Umbralisib, a PI3Kδ/CK1ε dual inhibitor demonstrates marked clinical activity in patients with relapsed or refractory indolent non-Hodgkin lymphoma: Results from the Phase 2 global UNITY-NHL trial

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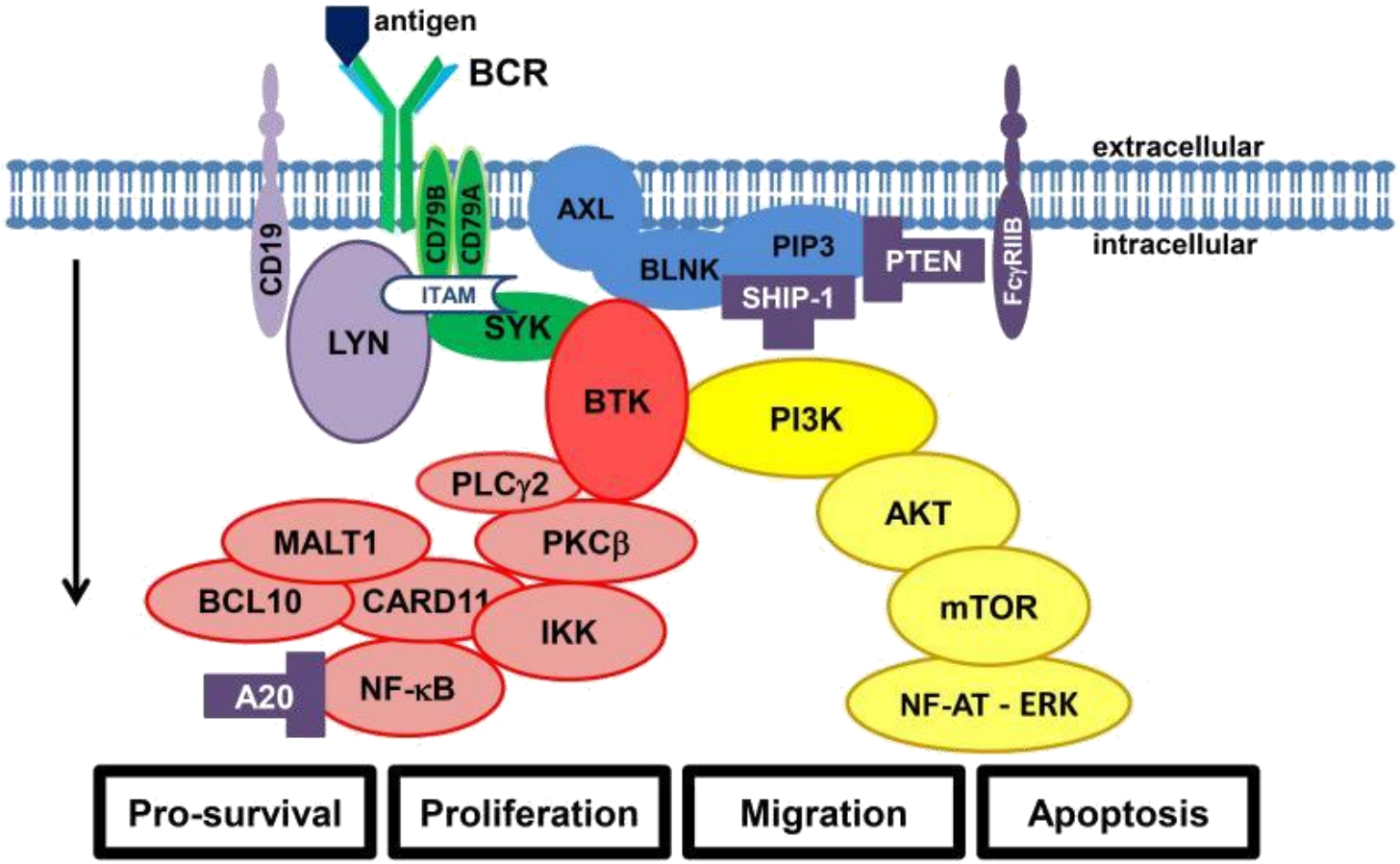
PI3K Signaling in iNHL

- B cell receptor (BCR) signaling is critical to the development of normal B cells and has been implicated in lymphomagenesis[1]
- PI3K is a downstream intermediary in the BCR pathway essential for BCR-dependent B cell survival[1]
- Recent evidence suggests the PI3K-mTOR pathway is sufficient for driving the pathogenesis of MZL[2]

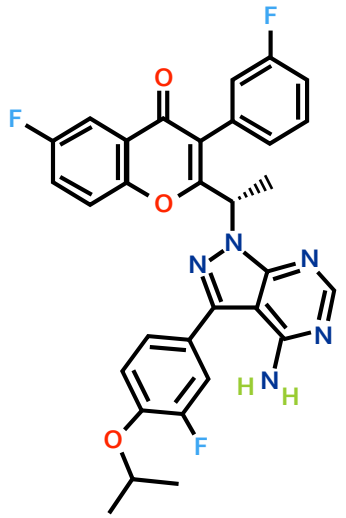
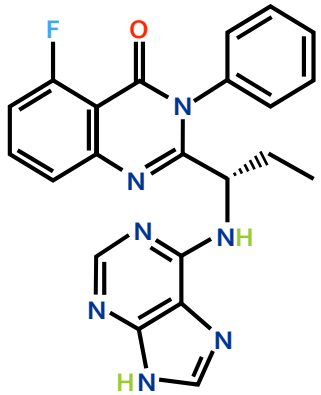
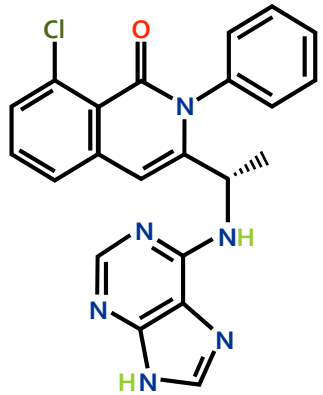
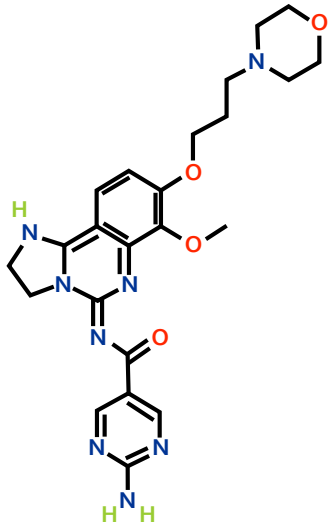
The B cell Receptor (BCR) and its Downstream Pathways[1]



PI3k: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; MZL: marginal zone lymphoma

1. Niemann CU, et al. *Seminars in Cancer Biology.* 2013;23(6):410–421.2. Sindel A, et al. *Blood.* 2018;132(supp 1):4125–4125.

Umbralisib Is a Dual Inhibitor of PI3Kδ and CK1ε

Umbralisib[1]	Idelalisib[1]	Duvelisib[1]	Copanlisib[2]
			

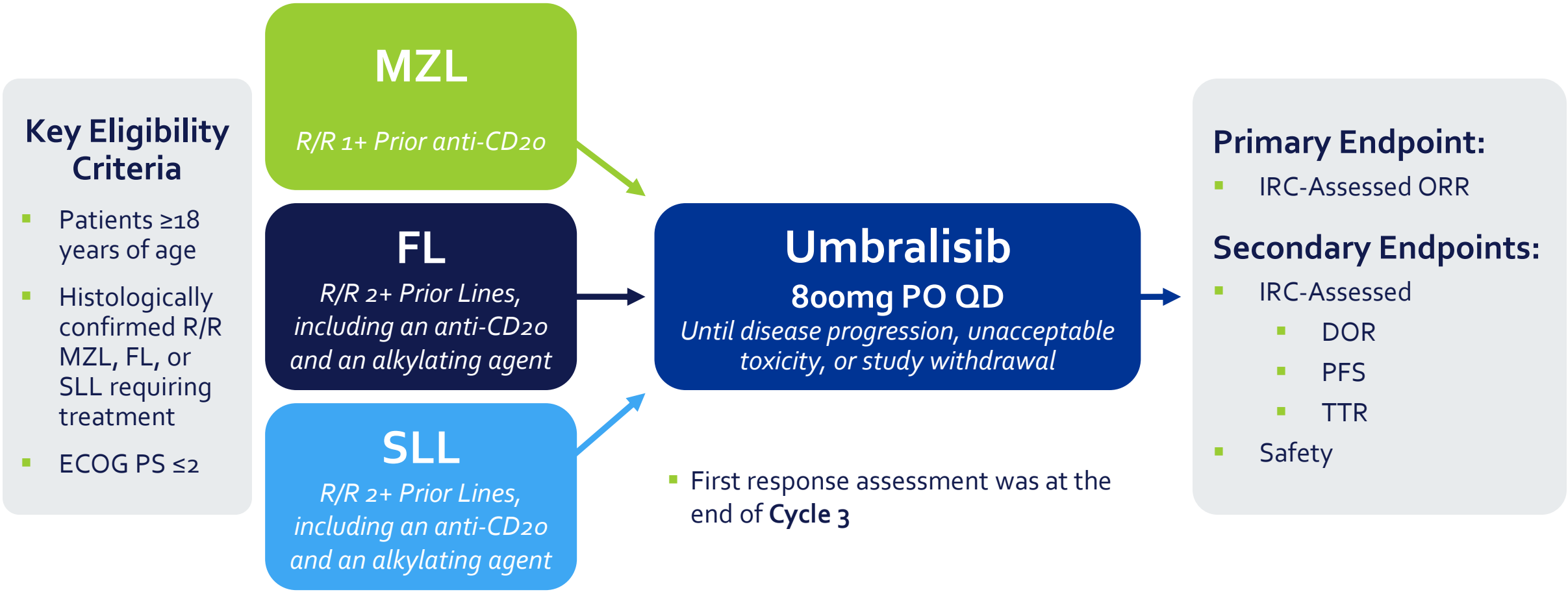
Isoform	K_d (nM)			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

- Umbralisib is an oral, once daily, dual inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms[3]
- Umbralisib is also **>200-fold** more selective for PI3Kδ relative to **PI3Kγ**

PI3k: phosphoinositide 3-kinase; CK1ε: casein kinase 1ε.

1. Burris HA, et al. *Lancet Oncol*. 2018;19(4):486-496. 2. Data on File [TGR 001]. TG Therapeutics, Inc, New York City, NY.

UNITY-NHL Study Design (UTX-TGR-205)



CD20: cluster of differentiation 20; DOR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; IRC: independent review committee; ORR: overall response rate; PFS: progression-free survival; PO: orally; QD: daily; TTR: time to response, FL: follicular lymphoma; ITT: intent to treat; MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma

Baseline Characteristics & Prior Therapies

Characteristic	MZL N=69	FL N=117	SLL N=22	Total N=208
Age, median (range), years	67 (34-88)	65 (29-87)	65 (49-86)	66 (29-88)
Male, n (%)	33 (48)	72 (61.5)	13 (59)	118 (57)
ECOG PS 0 | 1 | 2, %	55 | 42 | 3	56 | 41 | 3	64 | 36 | 0	56 | 41 | 3
Disease Stage III-IV, n (%)	56 (81)	85 (73)	19 (86)	160 (77)
FL Grade 1 | 2 | 3A, %	-	26 | 45 | 27	-	-
MZL Subtype MALT | Splenic | Nodal, %	55 | 16 | 29	-	-	-
Prior Therapies, median (range)	2 (1 – 6)	3 (1 – 10)	2 (1 – 4)	2 (1 – 10)
Anti-CD20 Therapies, n (%)	69 (100)	117 (100)	22 (100)	208 (100)
Chemoimmunotherapy, n(%)	52 (75)	117 (100)	20 (91)	189 (91)
Bendamustine based regimen, n (%)	24 (35)	72 (62)	15 (68)	111 (53)
Cyclophosphamide based regimen, n (%)	37 (54)	89 (76)	10 (45)	136 (65)
Refractory to Last Therapy, n (%)	18 (26)	42 (36)	11 (50)	71 (34)
Time Since Last Therapy, median, months	17	13	10	14

CD20: cluster of differentiation 20; ECOG PS: Eastern Cooperative Oncology Group performance status; FL: follicular lymphoma; ITT: intent to treat; MZL: marginal zone lymphoma; "-": not applicable; SLL: small lymphocytic lymphoma

Disposition & Exposure

	MZL N=69	FL N=117	SLL N=22	Total N=208
Treated with at least one dose, n (%)	69 (100)	117 (100)	22 (100)	208 (100)
Exposure, median (range), months	9.8 (0.2 – 27)	7.6 (1.0 – 27)	10.9 (0.7 – 25)	8.4 (0.2 – 27)
Median follow up, months	27.8	27.5	29.3	27.7
Treatment status, n (%)				
Ongoing	26 (38)	27 (23)	7 (32)	60 (29)
Discontinued	43 (62)	90 (77)	15 (68)	148 (71)
Adverse event	16 (23)	14 (12)	2 (9)	32 (15)
Death	0	0	1 (5)[a]	1 (0.5)
Non-compliance	0	1 (1)	0	1 (0.5)
Investigator decision	5 (7)	8 (7)	3 (14)	16 (8)
Progressive disease	19 (28)	62 (53)	7 (32)	88 (42)
Withdrew consent	3 (4)	2 (2)	1 (5)	6 (3)
Other	0	3 (3)	1 (5)	4 (2)

FL: follicular lymphoma; MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma. [a]One SLL patient had a fatal myocardial infarction unrelated to umbralisib; there were no other fatalities

All Causality AEs (>15%)

AEs, n (%) N=208	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	**123 (59.1)**	64 (30.8)	38 (18.3)	21 (10.1)	0	0
Nausea	**82 (39.4)**	52 (25.0)	29 (13.9)	1 (0.5)	0	0
Fatigue	**64 (30.8)**	38 (18.3)	19 (9.1)	7 (3.4)	0	0
Vomiting	**49 (23.6)**	29 (13.9)	19 (9.1)	1 (0.5)	0	0
Cough	**43 (20.7)**	35 (16.8)	8 (3.8)	0	0	0
ALT increased	**42 (20.2)**	13 (6.3)	15 (7.2)	11 (5.3)	3 (1.4)	0
AST increased	**39 (18.8)**	19 (9.1)	5 (2.4)	15 (7.2)	0	0
Decreased appetite	**39 (18.8)**	23 (11.1)	12 (5.8)	4 (1.9)	0	0
Dizziness	**38 (18.3)**	29 (13.9)	8 (3.8)	1 (0.5)	0	0
Neutropenia	**33 (15.9)**	5 (2.4)	4 (1.9)	10 (4.8)	14 (6.7)	0
Headache	**33 (15.9)**	22 (10.6)	9 (4.3)	2 (1.0)	0	0

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase

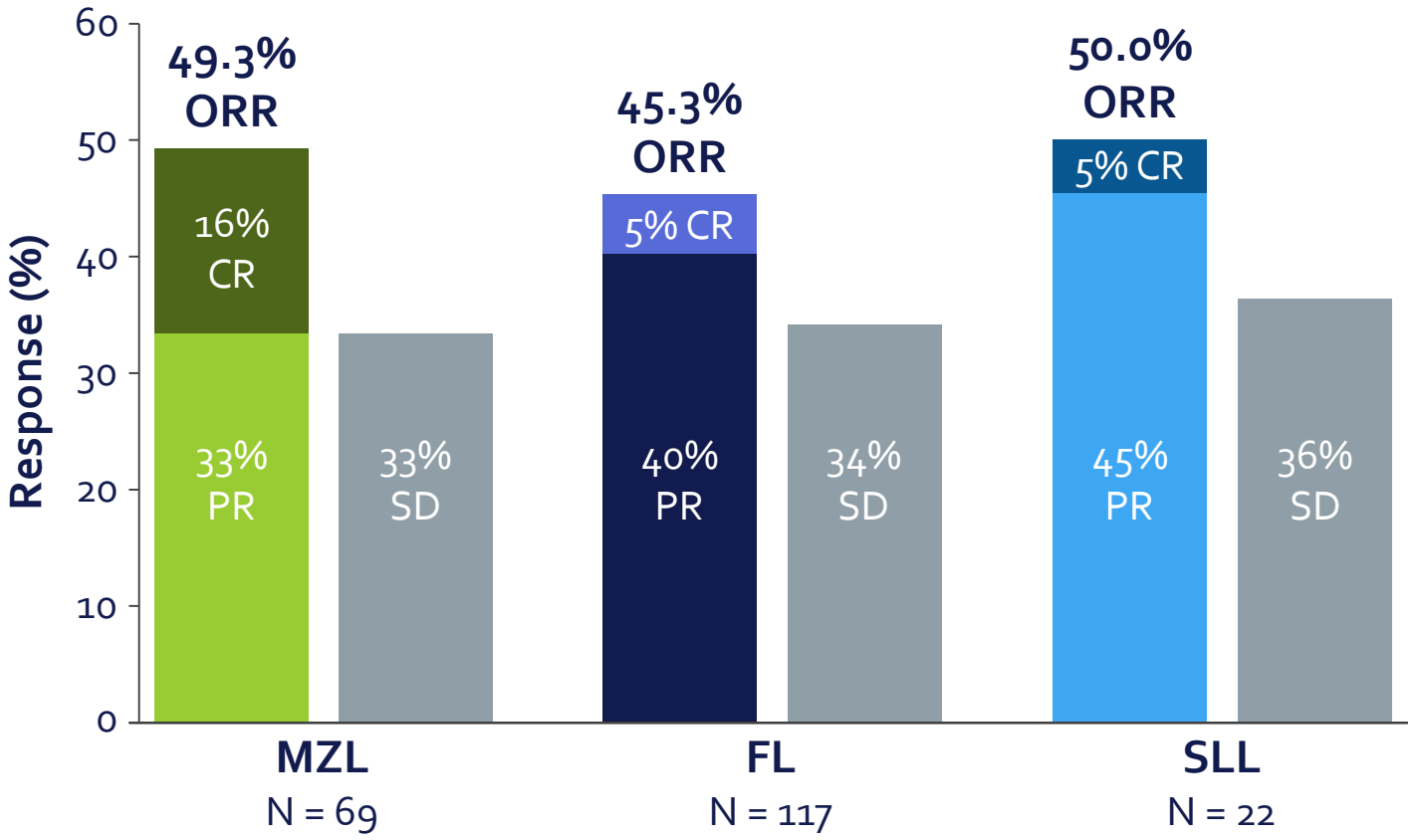
AEs of Special Interest

Safety profile distinct from prior generation PI3K inhibitors with extended follow-up (median 27+ months)

- Discontinuations due to ALT/AST elevations were limited at 2.9%
- Grade 3 diarrhea led to discontinuation of only 2.9% of patients
- Non-infectious colitis occurred in 4 patients (1.9%), of which 3 of 4 patients resolved and remained on umbralisib
- Grade 3/4 opportunistic infections: n=7 (3.4%)
- Grade 3/4 rash: n=4 (1.9%)
- Grade 3/4 pneumonitis: n=2 (1.0%)

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase. [a]Infectious colitis included 1 case of clostridium difficile colitis. *Includes multiple MedDRA terms.

IRC-Assessed Overall Response Primary Endpoint



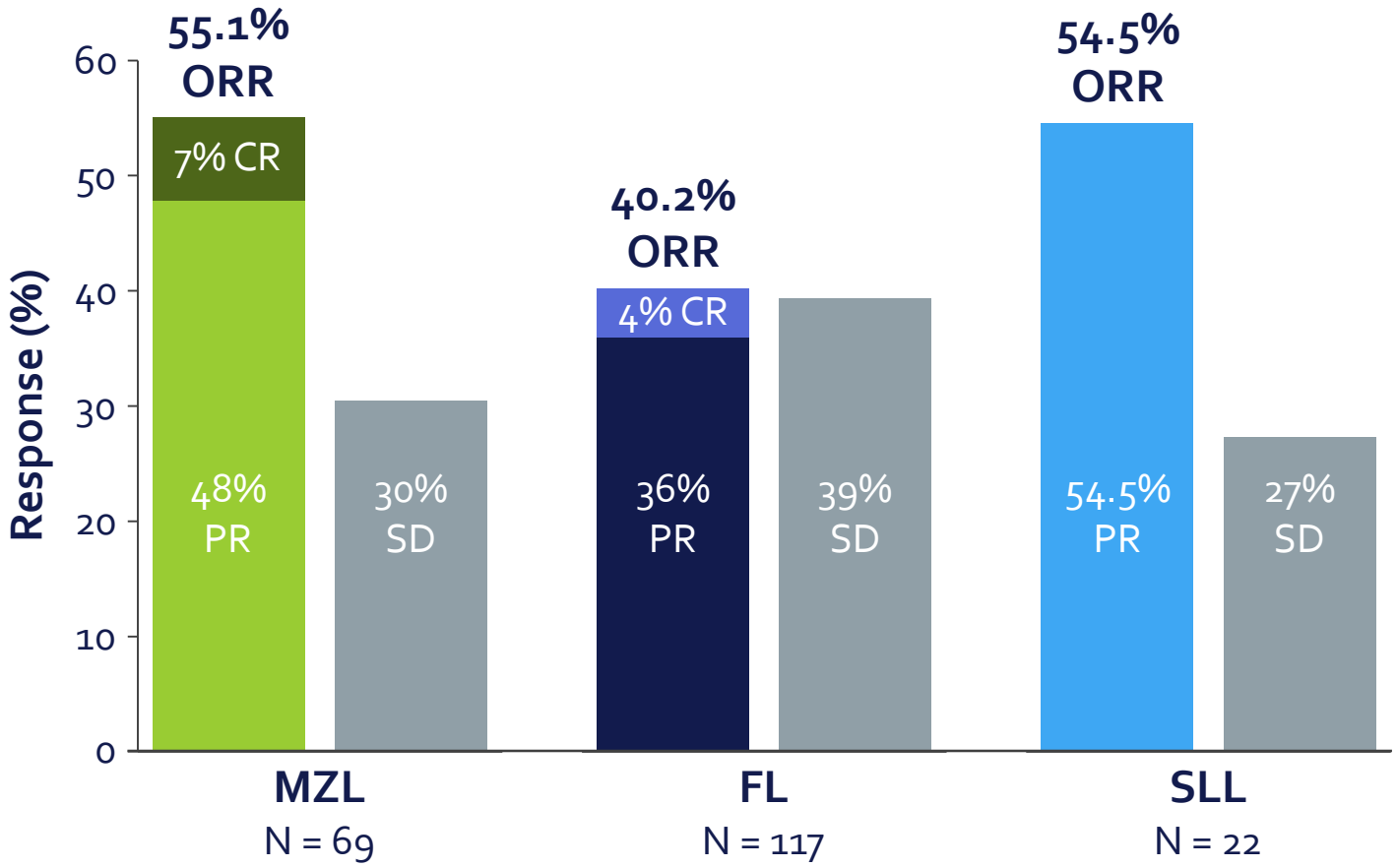
Cohort	DCR	Median TTR	Median FU
MZL	82.6 %	2.8 mo	27.8 mo
FL	79.5%	4.6 mo	27.5 mo
SLL	86.4%	2.7 mo	29.3 mo

Across entire indolent NHL population (n=208) umbralisib produced a **47.1%** ORR and **81.3%** DCR

CR: complete response; DCR: disease control rate (CR + PR + SD); FL: follicular lymphoma; FU: follow up; IRC: independent review committee; mo: months; MZL: marginal zone lymphoma; ORR: overall response rate; PR: partial response; SD: stable disease; TTR: time to response.

Investigator-Assessed Overall Response

Investigator assessed response rates were consistent with IRC-assessed responses



Cohort	DCR	Median TTR	Median FU
MZL	85.5%	2.8 mo	27.8 mo
FL	79.5%	2.9 mo	27.5 mo
SLL	81.8%	2.7 mo	29.3 mo

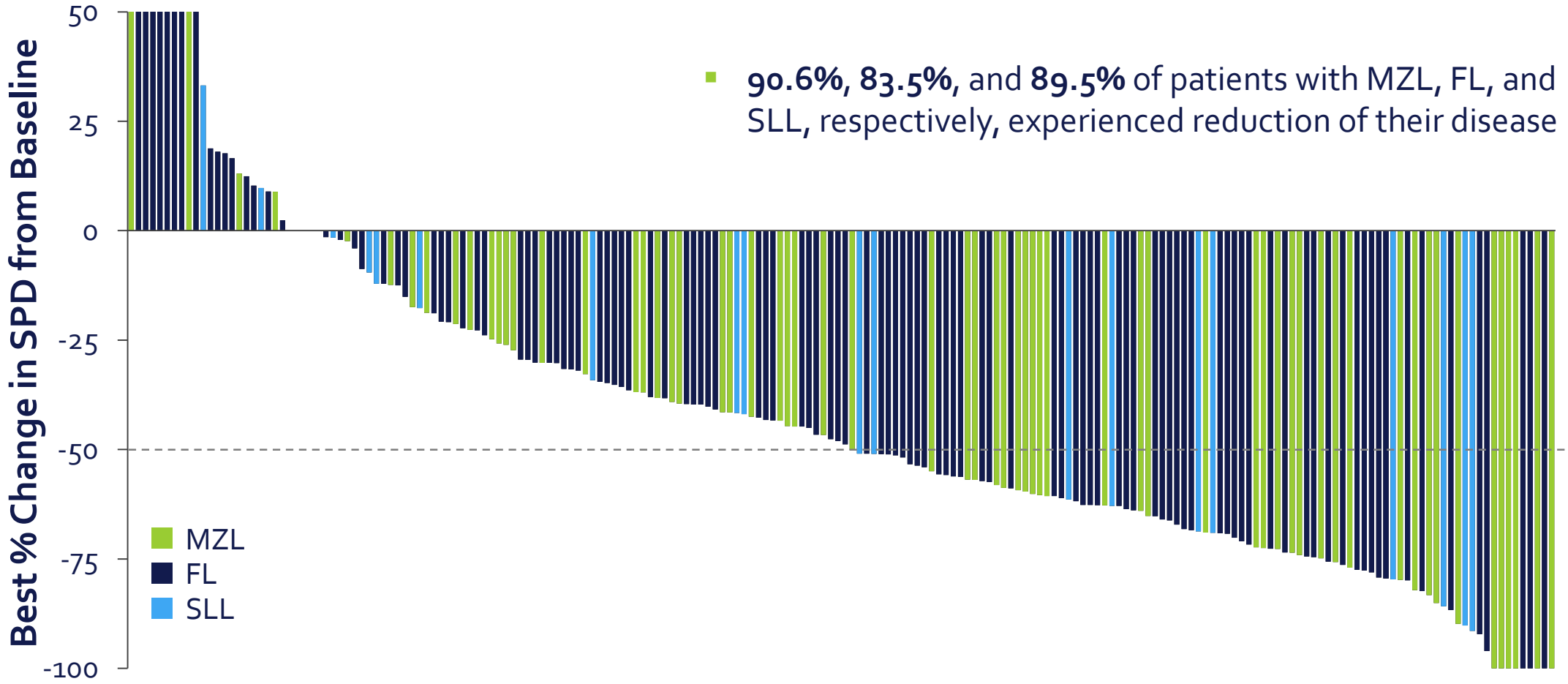
CR: complete response; DCR: disease control rate (CR + PR + SD); FL: follicular lymphoma; FU: follow up; IRC: independent review committee; mo: months; MZL: marginal zone lymphoma; ORR: overall response rate; PR: partial response; SD: stable disease; TTR: time to response.

IRC-Assessed ORR by Subgroup

Subgroup	MZL N=69		FL N=117		SLL N=22	
Number of Prior Therapies	**ORR (%)**	**n/N**	**ORR (%)**	**n/N**	**ORR (%)**	**n/N**
<3	**49**	(25/51)	**41**	(20/49)	**33**	(4/12)
≥3	**50**	(9/18)	**49**	(33/68)	**70**	(7/10)
Prior Therapy Type						
Anti-CD20 Antibody & Alkylating Agent	**48**	(25/52)	**45**	(53/117)	**45**	(9/20)
Lenalidomide	**75**	(3/4)	**39**	(7/18)	**-**	-
MZL Subtype						
MALT	**45**	(17/38)				
Splenic	**45**	(5/11)				
Nodal	**60**	(12/20)				
FL Grade						
1			**57**	(17/30)		
2			**45**	(24/53)		
3A			**34**	(11/32)		

BTK: Bruton's tyrosine kinase; CD20: cluster of differentiation 20; FL: follicular lymphoma; MALT: mucosa-associated lymphatic tissue; MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma.

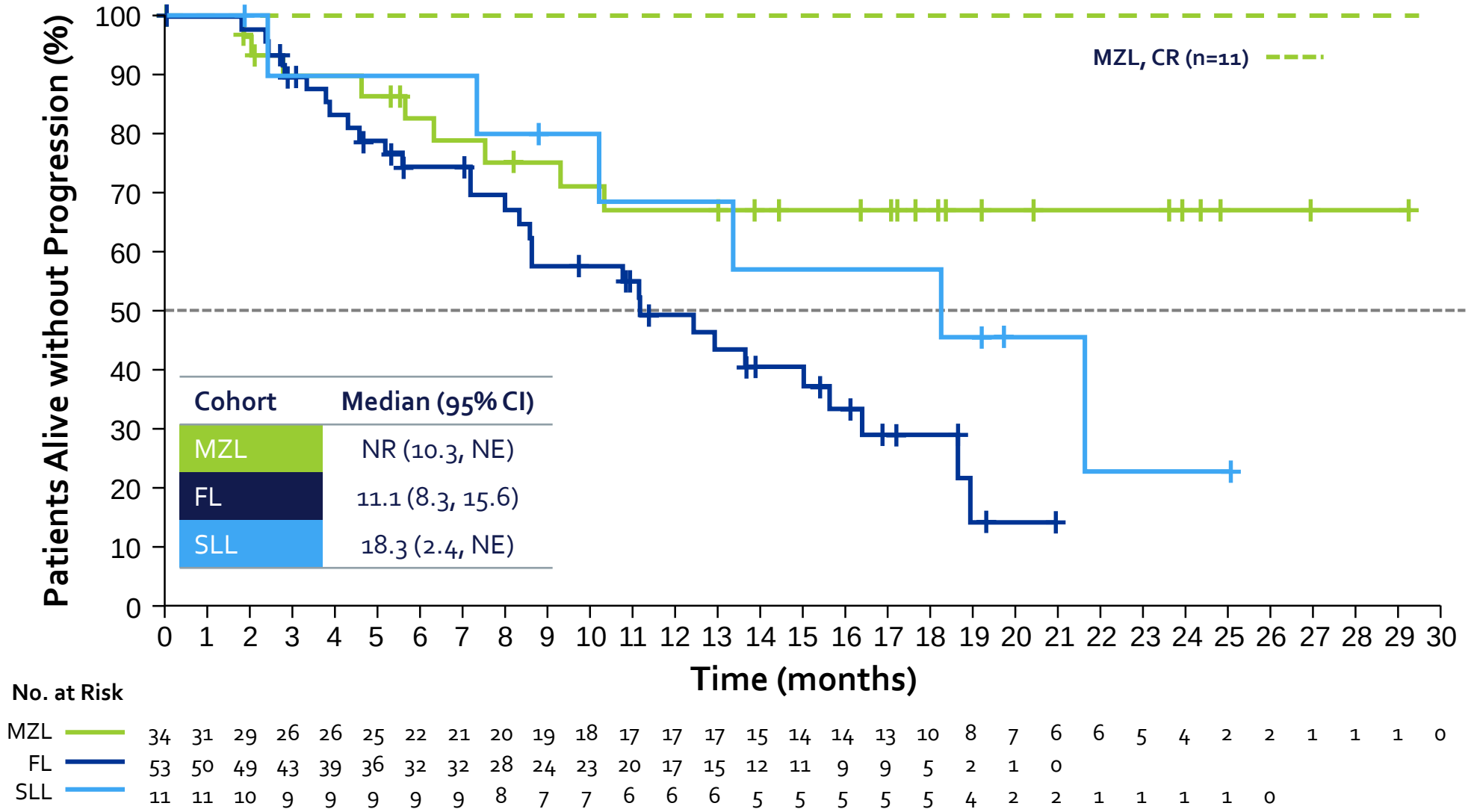
IRC-Assessed Response in Index Lesion Size



- **90.6%, 83.5%,** and **89.5%** of patients with MZL, FL, and SLL, respectively, experienced reduction of their disease

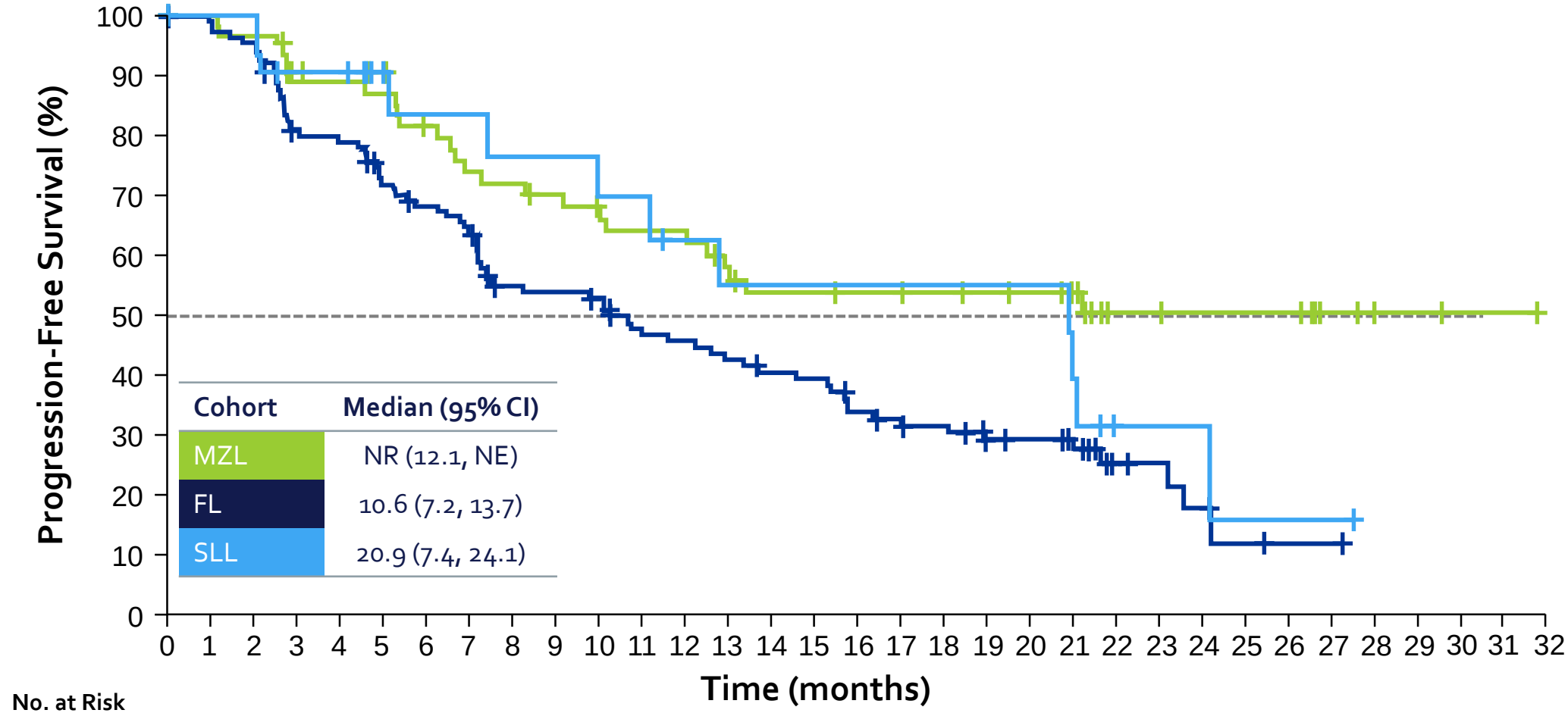
FL: follicular lymphoma; IRC: independent review committee; MZL: marginal zone lymphoma; SLL: small lymphocytic lymphoma; SPD: sum product diameters. Note: Waterfall plot includes all patients with an evaluable post-baseline scan (N=198).

IRC-Assessed Duration of Response



FL: follicular lymphoma; IRC: independent review committee; MZL: marginal zone lymphoma; NE: not estimable; NR: not reached; SLL: small lymphocytic lymphoma.

IRC-Assessed Progression-Free Survival



No. at Risk

MZL	69	64	62	51	50	48	43	39	38	36	34	32	32	28	25	25	24	24	23	22	21	18	10	10	9	9	9	4	2	2	1	1	0
FL	117	115	111	92	90	79	73	68	56	55	53	46	44	41	38	37	31	28	27	22	21	17	8	7	5	2	1	1	0				
SLL	22	21	21	18	18	13	12	12	11	11	10	10	8	7	7	7	7	7	7	7	7	5	2	2	2	1	1	1	0				

FL: follicular lymphoma; IRC: independent review committee; MZL: marginal zone lymphoma; NE: not estimable; NR: not reached; SLL: small lymphocytic lymphoma.

Conclusions

- In the UNITY-NHL study, umbralisib showed meaningful clinical activity in patients with R/R iNHL
  - Encouraging CR rate in MZL, with no patients in CR progressed to date
- The safety profile was acceptable, with manageable toxicities and a relatively low number of AE-related discontinuations.
- These results suggest that umbralisib has a favorable benefit-risk profile in this heavily pretreated patient population.
- Umbralisib is an effective and well-tolerated monotherapy treatment option for patients with R/R iNHL, serving as a platform for the development of highly active, safer combination regimens.
  - The UNITY-CLL trial investigating umbralisib combined with ublituximab for the treatment of newly diagnosed and previously treated CLL recently met its primary endpoint (abstract # 134783)

Acknowledgements

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- Thank you to the investigators, research staff, and entire UNITY-NHL study team