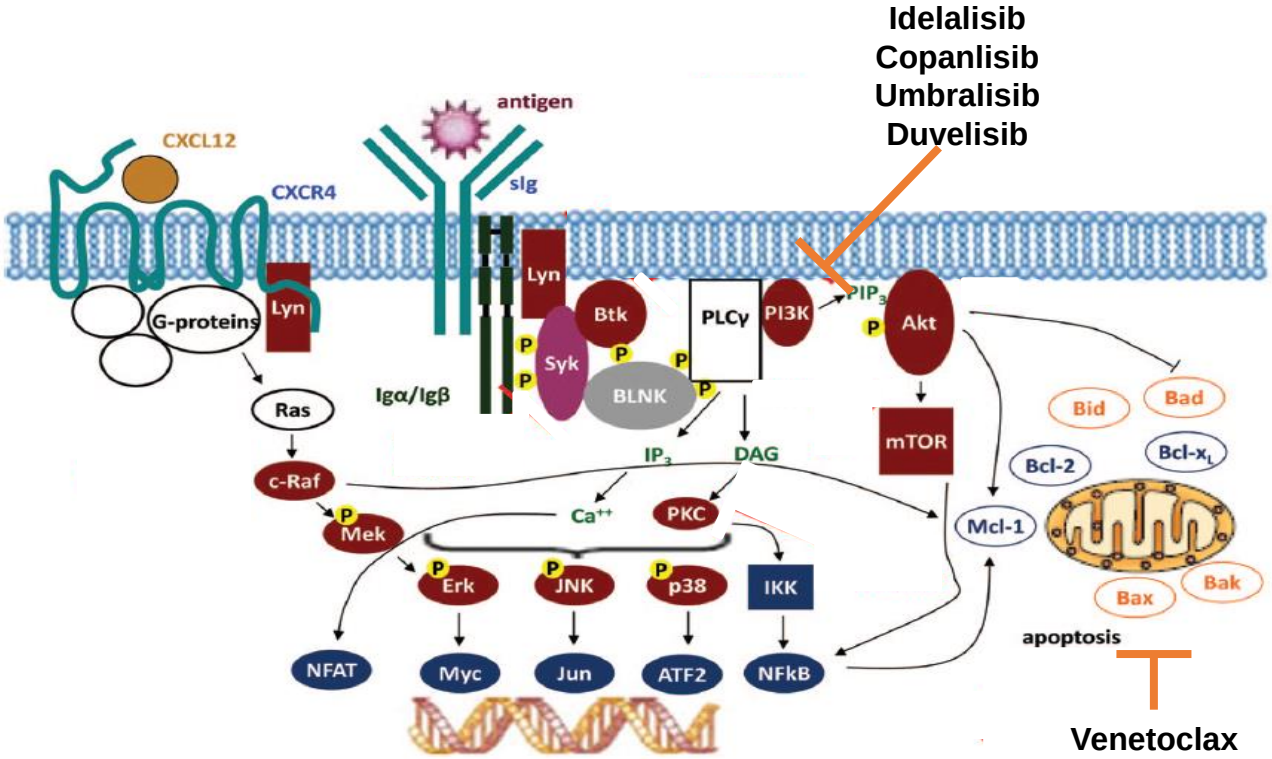
Tan. *Blood.* 2013 Aug 8;122(6):981-7



Treatment Options
Relapsed/Refractory FL in the US

Agent	Issues
Bendamustine; B-G	BR used upfront
Idelalisib/ Duvelisib	Toxicities
Copanlisib	Route/schedule
R^2	Relapsed, not refractory; RELEVANCE/ AUGMENT

B-cell Receptor Pathway



Idelalisib in R/R FL

Idelalisib is effective in early relapse FL

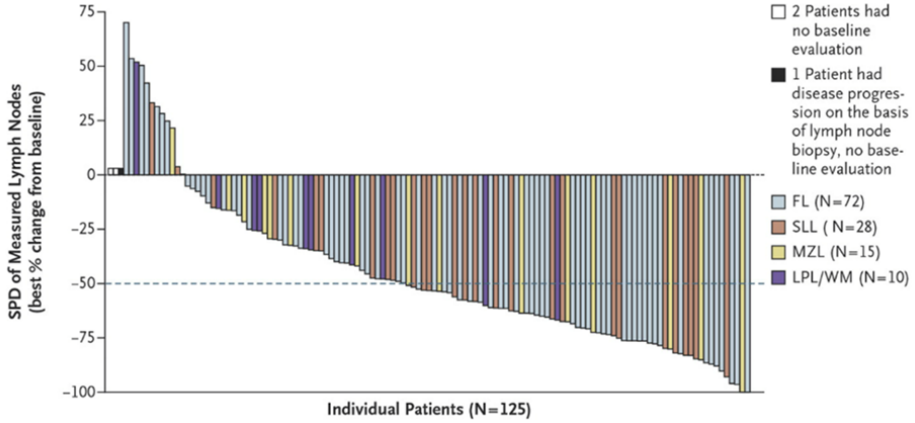
Enrolled April 2011 to October 2012

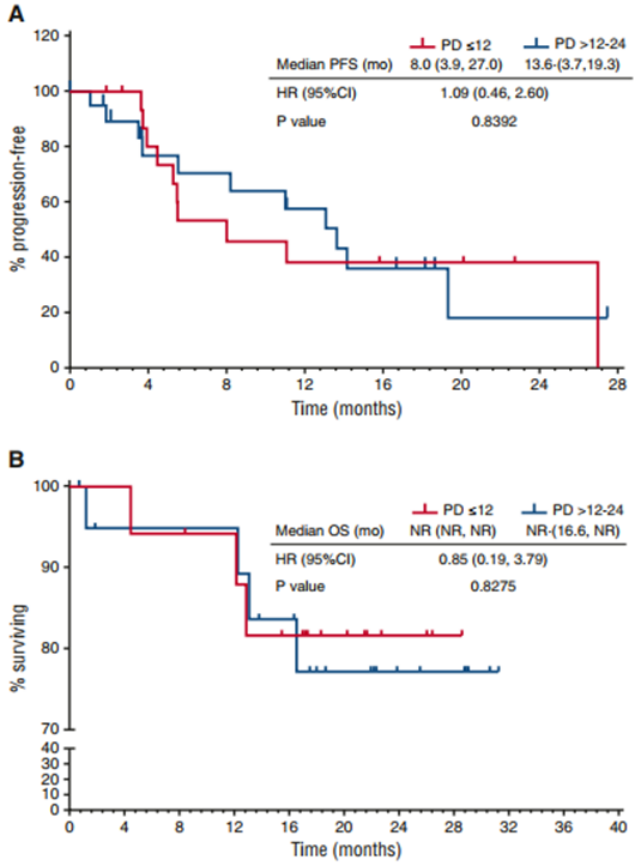
Idelalisib 150 mg BID

Therapy maintained until progression

Long-term follow-up

- 90% had improvement in lymphadenopathy
- 57% had ≥50% decrease from baseline



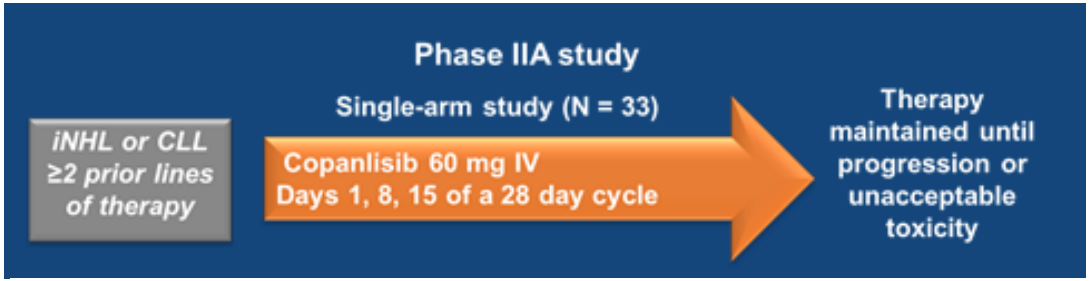


Idelalisib Toxicity Profile

AEs	Any grade N, %	Grade ≥3 N, %
Diarrhea	54 (43%)	16 (13%)
Fatigue	37 (30%)	2 (2%)
Nausea	37 (30%)	2 (2%)

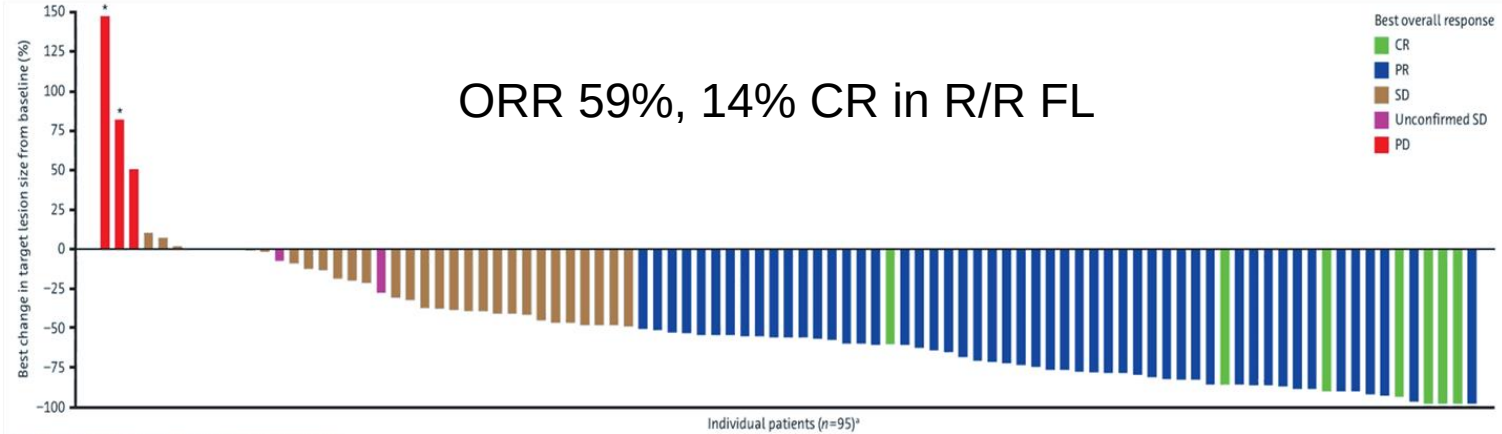
Transaminases, n (%)	Grade 1-2	Grade 3	Grade 4	Any grade
ALT or AST elevated	44 (35%)	13 (10%)	3 (2%)	60 (48%)

Copanlisib in R/R FL



Copanlisib is approved for patients with relapsed FL who have failed at least 2 prior lines of therapy.

ORR 59%, 14% CR in R/R FL



*Patient was assessed as having SD by independent review
ª1 patient classed by the investigator as having FL, but who was reclassified by independent assessment as having diffuse large B-cell lymphoma, is not shown in the plot (change in lesions: increase of 250%)
SD, stable disease

Toxicity Profile of Copanlisib

Incidence of TEAEs Occurring in ≥10% of Patients N (%)	Any grade (N = 104)	Grade 3 (N = 104)	Grade 4 (N = 104)
Hyperglycemia	50 (48.1)	33 (31.7)	9 (8.7)
Diarrhea	36 (34.6)	6 (5.8)	0
Hypertension	31 (29.8)	24 (23.1)	0
Decreased neutrophil count	31 (29.8)	6 (5.8)	19 (18.3)
Fatigue	29 (27.9)	0	0
Fever	28 (26.9)	5(4.8)	0
Decrease platelet count	26 (25.0)	7 (6.7)	1 (1.0)
Ling infection	24 (23.1)	15 (14.4)	3 (2.9)
Oral muscocitis	24 (23.1)	4 (3.8)	0
Nausea	23 (22.1)	0	0
Upper respiratory tract infection	20 (19.2)	3 (2.9)	0
Cough	17 (16.3)	0	0
Anemia	16 (15.4)	5 (4.8)	0
Constipation	14 (13.5)	0	0
Vomiting	14 (13.5)	0	0
Bronchial infection	13 (12.5)	1 (1.0)	0
Headache	13 (12.5)	1 (1.0)	0
Musculo-popular rash	11 (10.6)	1 (1.0)	0
Dyspnea	11 (10.6)	4 (3.8)	0
Flu-like symptoms	11 (10.6)	1 (1.0)	0
Anorexia	11 (10.6)	0	0
Skin infection	11 (10.6)	0	0

1. Dreyling MH., et al. J Clin Oncol 35, 2017 (suppl; abstr 7535)

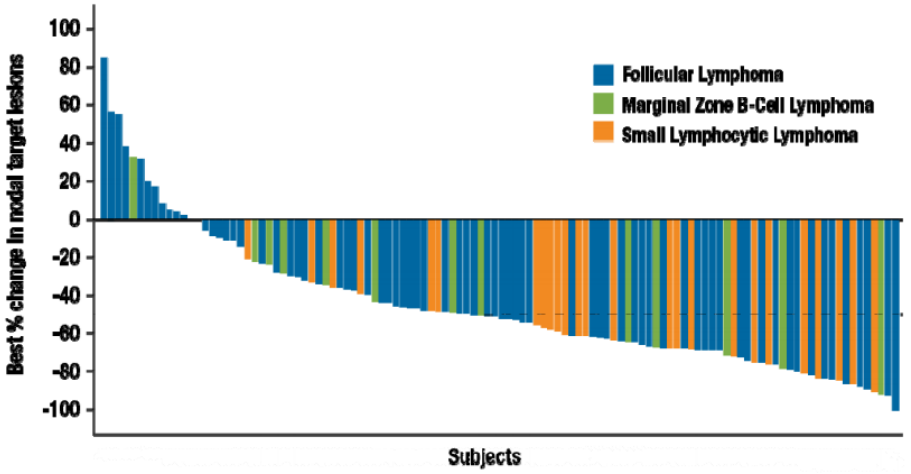
Duvelisib in R/R FL

Phase 2, Single arm, n=129

Accrual Complete; Analysis as of April 2016 (last pt enrolled + 6 mo.)

Duvelisib 25 mg BID Continuously

Treatment until progression or unacceptable toxicity



	OVERALL N = 129	FL N = 83	SLL N = 28	MZL N = 18
ORR per IRC, %	*46*	*41*	*68*	*33*
P-value	*p=0.0001**	--	--	--
95% CI	*(37-55)*	--	--	--
Complete Response	0	0	0	0
Partial Response	46	41	68	33
ORR per Investigator, %	*58*	*53*	*79*	*50*
Complete Response	2	1	4	0
Partial Response	57	52	75	50

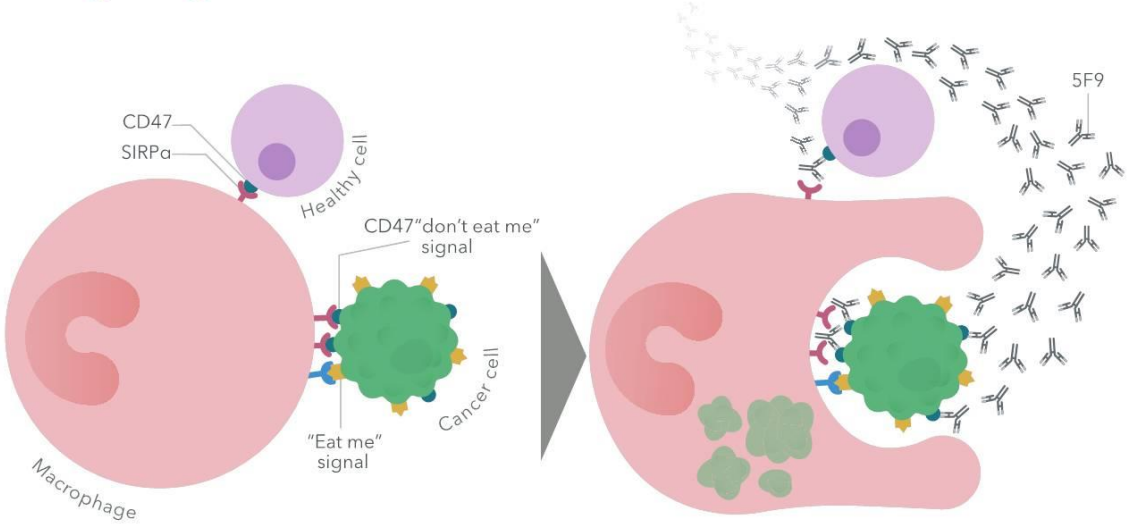
* The study met the primary endpoint (p=0.0001 against null hypothesis that ORR was ≤ 30% per IRC)

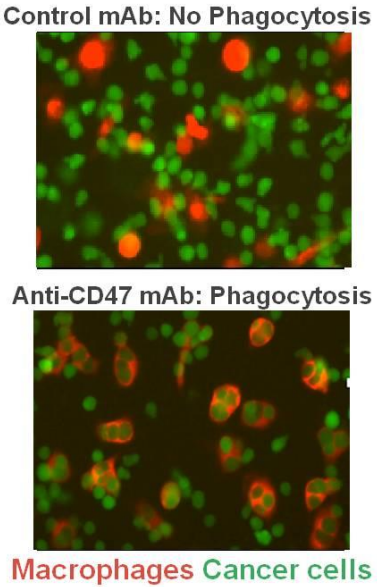
- 83% of pts had reduction in target lymph nodes (per IRC)

Toxicity Profile of Duvelisib

Preferred Term * ≥ Gr 3 AE occurring ≥ 5% of pts	All Grades %	Gr 3 %	Gr 4 %
Diarrhea *	44	14	1
Neutropenia *	32	9	14
Nausea	29	2	0
Cough	24	0	0
Fatigue *	24	5	0
Anemia *	23	10	2
Thrombocytopenia *	21	5	5
Pyrexia	21	0	0
Rash	18	4	0
Vomiting	17	4	0
Peripheral edema	15	2	0
Decreased appetite	15	1	0
Headache	15	0	0
Other Common ≥ Gr 3 AEs (≥ 5% of pts)			
Febrile neutropenia	9	7	2
Lipase increased	9	3	3
ALT increased	14	5	1

5F9 is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47





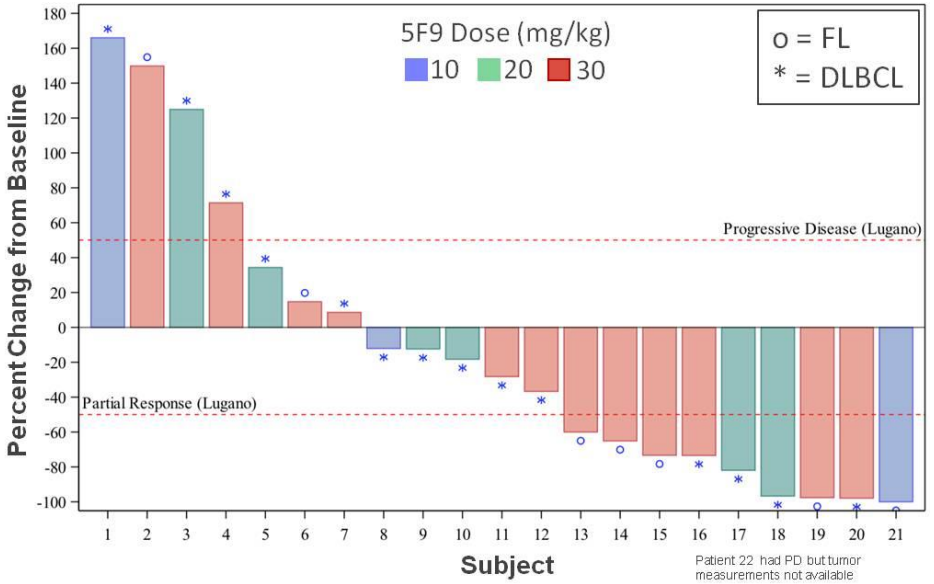
- 5F9 is a humanized IgG4 antibody against CD47, a don't eat me signal, that induces tumor cell phagocytosis
- 5F9 eliminates cancer cells through blockade of CD47 to its binding partner SIRP-alpha on macrophages
- Cancer cells express pro-phagocytic (eat me) signals while most normal cells do not; this allows 5F9 to selectively eliminate cancer cells
- 5F9/CD47 blockade induces anti-tumor activity in over 25 tumor models

Advani. ASCO abstract 2018

Anti-tumor Activity is Observed with 5F9 and Rituximab in Relapsed or Refractory NHL

	Phase 1b		
Response	All patients n=22	DLBCL n=15	Follicular Lymphoma n=7
Objective Response Rate (ORR)	11 (50%)	6 (40%)	5 (71%)
Partial Response (PR)	3 (14%)	1 (7%)	2 (29%)
Complete Response (CR)	8 (36%)	5 (33%)	3 (43%)
Disease control rate (CR+PR+SD)	14 (64%)	9 (60%)	5 (71%)

Data cutoff April 2018



- The objective response rate across all patients is 50% according to Lugano criteria
- Multiple CRs have been observed in both DLBCL and FL Phase 1b populations
- Efficacy is observed in rituximab-refractory patients

Advani. ASCO abstract 2018

Nivolumab in R/R NHL

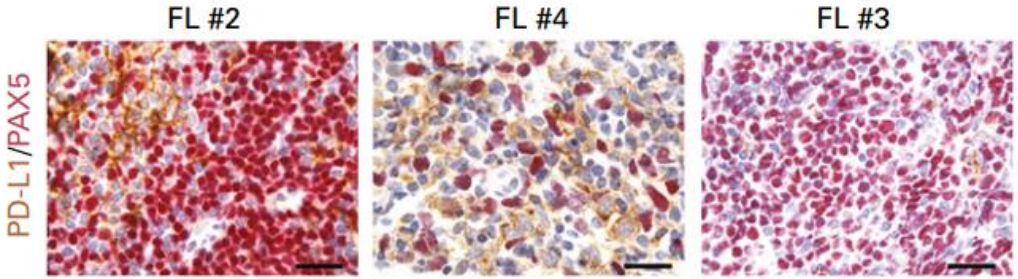
- PD-L1 expression is heterogeneous among lymphoma subtypes[1]
- Genetic alterations of the 9p24.1 locus is less frequently observed among NHL subytpes[2]
- Avoiding immune surveillance by modulating T cell activity may occur through expression of PD-L1/PD-L2 in the tumor microenvironment[3]

Table 3. Efficacy Results

Tumor	OR, No. (%)	CR, No. (%)	PR, No. (%)	SD, No. (%)	Median PFS, Weeks (95% CI)
B-cell lymphoma (n = 31)	8 (26)	3 (10)	5 (16)	16 (52)	23 (7 to 44)
DLBCL (n = 11)	4 (36)	2 (18)	2 (18)	3 (27)	7 (6 to 29)
FL (n = 10)	4 (40)	1 (10)	3 (30)	6 (60)	NR (7 to NR)
Other B-cell lymphoma (n = 10)	0	0	0	7 (70)	11 (3 to 39)
T-cell lymphoma (n = 23)	4 (17)	0	4 (17)	10 (43)	10 (7 to 33)
MF (n = 13)	2 (15)	0	2 (15)	9 (69)	10 (7 to 35)
PTCL (n = 5)	2 (40)	0	2 (40)	0	14 (3 to NR)
Other CTCL (n = 3)	0	0	0	0	7 (6 to NR)
Other non-CTCL (n = 2)	0	0	0	1 (50)	10 (2 to 18)
Multiple myeloma (n = 27)	1 (4)	1 (4)*	0	17 (63)	10 (5 to 15)

Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoides; NR, not reported; OR, objective response; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease.
*CR was obtained after radiotherapy. SD was the best response to nivolumab.

Positive PD-L1 expression among non malignant cells within the follicular lymphoma microenvironment[3]



[1]Chen. Clin Cancer Res. 19:3462-3473, 2013;[2]Green. Blood. 116:3268-3277,2010
[3]Lesokhin. JCO. 2016;34(23):2698-2704.

Conclusions

- Relapsed FL is heterogeneous.
- Goals of therapy remain the same, achieve a quality remission without significant toxicity or negative impact on QOL.
- Targeting the microenvironment appears to be a promising strategy.
- The most effective sequencing of therapy is not well understood.
- Enrichment of high risk patients on prospective clinical trial is advisable.

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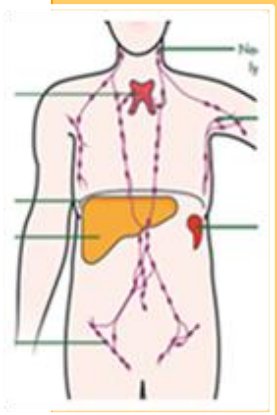
MD Anderson Cancer Center

Current Treatment Landscape Marginal Zone Lymphoma



Nodal

- Rituximab + Chemo
  - Bendamustine
  - CHOP
  - Fludarabine
- Ibrutinib

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Ibrutinib, First FDA-Approved Therapy for Marginal Zone Lymphoma

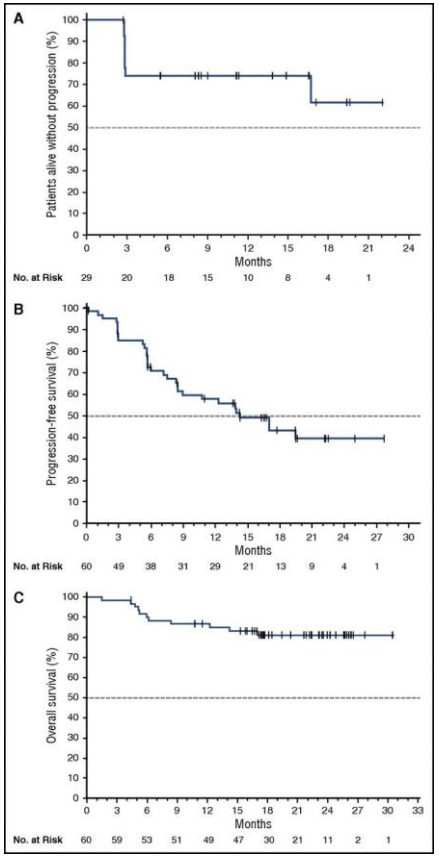
It is indicated in patients who require systemic therapy and have received at least one prior anti-CD20-based therapy

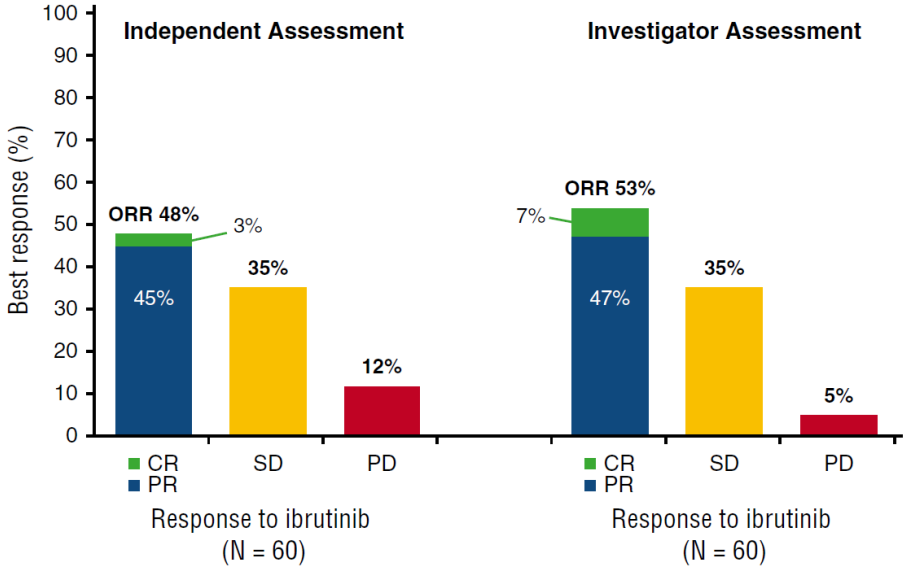
Date: 23 Jan 2017

Topic: **Haematologic malignancies** / **Anticancer agents & Biologic therapy**

On 19 January, 2017, the US Food and Drug Administration (FDA) has approved ibrutinib (IMBRUVICA®) for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. Accelerated approval was granted for this indication based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Ibrutinib is jointly developed and commercialised by Janssen Biotech, Inc., and Pharmacyclics LLC, an AbbVie company.

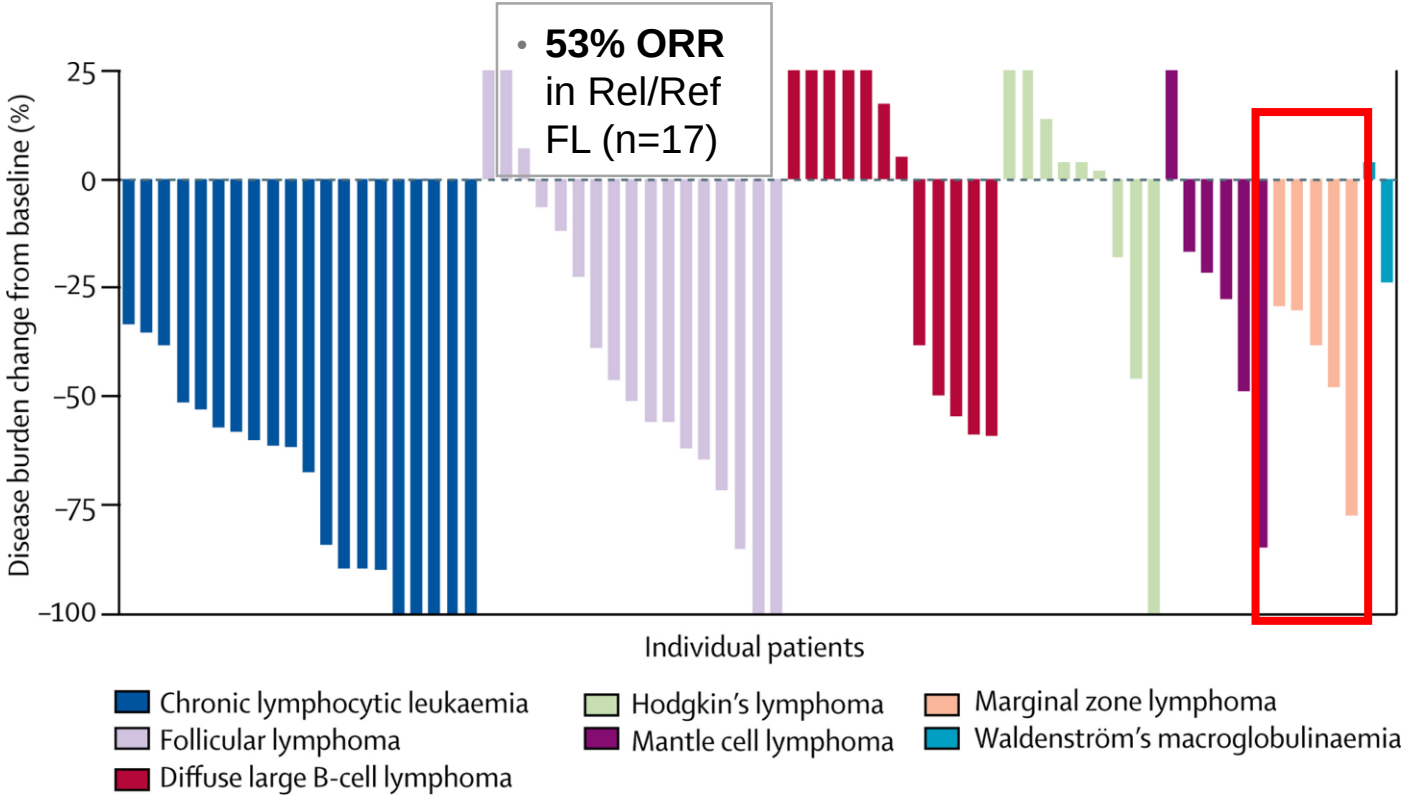
Ibrutinib in R/R MZL





Noy et al. Blood 2017;129:2224-2232

Umbralisib (PI3Kδ/CK1ε)
Phase I study in Relapsed/Refractory lymphoid malignancies



mITT, modified intention-to-treat.
Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

Umbralisib (PI3Kδ/CK1ε)
Phase I study in Relapsed/Refractory lymphoid malignancies

AE, n (%)	All Grades	Grade 1-2	Grade 3	Grade 4
Diarrhea	39 (43)	36 (40)	3 (3)	-
Nausea	38 (42)	37 (41)	1 (1)	-
Fatigue	28 (31)	25 (28)	3 (3)	-
Vomiting	25 (28)	25 (28)	-	-
Cough	19 (21)	19 (21)	-	-
Headache	19 (21)	17 (19)	2 (2)	-
Rash	17 (18)	13 (14)	4 (4)	-
Constipation	14 (16)	13 (14)	1 (1)	-
Decreased appetite	14 (16)	14 (16)	-	-
Hypokalemia	14 (16)	10 (11)	4 (4)	-
Anemia	13 (15)	5 (6)	8 (9)	-
Neutropenia	13 (15)	1 (1)	9 (10)	3 (3)

- Most common AEs were diarrhea (43%), nausea (42%) and fatigue 31%)
- Most diarrhea events were grade 1 (n=30; 77%) and resolved without intervention
- ALT/AST increase uncommon, occurring in 7 (8%) of patients (3% Grade ≥3)
- AEs of note occurring <15% of patients include pneumonia (8%, Grade 3/4 - 3%), febrile neutropenia (3%, Grade 4 - 1%), and colitis (2%)

Burris HA, et al. *Lancet Oncol.* 2018 Feb 20 [Epub ahead of print].

TG Therapeutics

The Future of Combination Therapy
U2 + Ibrutinib

Lorettta Nastoupil, MD

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

Tolerability and activity of chemo-free triplet combination of umbralisib (TGR-1202), ublituximab, and ibrutinib in patients with advanced CLL and NHL

Loretta Nastoupil, MD[1], Matthew A. Lunning, DO[2], Julie M. Vose, MD[2], Marshall T. Schreeder, MD[3], Tanya Siddiqi, MD[4], Christopher R. Flowers, MD[5], Jonathon B. Cohen, MD[5], Jan A. Burger, MD[1], William G. Wierda, MD[1], Susan O'Brien, MD[6], Peter Sportelli[7], Hari P. Miskin, MS[7], Michelle A. Purdom, RN, PhD[7], Michael S. Weiss[7] and Nathan H. Fowler, MD[1]

[1]MD Anderson Cancer Center, Houston, TX; [2]University of Nebraska Medical Center, Omaha, NE; [3]Clearview Cancer Institute, Huntsville, AL; [4]City of Hope National Medical Center, Duarte, CA; [5]Emory University/Winship Cancer Institute, Atlanta, GA; [6]University of California Irvine Cancer Center, Orange, CA; [7]TG Therapeutics, Inc., New York, NY

Presented at the 14th International Conference on Malignant Lymphoma
Lugano, Switzerland ● June 14 – 17, 2017

Safety

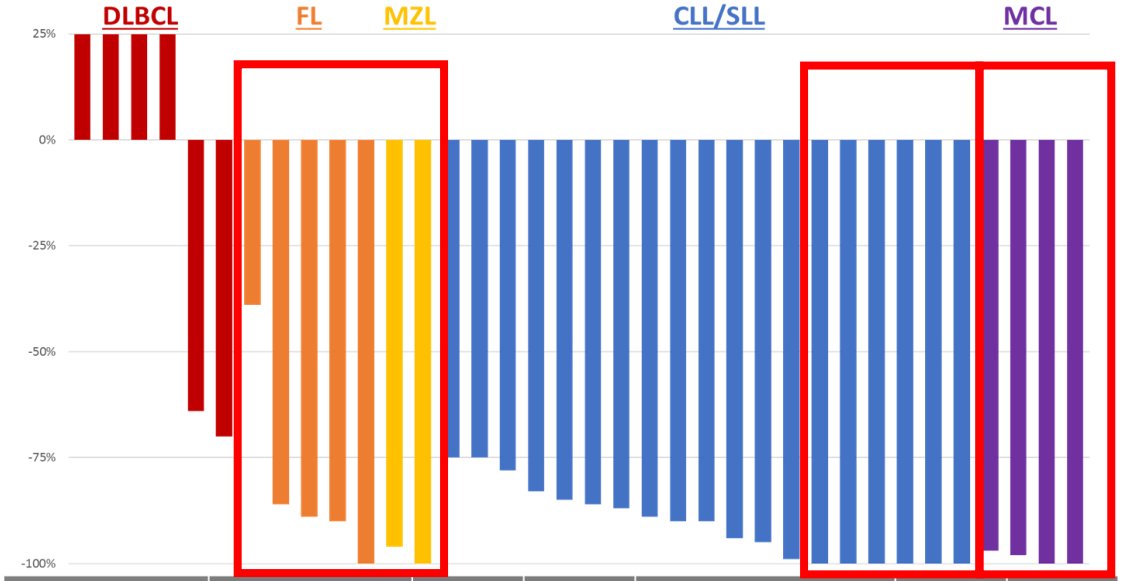
Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	18	47%	1	3%
Fatigue	18	47%	-	-
Dizziness	14	37%	1	3%
Insomnia	13	34%	-	-
Nausea	13	34%	-	-
Neutropenia	12	32%	7	18%
Cough	12	32%	-	-
Infusion related reaction	12	32%	-	-
Thrombocytopenia	11	29%	3	8%
Pyrexia	11	29%	1	3%
Rash	11	29%	1	3%
Anemia	10	26%	1	3%
Sinusitis	9	24%	-	-
Dyspnea	8	21%	1	3%
Stomatitis	8	21%	1	3%

- 1 DLT (reactivated varicella zoster) occurred CLL cohort level 1. No other DLT's were observed.
- Diarrhea majority Gr. 1 (32%) and Gr. 2 (13%), with no Gr. 4 event reported.
- Pneumonia (11% Gr. 3/4) and neutropenia were the only Gr. 3/4 AE's in >10% of patients
- Two patients discontinued due to an AE (sepsis and pneumonia)
- Median time on study 11.1 months (range 0.4 – 30+ months)

Nastoupil et al, ICML 2017

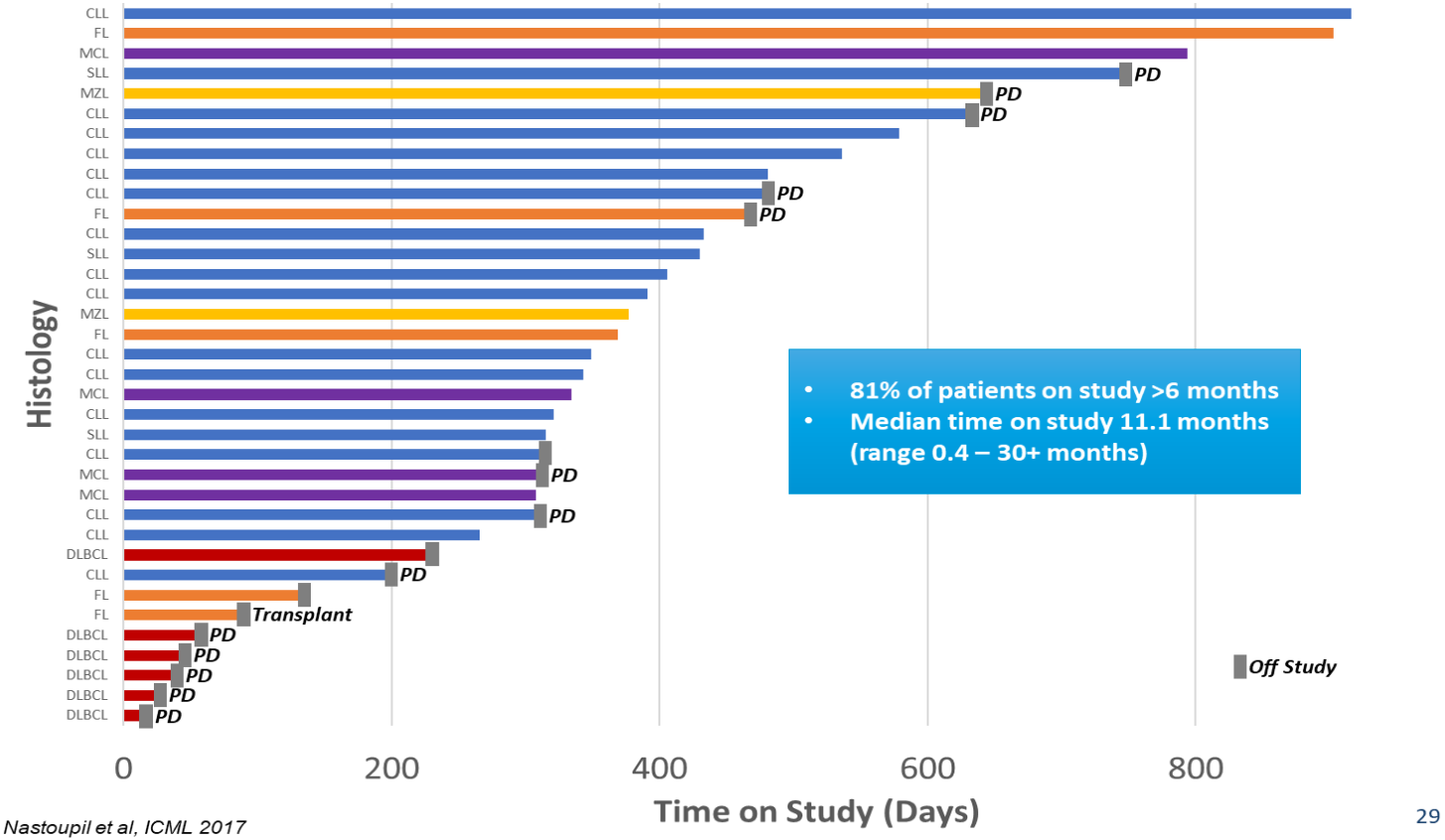
Efficacy: Waterfall Plot

Best Percent Change from Baseline in Disease Burden



Type	Pts (n)	CR† (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	19	6	13	**19 (100%)**	-	-
MZL	2	1	1	**2 (100%)**	-	-
MCL	4	2	2	**4 (100%)**	-	-
FL	5	1	3	**4 (80%)**	1	-
DLBCL	6	-	1	**1 (17%)**	-	5
Total	**36**	**10**	**20**	**30 (83%)**	**1**	**5**

Efficacy: Time on Study



Nastoupil et al, ICML 2017

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Conclusions

- With a median follow up of 11.1 months, the combination of ublituximab, umbralisib (TGR-1202), and ibrutinib appears to be well tolerated and demonstrates favorable efficacy in advanced CLL and NHL.

- The safety profile of this novel combination was favorable suggesting that TGR-1202 may be safely combined with targeted agents to overcome mechanisms of resistance.

- Many patients continue on therapy, with approximately half beyond 1 year and are experiencing a manageable safety profile.

Nastoupil et al, ICML 2017

TG Therapeutics

U2 + Bendamustine

Matthew Lunning, DO
University of Nebraska Medical Center

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

U2 + Bendamustine: Demographics

Evaluable for Safety (n)	33	
Evaluable for Efficacy† (n)	24	
Median Age, years (range)	68 (31 – 81)	
Male/Female	20/13	
Histology	DLBCL	23
	FL	10
ECOG, 0/1/2	7/24/2	
Prior Therapy Regimens, median (range)	2 (1 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	10 (30%)	
Refractory to Prior Therapy, n (%)	21 (64%)	
Refractory to Rituximab, n (%)	20 (61%)	

- 17/23 (74%) DLBCL patients refractory to immediate prior therapy

Lunning et al, ICML 2017

TG Therapeutics

U2 + Bendamustine: Safety

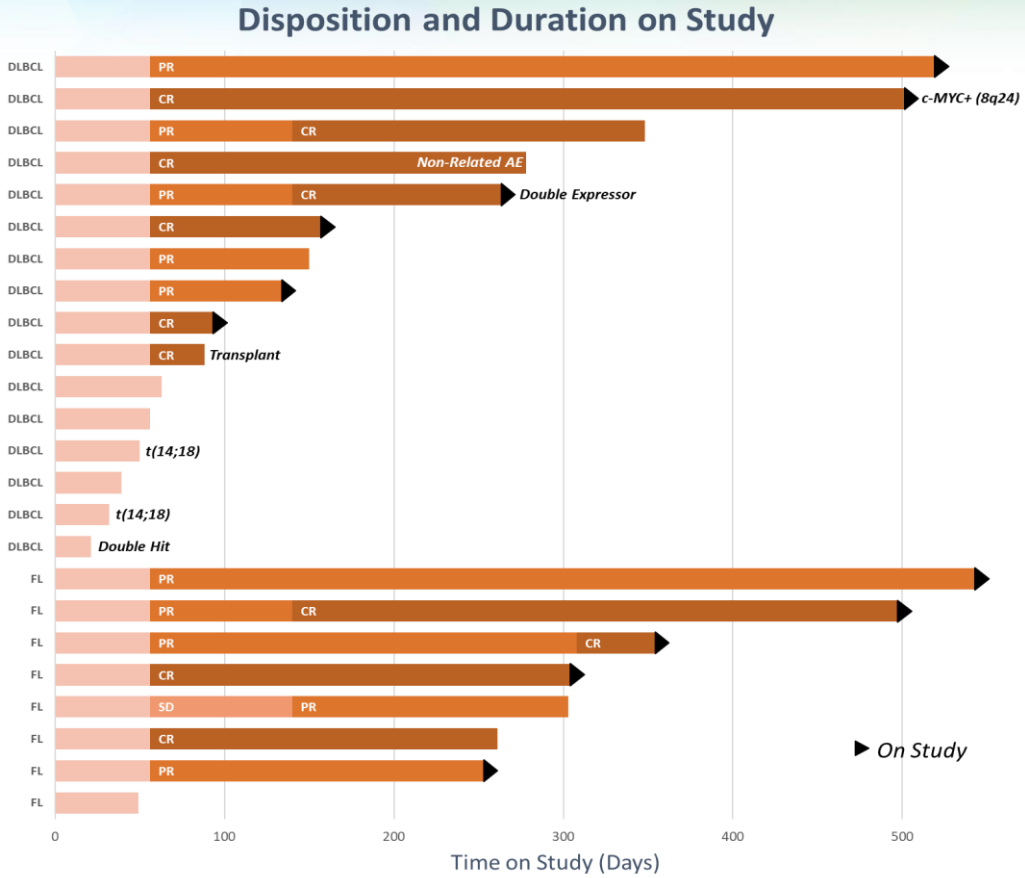
All Causality AE's Occurring in ≥ 10% of Patients (n = 33)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	12	36%	3	9%
Decreased appetite	9	27%	1	3%
Nausea	8	24%	1	3%
Neutropenia	8	24%	8	24%
Asthenia	6	18%	1	3%
Hypomagnesaemia	6	18%	1	3%
Thrombocytopenia	5	15%	2	6%
Vitamin D decreased	5	15%	-	-
Hypokalemia	4	12%	3	9%
Anemia	4	12%	2	6%
Arthralgia	4	12%	-	-
Bone pain	4	12%	-	-
Hypophosphatasemia	4	12%	-	-
Infusion related reaction	4	12%	-	-
Pyrexia	4	12%	-	-
Vomiting	4	12%	-	-

- Mean time on study 6 cycles
- Growth factor support was initially restricted during Cycle 1 for DLT evaluation purposes; now allowed prophylactically
- No events of febrile neutropenia were reported

Lunning et al, ICML 2017

U2 + Bendamustine: Efficacy



Lunning et al, ICML 2017

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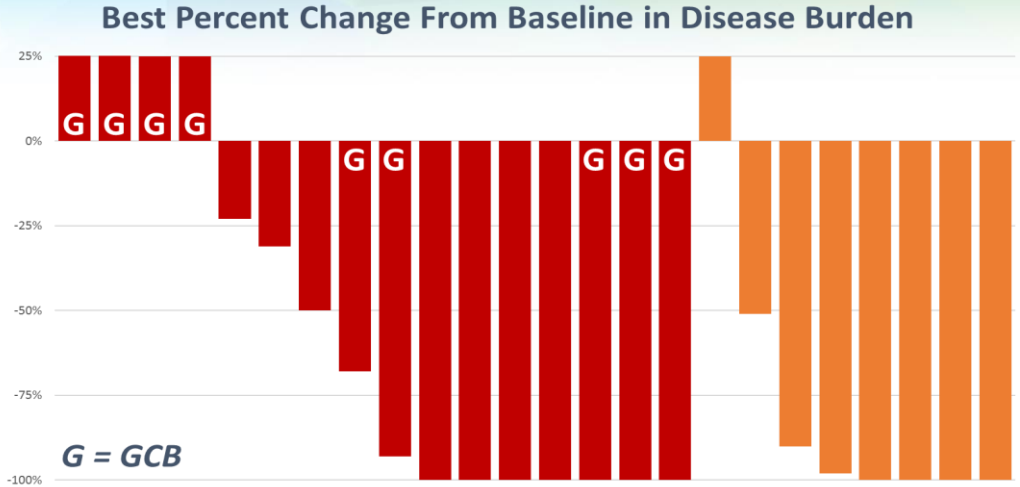

Best Overall Response Rate at Month 3

Type	Pts n	CR n (%)	PR n (%)	ORR n (%)	SD n	PD n
DLBCL (Rel)	4	2 (50%)	2 (50%)	**4 (100%)**	-	-
DLBCL (Ref)	12	5 (42%)	1 (8%)	**6 (50%)**	1	5
FL (Rel)	5	3 (60%)	1 (20%)	**4 (80%)**	-	1
FL (Ref)	3	1 (33%)	2 (67%)	**3 (100%)**	-	-
Combined	**24**	**11 (46%)**	**6 (25%)**	**17 (71%)**	**1**	**6**

Lunning et al, ICML 2017

Patient Case Studies

FL Case Studies

- 77 y/o Male with 3 prior lines: R-Benda (refractory), R-idelalisib (refractory), and an investigational EZH2 inhibitor (refractory)
  - Attained a PR (72% reduction) at first assessment, CR by Week 44, now ongoing for ~12+ months

- 57 y/o Male with 3 prior lines of therapy: CHOP, R-ICE, and ASCT
  - Attained a PR (88% reduction) at first response, and PET-negative CR at second assessment, ongoing for 16+ months

U2 + Bendamustine: ASH 2018 Abstract Data

Table 1

	N	CR *N (%)*	PR *N (%)*	ORR *N (%)*	SD *N (%)*
DLBCL	25	8 (32%)	4 (16%)	12 (48%)	3 (12%)
FL	13	7 (54%)	4 (31%)	11 (85%)	1 (8%)

Full Poster Presentation Tomorrow Evening!

- **Date: Monday December 3, 2018**
- **Time: 6:00 PM - 8:00 PM PT**
- **Abstract Number: 4197**

Lunning et al. ASH 2018 Abstract Data

TG Therapeutics

U2 + Pembrolizumab

Mato et. Al. ASH 2018

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PHASE 3 TRIAL IN CLL

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PREVIOUSLY TREATED NHL PATIENTS

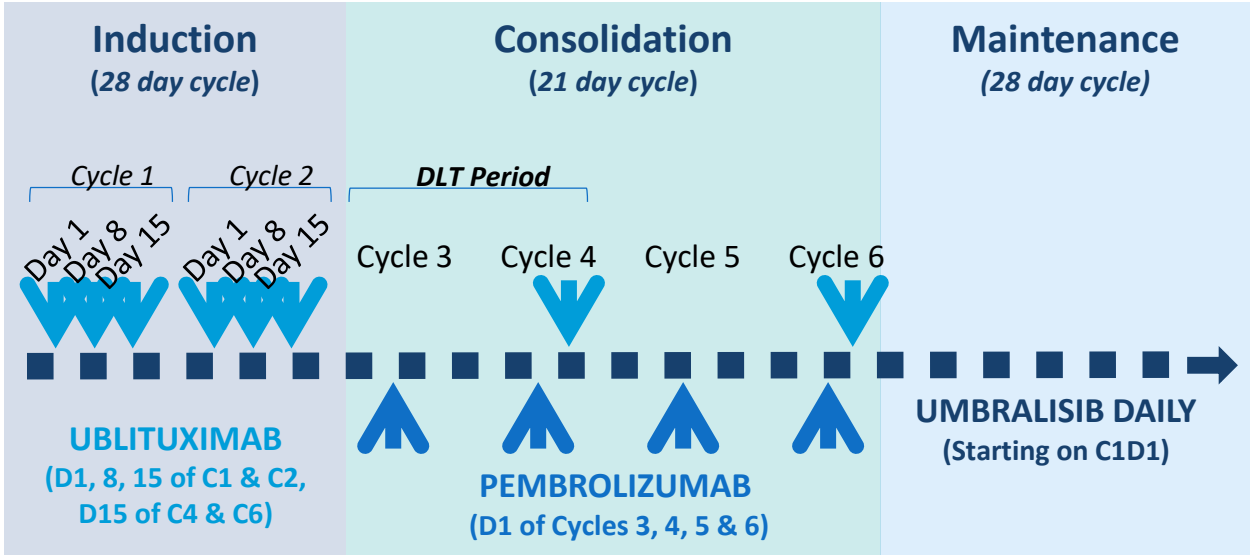
Phase I/II Study of Umbralisib (TGR-1202) in Combination with Ublituximab (TG-1101) and Pembrolizumab in Patients with Relapsed/Refractory CLL and Richter's Transformation

Anthony R. Mato, MD MSCE[1], Jakub Svoboda, MD[2], Eline T. Luning Prak, MD, PhD[3], Stephen J. Schuster, MD[2], Patricia Tsao, MD, PhD[3], Colleen Dorsey, BSN, RN[1], Pamela S. Becker, MD[4], Danielle M. Brander, MD[5], Sunita Dwivedy Nasta, MD[2], Daniel J. Landsburg, MD[2], Cara M King, MPH[2], Beth Morrigan[4], Jill Elwell[4], Kaitlin Kennard, RN, BSN[2], Lindsey E. Roeker, MD[1], Andrew D. Zelenetz, MD, PhD[6], Michelle Purdom, PhD, RN[7], Dana Paskalis[7], Peter Sportelli[7], Hari P Miskin, MSc[7], Michael S. Weiss[7] and Mazyar Shadman, MD, MPH[4]

[1]CLL Program, Leukemia Service, Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [3]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [4]Fred Hutchinson Cancer Research Center, Seattle, WA; [5]Duke Cancer Institute, Duke University Health System, Durham, NC; [6]Lymphoma Service, Memorial Sloan-Kettering Cancer Center, New York, NY; [7]TG Therapeutics, Inc., New York, NY

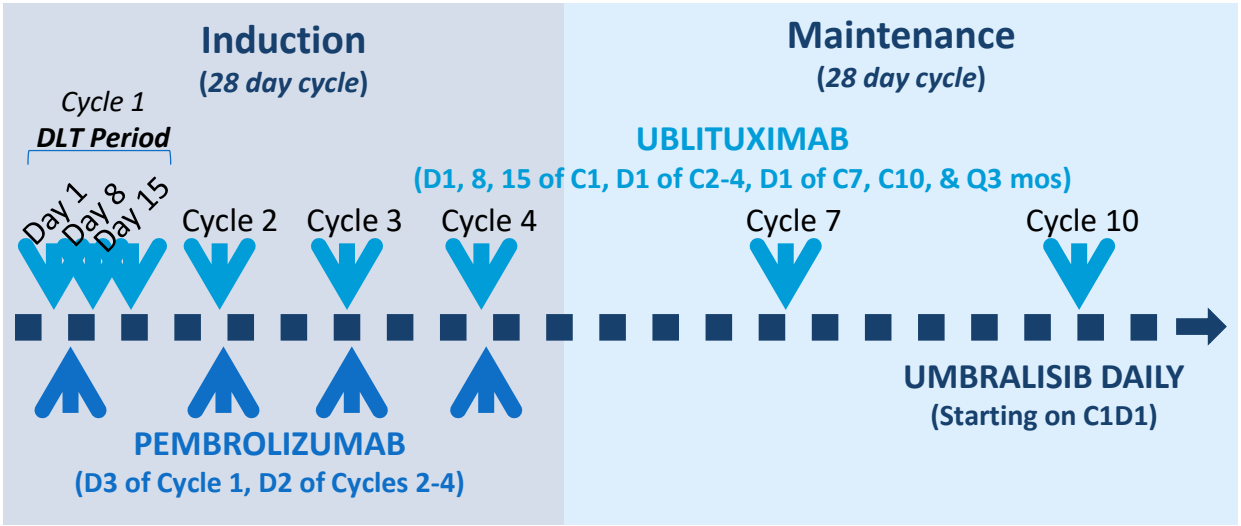
Presented at the 60th Annual ASH Meeting and Exposition
December 1 – 4, 2018 ● San Diego, CA

Study Design: Treatment Schedule for CLL



- Efficacy assessed at the end of Cycles 2, 6 & 12. After Month 12, efficacy is assessed per investigator discretion.

Study Design: Treatment Schedule for RT



- Efficacy assessed at the end of Cycles 2 & 4 and Q3 cycles thereafter until Month 12. After Month 12, efficacy assessed per investigator discretion.

Demographics

Chronic Lymphocytic Leukemia

Evaluable for Safety & Efficacy, n	10
Median Age, years (range)	70 (60 - 81)
Male/Female	6 / 4
ECOG, 0/1/2	4 / 6 / 0
Prior Therapy Regimens, median (range)	2 (1 – 4)
Prior BTK (ibrutinib or acalabrutinib), n (%)	6 (60%)
Refractory to prior BTK	5/6 (83%)
Refractory to immediate prior therapy, n (%)	7 (70%)
At least 1 high risk feature (del17p, del11q, TP53*mut*, NOTCH1*mut* or Complex karyotype)	8 (80%)
≥2 high risk features	6 (60%)
17p del/TP53 mutated, n (%)	3 (30%)
Complex Karyotype, n (%)	5 (50%)
NOTCH1/ATM/SF3B1*mut*, n (%)	5 (50%)
IGHV Unmutated, n (%)	5 (50%)
Bulky Disease, n (%)	6 (60%)

Richter's Transformation

Evaluable for Safety, n	5
Evaluable for Efficacy[†], n	4
Median Age, years (range)	70 (53 - 73)
Male/Female	4 / 1
ECOG, 0/1/2	3 / 1 / 1
Prior Therapy Regimens, median (range)	7 (2 – 9)
Prior ibrutinib	5 (100%)
Refractory to prior ibrutinib	5 (100%)
Prior idelalisib + rituximab	2 (40%)
Prior venetoclax	1 (20%)
Prior CAR-T / Allo Transplant	3 (60%)
Refractory to immediate prior therapy	5 (100%)
Bulky Disease, n (%)	5 (100%)

[†]1 RT patient is too early to evaluate.

Disposition and Safety

Enrollment by Cohort

Pembro Dose	CLL	RT	Total
100 mg	4	3	7
200 mg	6	2	8

- 1 DLT at 200 mg pembro dose (transient elevated LFT - resolved); MTD not reached
- Grade 3/4 LFT elevations occurred in 3 patients (20%)
- No Grade 3/4 diarrhea and no events of colitis observed
- No Grade 3/4 pembro associated autoimmune events
- Median follow-up: 15.6+ mos

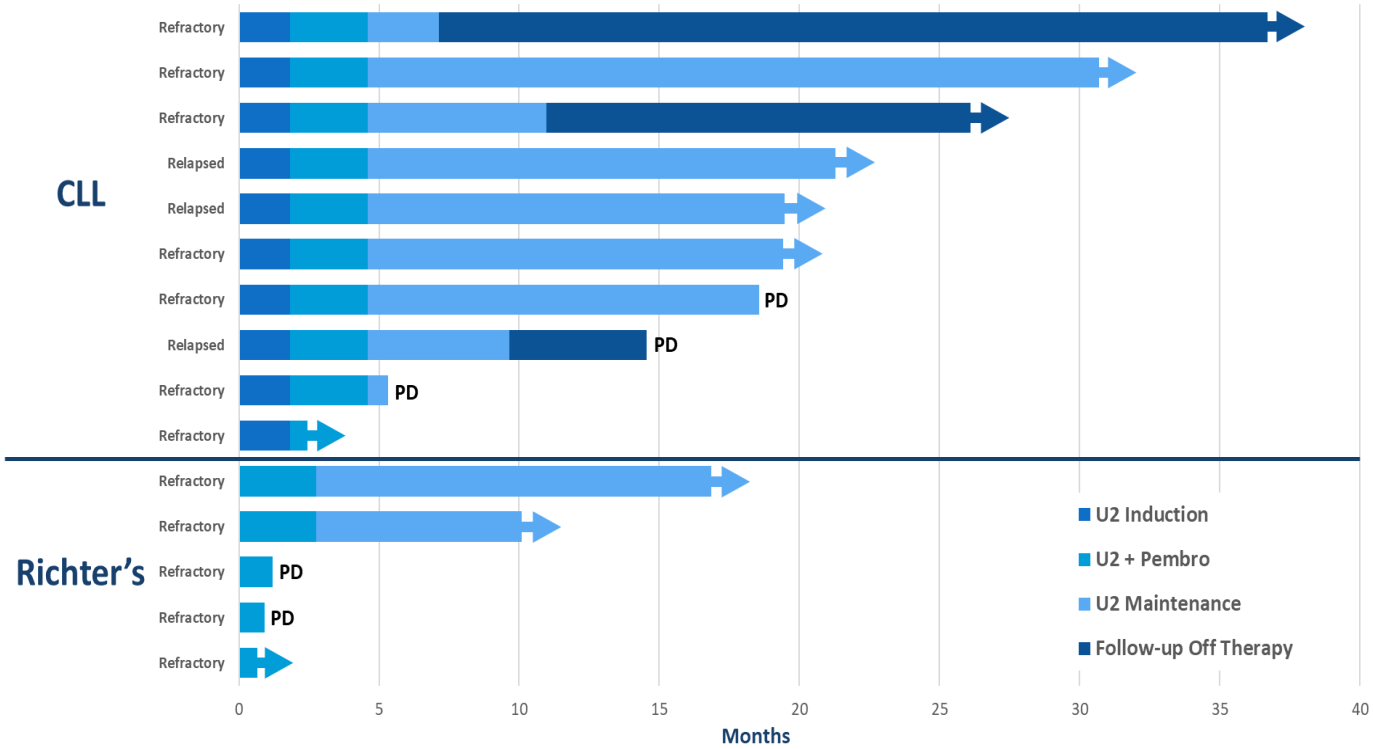
Dose Modifications

	Delay	Withdrawn
Pembro	3	1
Umbralisib	8	5

Adverse Events for (All Causality) >20% (N=15)

	All Grades		Grade 3/4	
	N	%	N	%
Neutropenia	10	67%	5	33%
Pyrexia	8	53%	-	-
Decreased appetite	7	47%	-	-
Diarrhea	7	47%	-	-
Fatigue	7	47%	1	7%
Infusion related reaction	7	47%	-	-
Anemia	6	40%	1	7%
Blood alk phos increased	6	40%	-	-
Chills	6	40%	-	-
Cough	6	40%	-	-
Nausea	6	40%	1	7%
Thrombocytopenia	6	40%	2	13%
Headache	5	33%	-	-
Nasal congestion	5	33%	-	-
Peripheral Edema	5	33%	-	-
Arthralgia	4	27%	-	-
Dysgeusia	4	27%	-	-
Myalgia	4	27%	-	-

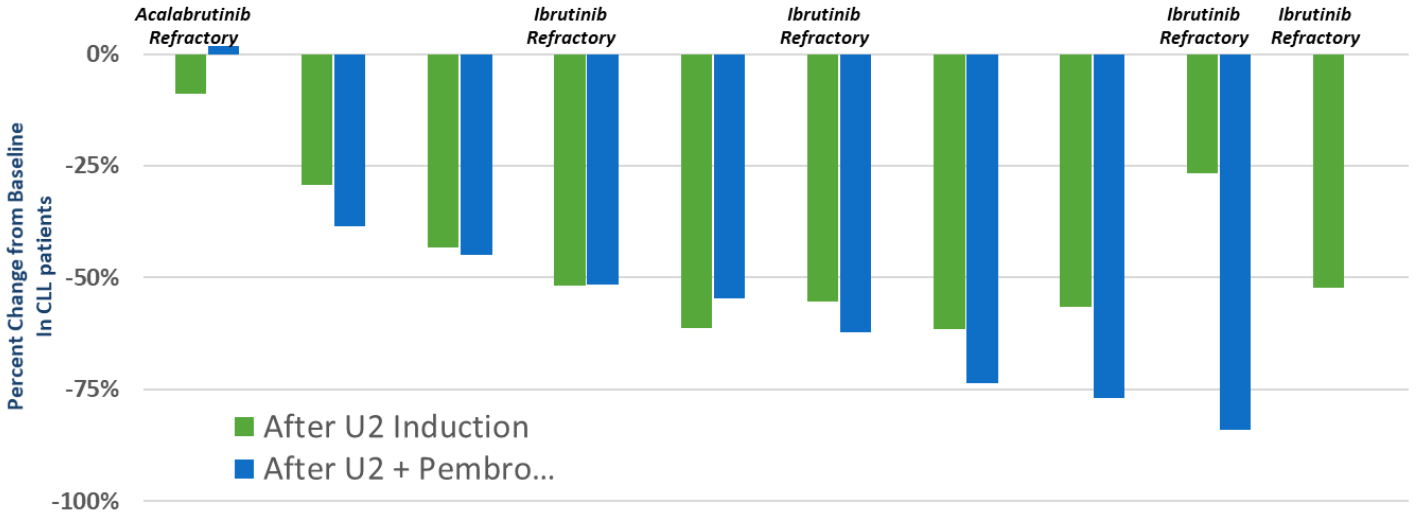
Efficacy & Tolerability: Duration of Exposure



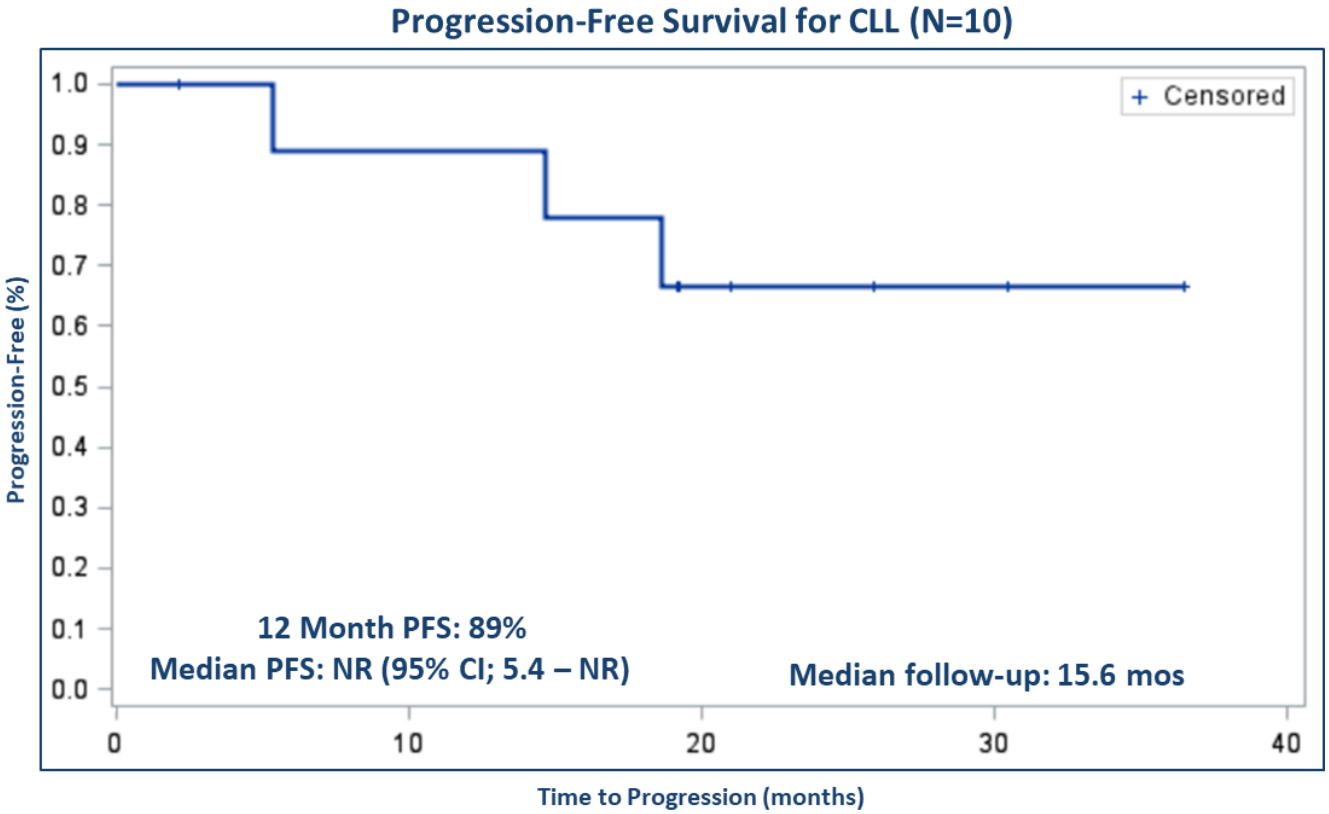
Efficacy: ORR

Group	N	CR N (%)	PR N (%)	ORR N (%)
CLL	10	1 (10%)	8 (80%)	9 (90%)
RT	4	2 (50%)	0	2 (50%)

- BTK Refractory CLL
  - **ORR: 80% (4/5)**
  - 3/4 BTK Refractory responders achieved response after U2 Induction, prior to pembro



Efficacy: PFS



Conclusions

- Triplet combination of umbralisib + ublituximab (“U2”) + pembrolizumab was well tolerated
  - Immune mediated toxicities were not increased above what would be expected with either umbralisib or pembrolizumab alone
- Responses were durable in BTK refractory, high-risk pts, including two durable CRs in RT pts
  - Data suggest that CLL pts who achieve less than CR with a checkpoint inhibitor-containing regimen can achieve durable remissions and that time-limited schedules should be explored
- Maintenance of T-regs throughout therapy may explain limited autoimmune sequelae
- Enrollment is ongoing in both the CLL (BTK refractory only) and RT cohorts
  - Protocol amendment underway to replace pembro with novel anti-PD-L1 (TG-1501)

TG Therapeutics

Questions & Answer Session

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Concluding Remarks

Michael S. Weiss
Chief Executive Officer, TG

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