Efficacy and Safety of Umbralisib and Ublituximab (U2), and U2 Plus Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

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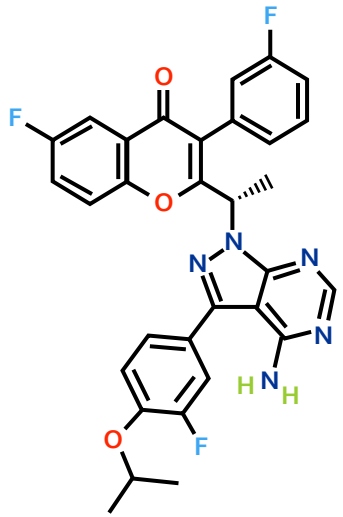
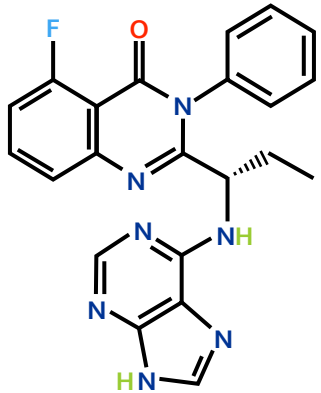
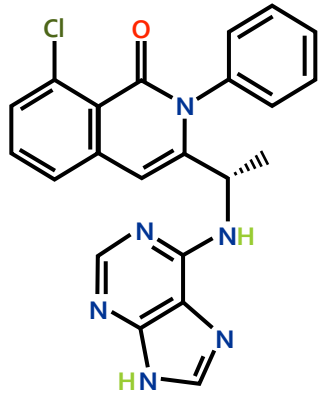
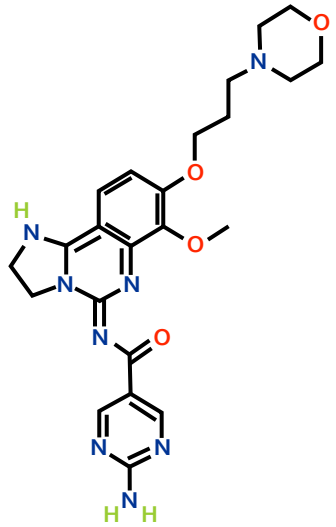
Disclosures for John M. Burke, M.D.

- **Advisory Boards: Adaptive Biotech, Roche/Genentech, Epizyme, Kura, Abbvie, Morphosys, Beigene, SeaGen, Kymera, BMS, X4, AstraZeneca, TG Therapeutics**

- **Speakers' Bureaus: SeaGen, Beigene**

Umbralisib is a Selective Inhibitor of PI3Kδ and CK1ε

- 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[1]

Umbralisib[2]	Idelalisib[2]	Duvelisib[2]	Copanlisib[3]
			

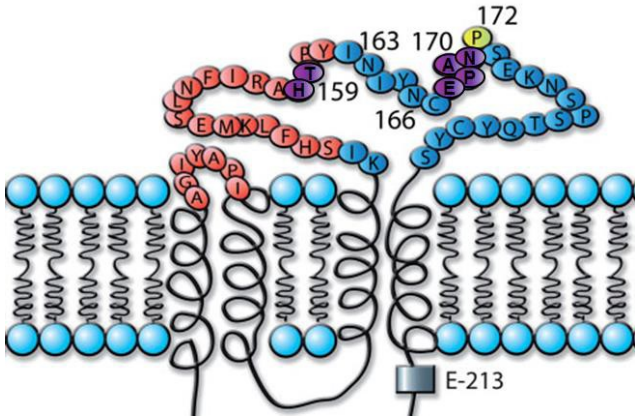
Isoform	K_d (nM)			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

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

Ublituximab is a Novel Glycoengineered Anti-CD20 mAb

- Ublituximab (TG-1101, UTX) is a novel, glycoengineered, Type I, anti-CD20 monoclonal antibody with several defining features:
  - Targets a unique epitope on the CD20 antigen
  - Type I maintains complement-dependent cytotoxicity (CDC)
  - Glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, thereby demonstrating greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab including in 17p deleted CLL cells[1]

Ublituximab



Red: Key ofatumumab epitope amino acids
Purple: Core amino acids of ublituximab epitope

Figure adapted from Ruuls et al, 2008[2]

CLL: chronic lymphocytic leukemia

1. Le Garff-Tavernier M, et al. *Leukemia*. 2014;28:230-233; 2. Ruuls S, et al. *Biotechnology J.* 2008; 3:1157-1171.

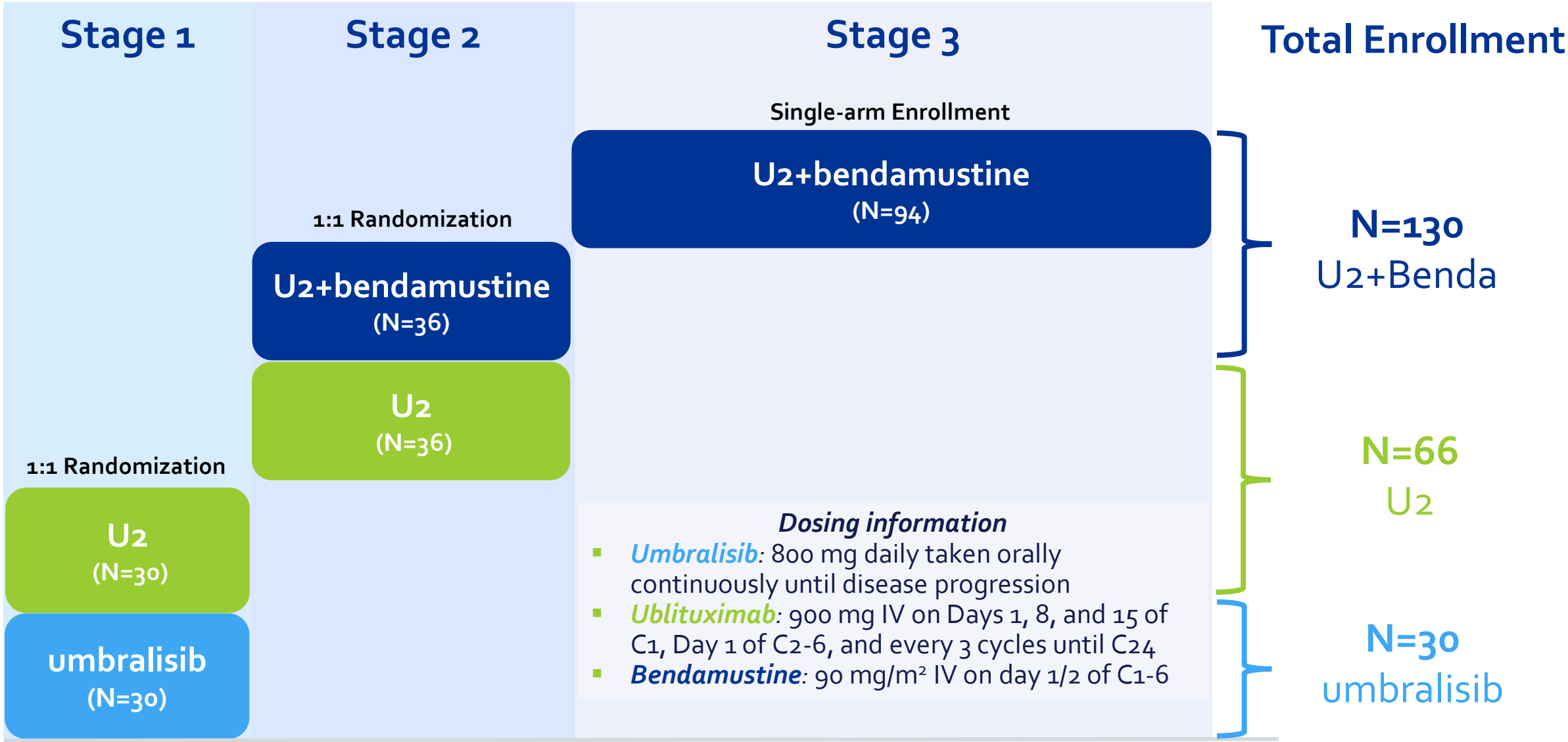
Rationale for Combining Ublituximab + Umbralisib (U2) + Bendamustine in DLBCL

- **Ublituximab** Phase 1-2 trial in R/R CLL and NHL[1]
  - Overall response rate 45%, but only 1 DLBCL patient
- **Umbralisib + ublituximab** phase 1 trial in R/R B-cell malignancies, n=22 with DLBCL[2]
  - Overall response rate 23%
  - Complete response rate 14%
- Phase 1 trial of **U2 + bendamustine**, n=25 with DLBCL[3]
  - Overall response rate 48%
  - Complete response rate 32%
- Hypothesis: U2 + bendamustine is an effective regimen in R/R DLBCL

CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma; DLBCL: diffuse large B-cell lymphoma

1. Sawas A, et al. Br J Hematol 2017;177(2):243-253, 2. Lunning M., et al. *Blood* 2019; 134 (21): 1811–1820, 3. Lunning et al. *Blood* 2018; 132 (Supp.1): 4197

UNITY-NHL – DLBCL Cohorts



DLBCL: diffuse large B-cell lymphoma; IV: intravenous; D: Day; C: Cycle

Eligibility and Endpoints

Key Eligibility Criteria:

- Patients ≥18 years of age
- Histologically confirmed relapsed or refractory DLBCL ineligible for or had already received ASCT, including transformed indolent NHL
- No limit on number of prior therapies
- Prior bendamustine, CAR-T, or patients refractory to CD20 were not excluded
- 21-day washout from prior therapy, with palliative radiation allowed during washout
- ECOG PS ≤2

Primary Endpoint:

- Overall response rate, determined by independent review committee
  - Modified International Working Group criteria (Cheson et al. 2007)

Secondary Endpoints:

- Duration of response, progression-free survival, safety, overall survival

Exploratory Endpoint:

- Relationship between gene mutations and response

ASCT: autologous stem cell transplant; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NHL: non-Hodgkin's lymphoma; ORR: overall response rate; U2: umbralisib + ublituximab

Baseline Characteristics & Prior Therapies

Characteristic	Umbra N=30	U2 N=66	U2+B N=130
Age, median (range), years	**74 (41 – 95)**	**74 (39 – 90)**	**71 (32 - 91)**
ECOG-PS, 0 | 1 | 2, %	**33 | 53 | 13**	**23 | 56 | 21**	**33 | 55 | 12**
Male, %	**40**	**67**	**60**
Stage III-IV, n (%)	**24 (80)**	**42 (64)**	**78 (60)**
Transformed DLBCL, n (%)	**1 (3)**	**4 (6)**	**13 (10)**
Cell of origin, n (%)*			
GCB	10 (33)	24 (36)	58 (45)
ABC	8 (27)	26 (39)	47 (36)
Unknown	12 (40)	16 (24)	25 (19)
Prior therapies, median (range)	**2 (1 – 4)**	**2 (1 – 7)**	**2 (1 – 8)**
Bendamustine, n (%)	3 (10)	13 (20)	24 (18)
CAR-T, n (%)	-	1 (2)	4 (3)
Auto transplant, n (%)	1 (3)	3 (5)	5 (4)
Refractory to immediate prior therapy, n (%)	**13 (43)**	**43 (65)**	**76 (58)**
Refractory to prior anti-CD20, n (%)	**11 (37)**	**36 (55)**	**57 (44)**

*Cell of origin - Performed centrally using gene expression profiling. ABC: activated B-cell; DLBCL: diffuse large B-cell lymphoma; ECOG-PS: Eastern Cooperative Oncology Group performance status; GCB: germinal center B-cell–like DLBCL; umbra: umbralisib; U2: umbralisib + ublituximab; U2+B: umbralisib + ublituximab + bendamustine

Patient Disposition

Treatment status, n (%)	Umbra N=30	U2 N=66	U2+B N=130
Follow-up, median (range), mos	**54 (50 – 64)**	**50 (45 – 61)**	**43 (39 – 50)**
Ongoing treatment	**-**	**5 (8)**	**6 (5)**
Discontinued regimen	**30 (100)**	**61 (92)**	**124 (95)**
Progressive disease	26 (87)	40 (61)	86 (66)
Investigator decision	-	2 (3)	7 (5)
Withdrawal of consent	-	5 (8)	8 (6)
Adverse event	3 (10)	7 (11)	9 (7)
Other	1 (3)	4 (6)	8 (6)
Death	-	3 (5)[a]	6 (5)[b]

[a]3 deaths on U2 include: progressive disease (2), cardiopulmonary arrest (1). [b]6 deaths on U2+B include: progressive disease (2), COVID (2), caecal tumor (1), pneumonia (1).
umbra: umbralisib; U2: umbralisib + ublituximab; U2+B: umbralisib + ublituximab + bendamustine

Safety Overview

AE type, n (%)	Umbra N=30	U2 N=66	U2+B N=130
Any grade AE	29 (97)	66 (100)	129 (99)
Serious AEs	9 (30)	25 (38)	64 (49)
Grade 3/4	16 (53)	41 (62)	104 (80)
COVID-related fatal AEs	**-**	**-**	**2**
Non-COVID Grade 5 AEs	**1**	**4**	**3**
Unrelated to therapy	1	3	2
Treatment-related[a]	-	1	1
D/C due to AE	3 (10)	7 (11)	9 (7)

[a] Both Grade 5 AE's indicated as at least possibly related to treatment were pneumonia; Safety was assessed in all patients who received ≥1 dose of treatment. AE: adverse event; D/C: discontinuation; umbra: umbralisib; U2: umbralisib + ublituximab; U2+B: umbralisib + ublituximab + bendamustine

All Causality AEs (≥20%) in Any Treatment Arm

Median Tx Duration (mos)

- Umbra: 2.0
- U2: 2.1
- U2+B: 4.5

AEs, n (%)	Umbra N=30		U2 N=66		U2+B N=130	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	14 (47)	2 (7)	27 (41)	1 (2)	62 (48)	9 (7)
Nausea	12 (40)	1 (3)	30 (45)	1 (2)	59 (45)	7 (5)
Fatigue	10 (33)	3 (10)	20 (30)	1 (2)	54 (42)	6 (5)
Neutropenia	1 (3)	1 (3)	12 (18)	7 (11)	42 (32)	35 (27)
Vomiting	7 (23)	-	9 (14)	1 (2)	37 (28)	5 (4)
Decreased appetite	4 (13)	1 (3)	11 (17)	-	35 (27)	1 (1)
Anemia	4 (13)	1 (3)	9 (14)	4 (6)	35 (27)	22 (17)
Hypokalemia	2 (7)	-	7 (11)	-	27 (21)	5 (4)
Dyspnea	7 (23)	2 (7)	10 (15)	3 (5)	18 (14)	2 (2)
Peripheral edema	6 (20)	1 (3)	11 (17)	-	15 (12)	1 (1)
ALT increase	2 (7)	1 (3)	15 (23)	8 (12)	13 (10)	4 (3)
AST increase	2 (7)	1 (3)	15 (23)	3 (5)	14 (11)	6 (5)
Pleural effusion	6 (20)	4 (13)	3 (5)	-	3 (2)	1 (1)

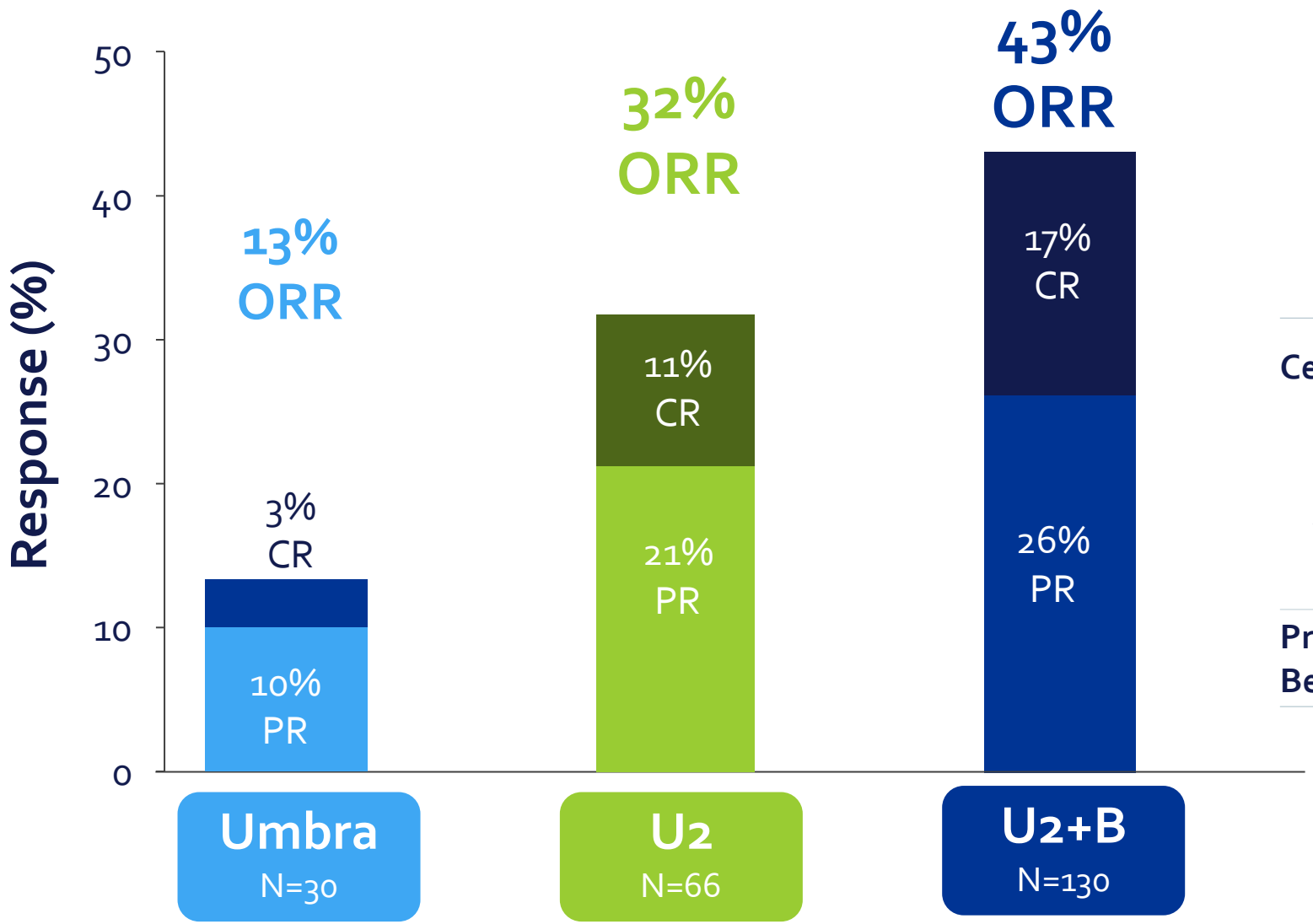
AEs are presented for specific MedDRA Preferred Terms. PJP and antiviral prophylaxis were required. GCSF support was permitted. AEs: adverse event; Tx: treatment; umbra: umbralisib; U2: umbralisib + ublituximab; U2+B: umbralisib + ublituximab + bendamustine

Events of Clinical Interest – PI3K-specific

AEs, n (%)	Umbra N=30			U2 N=66			U2+B N=130		
	Any Grade	Grade 3/4	Discontinued Umbralisib	Any Grade	Grade 3/4	Discontinued U2	Any Grade	Grade 3/4	Discontinued U2
ALT/AST increased	2 (7)	1 (3)	-	15 (23)	8 (12)	-	15 (12)	6 (5)	**1 (1)**
Non-infectious colitis	1 (3)	-	-	1 (2)	1 (2)	**1 (2)**	3 (2)	2 (2)	-
Diarrhea	14 (47)	2 (7)	**1 (3)**	27 (41)	1 (2)	-	62 (48)	9 (7)	-
Neutropenia	1 (3)	1 (3)	-	12 (18)	7 (11)	-	42 (32)	35 (27)	**2 (2)**
Pneumonitis	1 (3)	-	-	1 (2)	1 (2)	**1 (2)**	2 (2)	1 (1)	-
Rash	1 (3)	-	-	5 (8)	-	-	17 (13)	3 (2)	-

ALT/AST increased includes subjects that had ALT or AST. Non-infectious colitis includes Autoimmune colitis, colitis, colitis microscopic, enterocolitis and neutropenic colitis. Other AEs are presented for specific MedDRA Preferred Terms. AEs: adverse events; DLBCL: diffuse large B-cell lymphoma; umbra: umbralisib; U2: umbralisib + ublituximab; U2+B: umbralisib + ublituximab + bendamustine

IRC-assessed Response Rates



IRC-assessed ORR
% (n/N)

Cell of Origin	Umbra	U2	U2+B
GCB	**20** (2/10)	**38** (9/24)	**31** (18/58)
ABC	**13** (1/8)	**35** (9/26)	**57** (27/47)
Unknown	**8** (1/12)	**19** (3/16)	**44** (11/25)
Prior Bendamustine	-	**31** (4/13)	**42** (10/24)

ABC: activated B-cell; CR: complete response; DLBCL: diffuse large B-cell lymphoma; GCB: germinal center B-cell–like DLBCL; IRC: independent review committee; PR: partial response; ORR: overall response rate; umbra: umbralisib; U2: umbralisib + ublituximab; U2+B:umbralisib + ublituximab + bendamustine

Prevalence of Mutations & Response Rates

Pathway	Gene n (%)	Pooled N=156[a] Mutated	Pooled IRC-ORR[b]	Pooled by Pathway Mutated	Pooled by Pathway IRC-ORR[b]
NF-kappa B	MYD88	31 (20)	15 (48)	41 (26)	22 (54)
	TNFAIP3	14 (9)	9 (64)		
BCR	CD79A	4 (3)	1 (25)	33 (21)	13 (39)
	CD79B	19 (12)	9 (47)		
	SYK	4 (3)	2 (50)		
	BTK	7 (4)	2 (29)		
RAS/Raf	BRAF	3 (2)	2 (67)	5 (3)	3 (60)
	PTEN	1 (1)	1 (100)		
	KRAS	1 (1)	-		
	TP53	49 (31)	13 (27)		
	MYC	13 (8)	5 (38)		
	BCL2	6 (4)	1 (17)		
	BCL6	8 (5)	5 (63)		
	NOTCH1	7 (4)	4 (57)		
	CARD11	22 (14)	5 (23)		
	EZH2	15 (10)	4 (27)		
	PIM1	14 (9)	8 (57)		

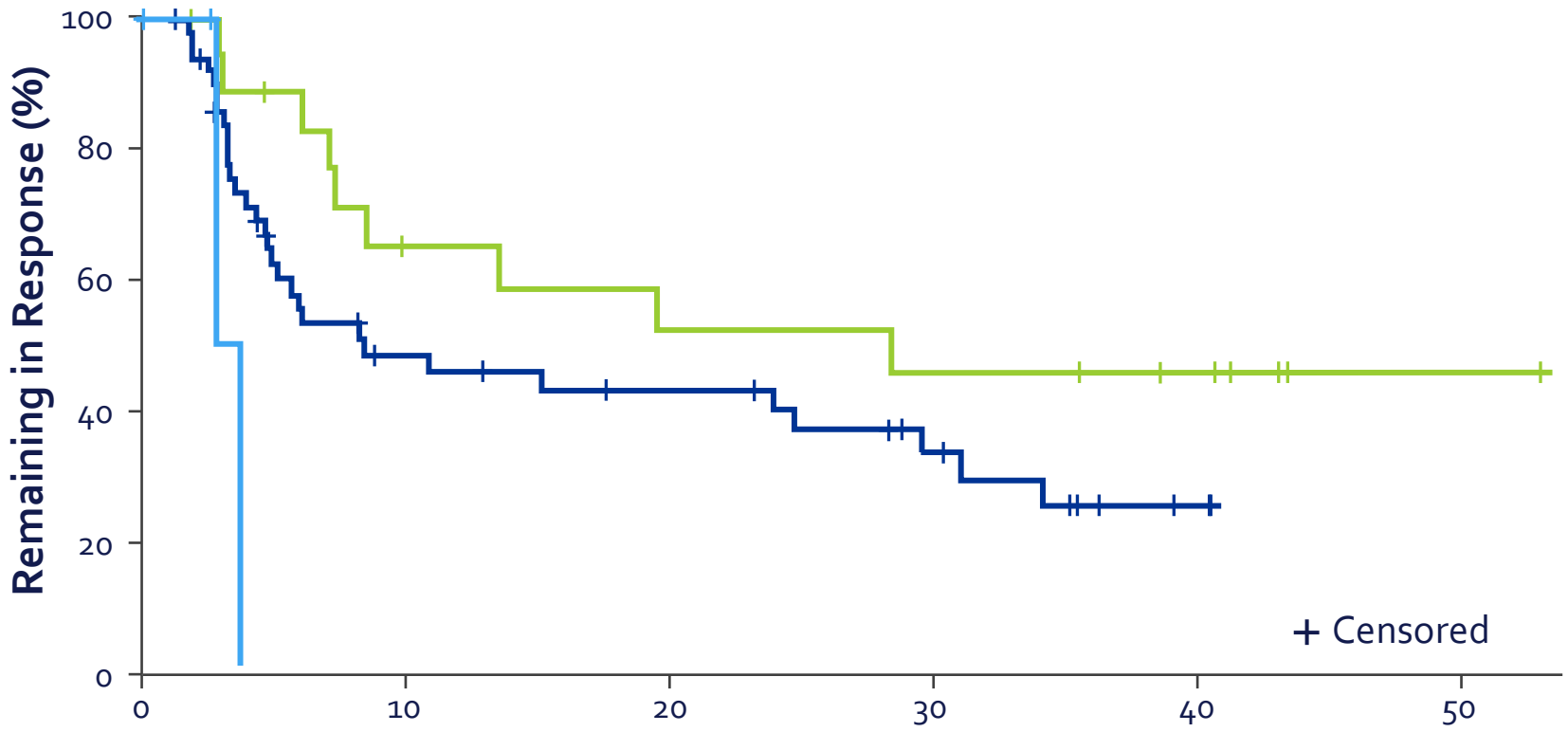
IRC-assessed ORR % (n/N)

	Umbra	U2	U2+B
c-Myc (8q24)			
Rearrangement	**33** (3/9)	**35** (11/31)	**43** (23/53)
Normal	-	**40** (8/20)	**45** (18/40)
t(8;14)			
Rearrangement	**20** (3/15)	**38** (14/37)	**40** (25/62)
Normal	-	**36** (5/14)	**50** (18/36)

- Among patients remaining progression-free at 30 months, 60% harbored NF-kappaB pathway mutations

[a]N represents number of patients that were tested with NGS panel. [b]Response percentages calculated as number of patients with respective mutation that achieved an IRC-response.
IRC: independent review committee; ORR: overall response rate; umbra: umbralisib; U2: umbralisib + ublituximab; U2+B: umbralisib + ublituximab + bendamustine

IRC-assessed Duration of Response



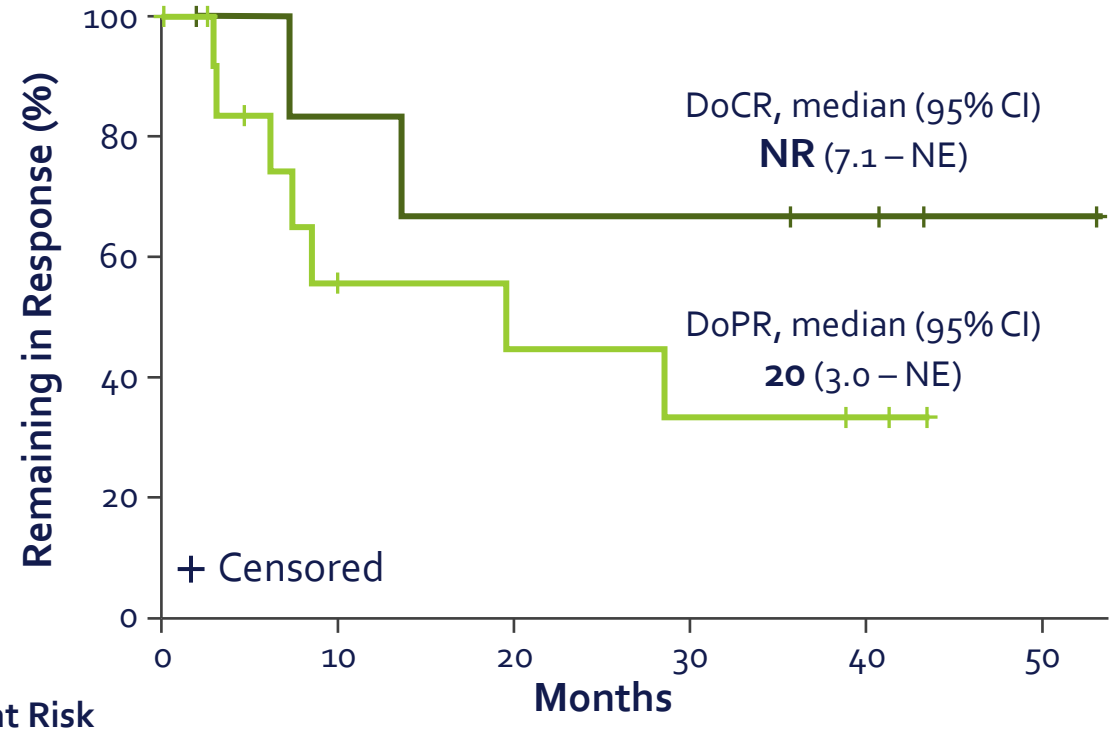
N at Risk						
Umbra	4	0				
U2	21	10	8	7	5	1
U2+B	56	19	15	9	2	0

Cohort	DOR, months Median (95% CI)
Umbra	3 (2.8 – NE)
U2	28 (7.1 – NE)
U2+B	8 (4.7 – 29.6)

CI: confidence interval; DOR: duration of response; IRC: independent review committee; NE: not estimable; umbra: umbralisib; U2: ublituximab + umbralisib; U2+B umbralisib + ublituximab + bendamustine

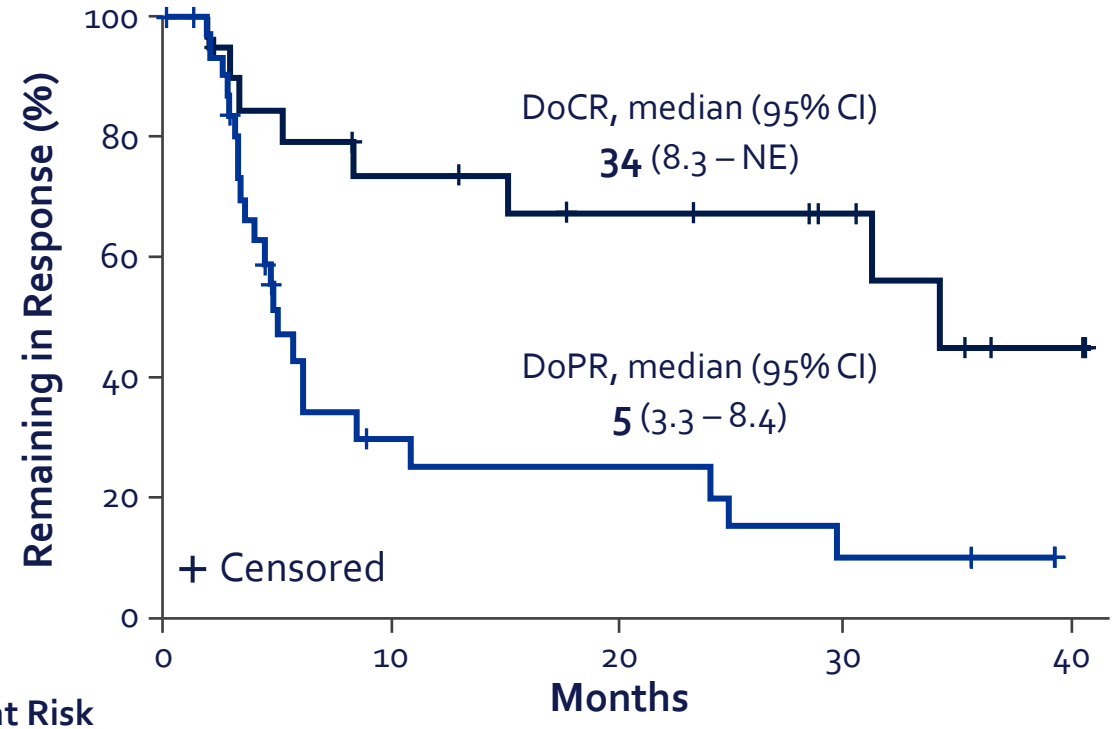
IRC-assessed DOR by Depth of Response

U2



N at Risk						
CR	7	5	4	4	3	1
PR	14	5	4	3	2	0

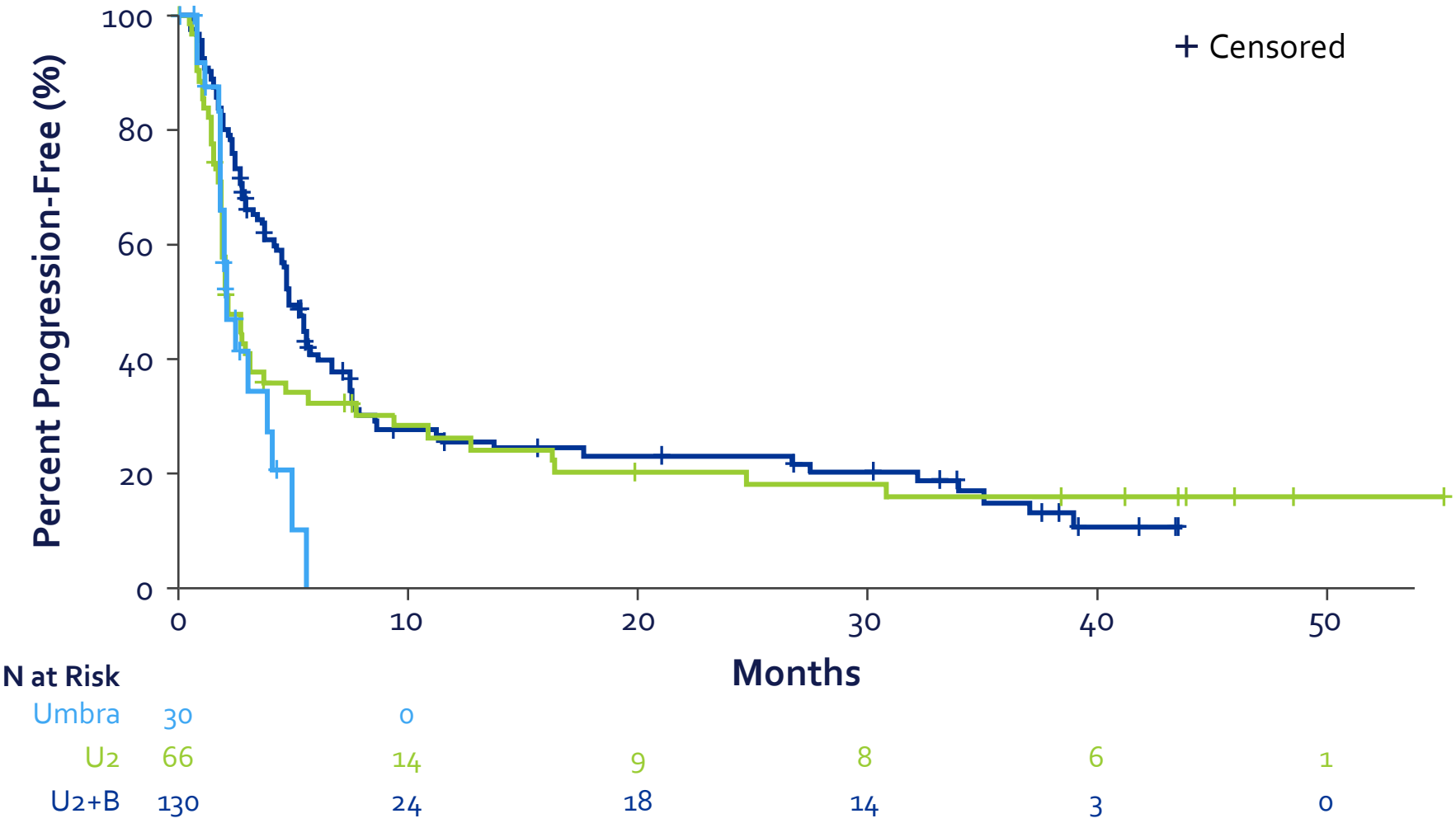
U2+B



N at Risk					
CR	22	13	10	7	2
PR	34	6	5	2	0

CI: confidence interval; DoCR: duration of complete response; DoPR: duration of partial response; DOR: duration of response; IRC: independent review committee; NE: not estimable, NR: not reached, U2: ublituximab + umbralisib, U2+B: umbralisib + ublituximab + bendamustine

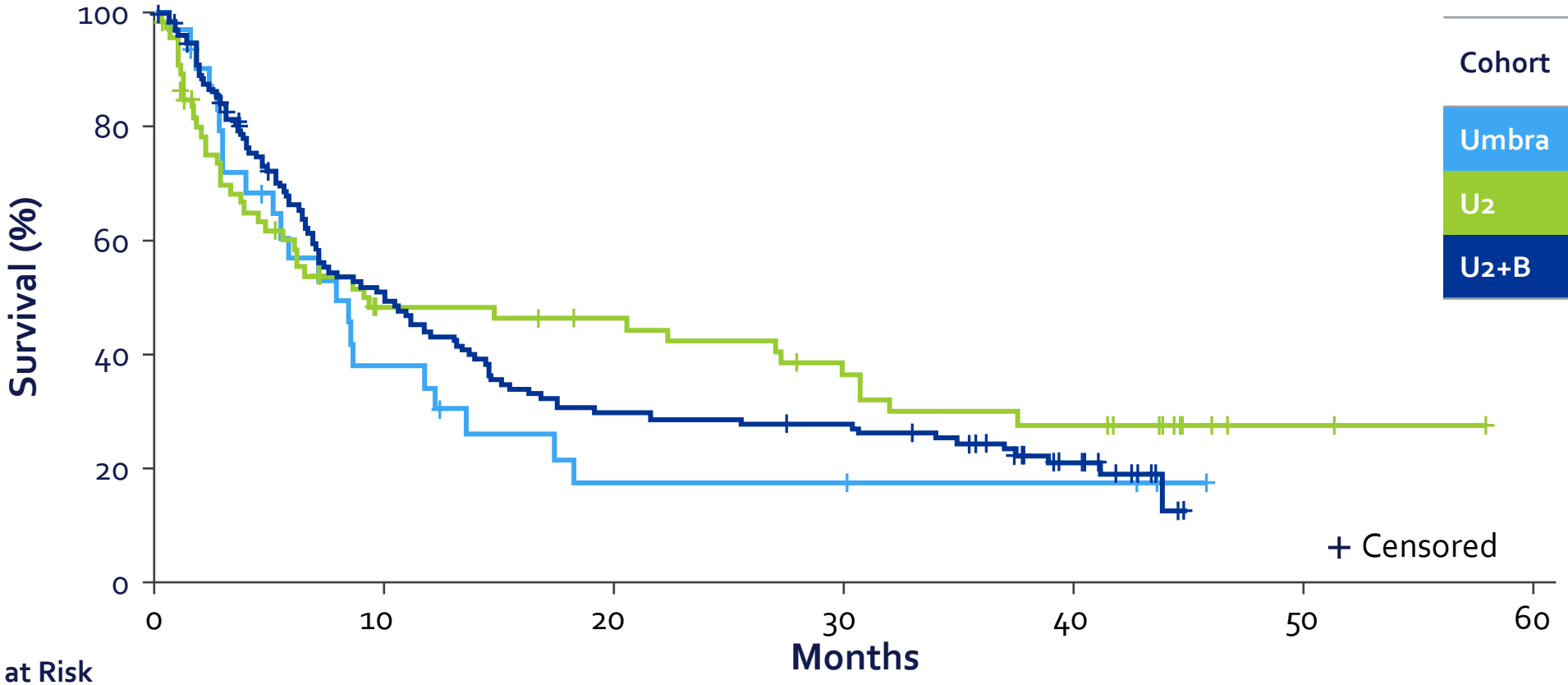
IRC-assessed Progression-free Survival



Cohort	PFS, month Median (95% CI)
Umbra	2 (1.8 – 3.8)
U2	2 (1.9 – 3.1)
U2+B	5 (4.2 – 5.7)

CI: confidence interval; IRC: independent review committee; PFS: progression-free survival; umbra: umbralisib; U2: ublituximab + umbralisib; U2+B: umbralisib + ublituximab + bendamustine

Overall Survival



Cohort	OS, months Median (95% CI)
Umbra	8 (4.0 – 12.3)
U2	9 (4.8 – 29.9)
U2+B	10 (7.0 –13.4)

N at Risk						
Umbra	30	10	4	4	3	0
U2	66	26	23	17	13	2	0
U2+B	130	60	35	32	14	0

CI: confidence interval; IRC: independent review committee; NE: not estimable; OS: overall survival; umbra: umbralisib; U2: ublituximab + umbralisib; U2+B umbralisib + ublituximab + bendamustine

Conclusions

- In patients with R/R DLBCL ineligible for transplant:
  - Single-agent umbralisib produced an ORR of 13% and CRR of 3%
  - Doublet of umbralisib + ublituximab improved ORR to 32% and CRR to 11%.
    - Median DOR was 28 months
  - Triplet of U2 + bendamustine improved ORR to 43% and CRR 17%

- Both U2 and U2 + bendamustine demonstrated activity and a manageable safety profile in patients with R/R DLBCL

- Further development plans are under discussion