The Combination of Umbralisib Plus Ublituximab is Active in Patients with Relapsed or Refractory Marginal Zone Lymphoma (MZL): Results from the Phase 2 Global UNITY-NHL Trial

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Disclosures

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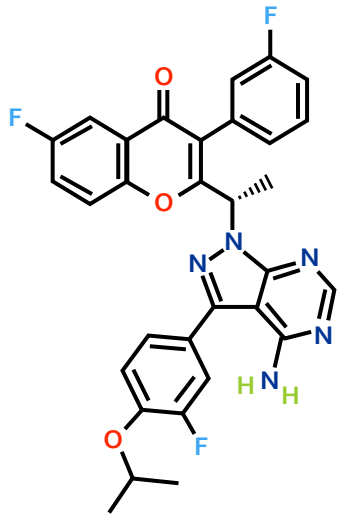
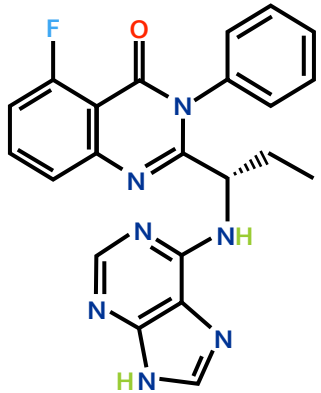
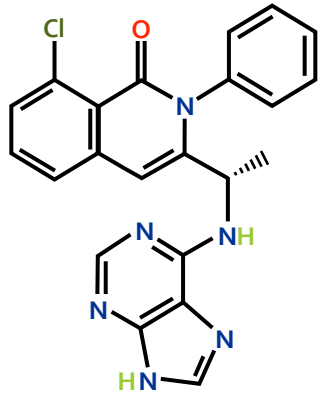
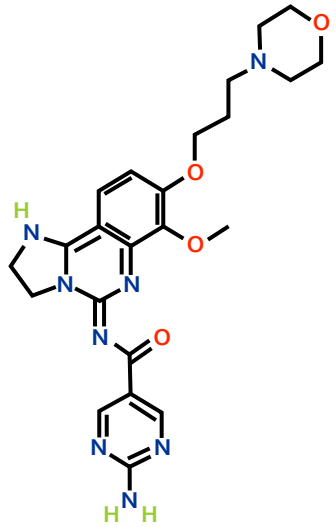
Umbralisib is a Selective Inhibitor of PI3Kδ and CK1ε

- Recent evidence suggests that the PI3K-mTOR pathway is sufficient for driving the pathogenesis of MZL[1]
- Umbralisib is a selective phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase-1epsilon (CK1ε) inhibitor that has recently been FDA approved for the treatment of previously treated marginal zone lymphoma (MZL) and follicular lymphoma (FL) based on reported data[2]

Umbralisib[3]	Idelalisib[3]	Duvelisib[3]	Copanlisib[4]
			

Isoform	K_d (nM)			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

1. Sindel A, et al. Blood. 2018;132(supp 1):4125–4125 2. Fowler N., et al. *JCO* 2021; 39(15): 1609-1618, 3. Burris HA, et al. *Lancet Oncol*. 2018;19(4):486-496. 4. Data on File [TGR 001]. TG Therapeutics, Inc, New York City, NY.

Ublituximab + Umbralisib (U2)

- Ublituximab is a novel anti-CD20 monoclonal antibody glycoengineered for enhanced ADCC that targets a unique epitope on CD20[1]
- In MZL patients, single agent umbralisib demonstrated a 49.3% ORR with 16% CR[2] and is currently approved for MZL patients who have received a CD20-directed therapy[3]
- The combination of umbralisib + ublituximab (U2) has been shown to be active, with a manageable safety profile in patients with relapsed/refractory (R/R) NHL[4]

ADCC: antibody-dependent cellular cytotoxicity; MZL: marginal zone lymphoma; NHL: non-Hodgkin's lymphoma; ORR: overall response rate. 1. Sawas A, et al. Br J Hematol 2017;177(2):243-253, 2. Zinzani P, et al. ASH 2934, 3. UKONIQ US Prescribing Information. 4. Lunning M., et al. *Blood* 2019; 134 (21): 1811–1820.

UNITY-NHL – U2 Marginal Zone Lymphoma Cohort

Key Eligibility Criteria

- Histologically confirmed R/R MZL (nodal, extranodal, and splenic) requiring treatment
- ≥1 anti-CD20 therapy (including CD20-refractory)
- Patients ≥18 years of age
- ECOG PS ≤2

U2

Umbralisib: 800 mg PO QD

Continuous: Until disease progression, unacceptable toxicity, or study withdrawal

Ublituximab: 900 mg IV D1, 8, and 15 of C1, D1 C2-6, and D1 every 3C

Time Limited: Until C24

- First response assessment was at the end of **Cycle 3**

Primary Endpoint:

- IRC-assessed ORR

Secondary Endpoints:

- IRC-assessed
  - DOR
  - PFS
  - TTR
- Safety

DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; IRC: independent review committee; MZL: marginal zone lymphoma; ORR: overall response rate; PFS: progression-free survival; PO: orally; QD: daily; R/R: relapsed or refractory; TTR: time to response; U2: umbralisib + ublituximab

Baseline Characteristics & Prior Therapies

Characteristic	MZL U2 N=72
Age, median (range), years	**70 (40 – 89)**
ECOG-PS, 0 | 1 | 2, %	**49 | 49 | 3**
Male, n (%)	**34 (47)**
Stage III-IV, n (%)	**53 (74)**
MZL subtype, extranodal | splenic | nodal, %	**46 | 11 | 43**
Prior therapies, median (range)	**2 (1 – 9)**
Refractory to immediate prior therapy, n (%)[a]	18 (25)
Chemotherapy, n (%)	61 (85)
BTKi, n (%)	6 (8)
Lenalidomide, n (%)	4 (6)
Prior CD20-containg regimens, median (range)	**2 (1 – 7)**
Refractory to CD20, n (%)	14 (19)
≥3 CD20 containing prior therapy, n (%)	14 (19)

ECOG-PS: Eastern Cooperative Oncology Group performance status; MZL: marginal zone lymphoma; a. Progressive Disease on prior therapy or within 6 months of discontinuation of prior therapy

Patient Disposition

Treatment status, n (%)	MZL U2 N=72
Follow-up, median (range), mos	**20 (9 – 29)**
Ongoing	**34 (47)**
Discontinued regimen	**38 (53)**
Progressive disease	16 (22)
Investigator decision	3 (4)
Death	6 (8)[a]
Adverse event	7 (10)
Other	4 (6)
Withdrawal of consent	2 (3)

MZL: marginal zone lymphoma. [a]6 deaths on U2 include: COVID-19 (4 patients), septic shock (1 patient), pneumonia (1 patient, unrelated)

All Causality AEs (≥15%)

AEs, n (%)	MZL U2 N=72 Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	15 (21)	11 (15)	9 (13)	-
Nausea	20 (28)	10 (14)	-	-
Fatigue	15 (21)	7 (10)	5 (7)	-
Headache	15 (21)	5 (7)	-	-
Neutropenia	-	7 (10)	7 (10)	6 (8)
ALT/AST increased	2 (3)	3 (4)	7 (10)	4 (6)
Dizziness	13 (18)	2 (3)	-	-
Back pain	12 (17)	1 (1)	1 (1)	-
Dyspnea	7 (10)	4 (6)	1 (1)	1 (1)
Infusion-related reaction	1 (1)	9 (13)	2 (3)	-
Vomiting	10 (14)	2 (3)	-	-
Decreased appetite	7 (10)	5 (7)	-	-

AE: adverse event; MZL: marginal zone lymphoma; ALT/AST increased includes subjects that had ALT or AST. Other AEs are presented for specific MedDRA Preferred Terms. PJP and antiviral prophylaxis were required. GCSF support was permitted

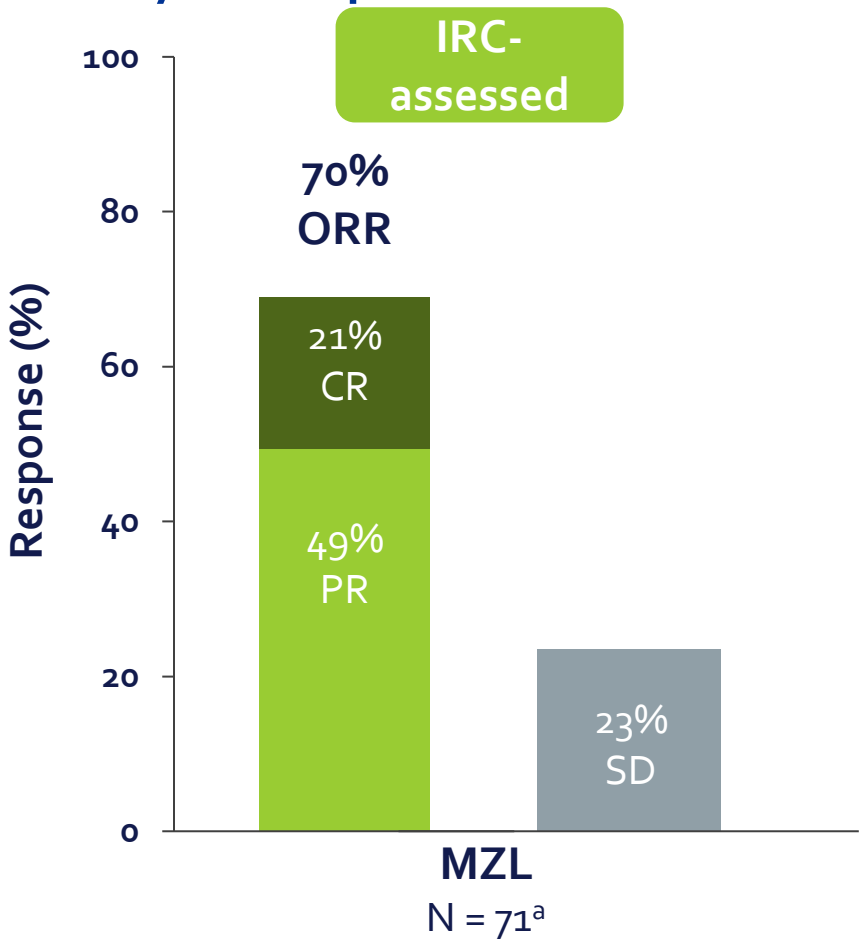
Events of Clinical Interest – PI3K Specific

AEs, n (%)	MZL U2 N=72 Any Grade	Grade 3/4	Discontinued U2
Diarrhea	35 (49)	9 (13)	2 (2.8)
Neutropenia	20 (28)	13 (18)	1 (1.4)
ALT/AST increased[a]	16 (22)	11 (15)	2 (2.8)
Rash	9 (13)	-	-
Non-infectious colitis[b]	2 (2.8)	2 (2.8)	-
Pneumonitis	-	-	-

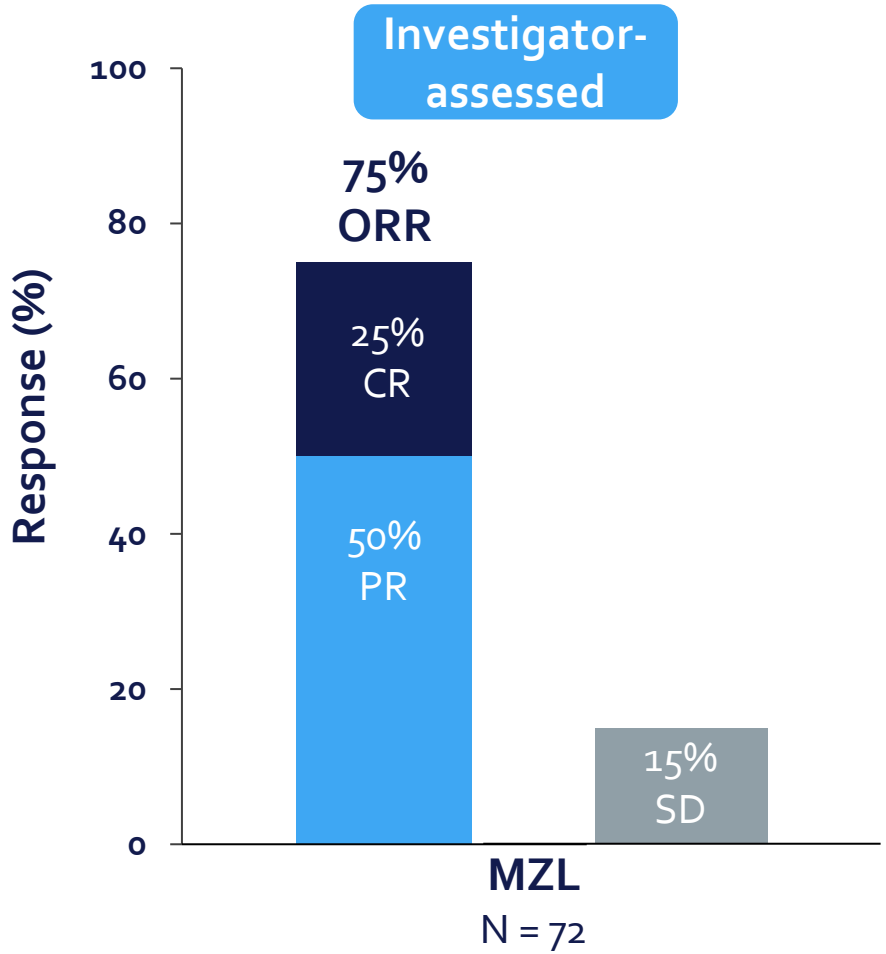
- Median follow-up is 20 months (range 9.5 – 29.3 months)
- Among patients who experienced Grade 3/4 diarrhea, only 1 patient was managed with steroids
- 22 (31%) patients were managed with dose reductions
  - Most common AEs leading to dose reduction: ALT/AST 8 (11%) and diarrhea 3 (4%)

AE: adverse event; MZL: marginal zone lymphoma; [a]ALT/AST increased includes subjects that had ALT or AST. [b]Grouped terms encompassing Non-infectious colitis includes Autoimmune colitis, colitis, colitis microscopic, enterocolitis and neutropenic colitis. MedDRA preferred terms. Other AEs are presented for specific MedDRA Preferred Terms.

IRC- & Investigator-assessed Overall Response Primary Endpoint



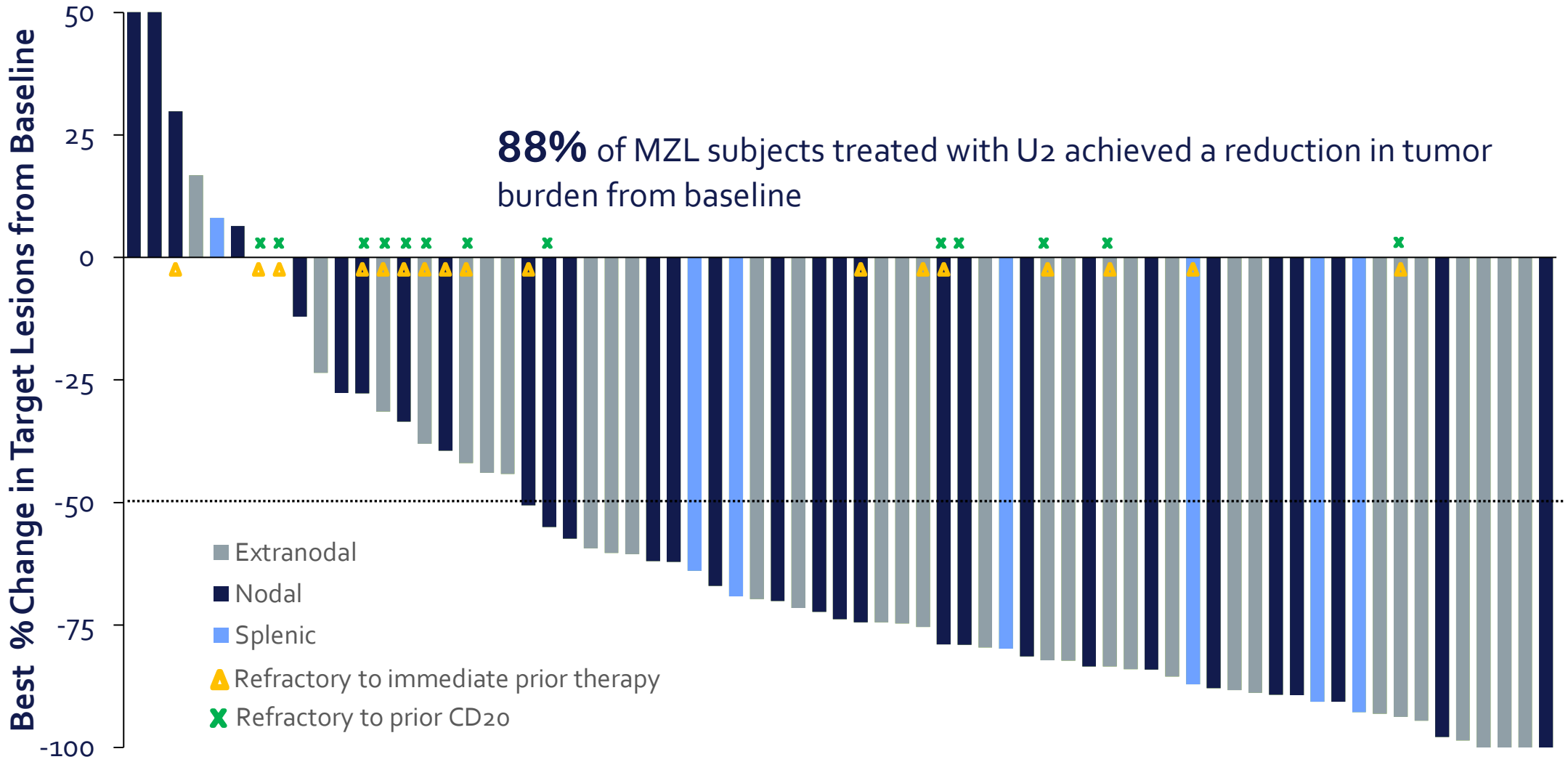
	DCR	Median FU
IRC-assessed	93.0 %	20 mos



	DCR	Median FU
Investigator-assessed	90.3%	20 mos

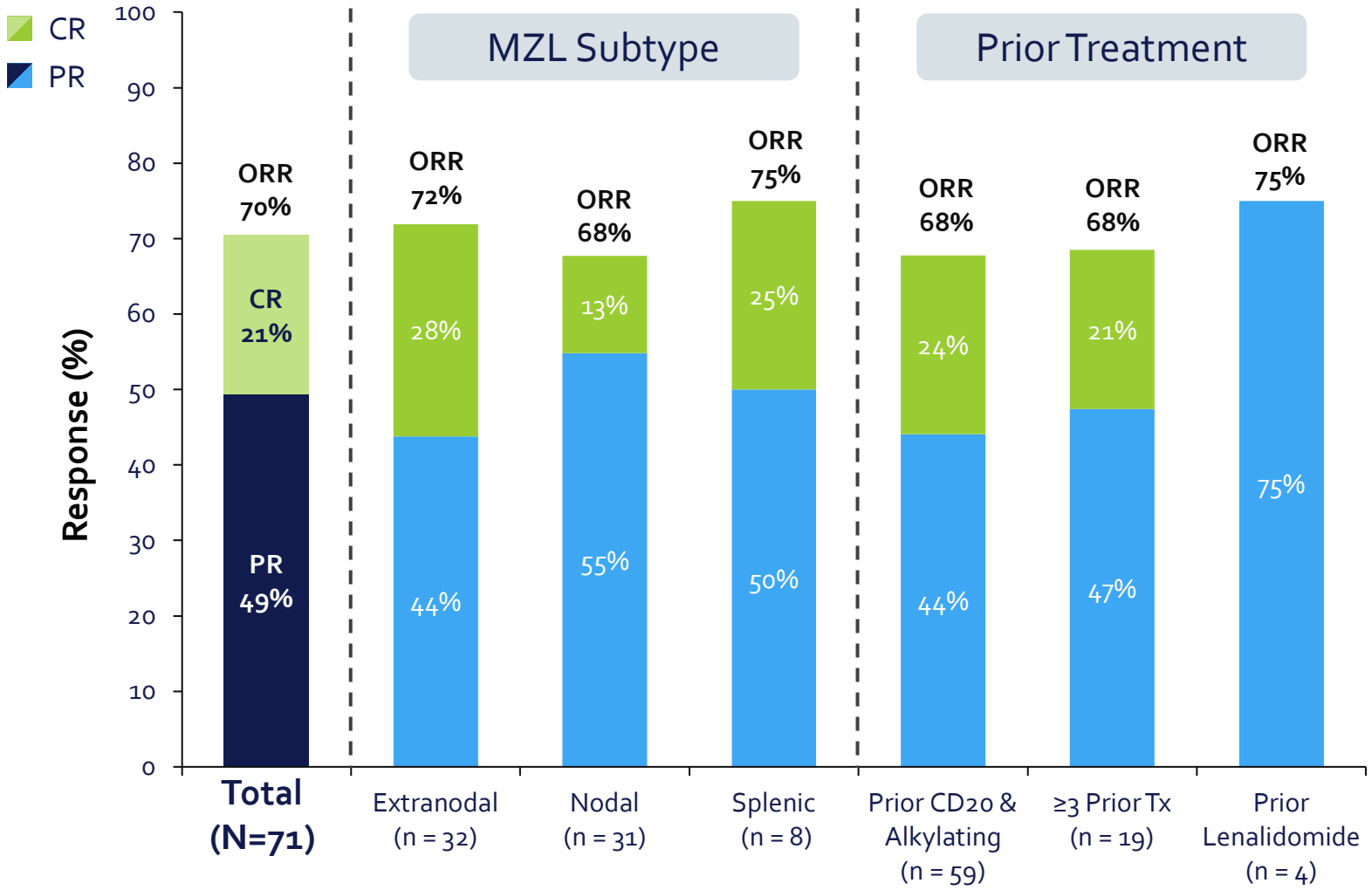
CR: complete response; DCR: disease control rate (CR + PR + SD); FU: follow-up; IRC: independent review committee; MZL: marginal zone lymphoma; ORR: overall response rate; PR: partial response; SD: stable disease; [a]Per IRC, one patient had no evaluable disease at baseline therefore is excluded in the overall response assessment

IRC-assessed Response in Index Lesion Size



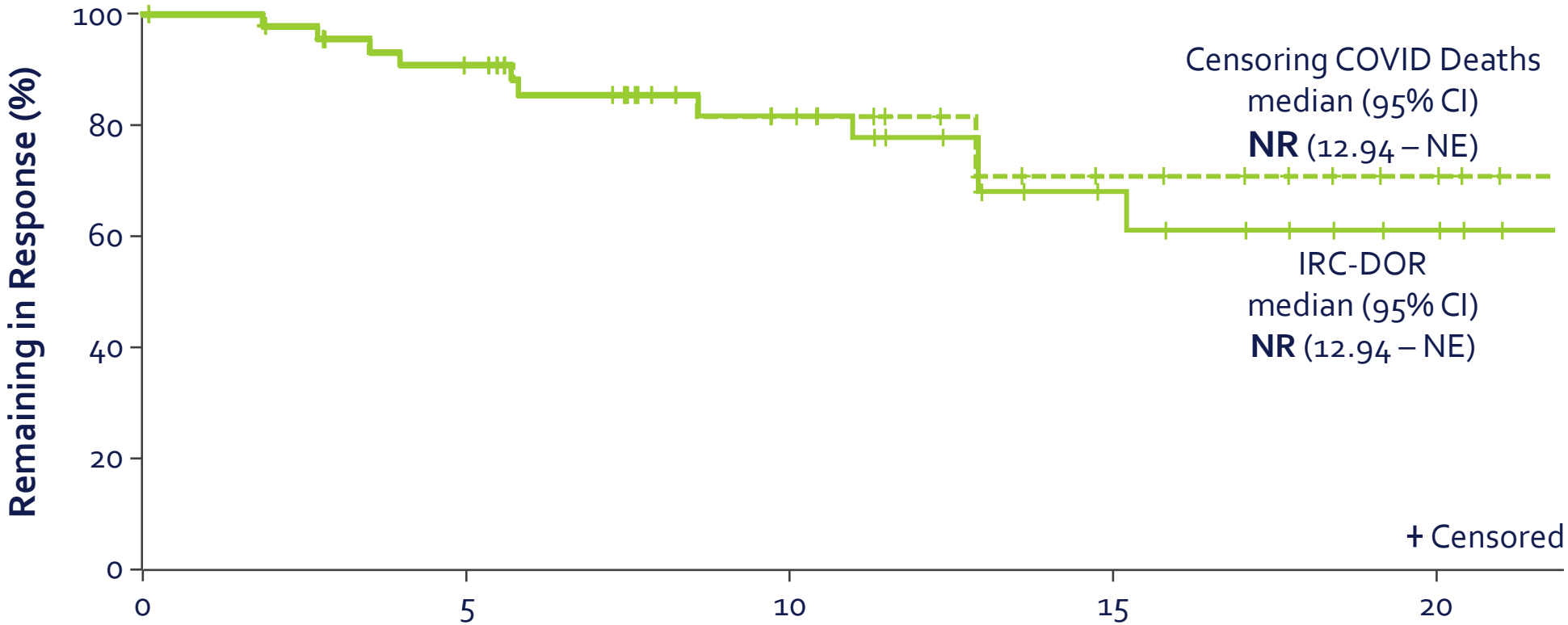
Data presented for patients that have at least 1 post-baseline scan (N=69); Scans were conducted by CT, MRI, or PET; MZL: marginal zone lymphoma

IRC-assessed Responses by Subgroup



CR: complete response; IRC: independent review committee; MZL: marginal zone lymphoma; ORR: overall response rate; PR: partial response.

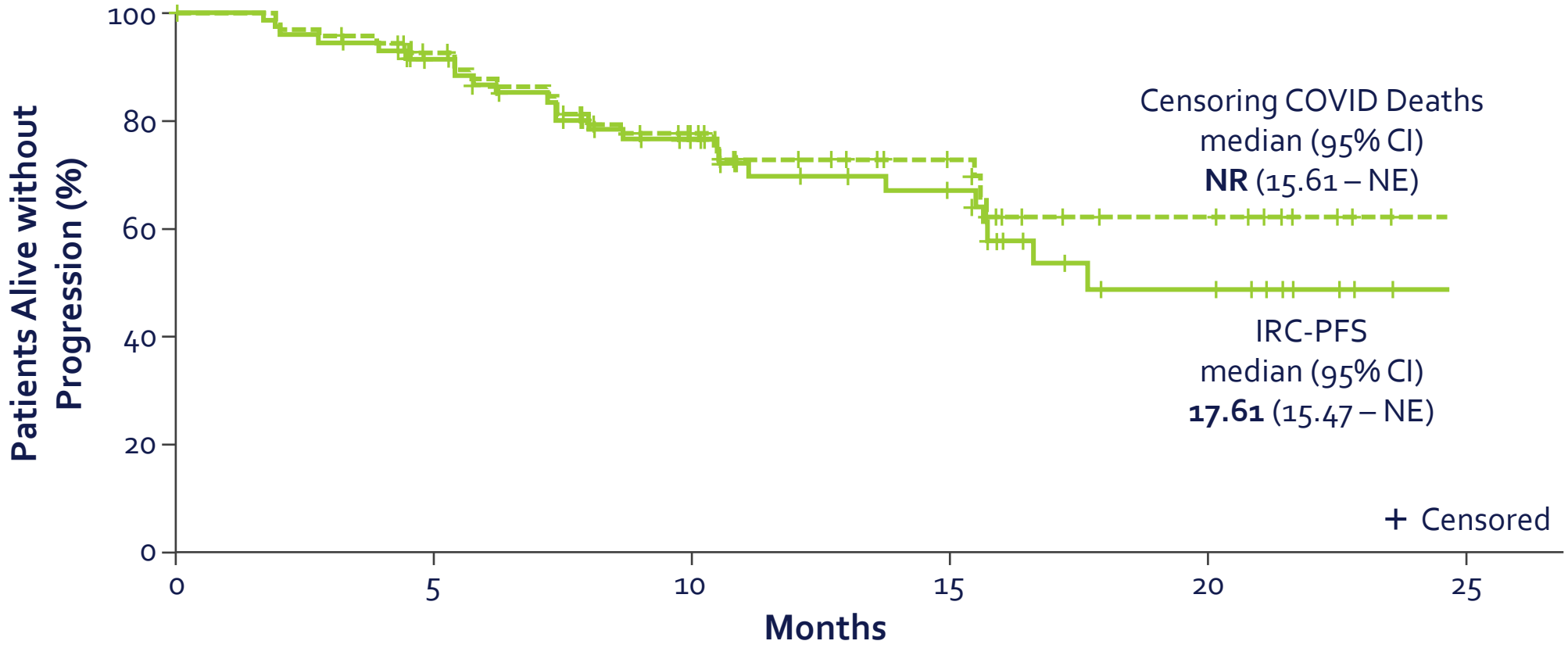
IRC-assessed Duration of Response



At Risk					
IRC-DOR	50	37	21	9	4
Censoring COVID Deaths	50	37	21	10	4

CI: confidence interval; DOR: duration of response; IRC: independent review committee; NR: not reached; NE: not estimable.

IRC-assessed Progression-free Survival



At Risk						
IRC-PFS	72	58	40	24	9	0
Censoring COVID Deaths	72	58	40	22	9	0

CI: confidence interval; IRC: independent review committee; NR: not reached; NE: not estimable; PFS: progression-free survival.

Conclusions

- In the UNITY-NHL study, U2 was highly active in patients with R/R MZL, with durable responses observed
  - U2 treatment resulted in an increased rate of response when compared to a prior cohort of MZL patients treated with umbralisib monotherapy
- The safety profile was acceptable, with low incidence of immune-mediated toxicities and AE-related discontinuations
- The U2 combination demonstrated favorable clinical activity and may constitute a novel non-chemotherapy treatment option for patients with R/R MZL