

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

Nathan H. Fowler<sup>1</sup>, Felipe Samaniego<sup>1</sup>, Wojciech Jurczak<sup>2</sup>, Ewa Lech-Maranda<sup>3</sup>, Nilanjan Ghosh<sup>4</sup>, Bertrand Anz<sup>5</sup>, Piers Patten<sup>6</sup>, James A. Reeves<sup>7</sup>, Lori A. Leslie<sup>8</sup>, Piotr Smolewski<sup>9</sup>, Julio C. Chavez<sup>10</sup>, Paolo Ghia<sup>11</sup>, Corrado Tarella<sup>12</sup>, John M. Burke<sup>13</sup>, Jeff Sharman<sup>14</sup>, Kathryn Kolibaba<sup>15</sup>, Owen A. O'Connor<sup>16</sup>, Chan Y. Cheah<sup>17</sup>, Hari P. Miskin<sup>18</sup>, Peter Sportelli<sup>18</sup>, Michael S. Weiss<sup>18</sup>, Pier Luigi Zinzani<sup>19</sup>

<sup>1</sup>MD Anderson Cancer Center, Houston, TX; <sup>2</sup>Jagiellonian University, Kraków, Poland; <sup>3</sup>Institute of Hematology and Transfusion Medicine, Warsaw, Poland; <sup>4</sup>Levine Cancer Institute, Charlotte, NC; <sup>5</sup>Sarah Cannon Research Institute/Tennessee Oncology, Chattanooga, TN; <sup>6</sup>King's College Hospital NHS Foundation Trust, London, United Kingdom; <sup>7</sup>Sarah Cannon Research Institute/Florida Cancer Specialists, Fort Myers, FL; <sup>8</sup>John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; <sup>9</sup>Copernicus Memorial Hospital, Lodz, Poland; <sup>10</sup>H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; <sup>11</sup>Università Vita-Salute San Raffaele and IRCCS Istituto Scientifico San Raffaele, Milan, Italy; <sup>12</sup>European Institute of Oncology, Milan, Italy; <sup>13</sup>Rocky Mountain Cancer Centers, US Oncology Research, Aurora, CO; <sup>14</sup>Willamette Valley Cancer Institute, US Oncology Research, Eugene, OR; <sup>15</sup>Compass Oncology, US Oncology Research, Vancouver, WA; <sup>16</sup>Center for Lymphoid Malignancies, Columbia University Medical Center, New York, NY; <sup>17</sup>Sir Charles Gairdner Hospital, Perth, Australia; <sup>18</sup>TG Therapeutics, Inc., New York, NY; <sup>19</sup>Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy

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  - Celgene
  
- Research funding
  - TG Therapeutics, Inc.

# Background / Rationale

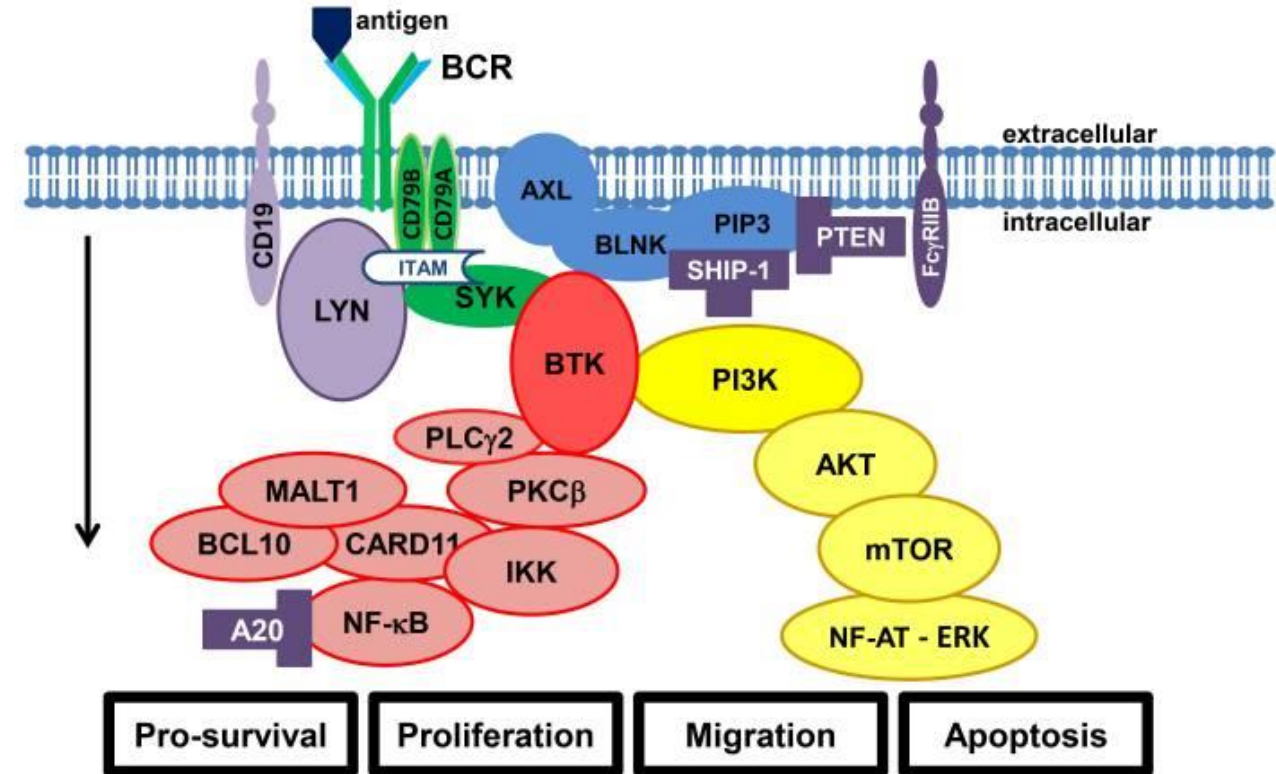
- Marginal Zone Lymphoma (MZL) is an indolent B-cell lymphoma accounting for ~10% of NHL
- Although responses are high to frontline therapy, most patients still relapsed following induction.
- Therapeutic options are limited for MZL pts who have progressed following anti-CD20-based therapy, and those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

<sup>1</sup>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<sup>2</sup>

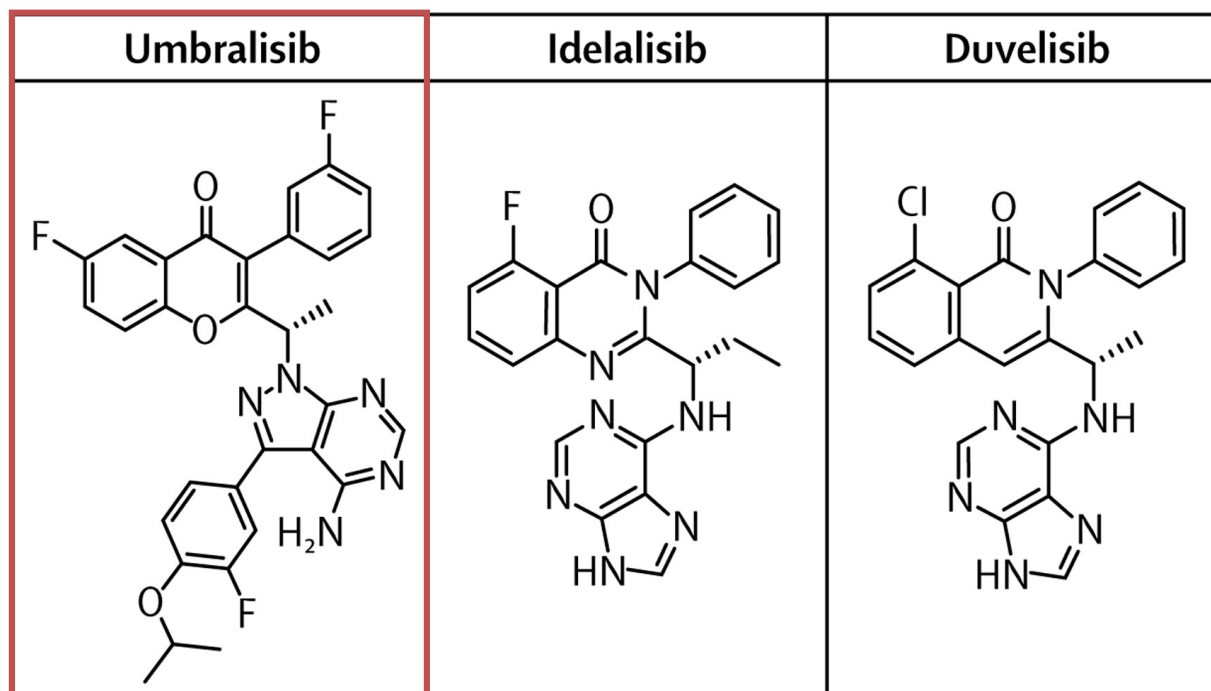
*The B cell Receptor (BCR) and its Downstream Pathways<sup>1</sup>*



<sup>1</sup>Niemann et al., Semin Cancer Biol. 2014. <sup>2</sup>Sindel et al., Blood. 2018

# Umbralisib (TGR-1202)

- Next generation PI3K $\delta$  inhibitor, with a unique structure and improved tolerability<sup>1</sup>
  - Improved selectivity to PI3K $\delta$  isoform
  - Inhibition of CK1 $\epsilon$ 
    - Potential regulator of Treg count and function
  - Ongoing long-term safety analysis demonstrate low rates of immune-mediated toxicity<sup>2</sup>
- Oral – once daily administration
- Phase 2/3 dose: 800 mg QD



Isoform	K <sub>d</sub> (nM)		
	Umbralisib	Idelalisib	Duvelisib
PI3K $\alpha$	>10 000	600	40
PI3K $\beta$	>10 000	19	0.89
PI3K $\gamma$	1400	9.1	0.21
PI3K $\delta$	6.2	1.2	0.047
CK1 $\epsilon$	180	>30 000	>30 000

<sup>1</sup>Burris et al., Lancet Oncology 2018; <sup>2</sup>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  $\leq 2$

## 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*
<b>N</b>	<b>69</b>	<b>42</b>
<b>MZL Subtype, n (%)</b>		
Extranodal	38 (55%)	23 (55%)
Nodal	20 (29%)	12 (29%)
Splenic	11 (16%)	7 (17%)
<b>Median Age, median (range)</b>	67 (34 – 81)	67 (34 – 81)
<b>Female, n (%)</b>	36 (52%)	25 (60%)
<b>Male, n (%)</b>	33 (48%)	17 (40%)
<b>ECOG 0/1/2, n</b>	39/30/0	23/19/0
<b>Prior Therapies, median (range)</b>	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%)
<b>Refractory to most recent therapy, n (%)</b>	18 (26%)	8 (19%)
<b>Refractory to prior anti-CD20, n (%)</b>	15 (22%)	6 (14%)
<b>Lactate dehydrogenase (LDH), ≥350 unit/L, n (%)</b>	17 (25%)	12 (29%)

## ■ Enrollment is complete

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

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

# 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

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

## Adverse Events of Interest Occurring After 6 Cycles on Umbralisib

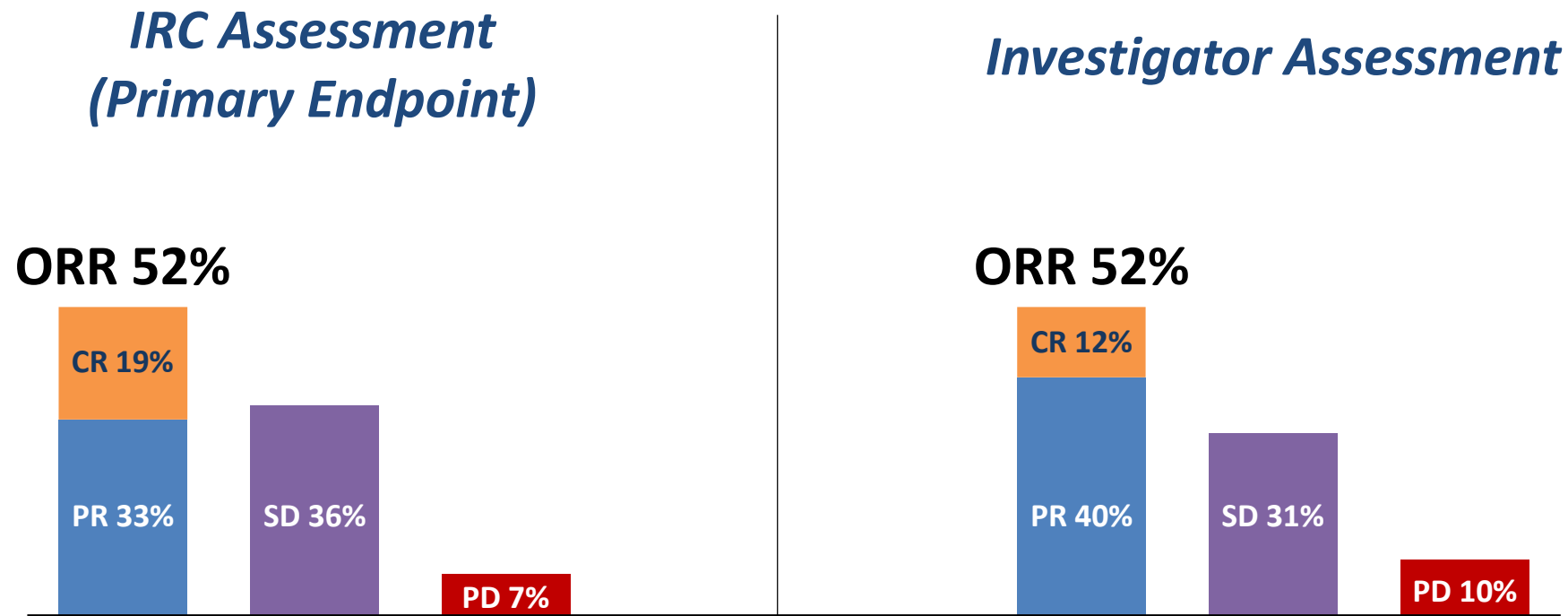
	All Grades		Grade 3/4	
	N	%	N	%
<b>Diarrhea</b>	10	24%	2	5%
<b>ALT increased</b>	1	2%	-	-
<b>AST increased</b>	-	-	-	-
<b>Pneumonitis</b>	1	2%	1	2%
<b>Pneumonia</b>	-	-	-	-

- 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)

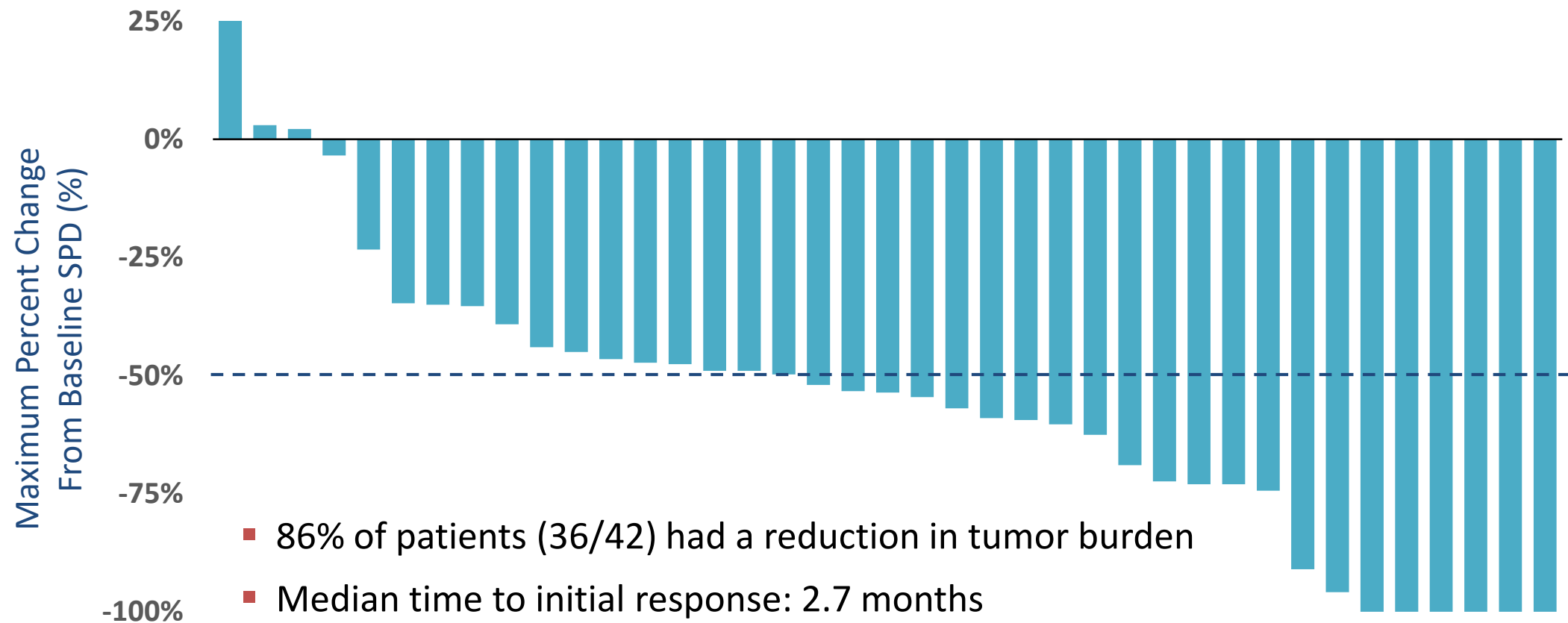


- Clinical benefit rate (PR+CR+SD) was 88% by IRC assessment
- All patients in CR by IRC remain on study (range 10.1+ – 15.7+ months)
- ORR by IRC was 57%, 42%, and 43% for the 3 MZL subtypes (extranodal, nodal, splenic), respectively
- ORR by IRC was 53% amongst patients with prior chemo-immunotherapy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

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

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

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



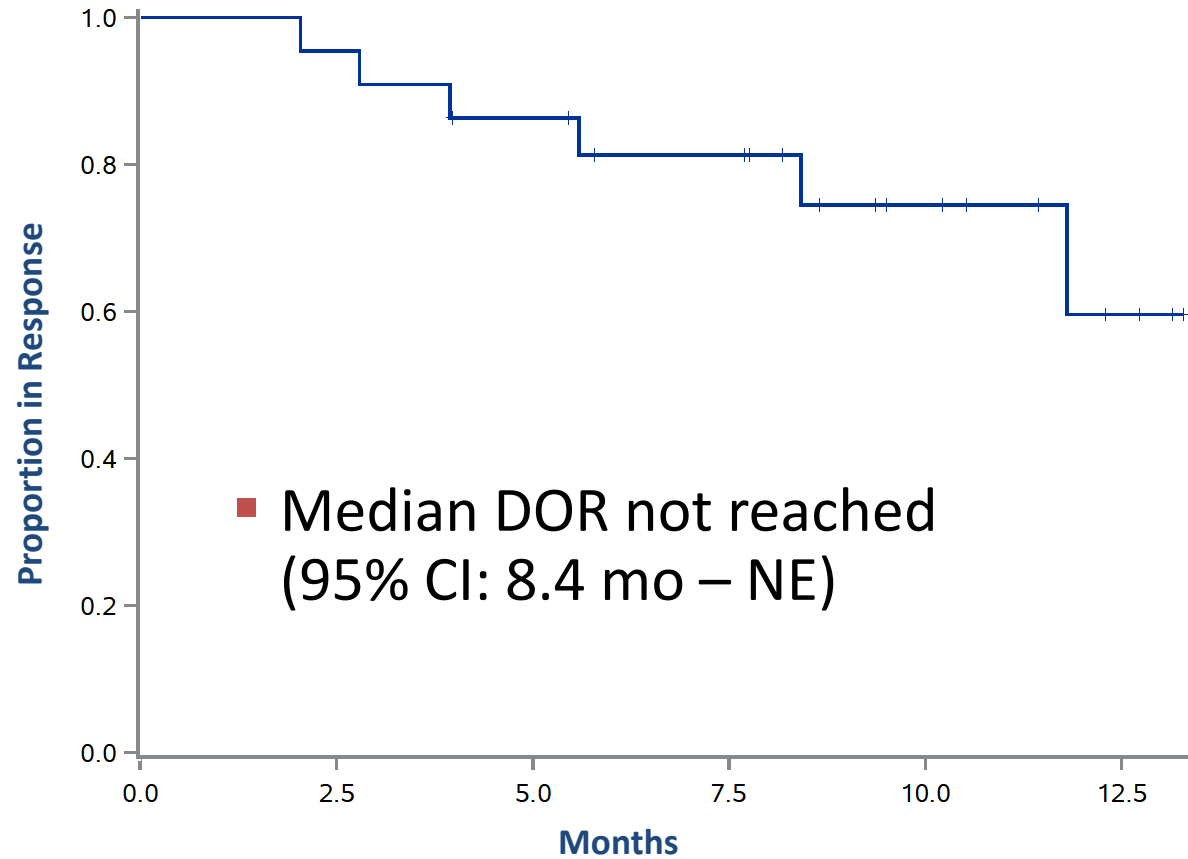
*\*Data based on investigator assessment for 39 subjects; 3 subjects who discontinued treatment prior to first response assessment were not evaluable and classified as non-responders for ORR.*

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

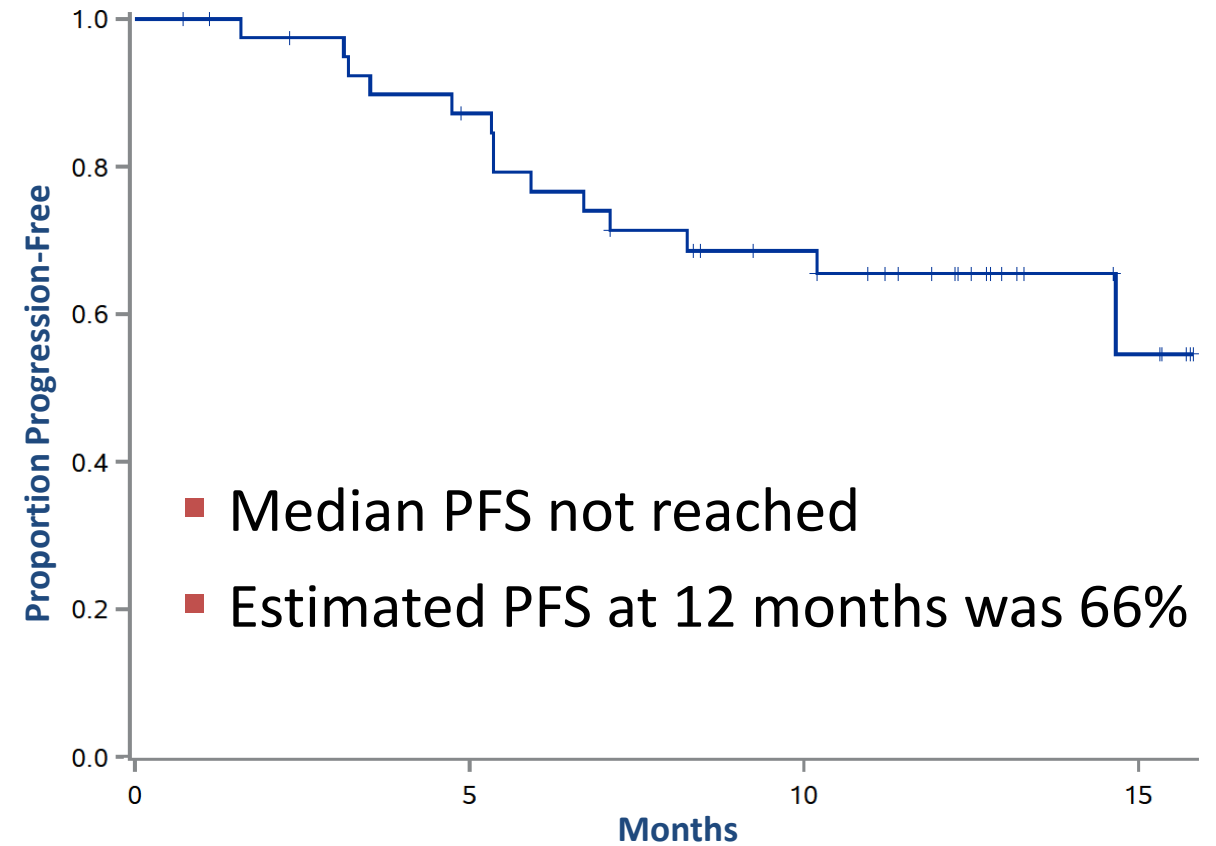
SPD: Sum of the Products of Diameters

# DOR & PFS by Investigator Assessment for Interim Efficacy Population

## Duration of Response (N=22)



## Progression-Free Survival (N=42)



# Conclusions

- The oral inhibitor of PI3K $\delta$ , 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

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