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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Background / Rationale

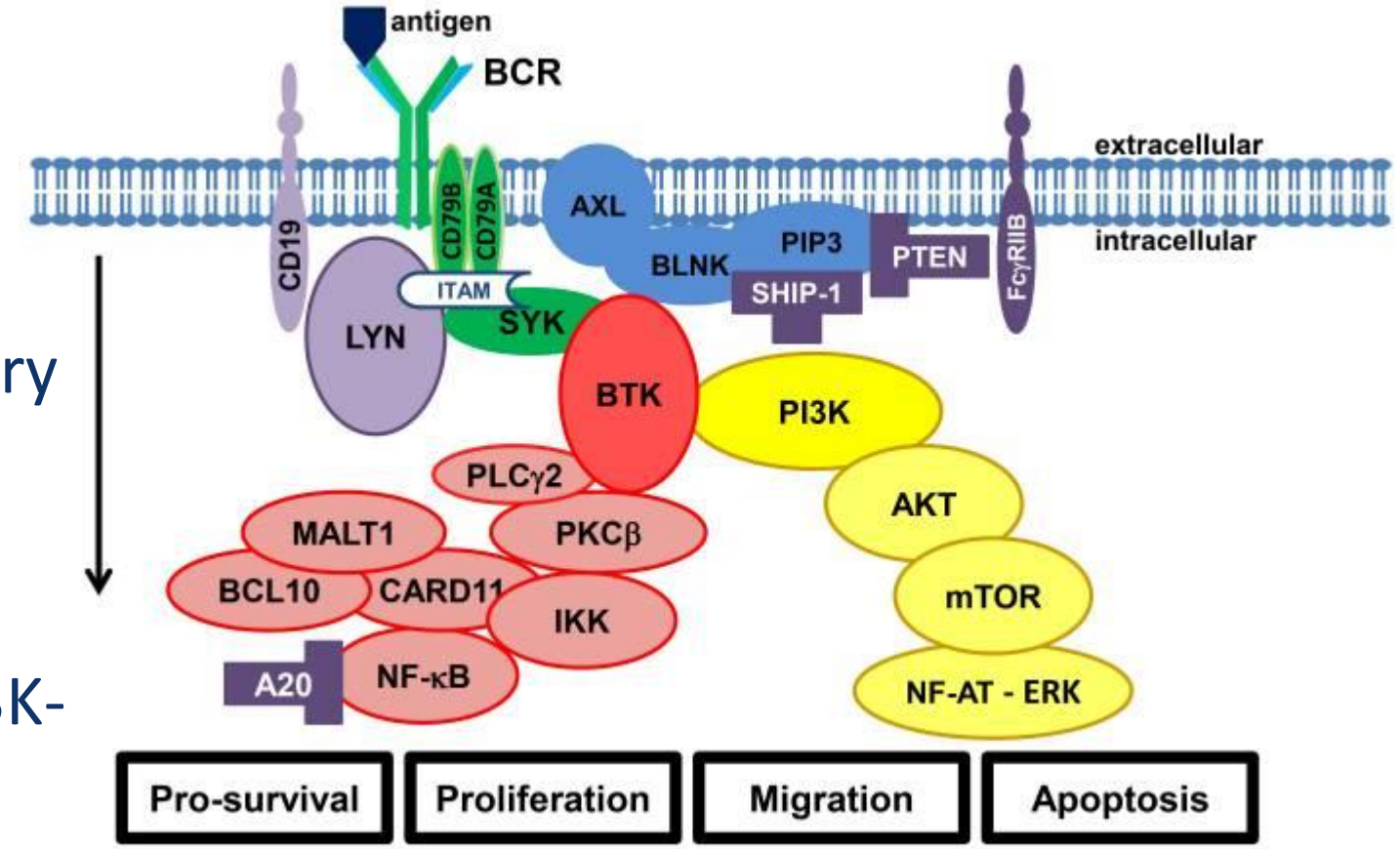
- Marginal Zone Lymphoma (MZL) is an indolent B-cell lymphoma accounting for ~10% of NHL
- Although responses are high to frontline therapy, most patients still relapse following induction
- Therapeutic options are limited for MZL pts who have progressed following anti-CD20-based therapy, and for those 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 of normal B cells and has been implicated in lymphomagenesis
- PI3K is a downstream intermediary in the BCR pathway essential for BCR-dependent B cell survival
- Recent evidence suggests the PI3K-mTOR pathway is sufficient for driving the pathogenesis of MZL[2]

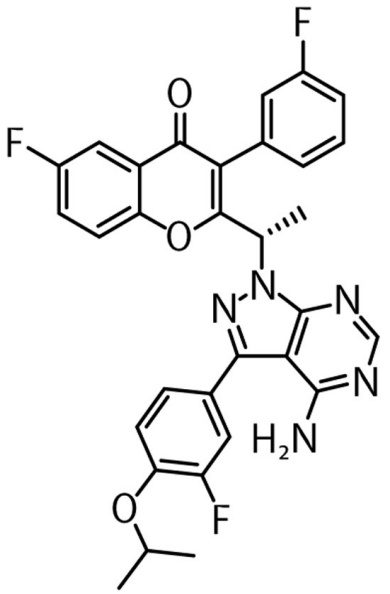
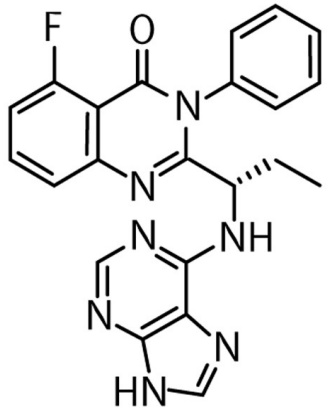
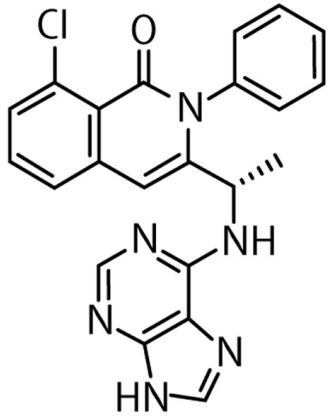
The B cell Receptor (BCR) and its Downstream Pathways[1]



[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 analyses 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

- UNITY-NHL is an ongoing Phase 2b, multicenter, multi-cohort trial evaluating umbralisib as monotherapy and in multiple combinations in previously treated NHL patients
- The MZL cohort receives 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 Nodal Splenic	 38 (55%) 20 (29%) 11 (16%)	 23 (55%) 12 (29%) 7 (17%)
Median Age, median (range)	67 (34 - 81)	67 (34 - 81)
Female, n (%) **Male, n (%)**	36 (52%) 33 (48%)	25 (60%) 17 (40%)
ECOG 0/1/2, n	39/30/0	23/19/0
Prior Therapies, median (range) 1 prior line 2 or more prior lines rituximab monotherapy only rituximab-based chemoimmunotherapy radiation stem cell transplant lenalidomide ibrutinib	2 (1 - 6) 34 (49%) 35 (51%) 16 (23%) 50 (72%) 5 (7%) 1 (1%) 3 (4%) 2 (3%)	2 (1 - 6) 19 (45%) 23 (55%) 7 (17%) 32 (76%) 3 (7%) 1 (2%) 2 (5%) 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 patients received therapy
    - 42 patients eligible to be followed for 9+ cycles as of data cutoff

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

- Umbralisib was well tolerated
- No events of colitis reported
- 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, n	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

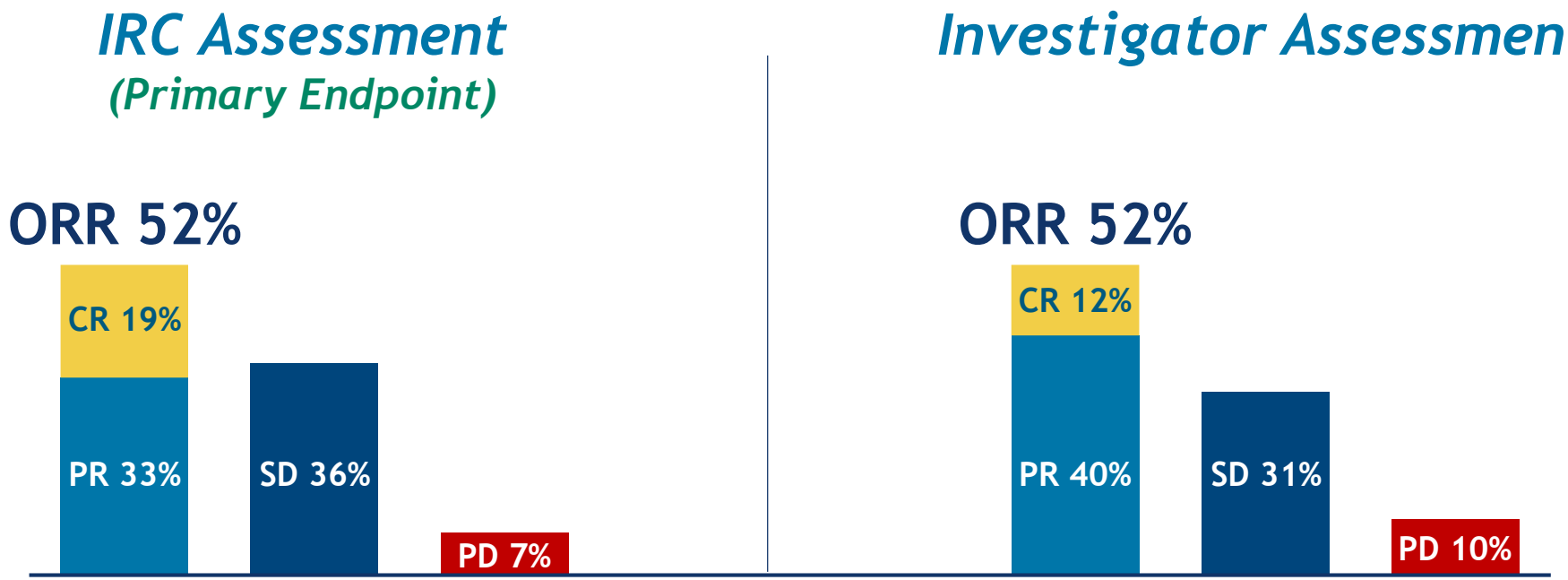
	All Grades		Grade 3/4	
	N	**%**	**N**	**%**
Diarrhea	10	24%	2	5%
ALT increased	1	2%	-	-
AST increased	-	-	-	-
Pneumonitis	1	2%	1	2%
Pneumonia	-	-	-	-

- ALT/AST elevations appeared to be time related, with all but one event occurring within first 6 cycles of therapy
- Grade 3/4 diarrhea did not appear to be 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)
- 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 on 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)

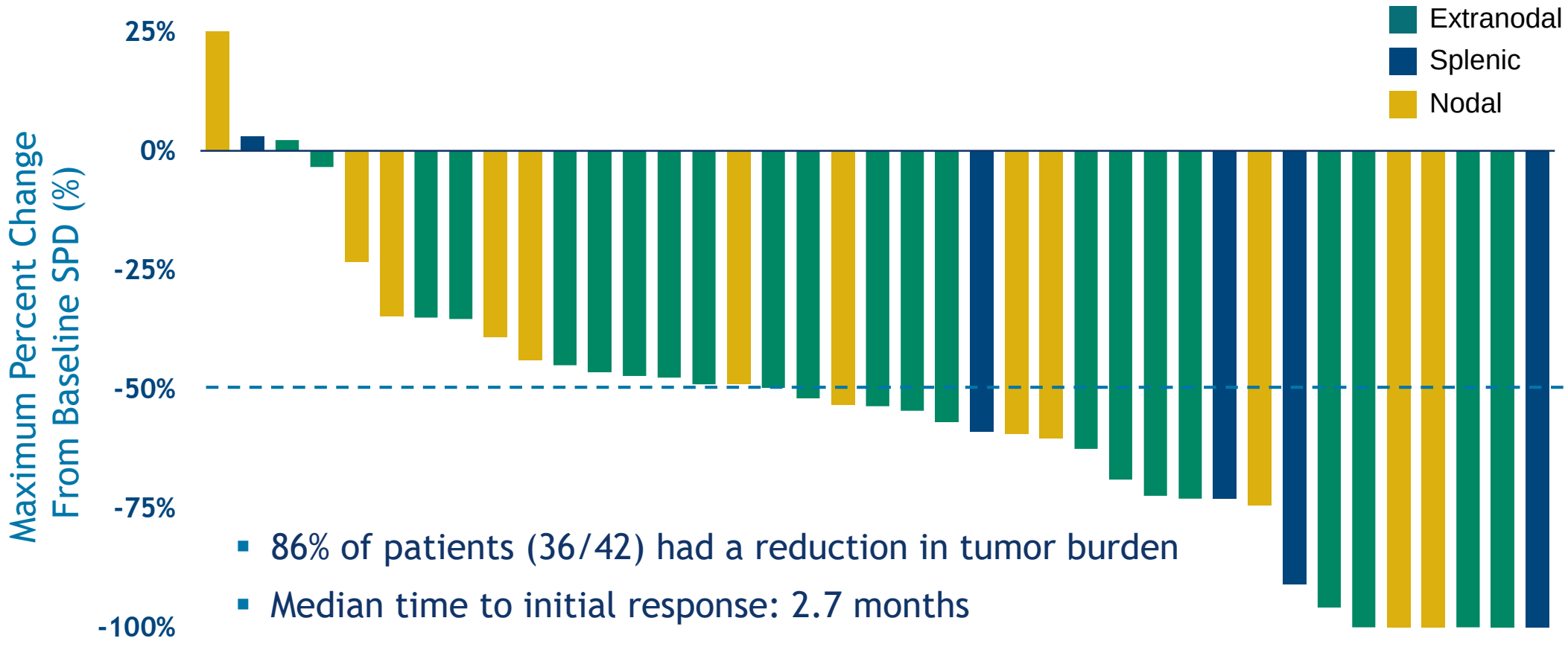


- Clinical benefit rate (PR+CR+SD) was 88% by IRC assessment
- All patients in CR by IRC assessment remain in continued response on study (range 10.1+ – 15.7+ months)
- ORR by IRC was 57%, 42%, and 43% for the 3 MZL subtypes (extranodal, nodal, splenic, respectively)
- ORR by IRC was 53% amongst patients with prior chemo-immunotherapy (n=32), 44% amongst those relapsed after at least 2 prior lines including an anti-CD20 and alkylating agent (n=18), 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

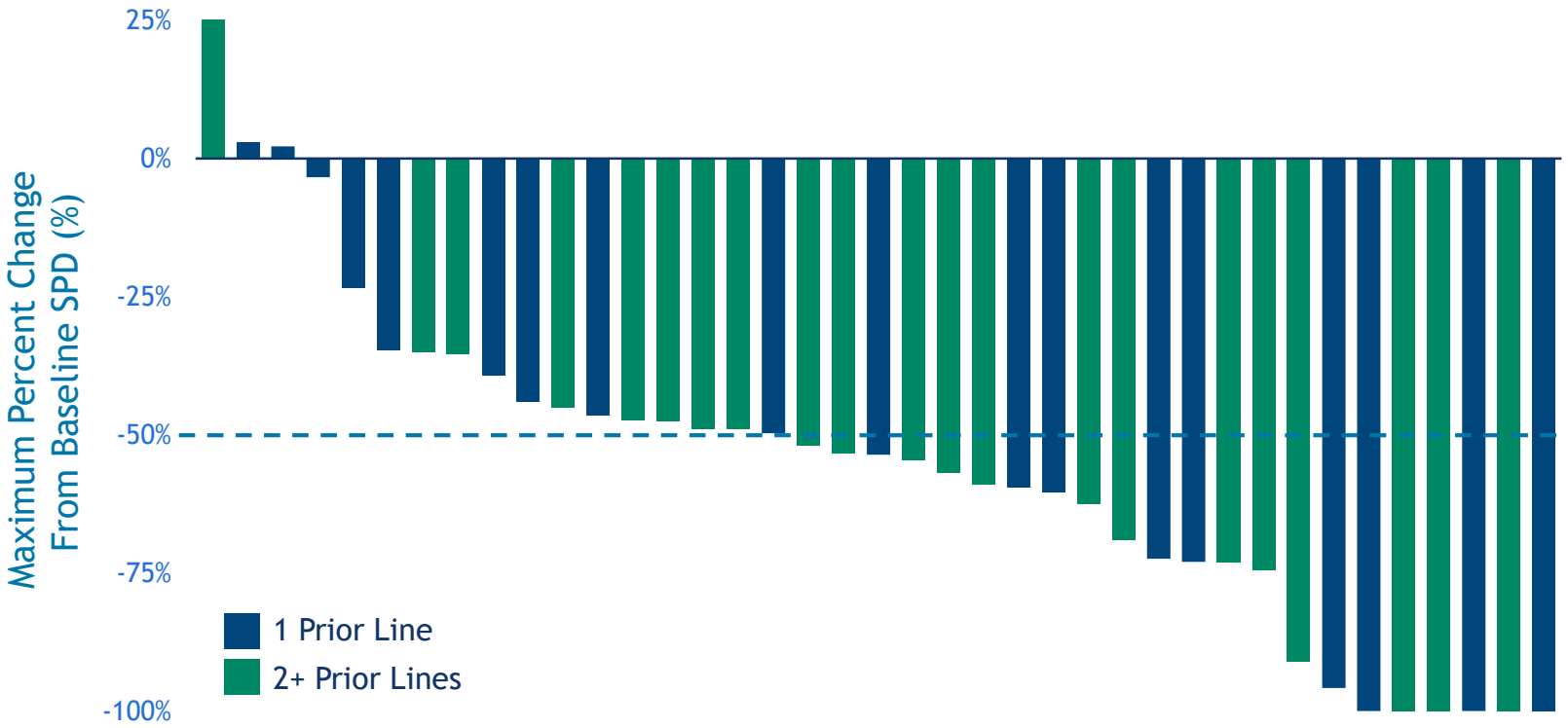


Data based on investigator assessment for 39 subjects; 3 subjects who discontinued treatment prior to first response assessment were not evaluable and were classified as non-responders for ORR.

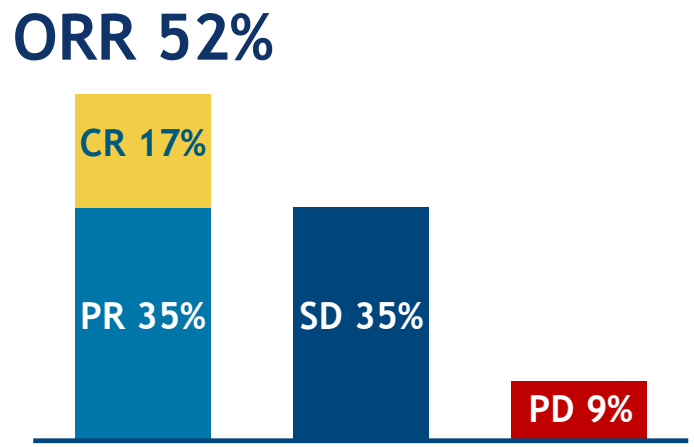
Investigator-assessed data were used given that IRC assessment included 2 separate sets of SPD data due to readings by 2 radiologists

SPD: Sum of the Products of Diameters

Best ORR For Patients with ≥2 Prior Lines in Efficacy Population (N=23)



IRC Assessment for ≥2 Prior Line Population



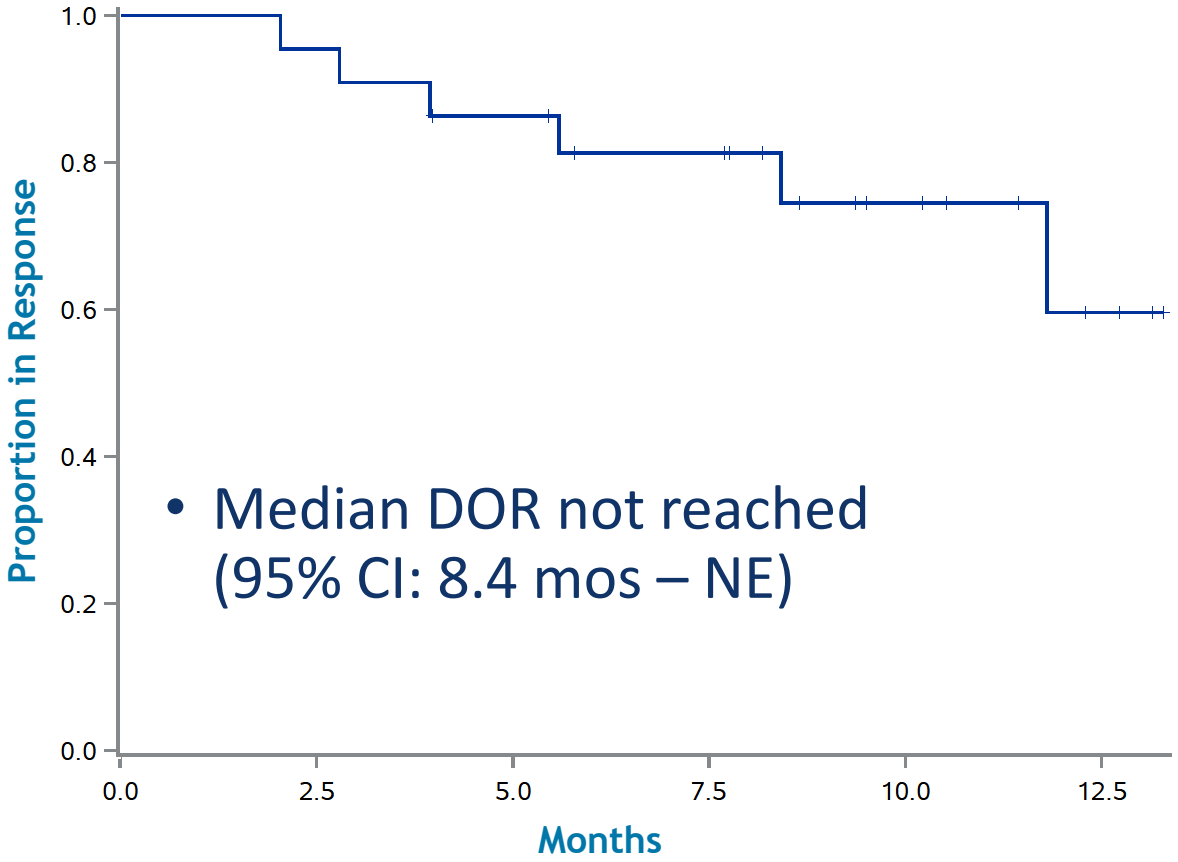
- ORR by IRC assessment was internally consistent among patients with 1 prior line and those with 2 or more prior lines of therapy

1 patient by IRC was Not Evaluable and is considered a non-responder

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

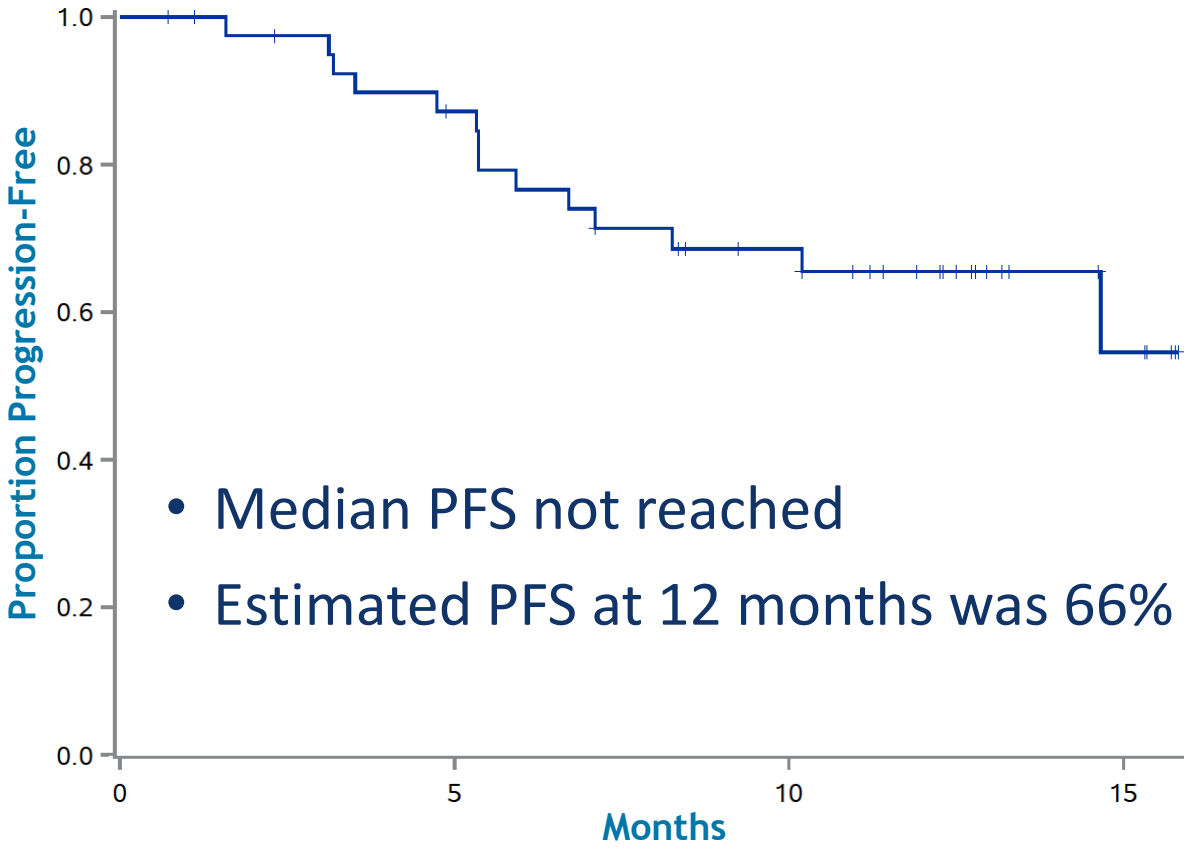
DOR & PFS by Investigator Assessment for Interim Efficacy Population

Duration of Response (N=22)



- Median DOR not reached (95% CI: 8.4 mos – 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.

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