TG Therapeutics

2019 American Association of Cancer Research (AACR)
Data Review Call
April 1, 2019

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AACR 2019 Umbralisib Data Review

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& Study Chair of the UNITY-NHL MZL Cohort

Umbralisib monotherapy demonstrates efficacy and safety in patients with relapsed/ refractory marginal zone lymphoma: a multicenter, open-label, registration directed phase 2 study

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  - TG Therapeutics, Inc.
  - Bayer
  - Gilead Sciences
  - Verastem Oncology
  - Celgene

- Research funding
  - TG Therapeutics, Inc.

Background / Rationale

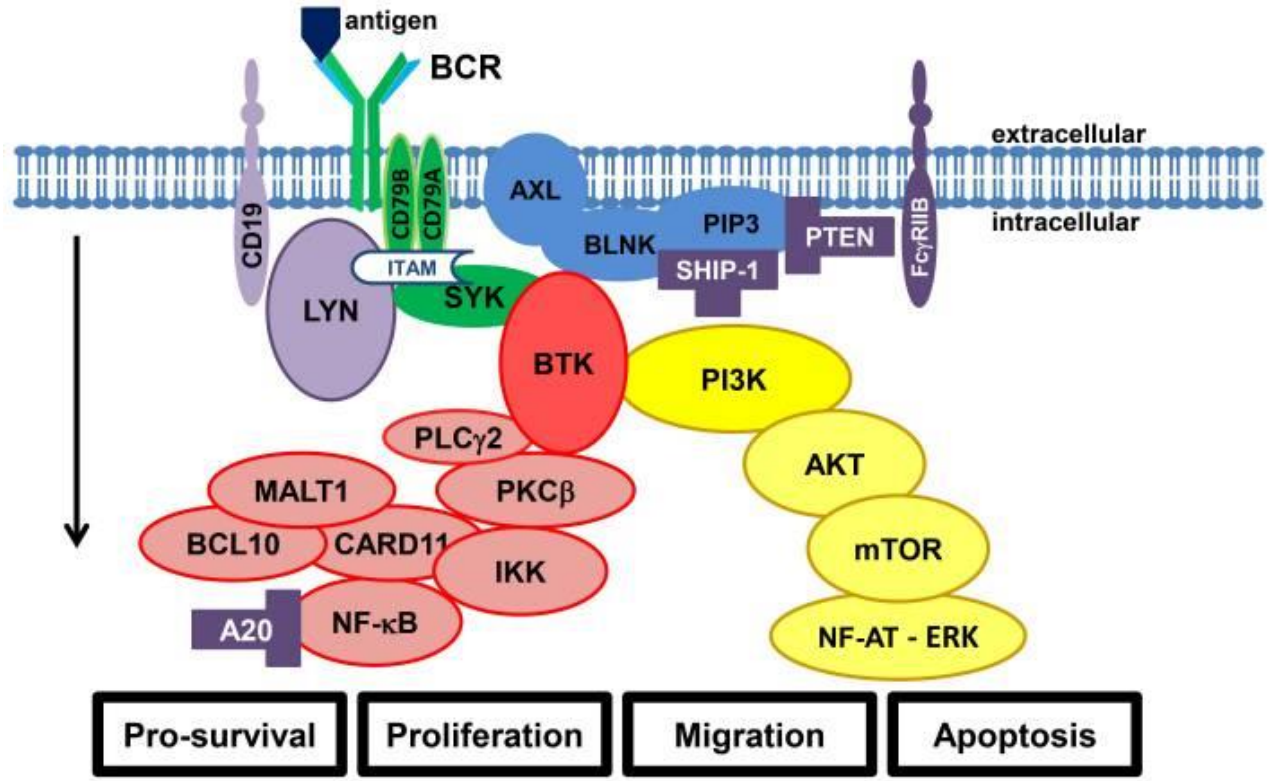
- Marginal Zone Lymphoma (MZL) is an indolent B-cell lymphoma accounting for ~10% of NHL
- Although responses are high to frontline therapy, most patients still relapsed following induction.
- Therapeutic options are limited for MZL pts who have progressed following anti-CD20-based therapy, and those who are poor candidates for chemo-based regimens
- Targeting components of the B-cell receptor pathway is effective in the treatment of MZL[1], however novel therapies are needed

[1]Noy et al., *Blood* 2017, 129(16), 2224-2232

PI3K Signaling in Marginal Zone Lymphoma

- B cell receptor (BCR) signaling is critical to the development and maturation of normal B cells and has been implicated in lymphomagenesis
- PI3K is a downstream intermediary in the BCR pathway that is essential for BCR-dependent B cell survival
- Recent evidence has shown that the PI3K-mTOR pathway is sufficient for driving the pathogenesis of marginal zone lymphomas[2]

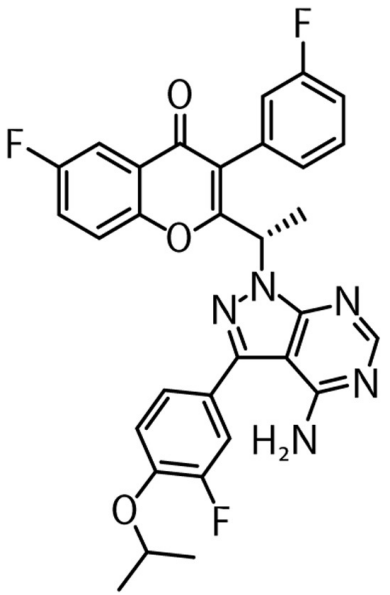
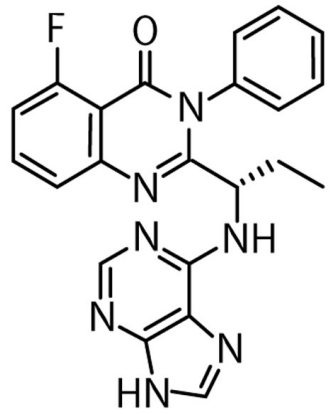
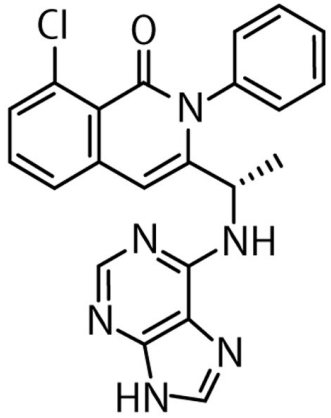
The B cell Receptor (BCR) and its Downstream Pathways[1]



[1]Niemann et al., Semin Cancer Biol. 2014. [2]Sindel et al., Blood. 2018

Umbralisib (TGR-1202)

- Next generation PI3Kδ inhibitor, with a unique structure and improved tolerability[1]
  - Improved selectivity to PI3Kδ isoform
  - Inhibition of CK1ε
    - Potential regulator of Treg count and function
  - Ongoing long-term safety analysis demonstrate low rates of immune-mediated toxicity[2]
- Oral – once daily administration
- Phase 2/3 dose: 800 mg QD

	Umbralisib	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
CK1ε	180	>30 000	>30 000

[1]Burris et al., Lancet Oncology 2018; [2]Davids et al., EHA 2018

UNITY-NHL Study Design

- Study UTX-TGR-205 (UNITY-NHL) is an ongoing Phase 2b, multicenter, multi-cohort trial evaluating umbralisib as monotherapy and in multiple combinations in previously treated NHL (NCT02742090)
- The MZL cohort enrolled patients to receive single agent umbralisib 800 mg oral QD until disease progression or unacceptable toxicity

Key Inclusion Criteria:

- Marginal Zone Lymphoma (splenic, nodal, or extranodal) requiring treatment
- Relapsed or refractory following treatment with one or more lines of therapy including at least one CD20-directed regimen (either as monotherapy or as chemoimmunotherapy)
- ECOG PS ≤2

Primary Endpoint:

- ORR by independent review committee (IRC) by 2007 IWG criteria

Secondary Endpoints:

- Duration of Response (DOR)
- Progression-free Survival (PFS)
- Time to Response (TTR)
- Safety

Demographics

	All Treated Patients (Safety Population)	Interim Efficacy Population*
N	**69**	**42**
MZL Subtype, n (%)		
Extranodal	38 (55%)	23 (55%)
Nodal	20 (29%)	12 (29%)
Splenic	11 (16%)	7 (17%)
Median Age, median (range)	67 (34 – 81)	67 (34 – 81)
Female, n (%)	36 (52%)	25 (60%)
Male, n (%)	33 (48%)	17 (40%)
ECOG 0/1/2, n	39/30/0	23/19/0
Prior Therapies, median (range)	2 (1 – 6)	2 (1 – 6)
rituximab monotherapy only	16 (23%)	7 (17%)
rituximab-based chemoimmunotherapy	50 (72%)	32 (76%)
radiation	5 (7%)	3 (7%)
stem cell transplant	1 (1%)	1 (2%)
lenalidomide	3 (4%)	2 (5%)
ibrutinib	2 (3%)	2 (5%)
Refractory to most recent therapy, n (%)	18 (26%)	8 (19%)
Refractory to prior anti-CD20, n (%)	15 (22%)	6 (14%)
Lactate dehydrogenase (LDH), ≥350 unit/L, n (%)	17 (25%)	12 (29%)

*Interim analysis for efficacy performed on all patients enrolled 9+ months prior to the data cutoff date

- Enrollment is complete
  - 72 patients enrolled between July 2017 and August 2018
    - 69 patient received therapy
    - 42 patients with 9+ months follow up

Adverse Events Regardless of Causality, All Treated Patients (N=69)

- Umbralisib was well tolerated
- No events of colitis reported (colonoscopies not mandated)
- AE's leading to dose reduction occurred in 6 subjects (9%)
- 10 subjects (14%) discontinued umbralisib due to an AE considered at least possibly related to treatment
- The median duration of exposure to umbralisib was 6.9 months as of data cutoff date
- No deaths occurred on study
- Grade 3 infections were limited, occurring in 3 patients (bronchitis, pneumonia, and influenza)

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	33%	19%	10%	-
Nausea	17%	14%	-	-
Fatigue	19%	9%	3%	-
AST increased	17%	3%	9%	-
ALT increased	6%	9%	9%	1%
Headache	16%	6%	3%	-
Cough	17%	4%	-	-
Decreased appetite	14%	7%	1%	-
Vomiting	12%	9%	-	-
Rash	12%	3%	3%	
Dysgeusia	14%	3%	-	-
Edema peripheral	12%	4%	-	-
Dizziness	7%	7%	-	-
Neutropenia	1%	-	7%	6%
Insomnia	9%	4%	-	-
Upper respiratory tract infection	1%	12%	-	-
Back pain	6%	3%	3%	-
Hyperuricemia	10%	-	-	-
Pyrexia	6%	4%	-	-

Adverse Events of Interest & Long Term Tolerability

Demographics
Patients on Study >6 Cycles

Evaluable for Safety	41
Age, median (range)	66 (34 - 80)
Prior Therapies, median (range)	2 (1 – 6)
Duration on Therapy, median (range)	10.1 mo (5.6 – 15.7)

Adverse Events of Interest
Occurring After 6 Cycles on Umbralisib

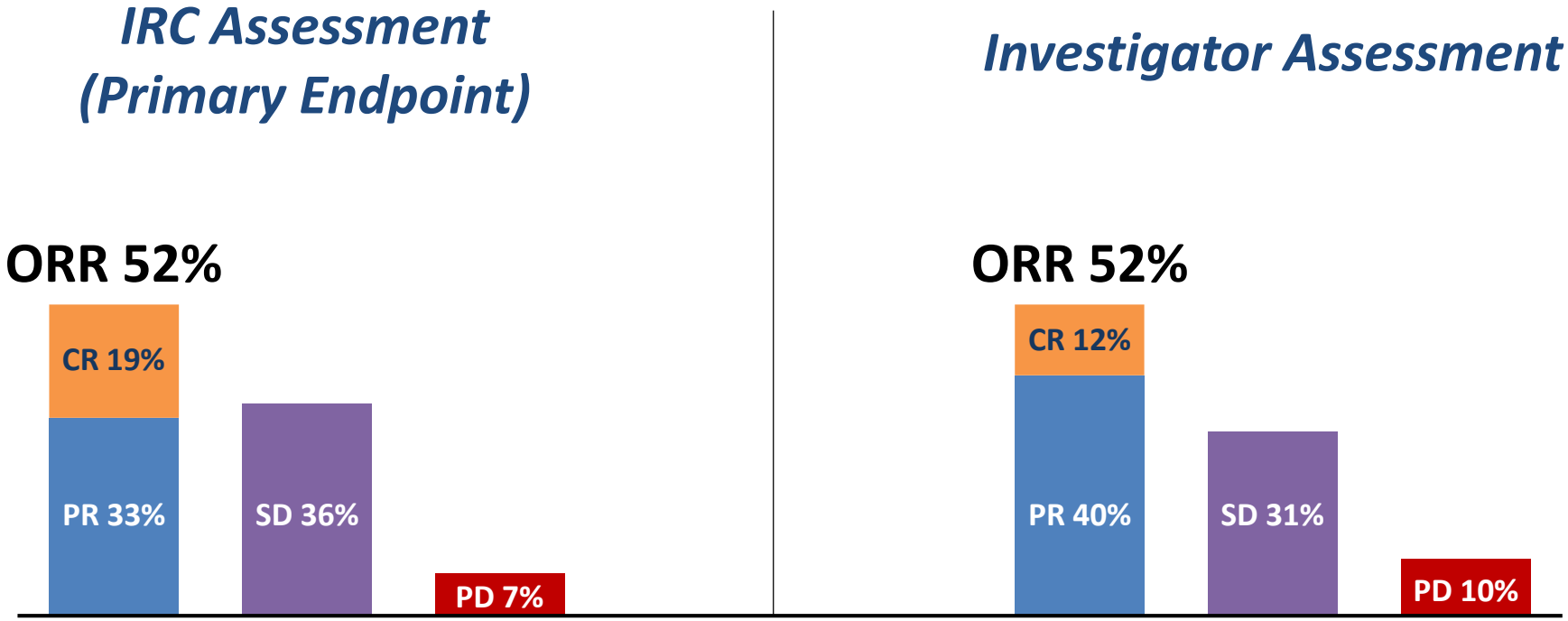
	All Grades		Grade 3/4	
	N	**%**	**N**	**%**
Diarrhea	10	24%	2	5%
ALT increased	1	2%	-	-
AST increased	-	-	-	-
Pneumonitis	1	2%	1	2%
Pneumonia	-	-	-	-

- ALT/AST elevations appeared time related, with all but one event occurring within first 6 cycles of therapy
- Grade 3/4 diarrhea did not appear time related, occurring both before and after 6 cycles of therapy
  - Both patients with Grade 3 diarrhea after Cycle 6 resolved and remain on study (10.9+ and 11.2+ months, each)
- No patients discontinued umbralisib after 6 months due to a treatment related AE

Disposition of Interim Efficacy Population (N=42)

- Median duration of umbralisib exposure was 10.1 months (range, 0.7 – 15.7)
- At a median follow-up of 12.5 months (range 8.3 – 18.5), 55% of patients continue study treatment
- Primary reasons for discontinuing umbralisib during study were
  - Disease progression (n=10, 24%)
  - Umbralisib related adverse event (n=5, 12%)
  - Not related adverse event (n=2, 5%)
  - Withdrawal of consent (n=1, 2%)
  - Investigator decision (n=1, 2%)

Best Overall Response of Interim Efficacy Population (N=42)

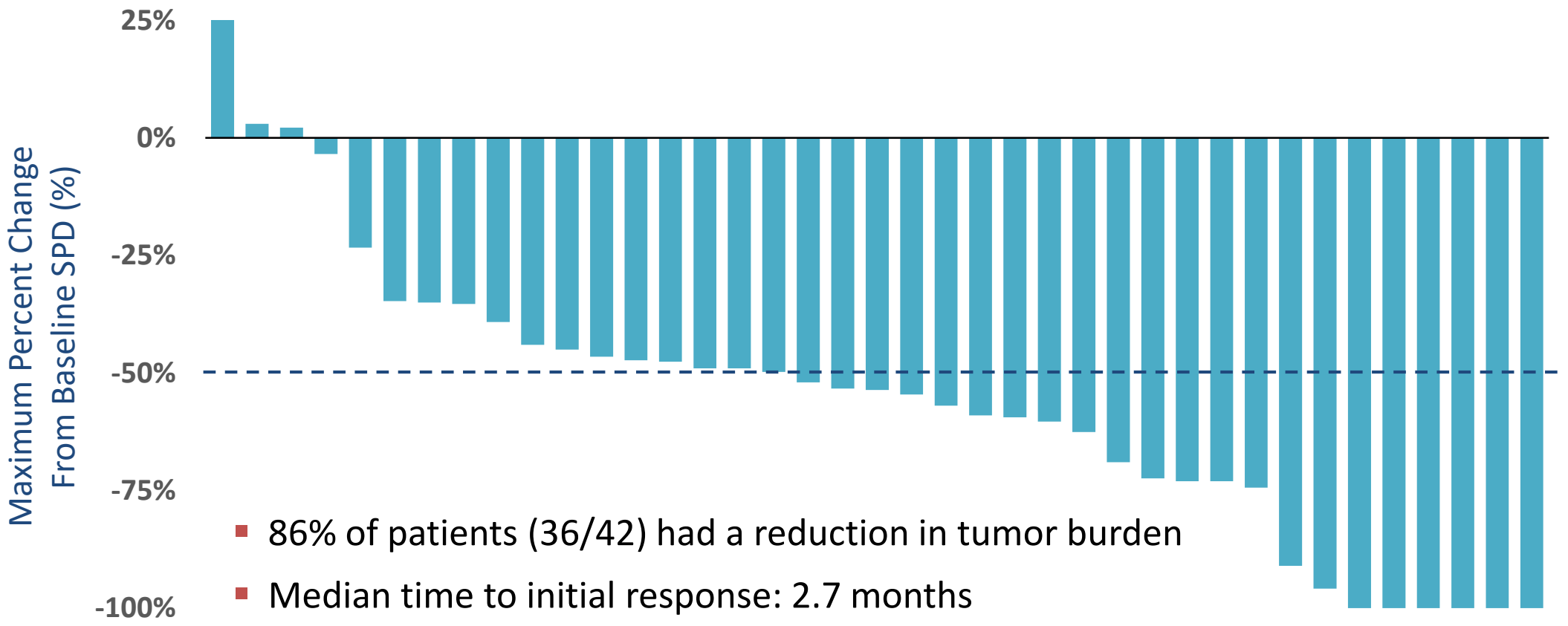


- Clinical benefit rate (PR+CR+SD) was 88% by IRC assessment
- All patients in CR by IRC remain on study (range 10.1+ – 15.7+ months)
- ORR by IRC was 57%, 42%, and 43% for the 3 MZL subtypes (extranodal, nodal, splenic), respectively
- ORR by IRC was 53% amongst patients with prior chemo-immunotherapy (n=32), and 38% amongst patients refractory to their last line of therapy (n=8)

2 patients by IRC, and 3 patients by Investigator Assessment were Not Evaluable, and are considered non-responders

IRC = Independent Review Committee; CR = complete response;
PR = partial response; SD = stable disease; PD = progressive disease;

Best Percent Change in Target Lesions from Baseline for Interim Efficacy Population



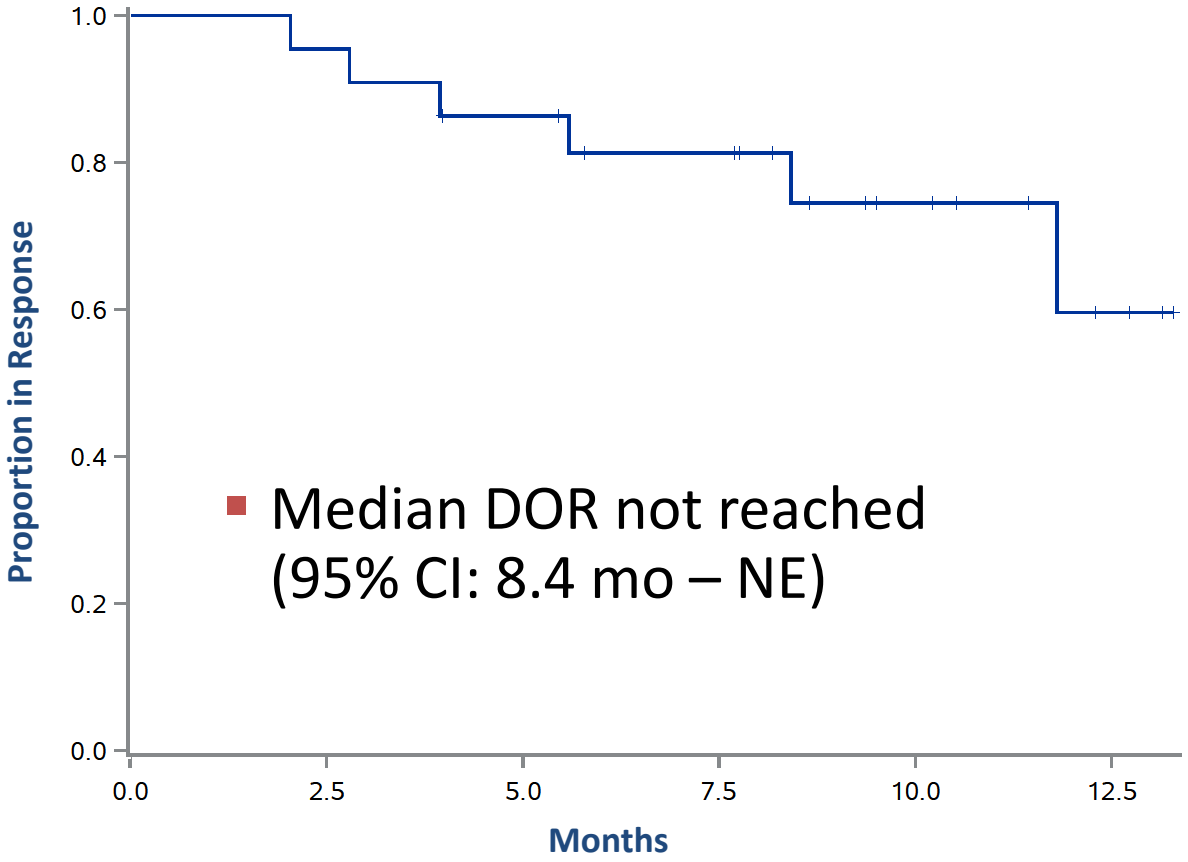
**Data based on investigator assessment for 39 subjects; 3 subjects who discontinued treatment prior to first response assessment were not evaluable and classified as non-responders for ORR.*

Investigator-assessed data were used given that IRC assessment included 2 separate sets of SPD data due to readings by 2 radiologists

SPD: Sum of the Products of Diameters

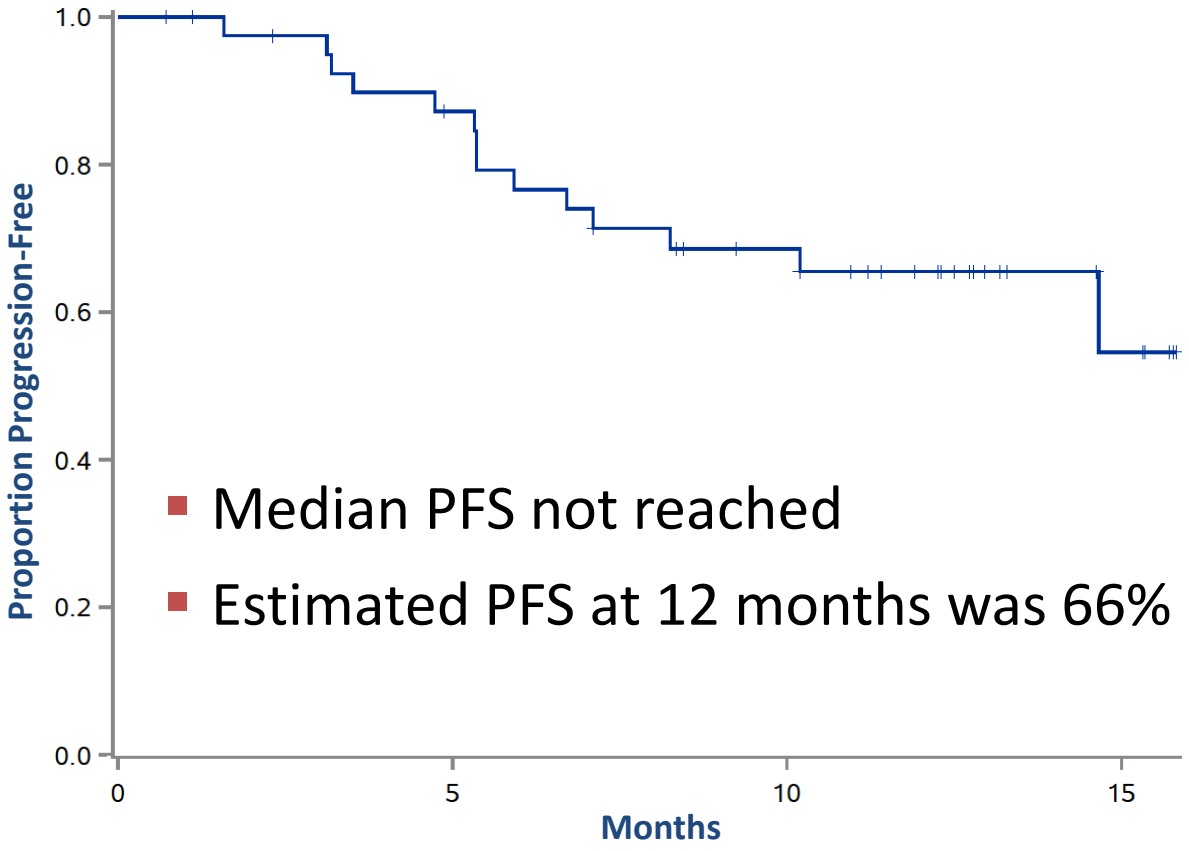
DOR & PFS by Investigator Assessment for Interim Efficacy Population

Duration of Response (N=22)



- Median DOR not reached (95% CI: 8.4 mo – NE)

Progression-Free Survival (N=42)



- Median PFS not reached
- Estimated PFS at 12 months was 66%

Conclusions

- The oral inhibitor of PI3Kδ, umbralisib, is highly active as a single agent with tolerable side effects in relapsed or refractory marginal zone lymphoma.
- Single agent dosing was active across subtypes, as well as in patients with extensive prior therapy.
- Durable responses were observed, and toxicity did not appear to worsen with prolonged exposure.
- Patients continue to be followed for mature overall response, duration, and toxicity analysis.
- Phase III studies are planned in marginal zone lymphoma and other indolent NHL subtypes.

Acknowledgements

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

- Thank you to the investigators, nurses, and study coordinators

- This study was sponsored by TG Therapeutics, Inc.

TG Therapeutics, Inc.

Michael S. Weiss
Executive Chairman &
Chief Executive Officer

Umbralisib in Relapsed/Refractory MZL

- Feb 2019 – Trial Met Primary Endpoint (ORR by IRC)
- Breakthrough Therapy Designation (BTD) recently granted for umbralisib to treat rel/ref MZL
  - Plan to meet with FDA to discuss filing for accelerated approval
  - Target NDA filing by YE-2019
- No fully approved therapies for MZL
  - Ibrutinib received accelerated approved with 46% ORR
  - No PI3K-delta inhibitors currently approved for MZL
- Approximately 7,500 new cases per year, with ~3,000 relapsed patients needing treatment each year

UNITY-NHL Trial
MZL Cohort

Umbralisib (TGR-1202) Monotherapy

Full Enrollment Complete	**69 patients**
Target ORR	40 – 50%
Enrollment Complete	3Q-18
Target Full Data Presentation	YE-19

Umbralisib & Ibrutinib Data in MZL[(1)]

Demographics and Duration of Exposure

	Umbralisib Interim Efficacy Population (n=42)	Ibrutinib Prescribing Information (n=63)
Median Prior Treatments (range)	2 (1-6)	2 (1-9)
Age (median)	67 (34 – 81)	66 (30 – 92)
Prior Rituximab Monotherapy Only	17%	27%
Refractory to Prior Therapy	19%	22%
Median duration of exposure (months)	10.1	11.6

Interim Efficacy Population (n=42):

- *Final median duration of exposure not yet reached*
  - *Currently at 10.1 months (55% remain on study)*

(1) Comparison for illustrative purposes only—Not based on a head to head study

Umbralisib & Ibrutinib Data in MZL[(1)]

	Umbralisib Interim Efficacy Population (n=42)	Ibrutinib Prescribing Information (n=63)
ORR	52%	46%
CR	***19%***	***3%***
PR	33%	43%
Clinical Benefit (CR + PR + SD)	88%	83%
% with reductions in tumor burden	86%	78%

- *Umbralisib appears at least comparable based on ORR by IRC in the interim efficacy population*
- *Median Time to Response for umbralisib 2.7 months (4.5 months for ibrutinib)*
- *Median DOR not reached for umbralisib with 12.5 months median follow-up*

(1) Comparison for illustrative purposes only—Not based on a head to head study

Ibrutinib Warnings and Precautions(1)

Ibrutinib

- **Hemorrhage: Serious, including fatal, bleeding events have occurred in 3% of** Imbruvica-treated patients**. Bleeding events of any grade occurred in 44%** of Imbruvica-treated patients.
- **Infections: Serious, including fatal, infections occurred in 24%** of Imbruvica-treated patients. **Cases of PML and PJP** have occurred.
- **Cytopenias: Grade 3 or 4 neutropenia (23%), thrombocytopenia (8%), and anemia (3%)** occurred in patients treated with single agent Imbruvica.
- **Cardiac Arrhythmias: Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2%** of patients, and **Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%** of Imbruvica-treated patients. **These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias**
- **Hypertension: Hypertension of any grade occurred in 12%** of Imbruvica-treated patients. **Grade 3 or greater hypertension occurred in 5%** of patients with a **median time to onset of 5.9 months**.
- **Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%)** have occurred in Imbruvica-treated patients. **The most frequent second primary malignancy was non-melanoma skin cancer (6%)**.

- *The major toxicity/tolerability concerns with ibrutinib and BTKs are generally not associated with umbralisib*

(1) Imbruvica Prescribing Information

Currently Approved PI3K Warnings and Precautions (1)

Idelalisib
Black-Box Warning(2)

- **Fatal and/or serious <u>hepatotoxicity</u> occurred in 16% - 18%** of Zydelig-treated patients
- **Fatal and/or serious <u>diarrhea or colitis</u> occurred in 14% - 20%** of Zydelig-treated patients
- Fatal and/or serious **<u>pneumonitis</u>** occurred in 4% of Zydelig-treated patients
- **Fatal and/or serious infections occurred in 21% - 48%** of patients treated with Zydelig monotherapy

Duvelisib
Black-Box Warning(3)

- **Fatal and/or serious <u>infections</u> occurred in 31%** of Copiktra-treated patients
- **Fatal and/or serious <u>diarrhea or colitis</u> occurred in 18%** of Copiktra-treated patients
- **Fatal and/or serious <u>cutaneous reactions</u> occurred in 5%** of Copiktra-treated patients
- **Fatal and/or serious <u>pneumonitis</u> occurred in 5%** of Copiktra-treated patients

Copanlisib
Warnings and Precautions(4)

- **<u>Infections:</u> Serious, including fatal, infections occurred in 19%** of Aliqopa-treated patients
- **<u>Hyperglycemia:</u> Grade 3 or 4 hyperglycemia occurred in 41%** of Aliqopa-treated patients
- **<u>Hypertension:</u> Grade 3 hypertension occurred in 26%** of Aliqopa-treated patients
- **<u>Non-Infection Pneumonitis:</u> Occurred in 5%** of Aliqopa-treated patients
- **<u>Severe Cutaneous Reactions:</u> Grade 3 and 4 cutaneous reactions occurred in 2.8% and 0.6%** of Aliqopa-treated patients, respectively

Interim Umbralisib MZL Safety Highlights (n=69):

- *No fatal adverse events*
- *No events of colitis reported*
  - *10% Gr. 3 diarrhea (no Gr. 4 events)*
- *Only 1 event of pneumonitis reported (patient remains on study)*
- *Gr. 3 infections were limited, occurring in 3 patients (bronchitis, pneumonia, and influenza)*
- *10% Gr. 3/4 ALT/AST Elevations*

(1) Comparison for illustrative purposes only—Not based on a head to head study
(2) Idelalisib Prescribing Information; (3) Duvelisib Prescribing Information; (4) Copanlisib Prescribing Information

QUESTIONS?

TG Therapeutics

Thank you!