

Mantle cell lymphoma with poor prognosis (blastoid morphology, p53 mutation, high proliferation index): How can we exploit target therapies (BKTi, BCL2i, T-cell-engagers)?

CARLO VISCO



UNIVERSITÀ
di **VERONA**



ROMA
HEMATOLOGY
CONFERENCE
the lymphomas

Rome

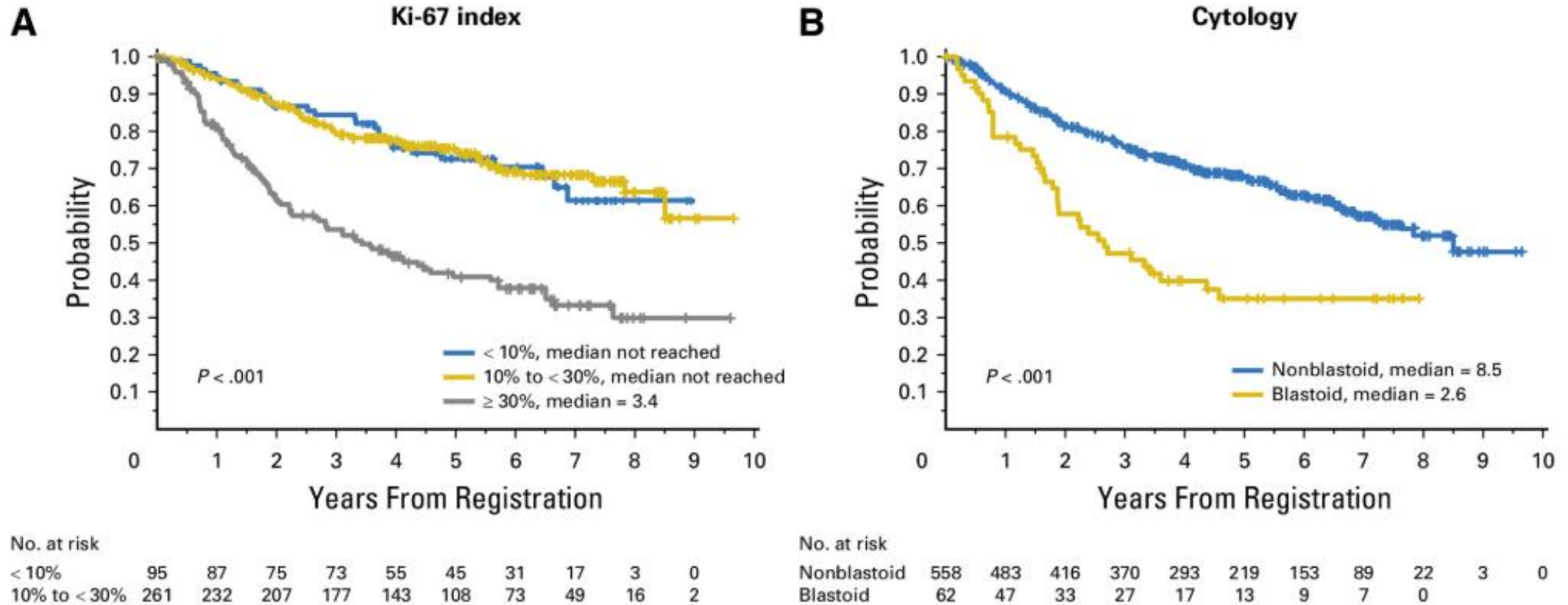
October 15-16, 2026

Hotel nhow Roma

Disclosure: Carlo Visco

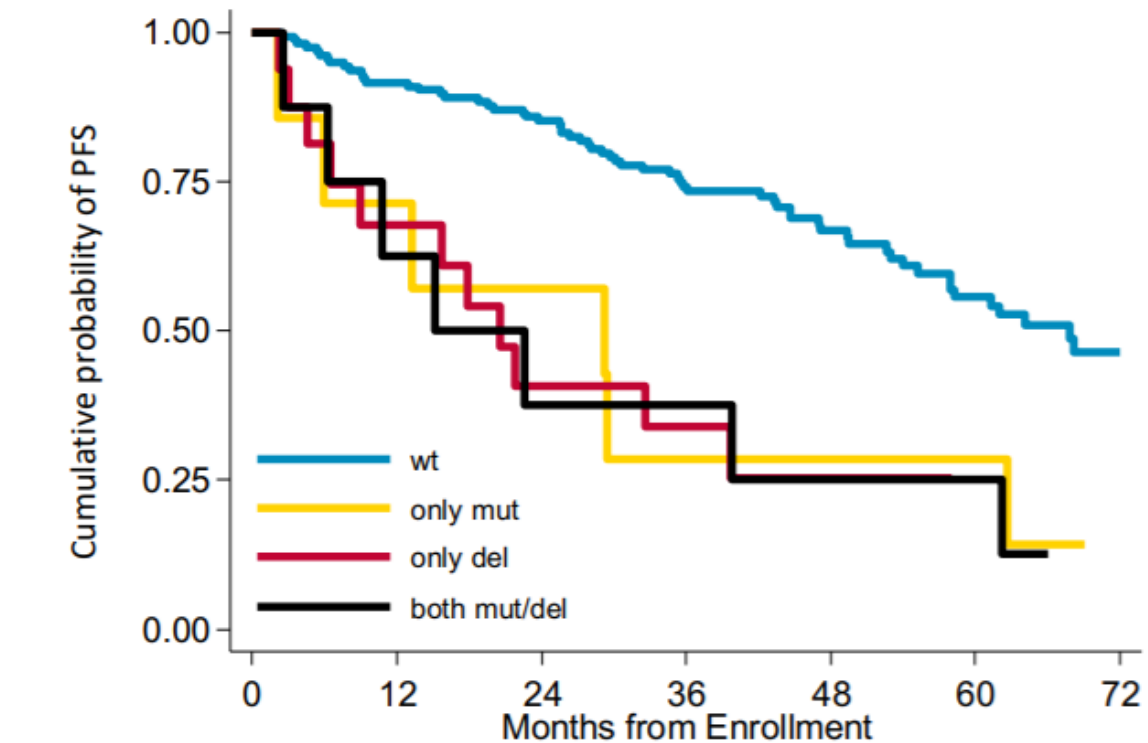
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X				X	X	
Kite-Gilead					X	X	
Janssen	X		X		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			X		X	X	
Roche					X	X	
Incyte					X	X	
Servier					X		
Astra Zeneca					X		
BMS						X	
Kyowa Kirin					X		
Beigene					X		
Lilly			X		X	X	

Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in MCL: Results From Randomized Trials of the EMCLN



Hoster E et al, JCO 2016

TP53 disruptions (and KMT2D mutations) are poor prognostic biomarkers with ASCT



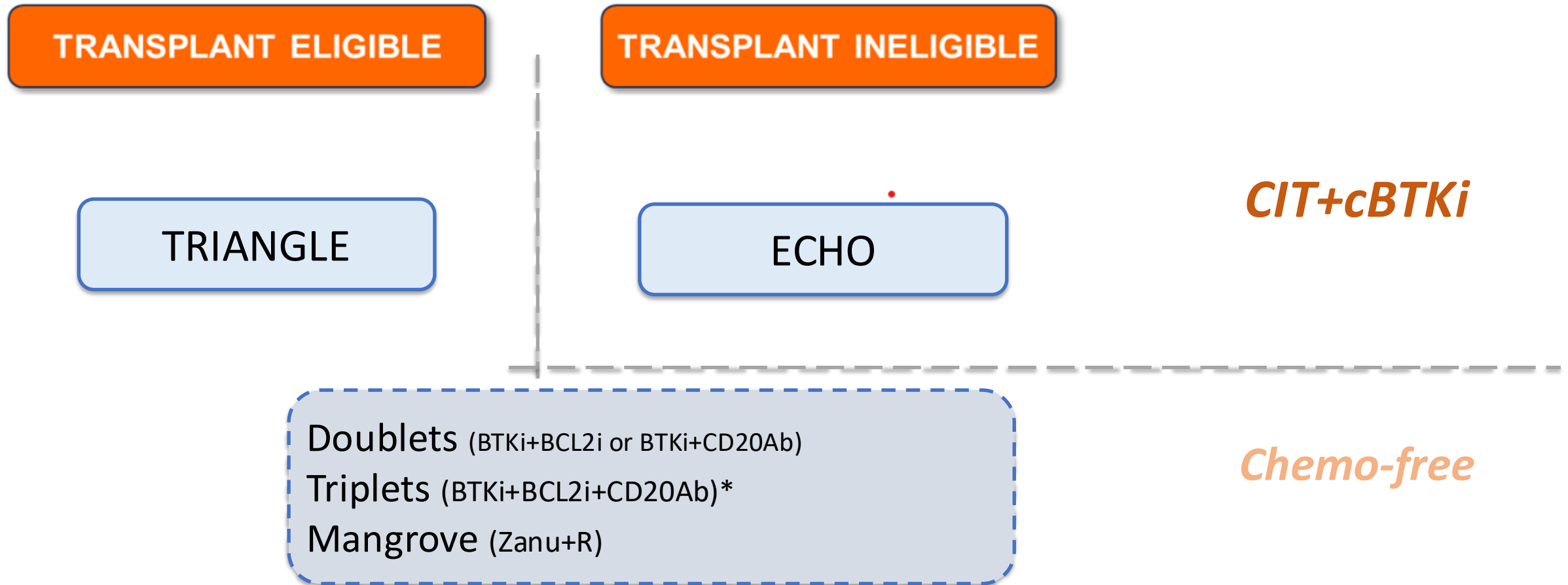
At risk:

wt	155	142	130	98	64	38	16
only mut	7	5	4	2	2	2	0
only del	16	10	6	4	1	0	0
both mut/del	8	5	3	3	2	2	0

P53 mutations 8%
P53 deletions 13%
KMT2D mut/del 14%

Ferrero S et al, Haematologica 2019

Evolving MCL treatment: first line

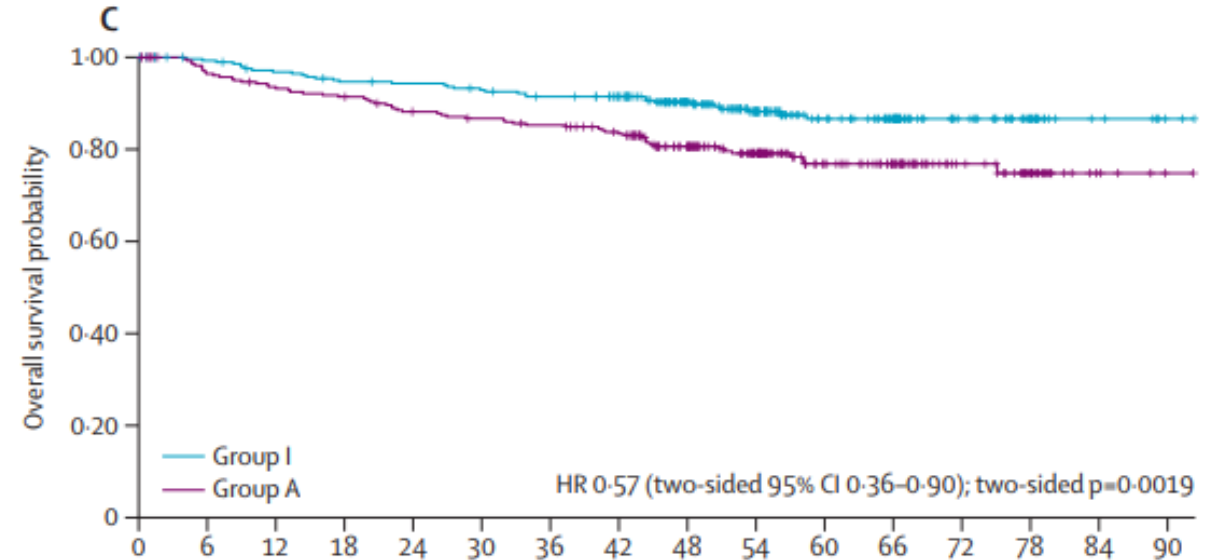
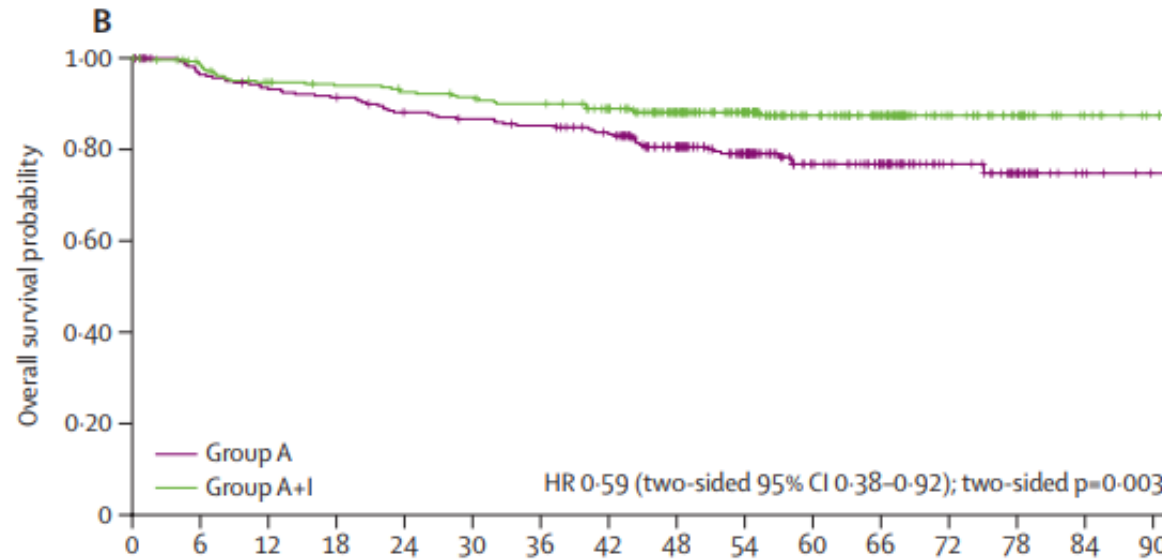


*recently incorporated by NCCN Guidelines for TP53 disrupted disease

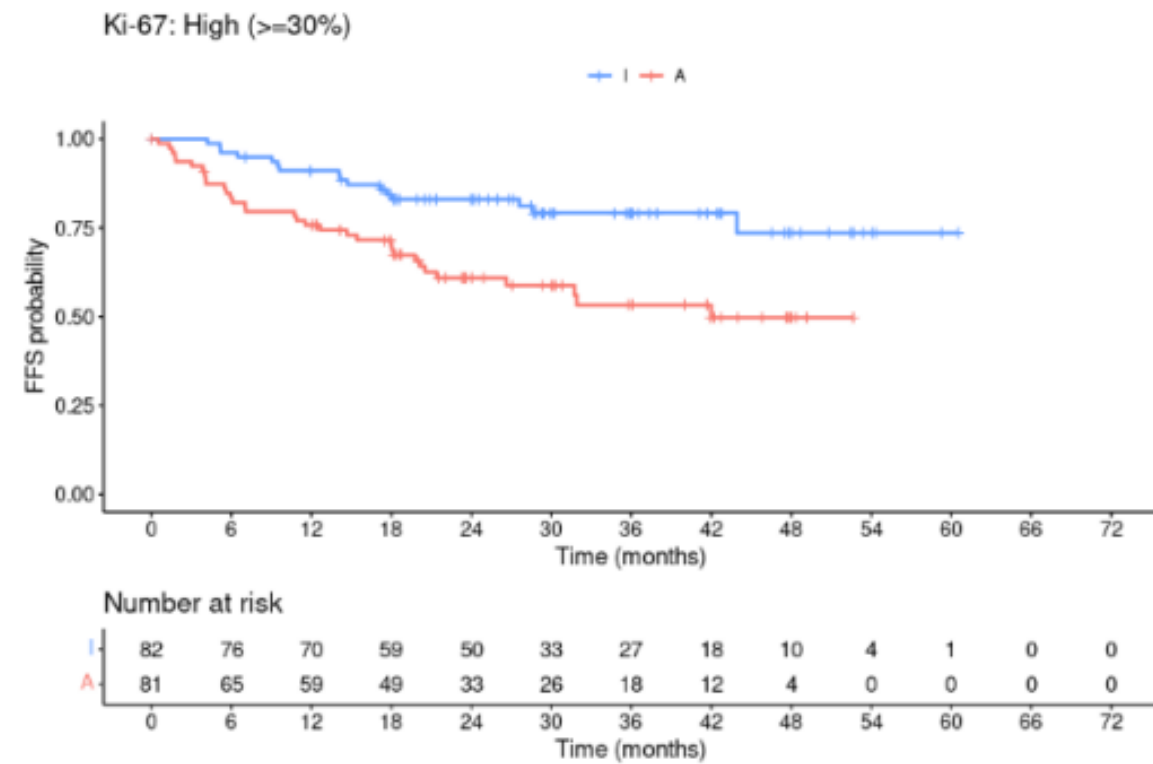
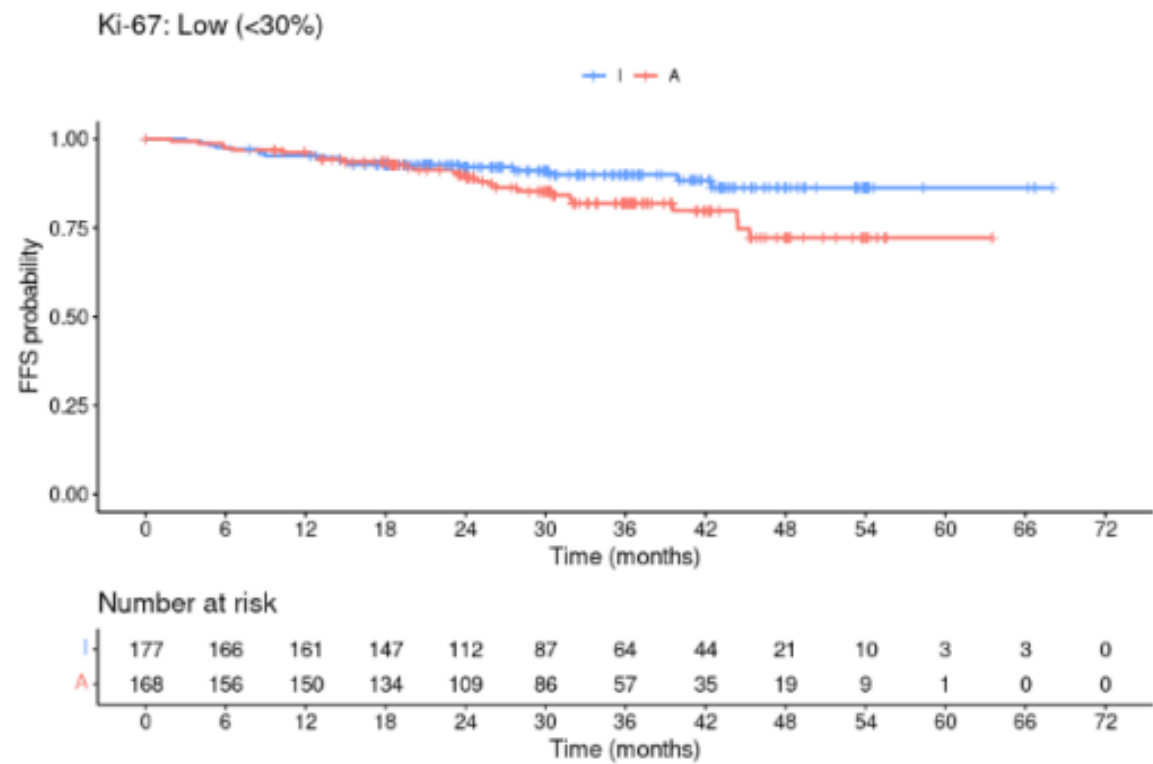
Addition of autologous stem-cell transplantation to an ibrutinib-containing first-line treatment in patients aged 18–65 years with mantle cell lymphoma (TRIANGLE): 4.5-year follow-up of a three-arm, randomised, open-label, phase 3 superiority trial of the European MCL Network

Martin Dreyling, Jeanette Doorduijn, Eva Giné, Mats Jerkeman, Jan Walewski, Martin Hutchings, Ulrich Mey, Jon Riise, Marek Trneny, Vibeke K J Vergote, Ofer Shpilberg, Maria Gomes da Silva, Sirpa Leppä, Linmiao Jiang, Stephan Stilgenbauer, Andrea Kerkhoff, Ron D Jachimowicz, Georg Heß, Tom van Meerten, Stefan Wirths, Peter Herhaus, Urban Novak, Judith Dierlamm, Mathias Hänel, Christine Hanoun, Kristina Sonnev, Carlo Visco, Daniela Donnarumma, Andrés J M Ferreri, Caterina Patti, Piero Maria Stefani, Christiane Pott, Wolfram Klapper, Christian Schmidt, Michael Unterhalt, Tobias Tix, Marco Ladetto*, Eva Hoster*, on behalf of the European Mantle Cell Lymphoma Network

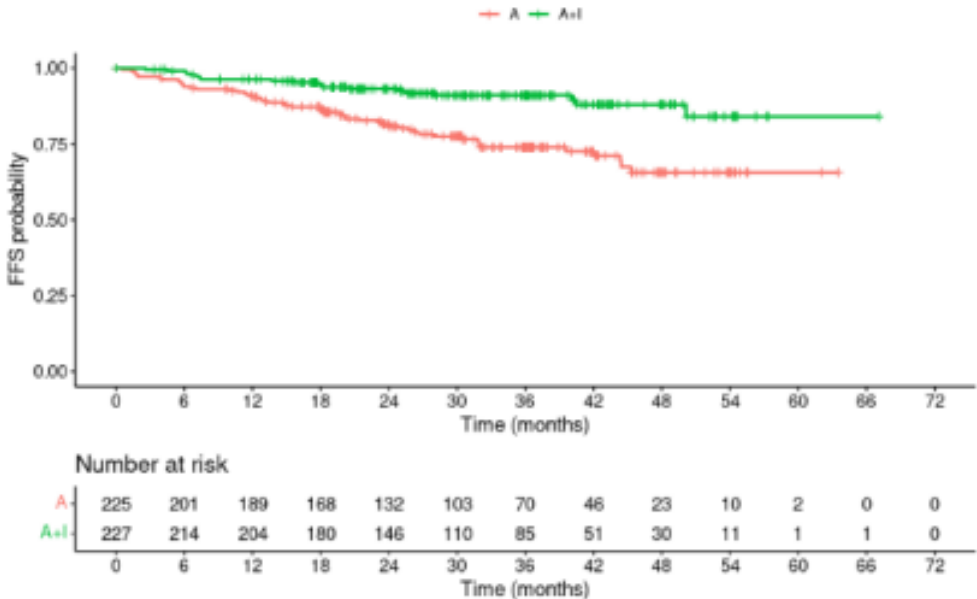
The Lancet, 2026



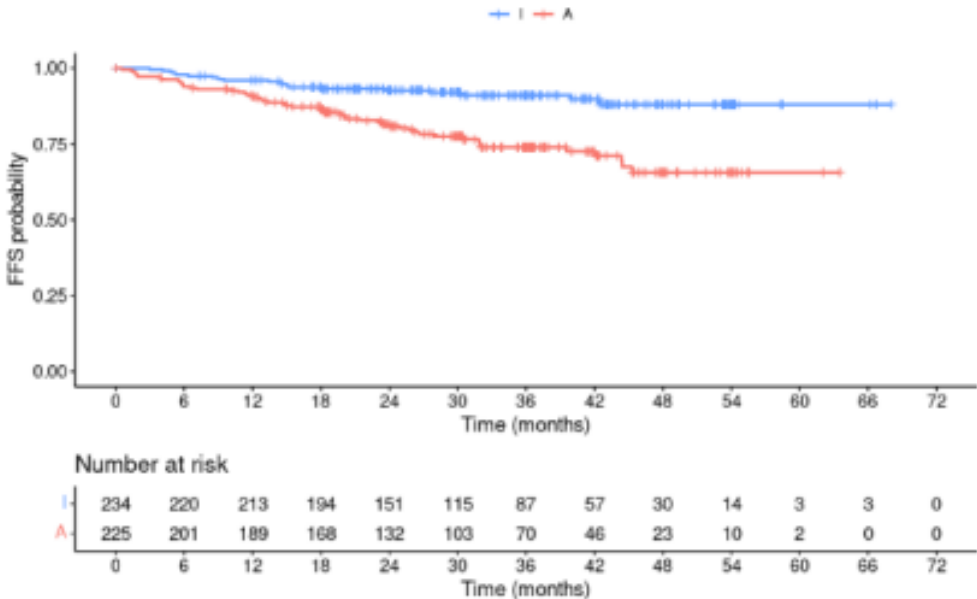
The introduction of cBTKi upfront improves the outcome of highly proliferative tumors



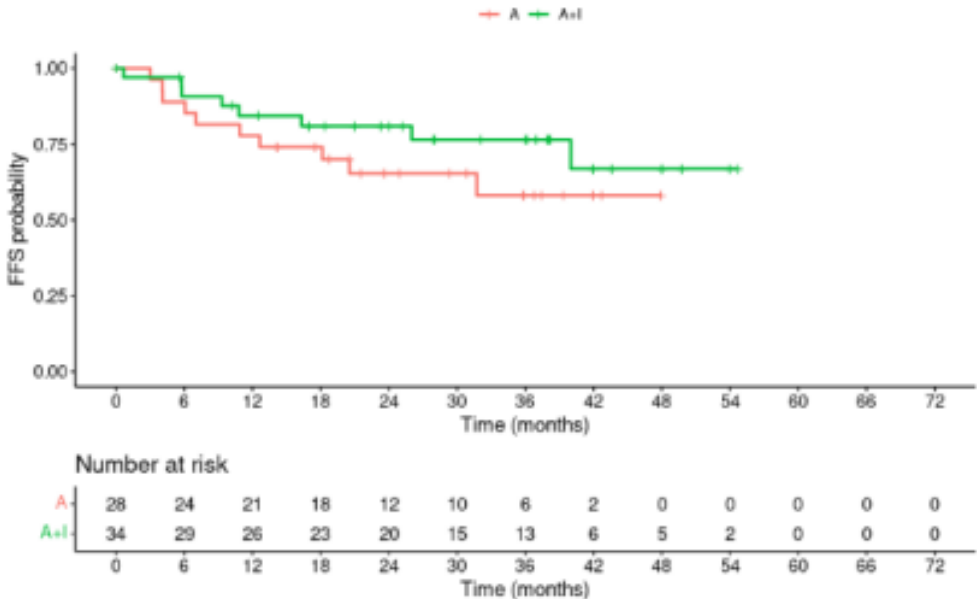
Cytology: Non-blastoid



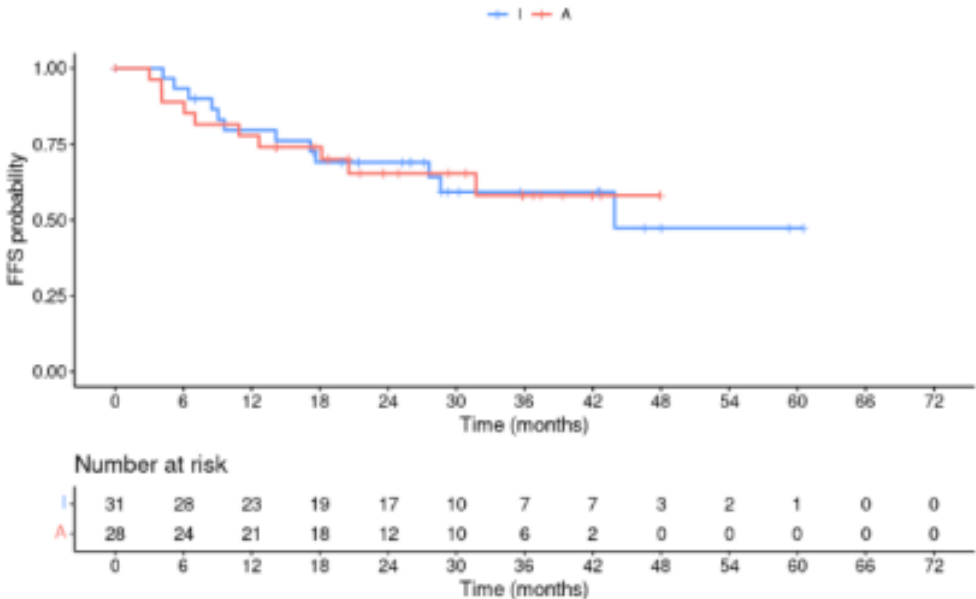
Cytology: Non-blastoid



Cytology: Blastoid

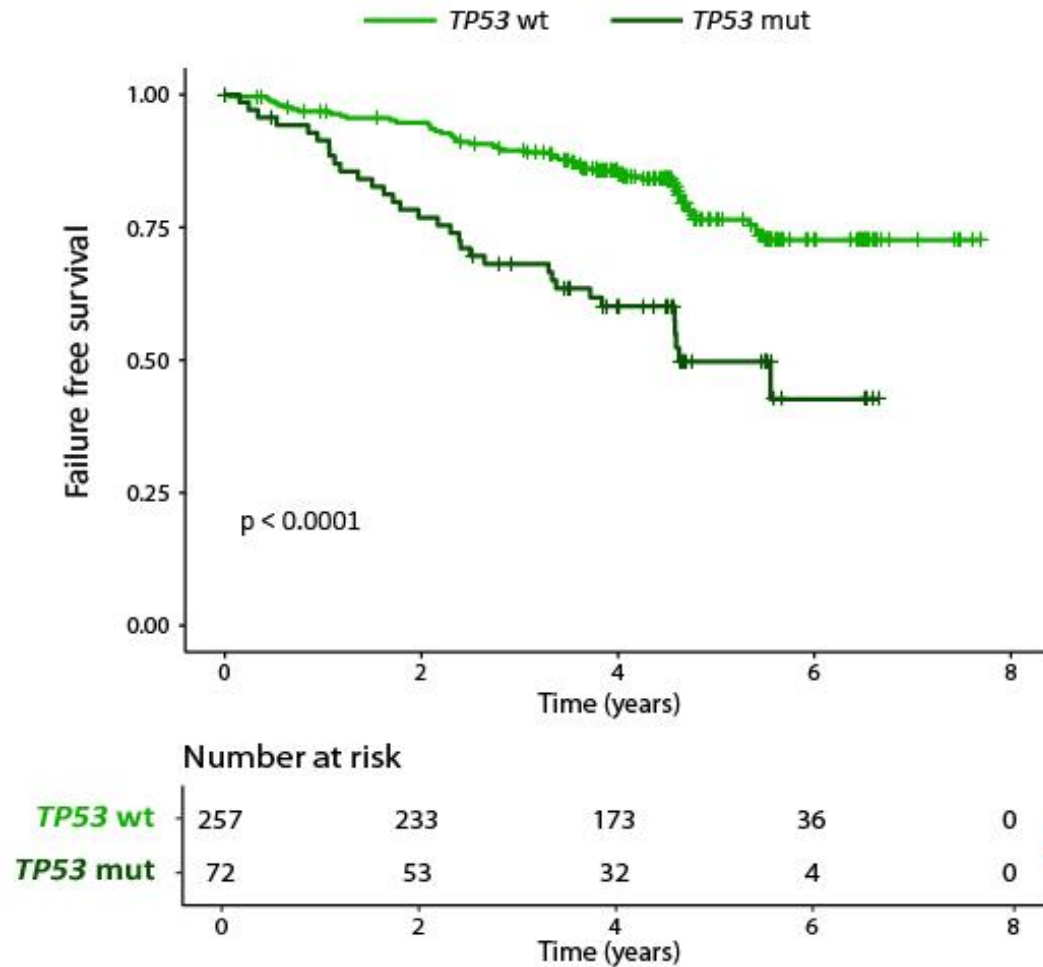


Cytology: Blastoid

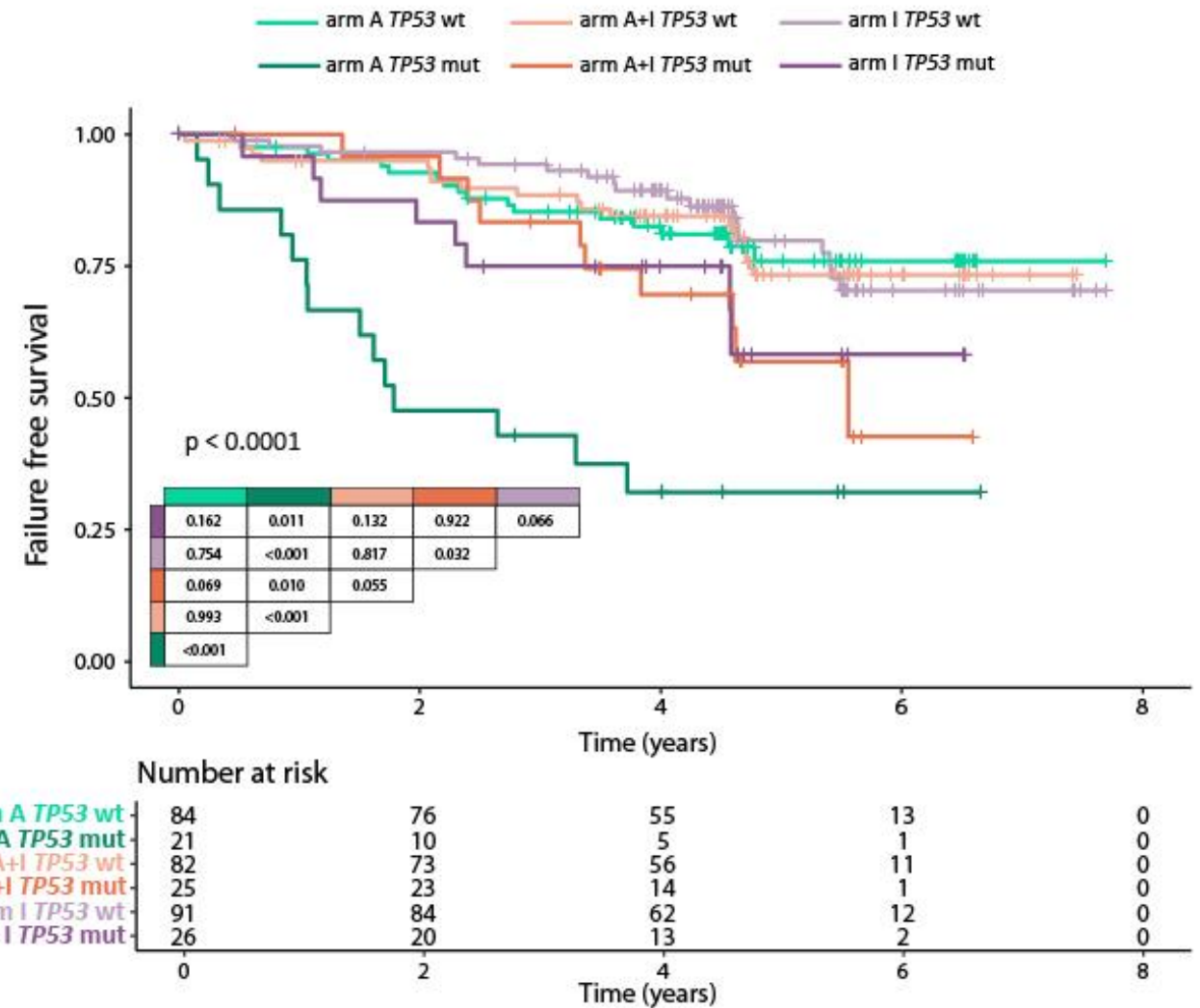


TP53 mutation (first analysis on TRIANGLE at EHA2026)

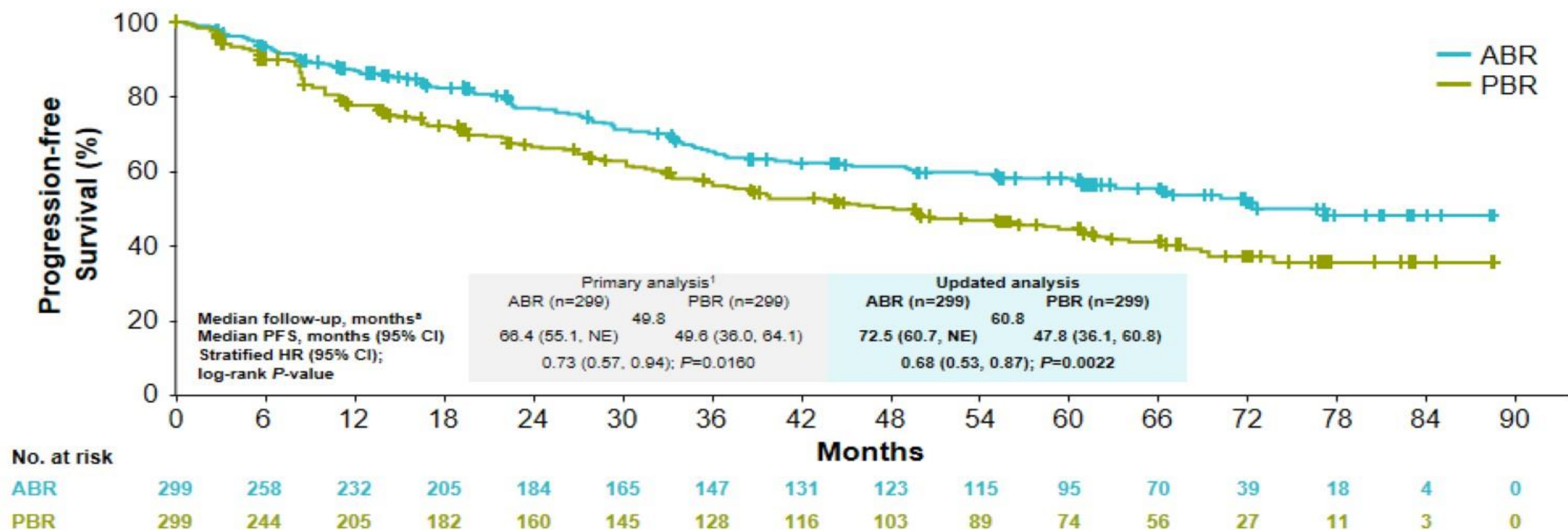
A.



B.



At 60.8 Months of Follow-up, PFS Further Improved With ABR vs PBR



- PFS risk reduction with ABR vs PBR increased from 27% (primary analysis) to 32% (updated analysis)
- Median PFS was longer with ABR vs PBR (6 years vs 4 years)

^aMedian follow up for PFS estimated using the reverse K-M method.

ABR, acalabrutinib plus bendamustine-rituximab; CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; NE, not estimable; PBR, placebo plus bendamustine-rituximab;

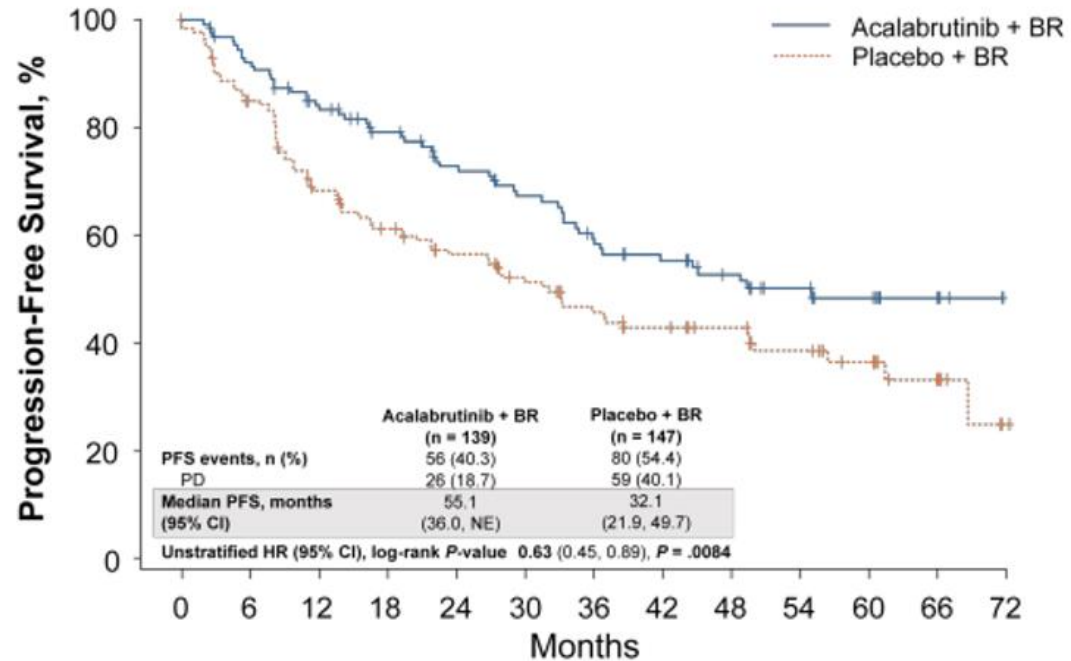
PFS, progression-free survival.

1. Wang M, et al. *J Clin Oncol*. 2025;43:2276-84.



ABR improved survival in patients with high-risk MCL compared with PBR

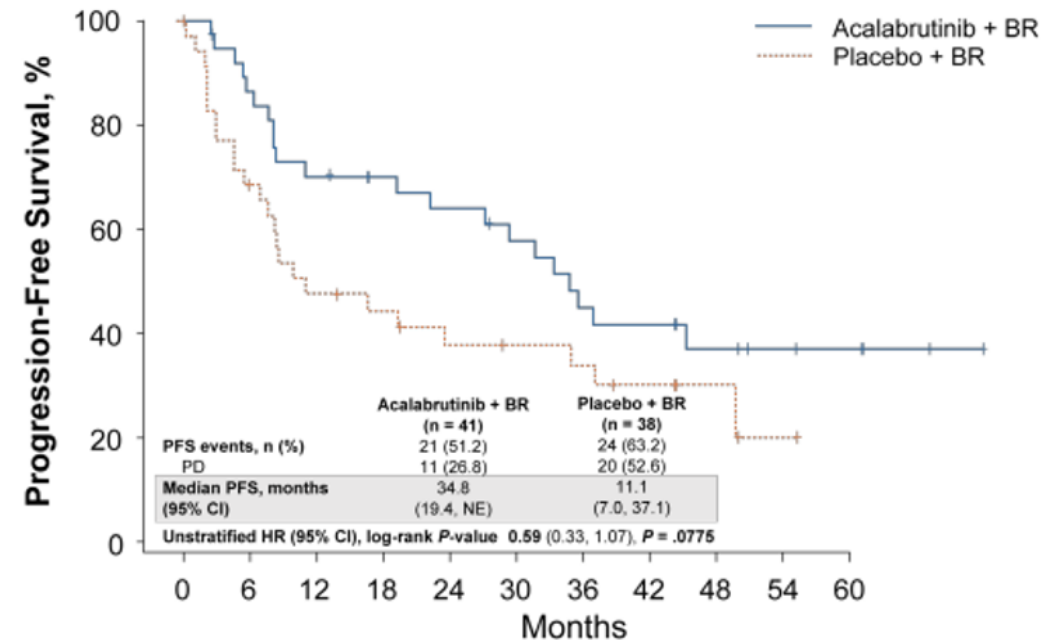
PFS in Patients With Ki-67 Index $\geq 30\%$



Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72
Acalabrutinib + BR	139	117	103	91	80	69	61	53	40	30	22	15	0
Placebo + BR	147	117	91	78	68	60	48	40	33	24	17	9	1

PFS in Patients With Blastoid/Pleomorphic Histology

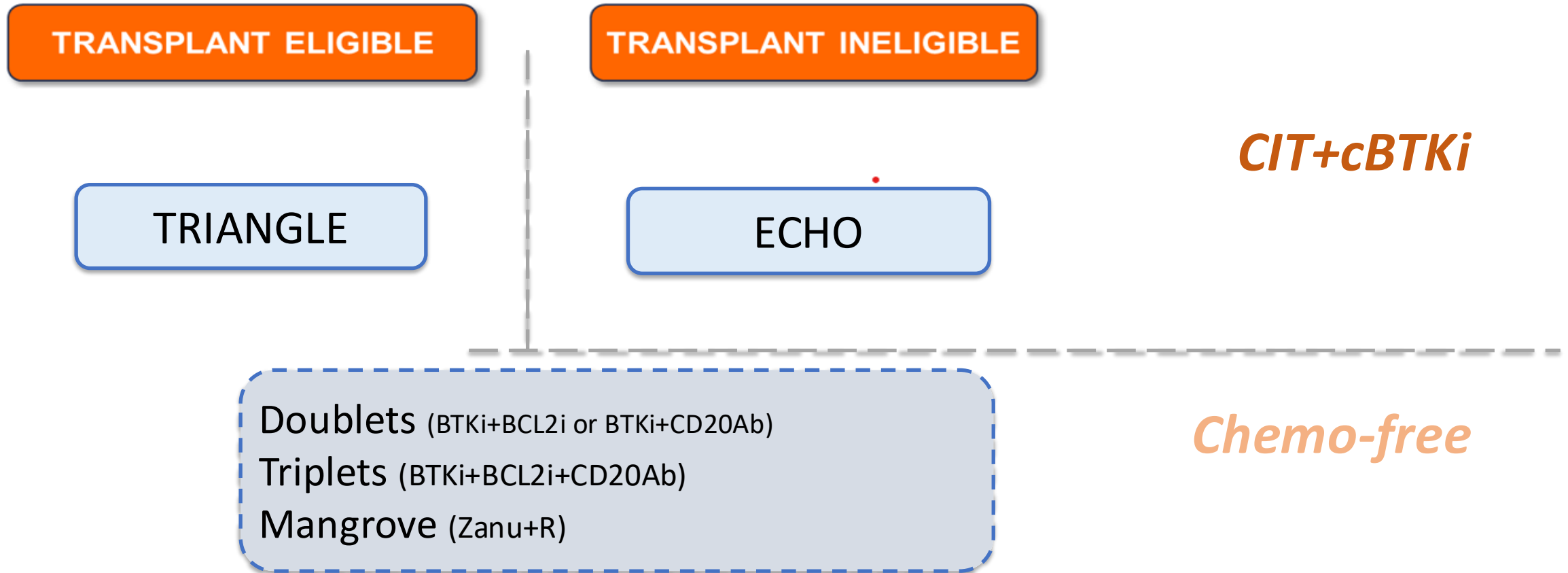


Number at risk

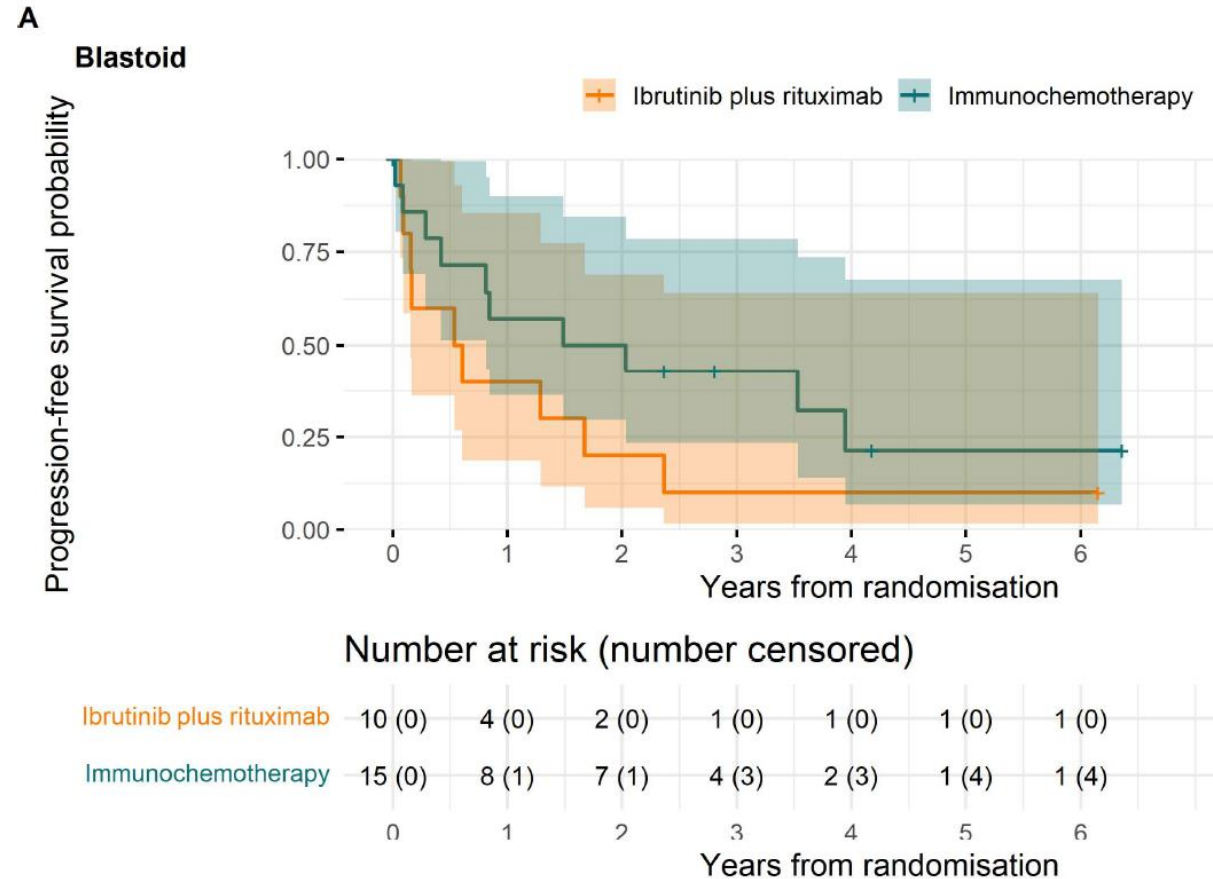
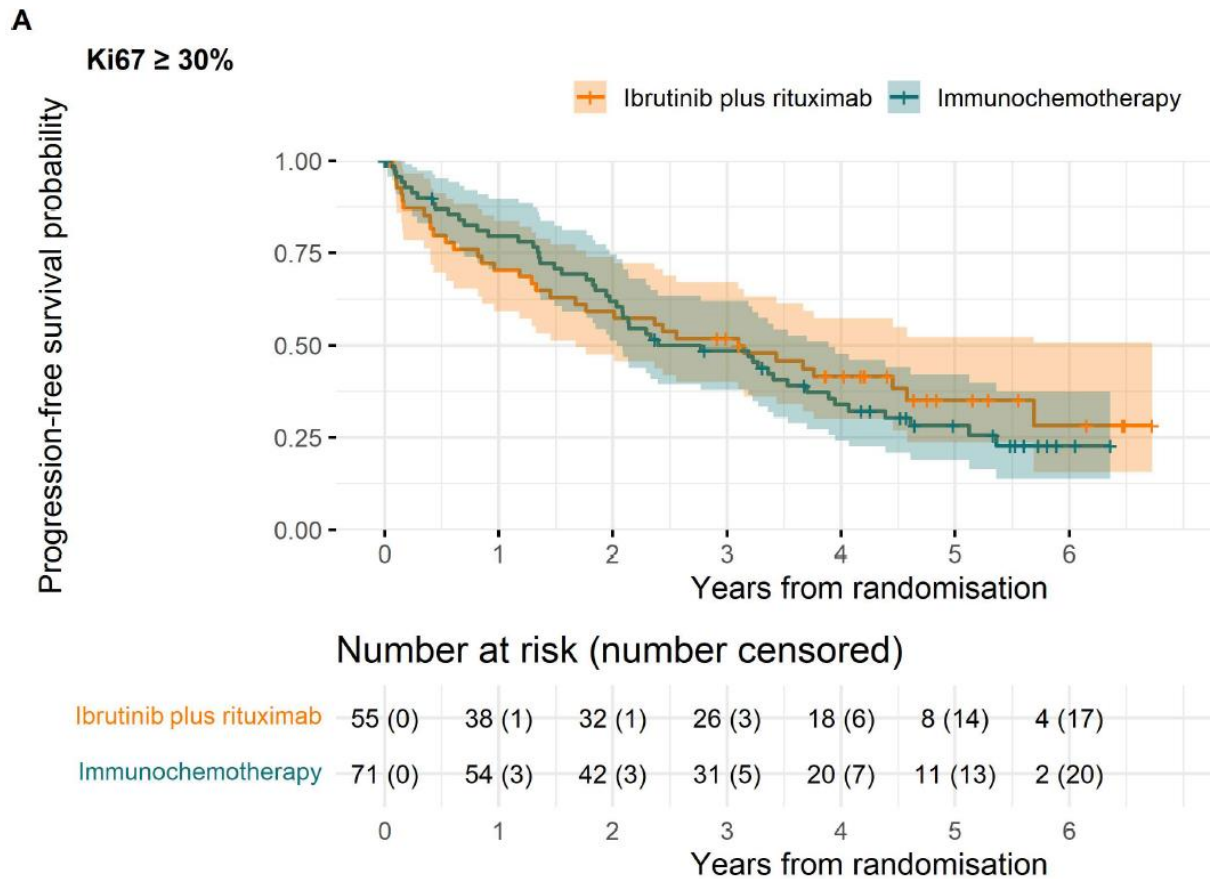
	0	6	12	18	24	30	36	42	48	54	60
Acalabrutinib + BR	41	32	26	23	21	18	14	13	8	6	5
Placebo + BR	38	23	16	14	11	10	9	6	3	1	0

Dreyling M et al, EHA 2025

Evolving MCL treatment: first line



Ibrutinib + Rituximab vs R-Chemo: ENRICH Subgroup Results



Lewis D et al, Lancet 2025

ALTAMIRA Results by Risk Category

A phase 2, single-arm study of **acalabrutinib + R**

Risk Groups

Low Risk

n=51 (63%)

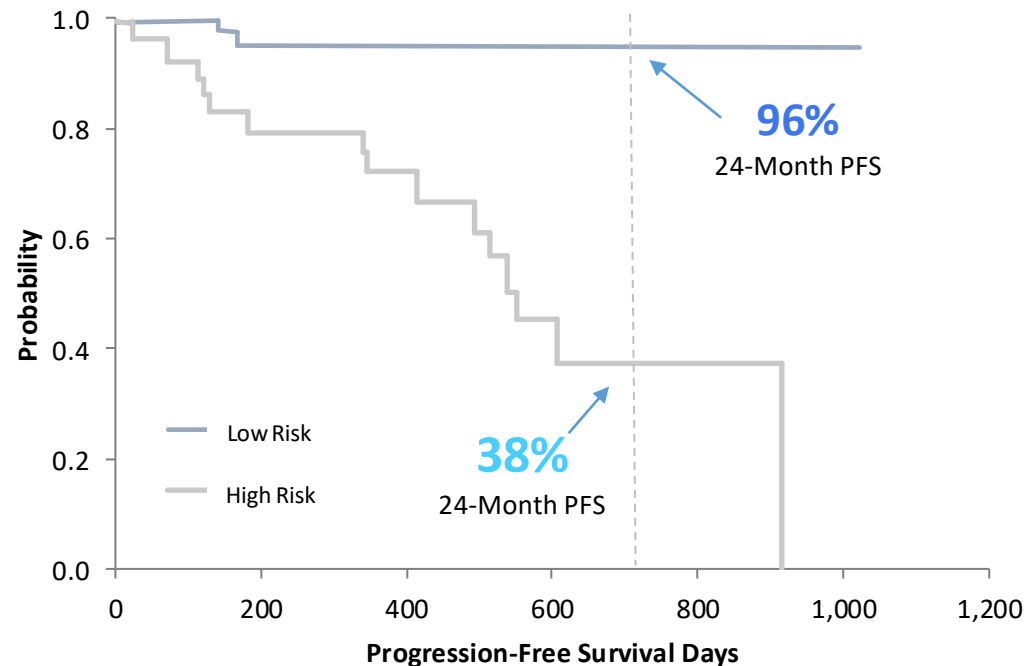
- TP53-wild type
- Classical histology
- Ki67 $\leq 30\%$
- → stop acalabrutinib when MRD negative (after minimum 1 year)

High Risk

N=30 (37%)

- TP53-mutation
- Blastoid histology
- Ki67 $>30\%$
- → treatment until progression

Progression-Free Survival



The two events in Low Risk included:



1 AE of cardiac failure



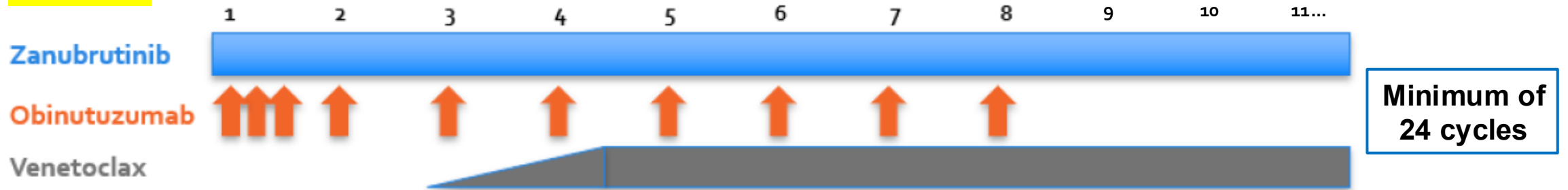
1 AE of aplastic anemia

Jerkeman M, et al. ASH 2024

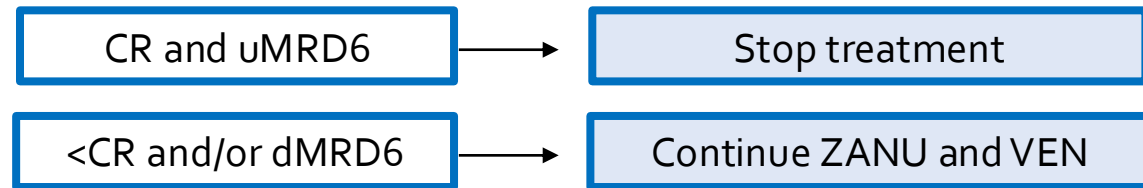
Triplets upfront in MCL

BOVEN

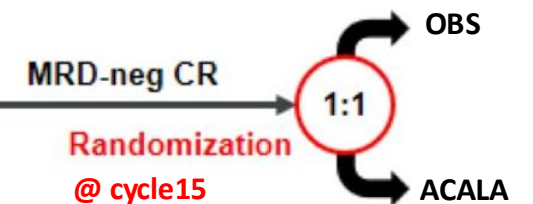
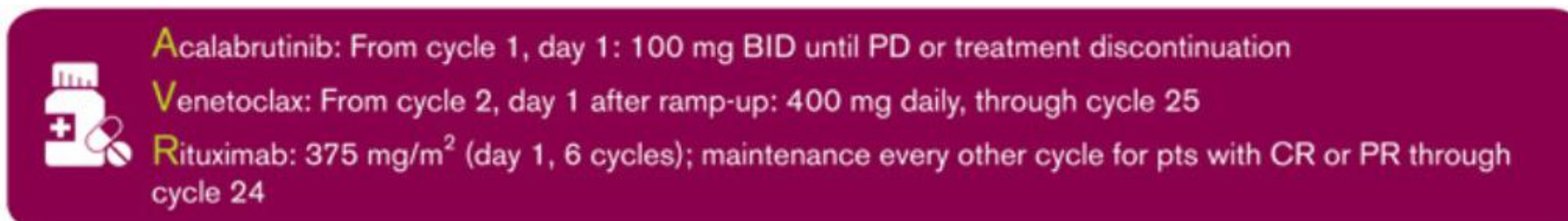
Age 47-89



After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:



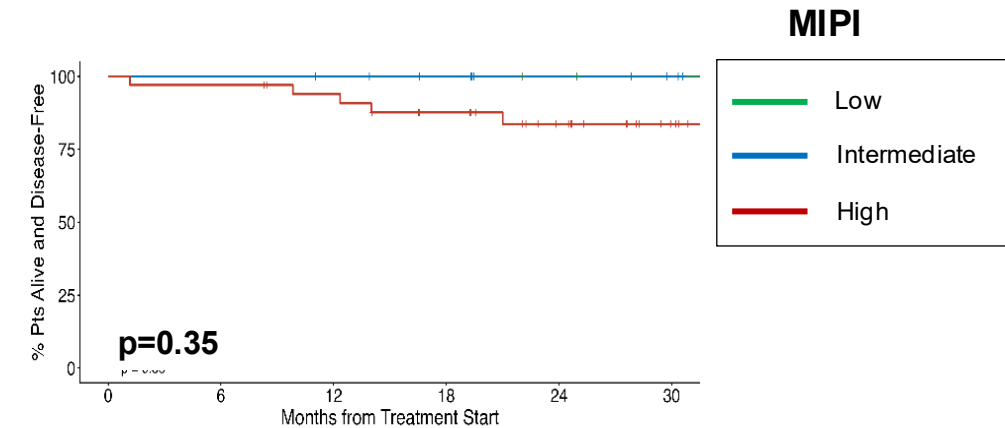
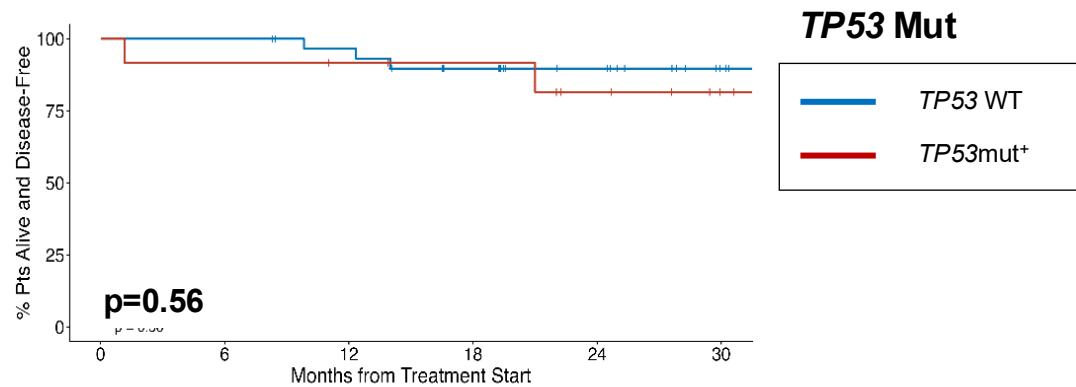
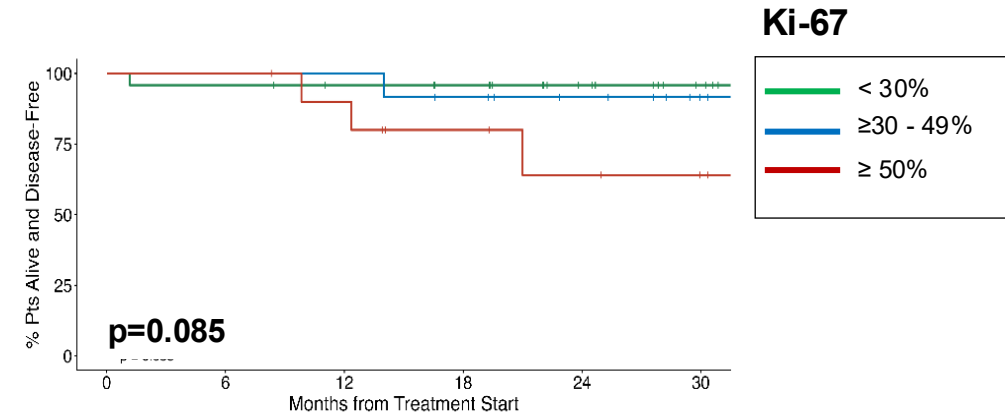
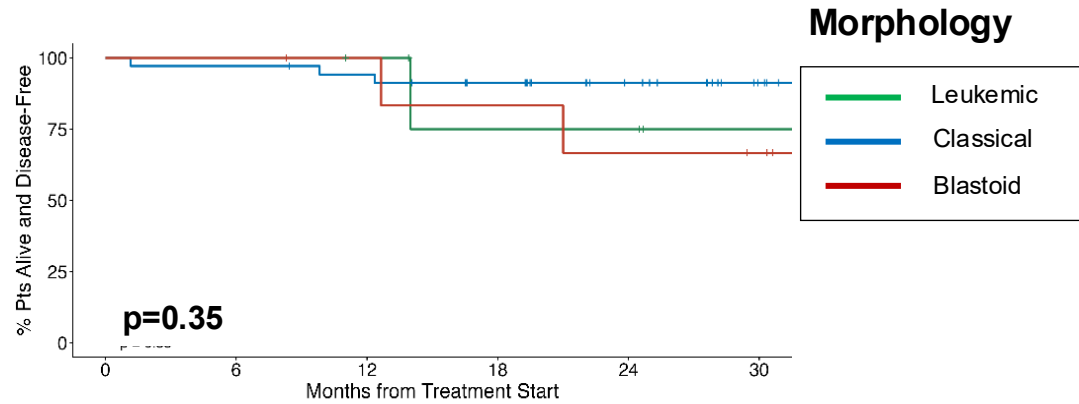
TRAVERSE



Age 40-89

PFS by risk factors, n=50

BOVEN [Zanu-Ven-Ob]



Kumar A et al, ASH 2025



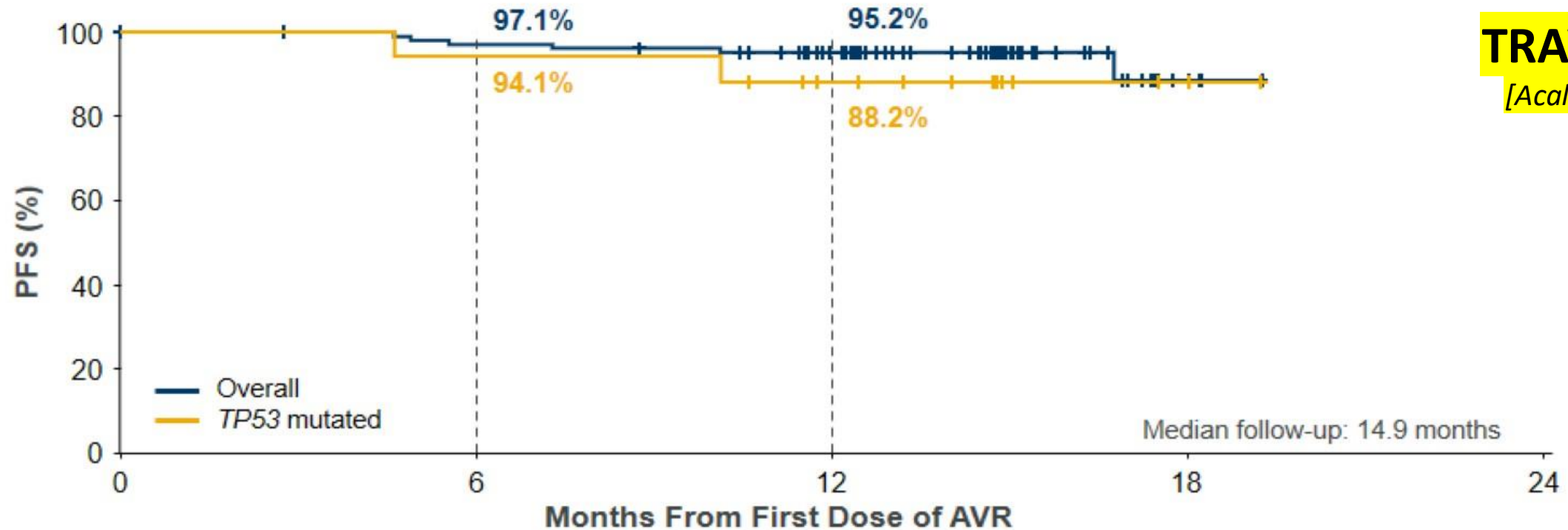
ROMA HEMATOLOGY
CONFERENCE

the lymphomas

Rome Hotel nhow Roma
October 15-16, 2026

Progression-free Survival

PFS rates were high, regardless of TP53 mutation status



TRAVERSE

[Acala-Ven-R]

No. at risk	
Overall	108
TP53 mutated	17

102
16

90
12

3
2

0
0

11 PFS, progression-free survival.

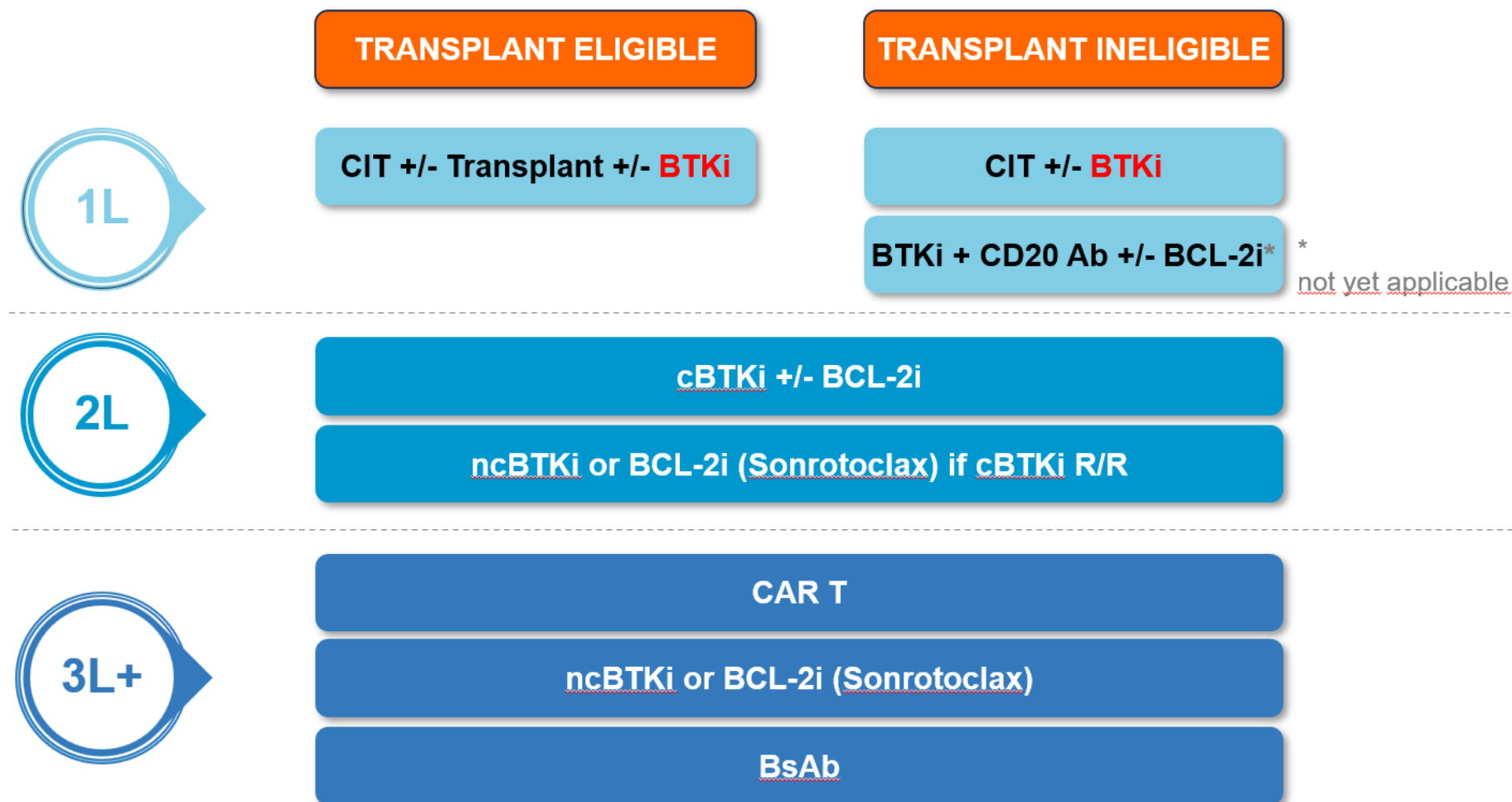


ROMA HEMATOLOGY
CONFERENCE

the lymphomas

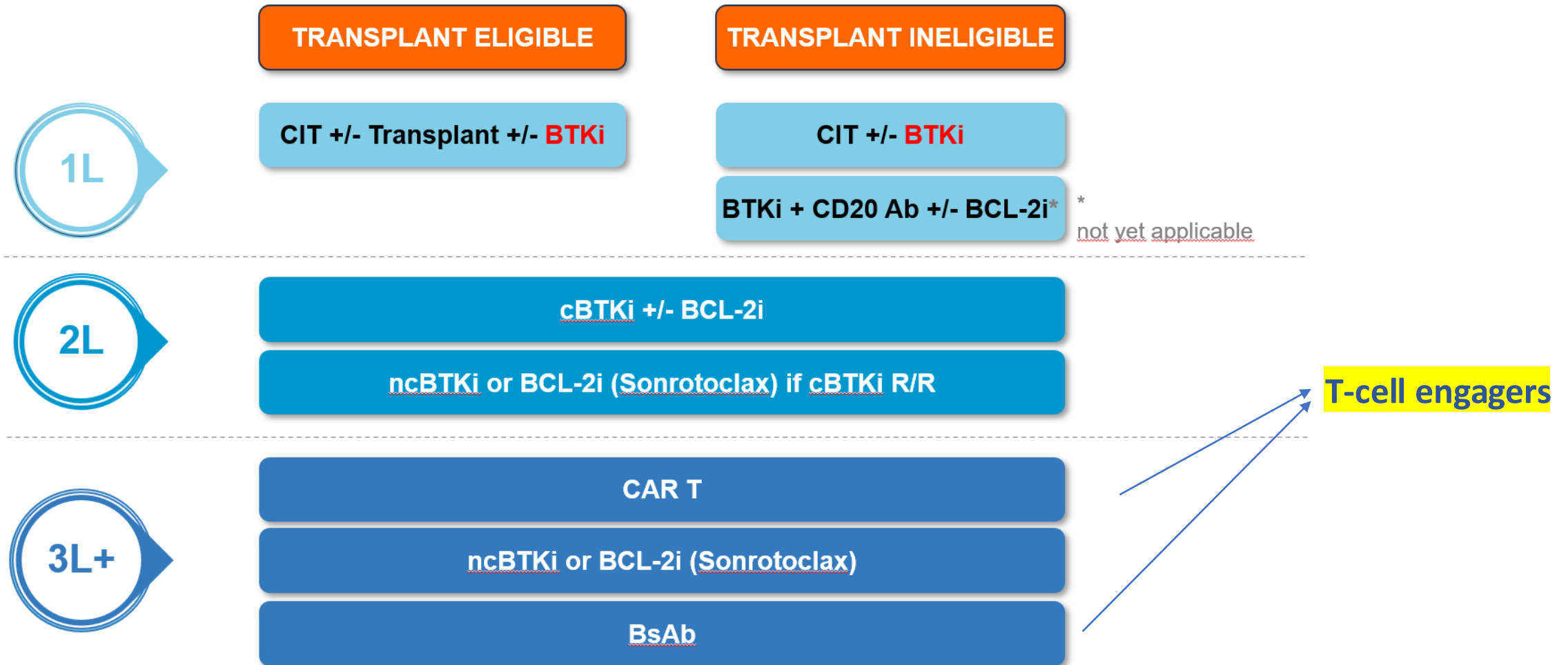
Rome Hotel nhow Roma
October 15-16, 2026

Evolving MCL Treatment Algorithm



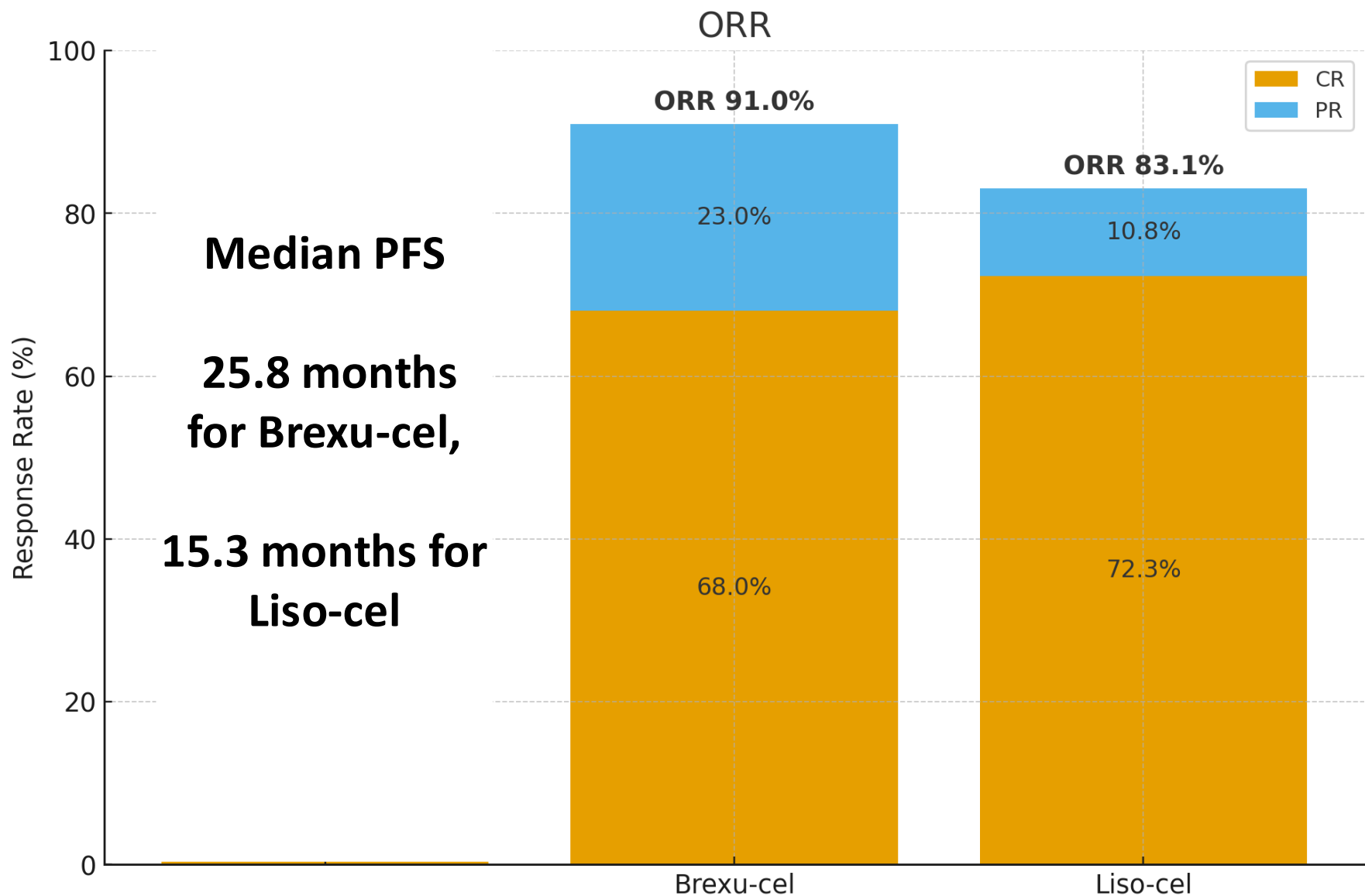
1L/2L/3L=First/Second/Third Line (of therapy). Ab=Antibody. BCL-2i=BCL-2 Inhibitor. BsAb=Bispecific Ab. CAR T=Chimeric Antigen Receptor T-cell Therapy. CIT=Chemoimmunotherapy. c/ncBTKi=Covalent/Non-Covalent BTK Inhibitor. MCL=Mantle Cell Lymphoma

Evolving MCL Treatment Algorithm



1L/2L/3L=First/Second/Third Line (of therapy). Ab=Antibody. BCL-2i=BCL-2 Inhibitor. BsAb=Bispecific Ab. CAR T=Chimeric Antigen Receptor T-cell Therapy. CIT=Chemoimmunotherapy.
c/ncBTKi=Covalent/Non-Covalent BTK Inhibitor. MCL=Mantle Cell Lymphoma

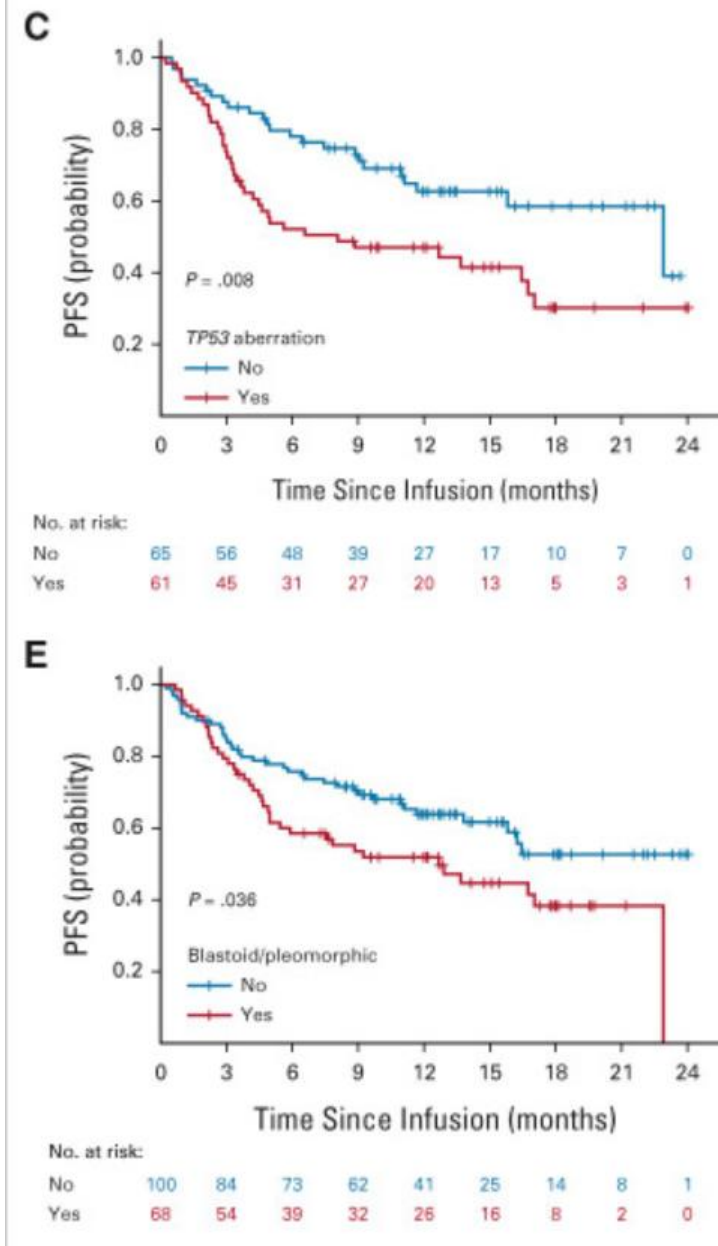
CAR T in R/R MCL: Efficacy with the two available compounds



Cohen et al.; ASH 2023
Wang M et al. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. JCO 41, 555-567(2023).
Wang M et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study. J Clin Oncol. 2024 Apr 1;42(10):1146-1157.

Brexu-Cel real-world from US Lymphoma CAR T Consortium

Wang Y et al, JCO 2023



ROMA HEMATOLOGY
CONFERENCE

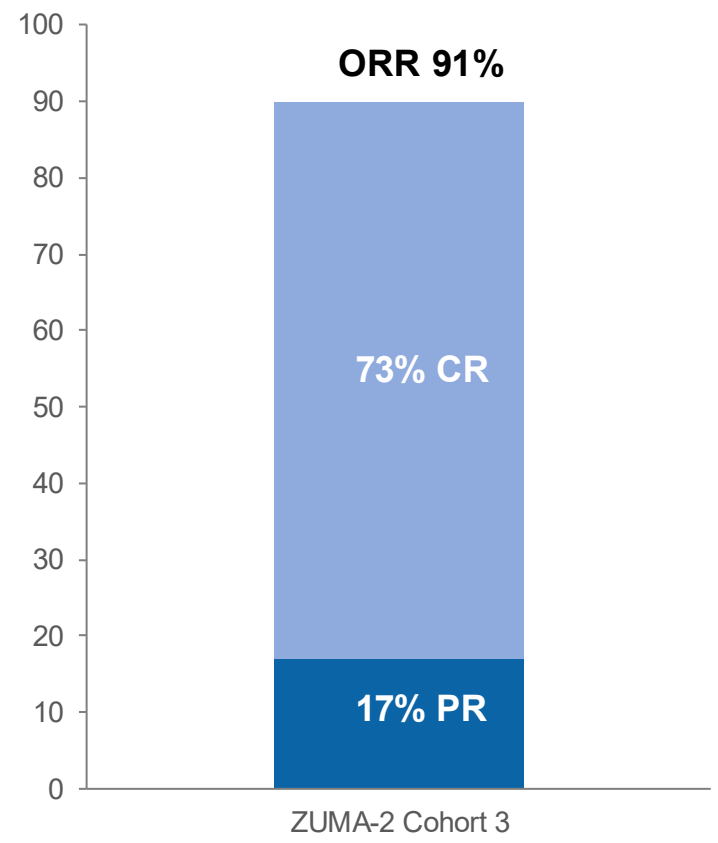
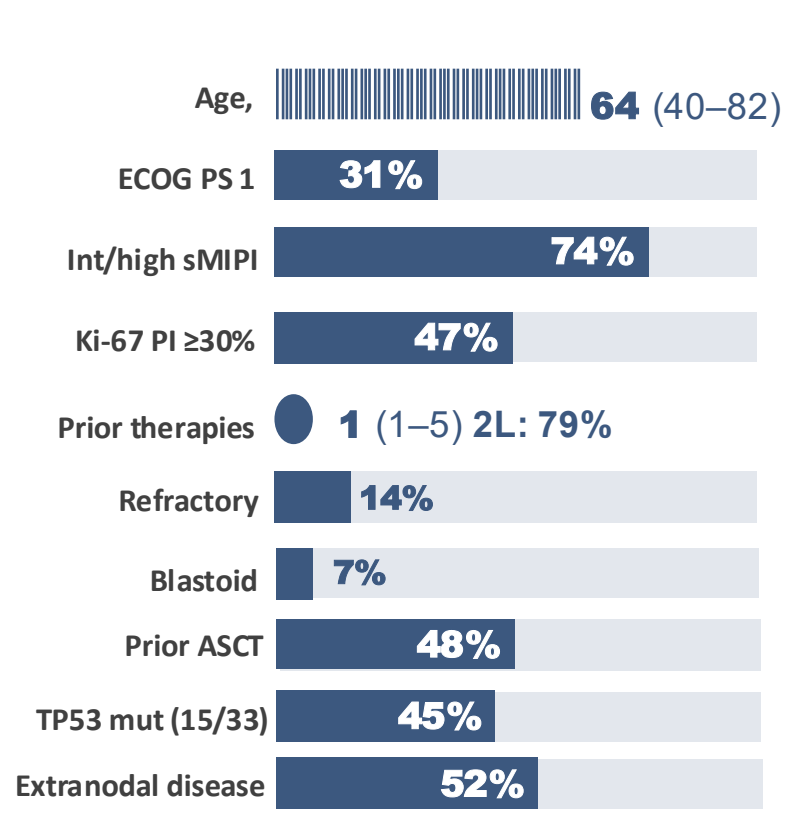
the lymphomas

Rome Hotel nhow Roma
October 15-16, 2026

ZUMA-2 Cohort 3: BTKi-naïve

ZUMA-2 Cohort-3

Cohort 3 BTKi naïve (N=86). Median follow-up 26,4 months



van Meerten T. et al. Blood 20267



ROMA HEMATOLOGY CONFERENCE

the lymphomas

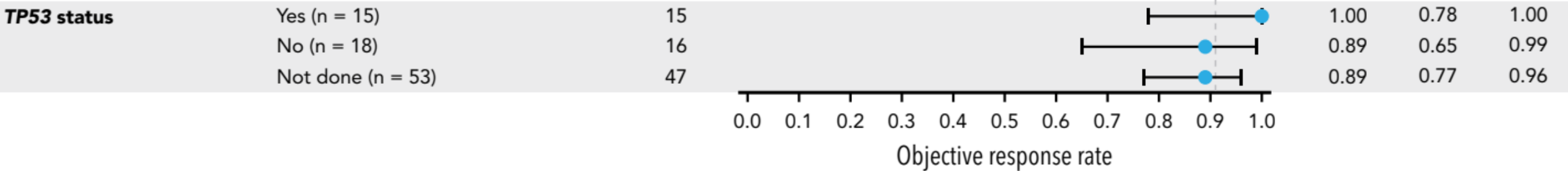
Rome Hotel nhow Roma
October 15-16, 2026

tecavus is indicated for the treatment of adult patients with R/R MCL after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor

ZUMA-2 Cohort 3: BTKi-naïve

ZUMA-2 Cohort-3

Cohort 3 BTKi naïve (N=86). Median follow-up 26,4 months



van Meerten T. et al. Blood March 2026 Vol 147

Glofitamab Monotherapy in R/R MCL

	Ki67 index			TP53 status			
	Low (<30%)	High (≥30%)	Not done	WT	Abnormal	Unknown*	Missing†
Response (INV-assessed)	(n = 6)	(n = 28)	(n = 13)	(n = 1)	(n = 5)	(n = 26)	(n = 28)
Overall response rate							
n (%)	5 (83.3)	22 (78.6)	12 (92.3)	1 (100)	3 (60.0)	24 (92.3)	23 (82.1)
95% CI	35.9 to 99.6	59.1 to 91.7	64.0 to 99.8	2.5 to 100	14.7 to 94.7	74.9 to 99.1	63.1 to 93.9
Complete response rate							
n (%)	5 (83.3)	20 (71.4)	10 (76.9)	1 (100)	3 (60.0)	21 (80.8)	22 (78.6)
95% CI	35.9 to 99.6	51.3 to 86.8	46.2 to 95.0	2.5 to 100	14.7 to 94.7	60.7 to 93.5	59.1 to 91.7

Phillips TJ et al, JCO 2025



ROMA HEMATOLOGY
CONFERENCE

the lymphomas

Rome Hotel nhow Roma
October 15-16, 2026

Take home messages (for new drugs in HR patients)

FRONTLINE: the addition of a cBTKi to ICT improves outcome of high risk patients
doublets (cBTKi+ABCD20) not enough, for cBTKi+BCL2i more data needed
triplets seem to work and provide a winning platform!

R/R SETTING: CarT cells are the best therapy, but should be considered early on
Not enough data for bispecifics, though initial response seems promising



Thanks for your
attention



FONDAZIONE
ITALIANA
LINFOMI



UNIVERSITÀ
di **VERONA**



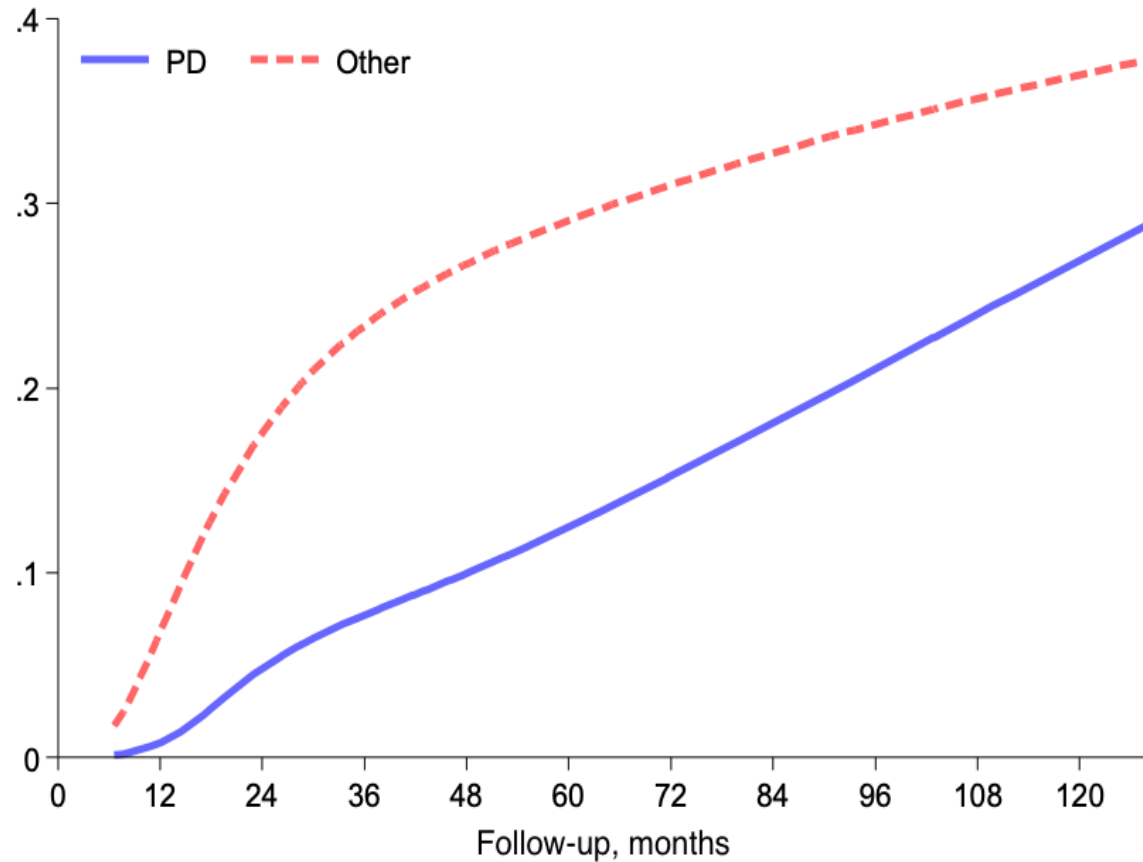
ROMA HEMATOLOGY
CONFERENCE

the lymphomas

Rome Hotel nhow Roma

October 15-16, 2026

Cumulative incidence of death for PD or other causes

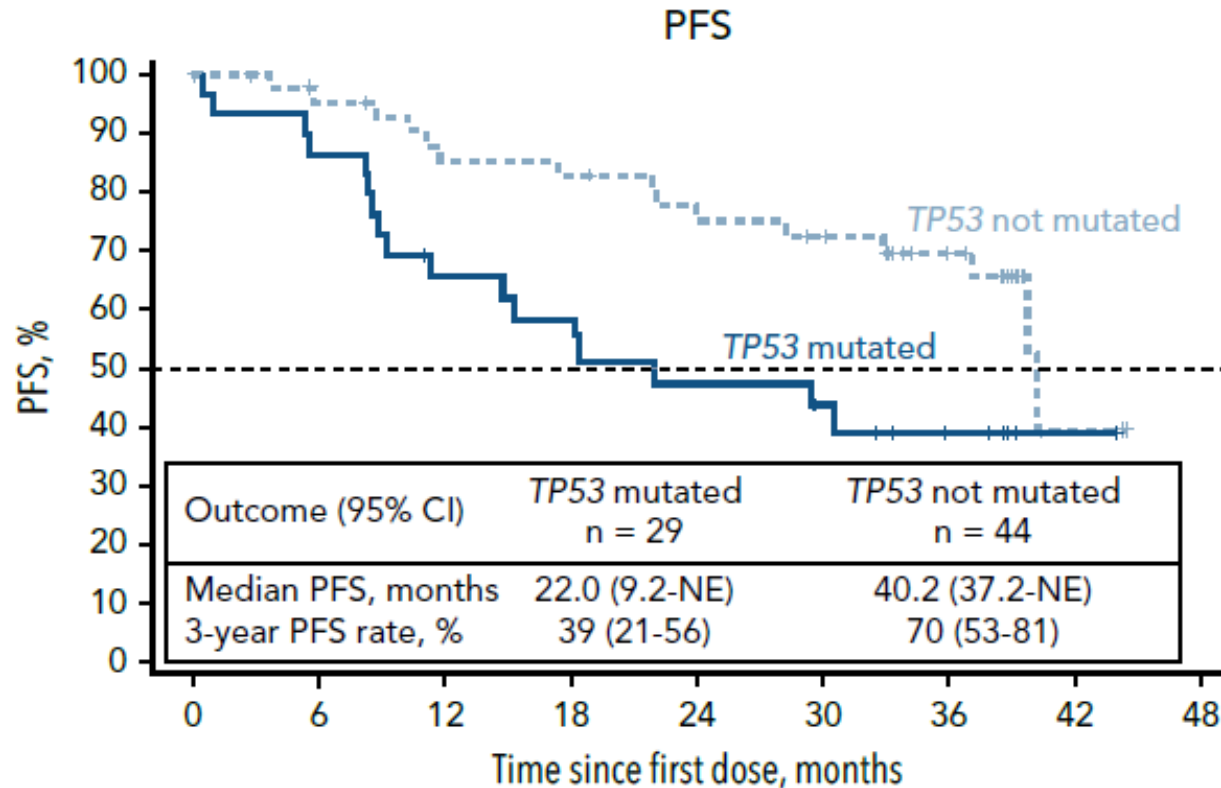


Better outcome if
not aGVHD,
≤2 prior lines,
Age<60



The phase 3 SYMPATICO study

B



**First-line ibrutinib plus venetoclax
in patients with nonblastoid MCL**

Patients at risk:

TP53 mutated	29	25	18	16	13	9	5	1	0
TP53 not mutated	44	39	34	33	30	27	18	2	0

Wang M, et al. Blood 2026