3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

Mantle Cell Lymphoma

How I treat relapsed/refractory mantle cell lymphoma and new perspectives with CAR-T therapy

C. Visco

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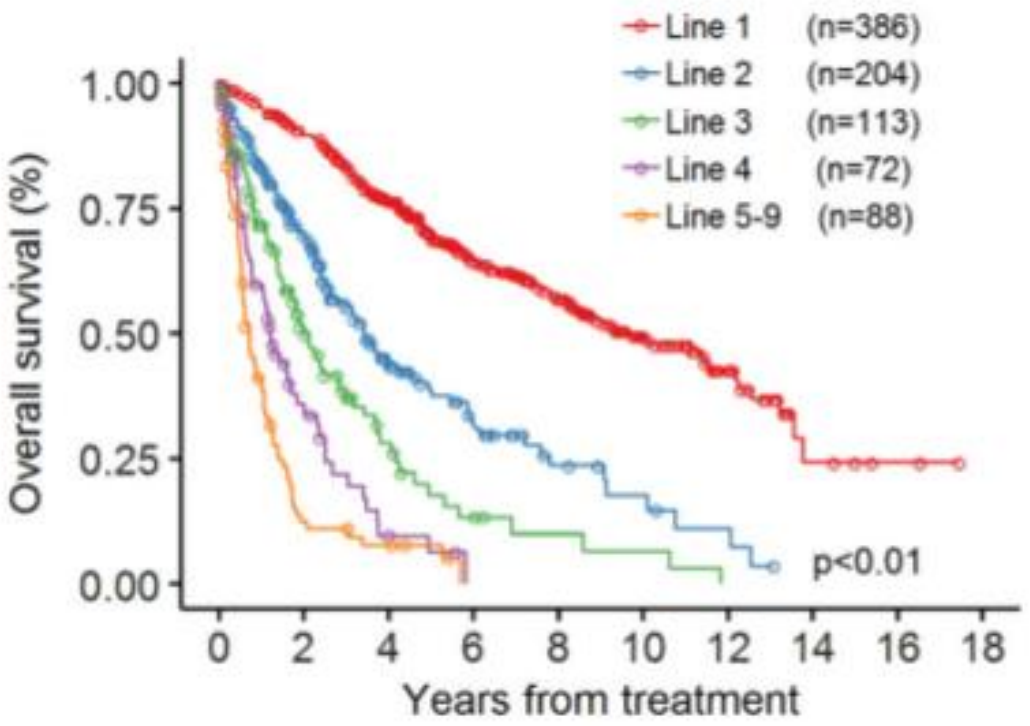
Disclosures of CARLO VISCO

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

Life expectancy and number of previous lines



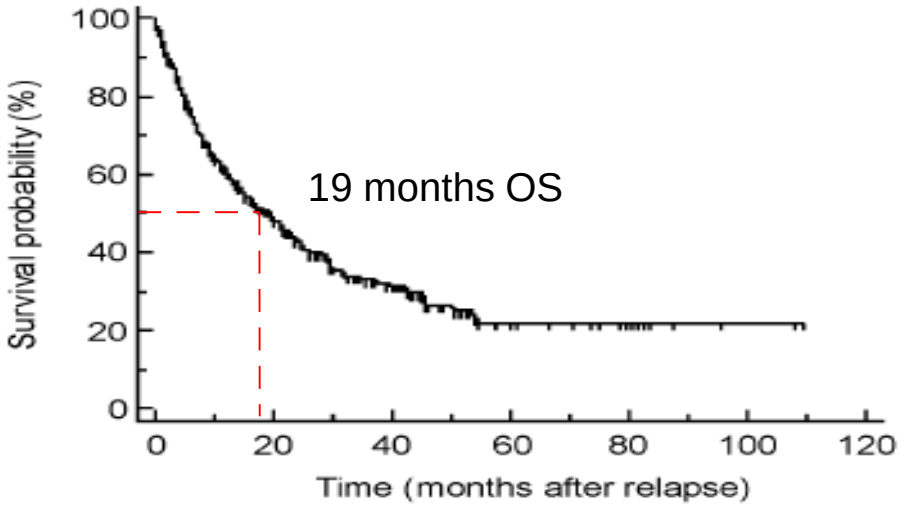
Number at risk

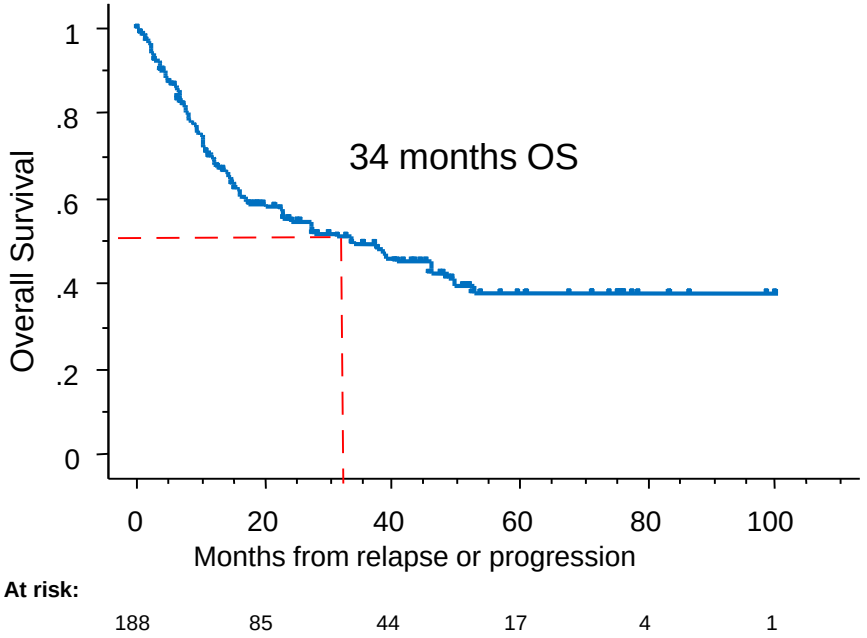
	386	329	242	142	101	53	28	5	2	0
	204	111	45	23	11	6	3	0	0	0
	113	38	15	6	3	2	0	0	0	0
	72	16	4	0	0	0	0	0	0	0
	88	9	5	0	0	0	0	0	0	0

Kumar et al. Blood Cancer Journal 2019

Patients relapsed after Auto transplant

Previous versus modern therapeutic era (HD-AraC, Benda, BTK-i etc)





EBMT registry 2000-2009 (n=360)

FIL study 2007-2017 (n=188)

Dietrich S, Ann Oncol 2014

Visco C, BJH 2019

Relapsed setting

BTKi at first relapse

Later relapses and peculiar features:

-TP53 mutations
-What to do when ibrutinib fails
-CAR T-cell therapy

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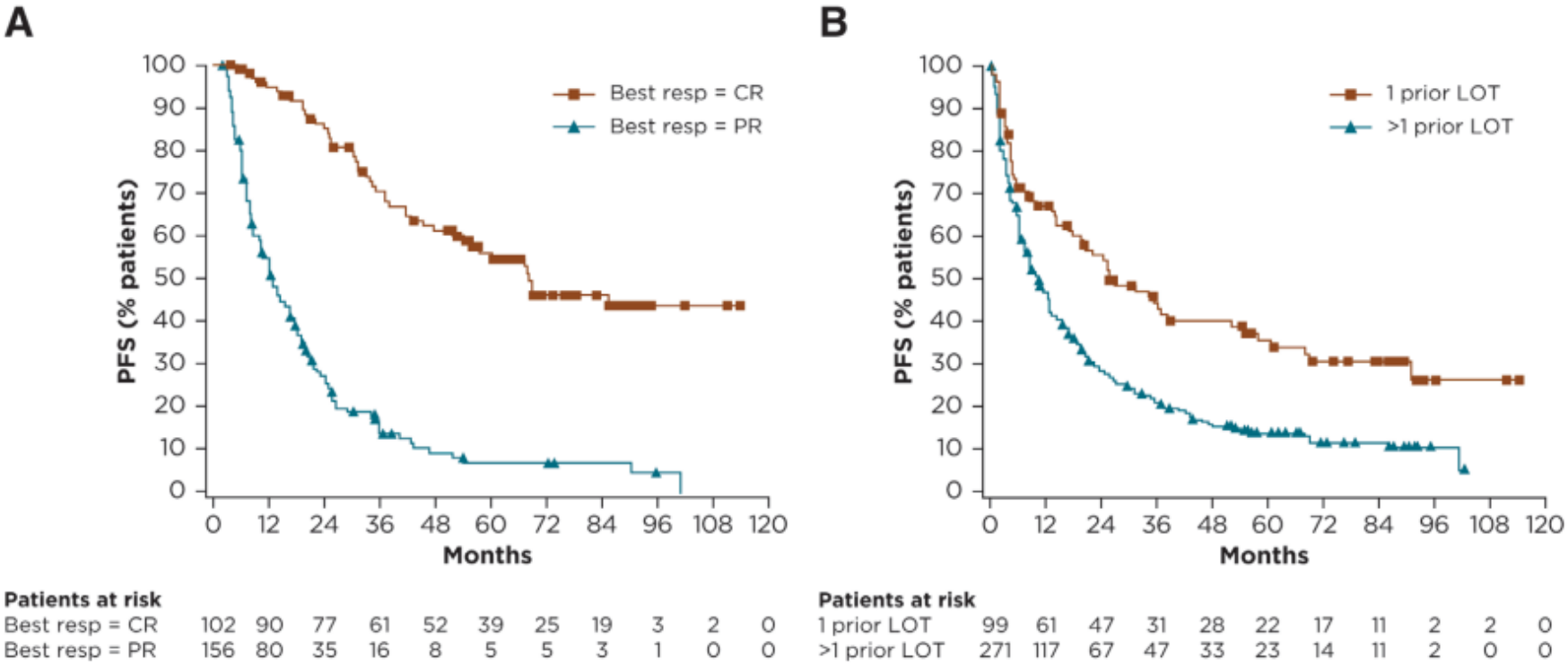
Long-term Outcomes With Ibrutinib Treatment for Patients With R/R MCL

Response to BTKi

N prior Tx

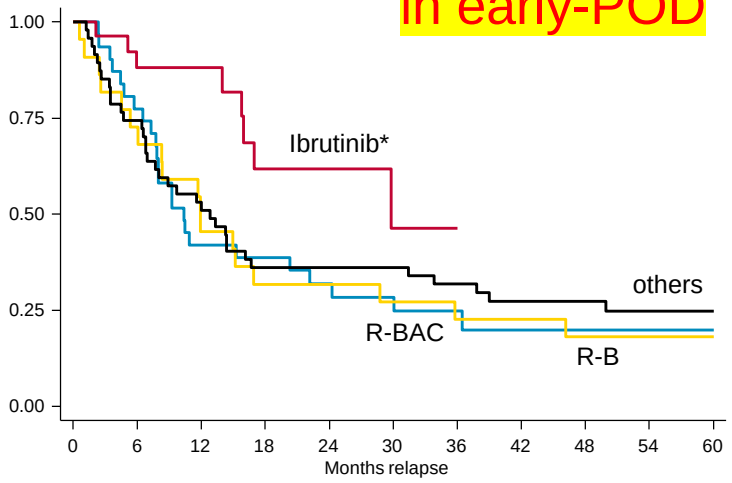


Dreyling M et al, Hemasphere 2022

OS, early versus late POD

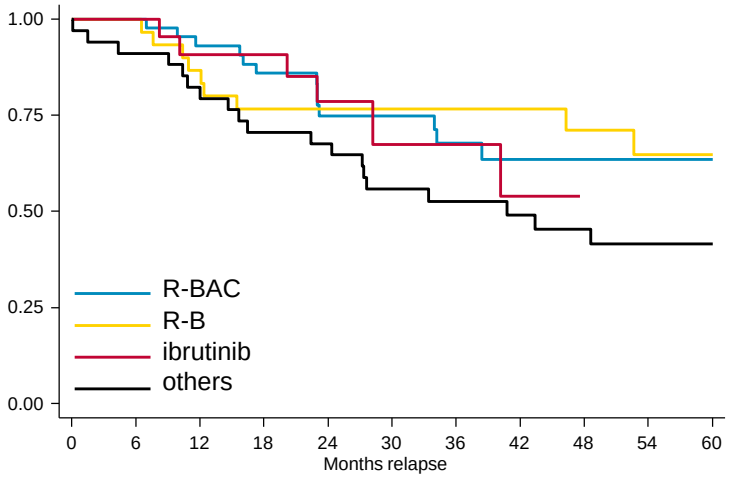
Ibrutinib best choice in early-POD

Early POD



At risk:											
BAC	31	24	13	12	9	8	5	4	3	3	3
BR	22	16	10	7	7	6	5	5	4	3	2
ibru	27	21	16	8	5	3	0	0	0	0	0
other	47	35	24	17	17	17	15	11	11	10	6

Late-POD



At risk:											
BAC	45	45	40	35	26	23	16	14	12	8	7
BR	32	30	26	23	22	20	16	15	13	10	9
ibru	23	22	20	18	10	6	6	4	0	0	0
other	34	31	27	24	23	19	16	13	12	8	7

*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)

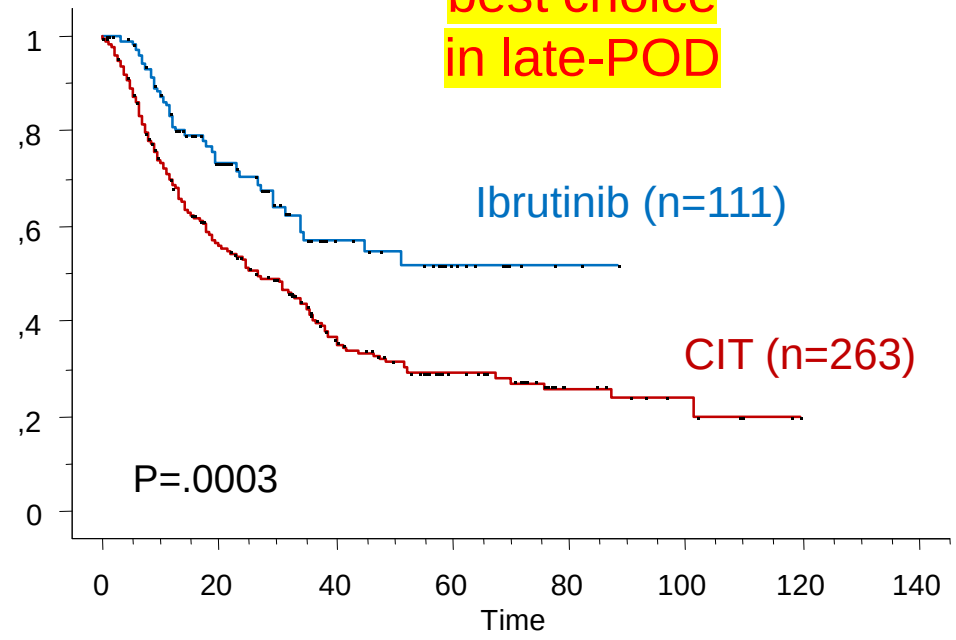
Visco et al, Leukemia 2020

Survival curves of late-POD patients according to second line treatment

Ibrutinib *vs* **Chemoimmunotherapy (CIT)**

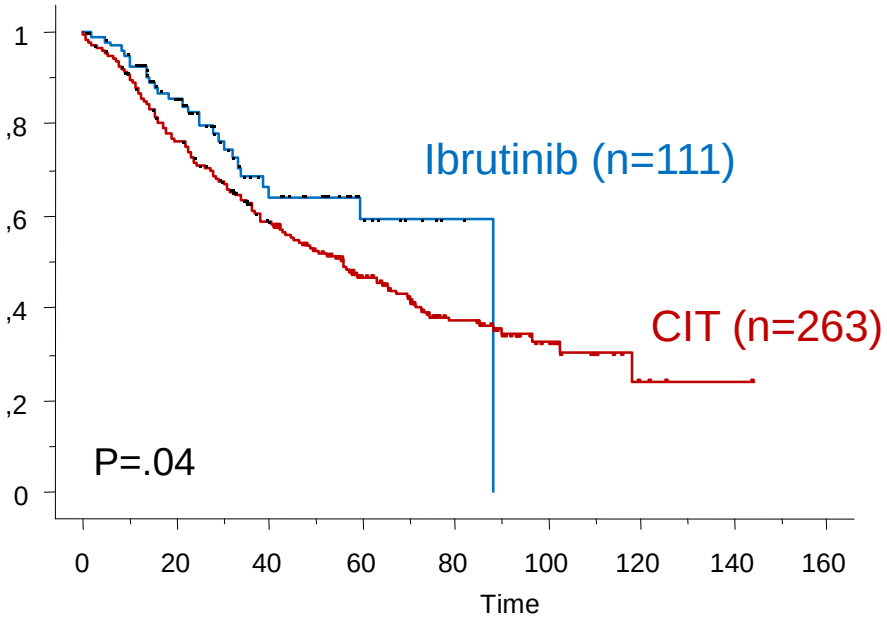
PFS-2

Ibrutinib
best choice
in late-POD



Median 26 months for CIT;
NR for Ibrutinib

OS-2

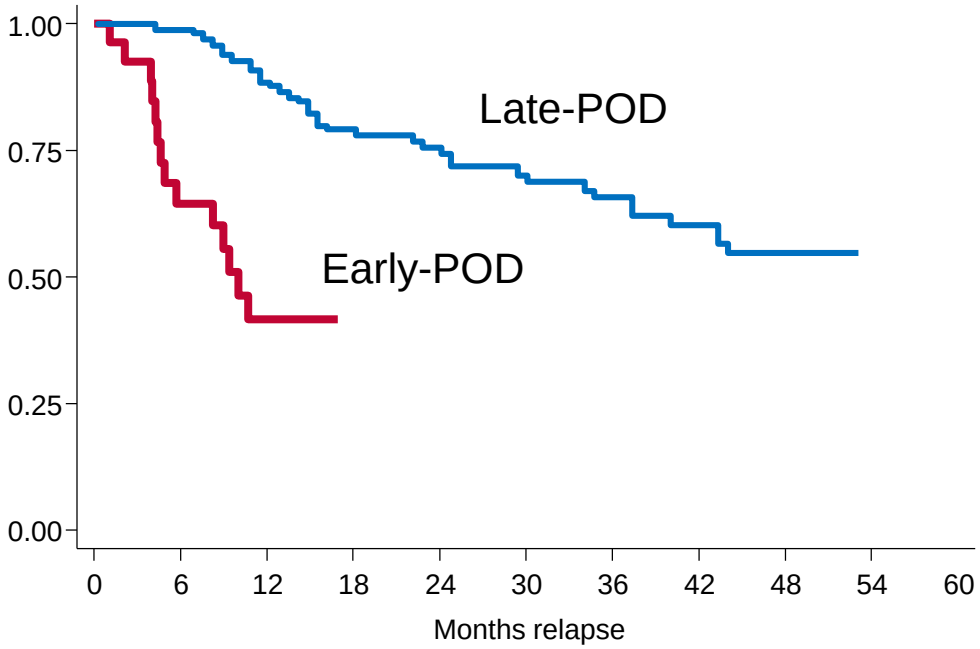


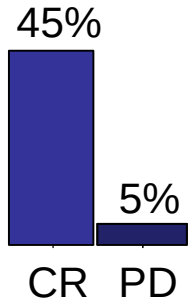
Median 56 months for CIT;
88 for Ibrutinib

Visco, ICML 2023

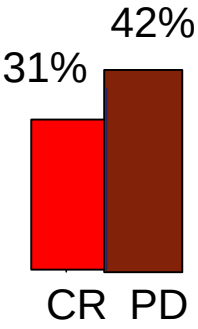
Ibrutinib at first relapse: late versus early POD

PFS





Late-POD



Early-POD

Visco, modified from Leukemia 2021
And late-POD, ICML 2023

Relapsed setting

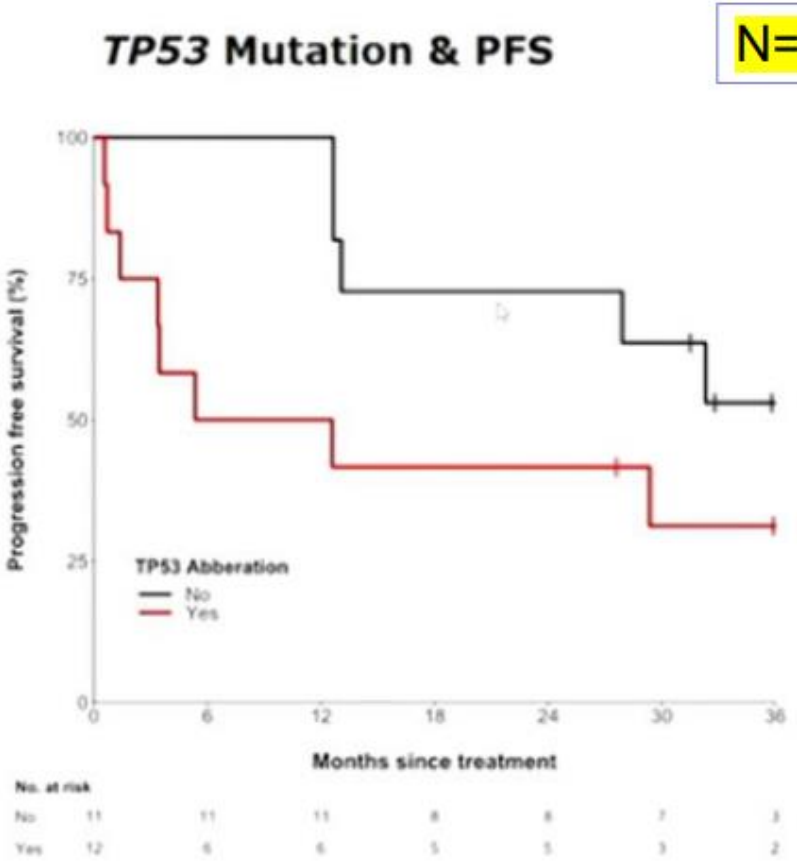
BTKi at first relapse

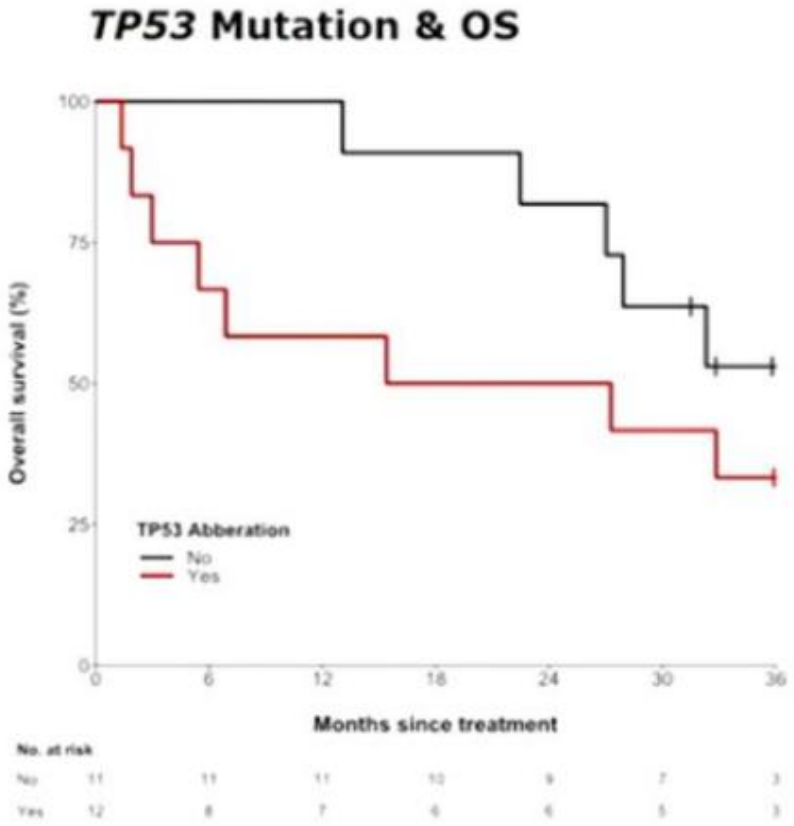
Subsequent relapses, tumor biology:

-TP53 mutations
-What to do when ibrutinib fails
-CAR T-cell therapy

Three Year Update of the Phase II ABT-199 (Venetoclax) and Ibrutinib in Mantle Cell Lymphoma (AIM) Study

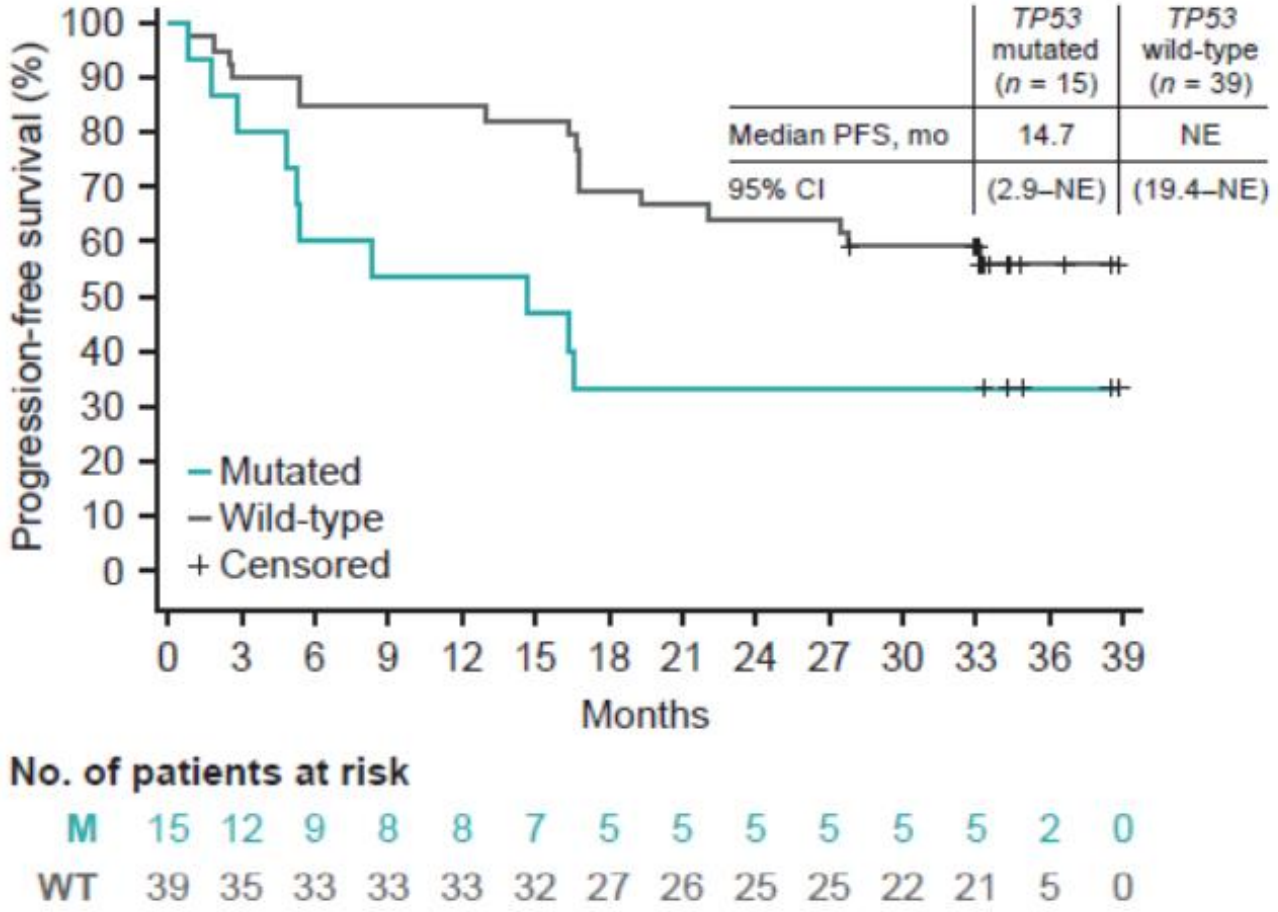
N=12





Sasanka M. Handunnetti, et al, ASH 2019

Zanubrutinib in R/R MCL: long-term efficacy results



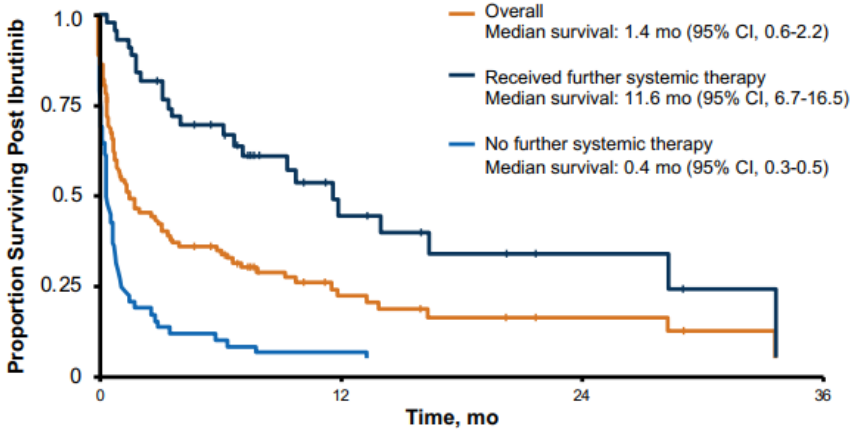
ORR 80.0%

Song Y, Blood 2022

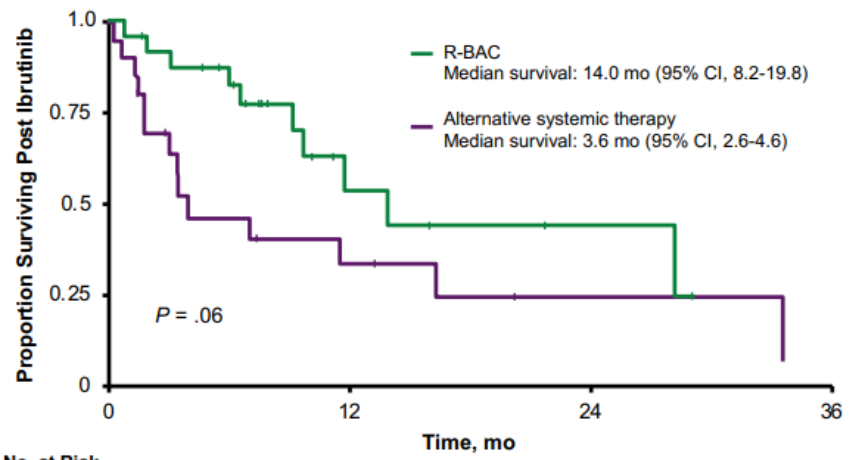
Treatment after BTKi failure

OS post-ibrutinib failure

- Progression on BTKi likely involves therapeutic resistance
- Overall, post-ibrutinib OS was 1.4 months for patients receiving no further therapy



No. at Risk				
Overall	100	10	3	0
Systemic therapy	45	9	3	0
No systemic therapy	56	1	0	0

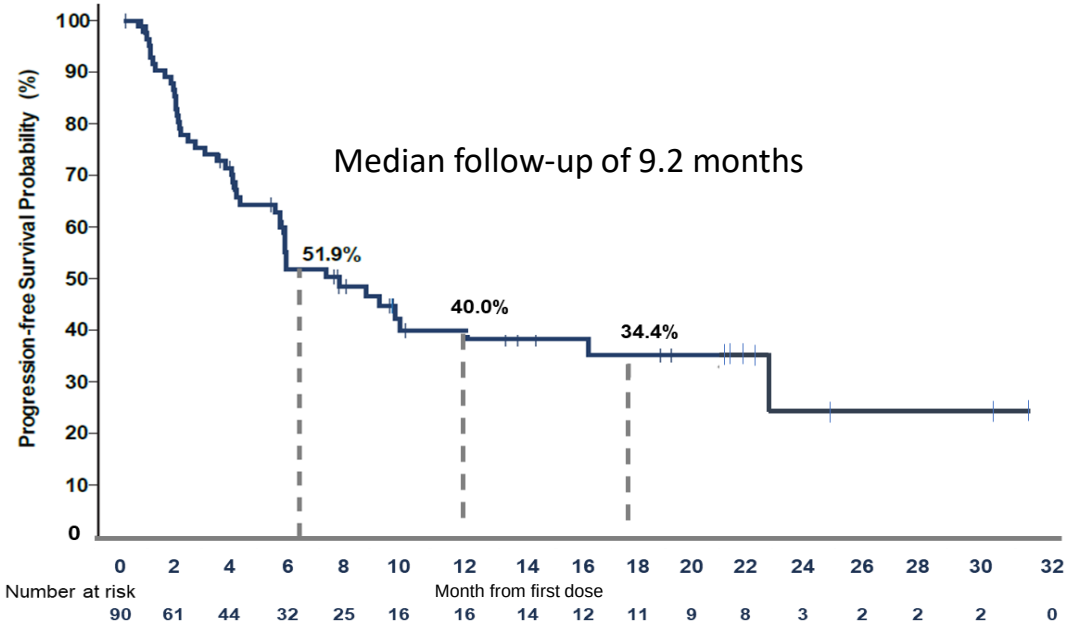


No. at Risk				
R-BAC	23	5	2	0
Alternative therapy	19	4	1	0

1. McCulloch R et al. *Br J Haematol*. 2021;193:290-298.

Pirtobrutinib Monotherapy

Phase I/II, first-in-human, open-label, multicenter, BRUIN study evaluating the efficacy of **pirtobrutinib (n=90)** in patients with covalent BTK inhibitor pretreated MCL



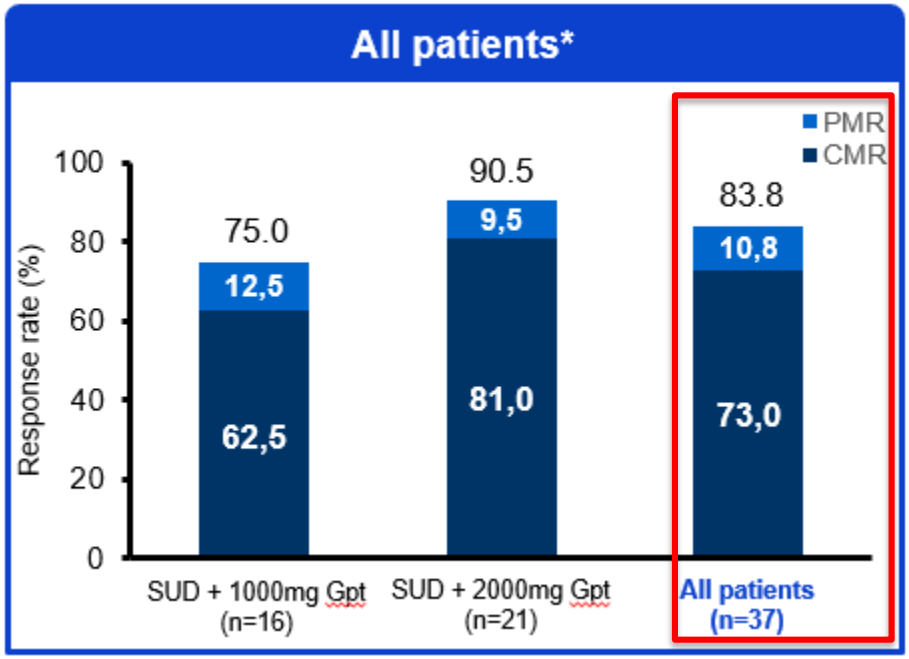
ORR in BTK pretreated 51%

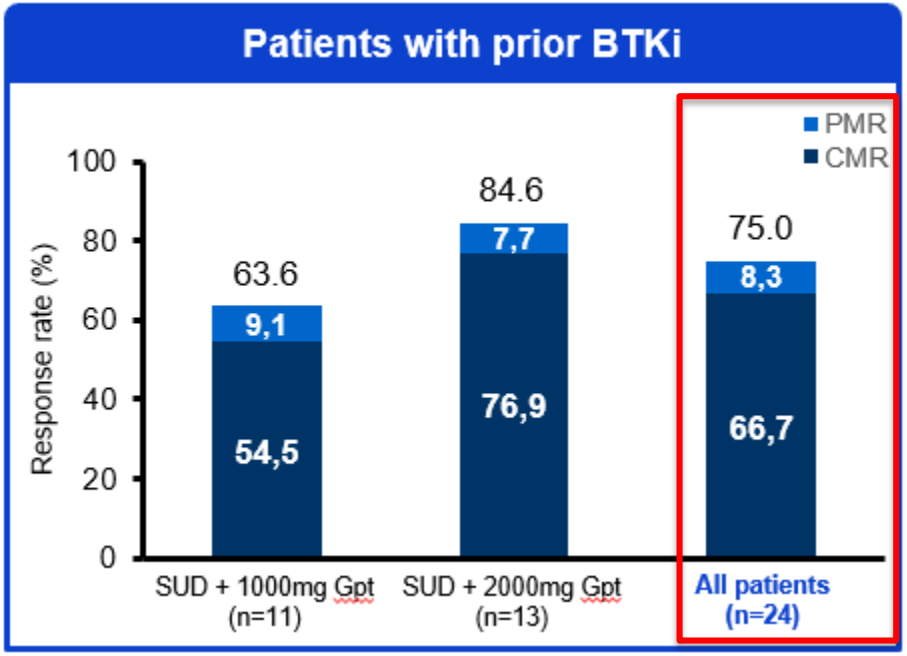
PFS	Median PFS (95% CI), mo
12-month PFS	7.4 (5.3 – 12.5)

BTK, Bruton kinase; CI, confidence interval; MCL, mantle cell lymphoma mo, months; PFS, progression-free survival; R/R, relapsed/refractory.
Wang M et al. *J Clin Oncol*. 2023. Online ahead of print.

Glofitamab Monotherapy Induces High CR Rates in Patients with Heavily Pretreated R/R MCL

N=37; Median age 72 (41-84)





Phillips TJ, ASH 2022

FONDAZIONE ITALIANA LINFOMI

COLUMN- Final Study Design

Single arm phase II study conducted in 20 centers (Italy and 1 European country within the EU MCL network)

BTKi R/R MCL (first, second or third salvage treatment)*

→ **2 R-BAC ****

→ CR/PR/SD → ADCT 402 **(loncastuximab tesirine)** 150 µg/kg Q3W
Two doses, followed by two doses at 75 µg/kg Q3W

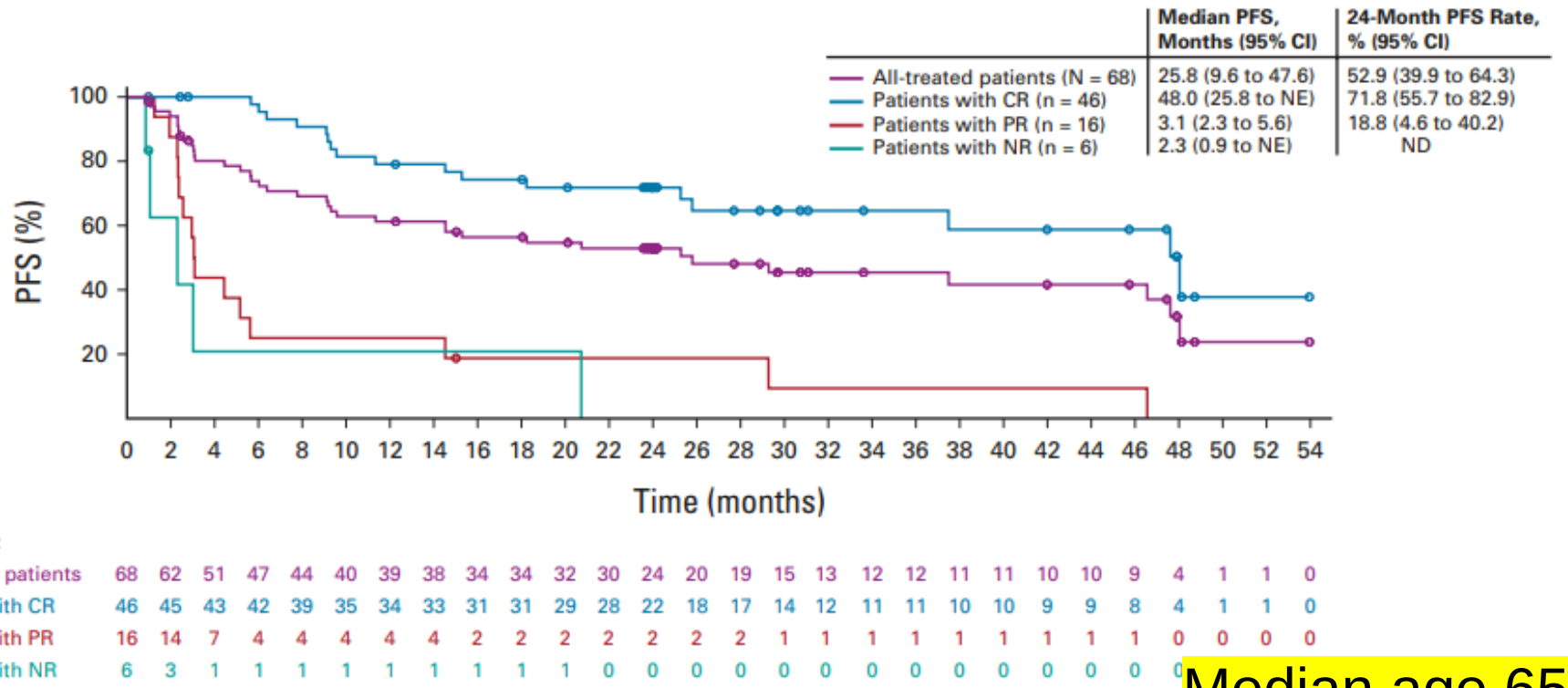
→ PD → Off study

*Previous treatment with BTKi monotherapy or BTKi containing regimens with R/R disease; and/or patients who discontinued BTKi monotherapy or BTKi containing regimens for adverse events.

**A patient with CR, PR or SD after one R-BAC course, which is unable to undergo a second course due to toxicity to chemotherapy, can be considered to proceed for consolidation.

CarT-cell therapy in R/R MCL (ZUMA-2 long term)

B



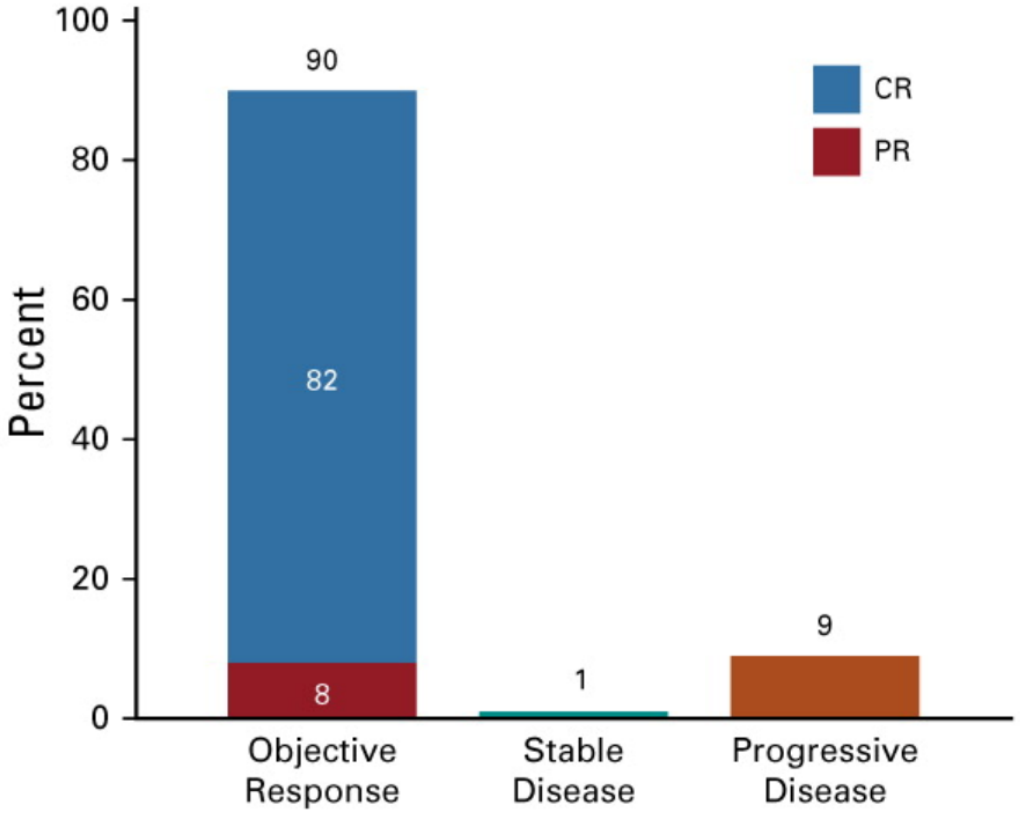
Median age 65 (38-79)

Median follow-up of 35.6 months

Late-onset toxicities were infrequent; only 3% of treatment-emergent adverse events of interest in ZUMA-2 occurred during this longer follow-up period.

Wang M et al, JCO 2022

Brexucabtagene Autoleucel for R/R MCL in Standard-of-Care Practice



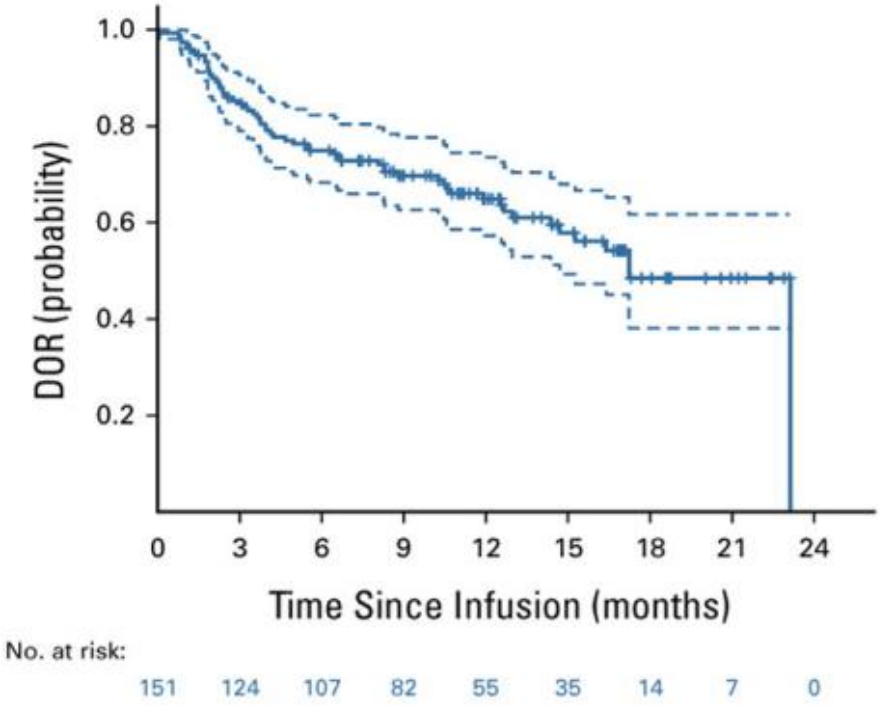
Patients who underwent leukapheresis (August 18, 2020-December 31, 2021; N = 189)

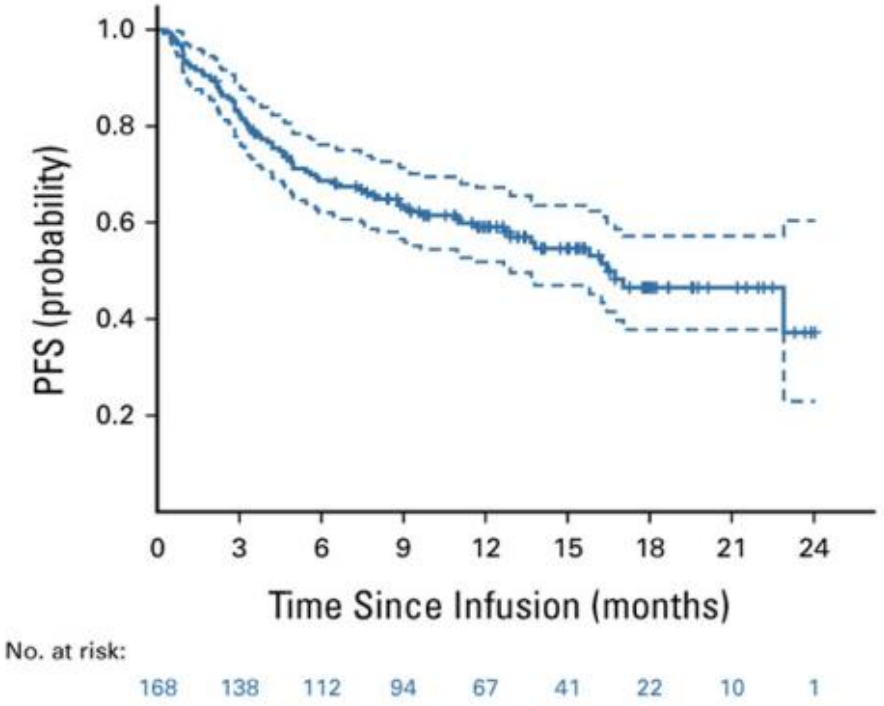
Patients who did not receive CAR T-cell infusion (n = 21)
- Death (n = 9, all lymphoma-related)
- Manufacture failure (n = 7)
- Disease progression (n = 2)
- Organ dysfunction (n = 1)
- CR to bridging therapy (n = 1)
- Patient declined (n = 1)

Patients who received CAR T-cell infusion (n = 168)
- Standard-of-care (n = 159)
- Expanded access program (n = 2)
- Single-patient IND protocol (n = 7)

Wang Y et al, JCO 2023

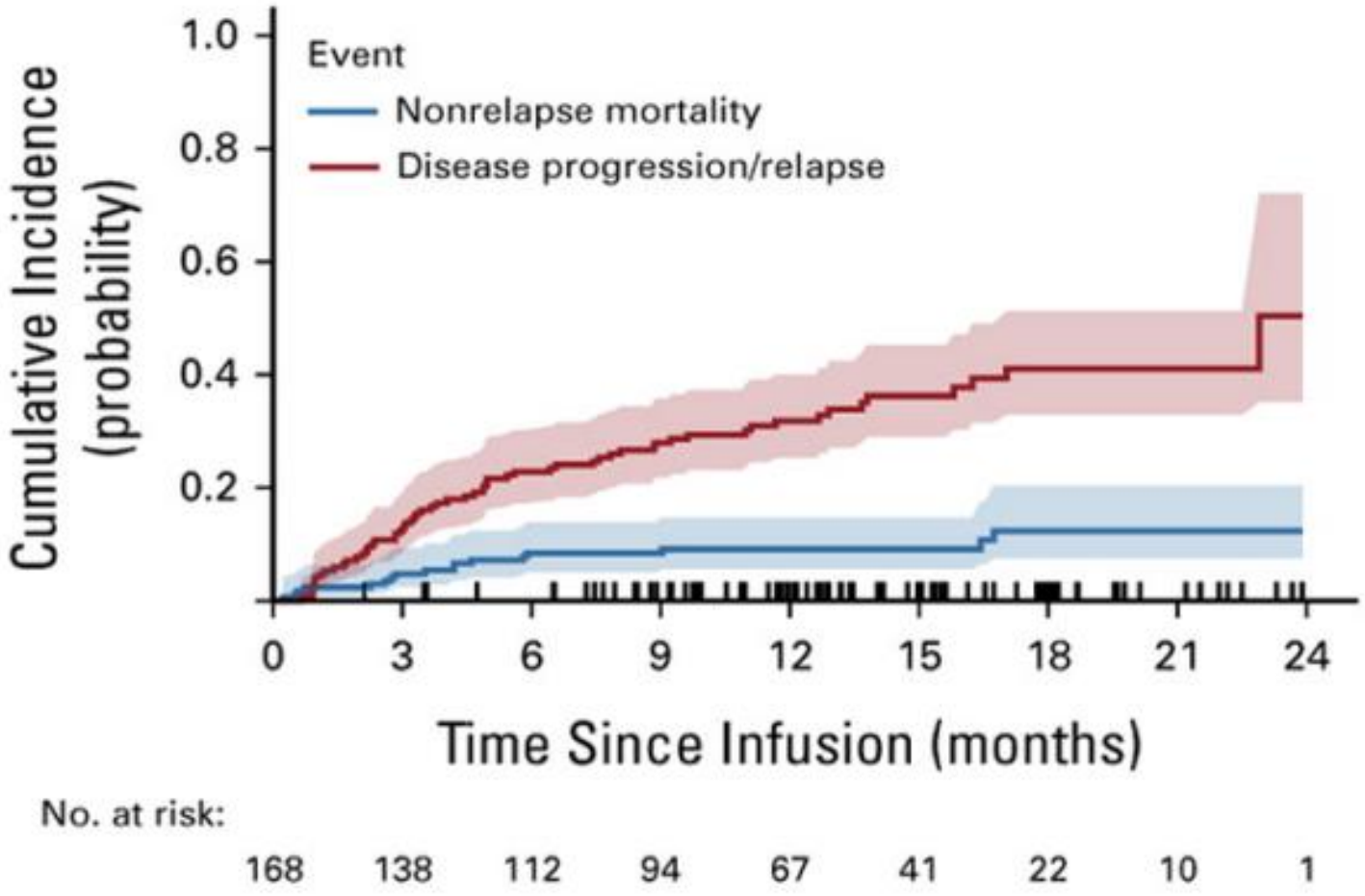
Brexucabtagene Autoleucel for R/R MCL in Standard-of-Care Practice





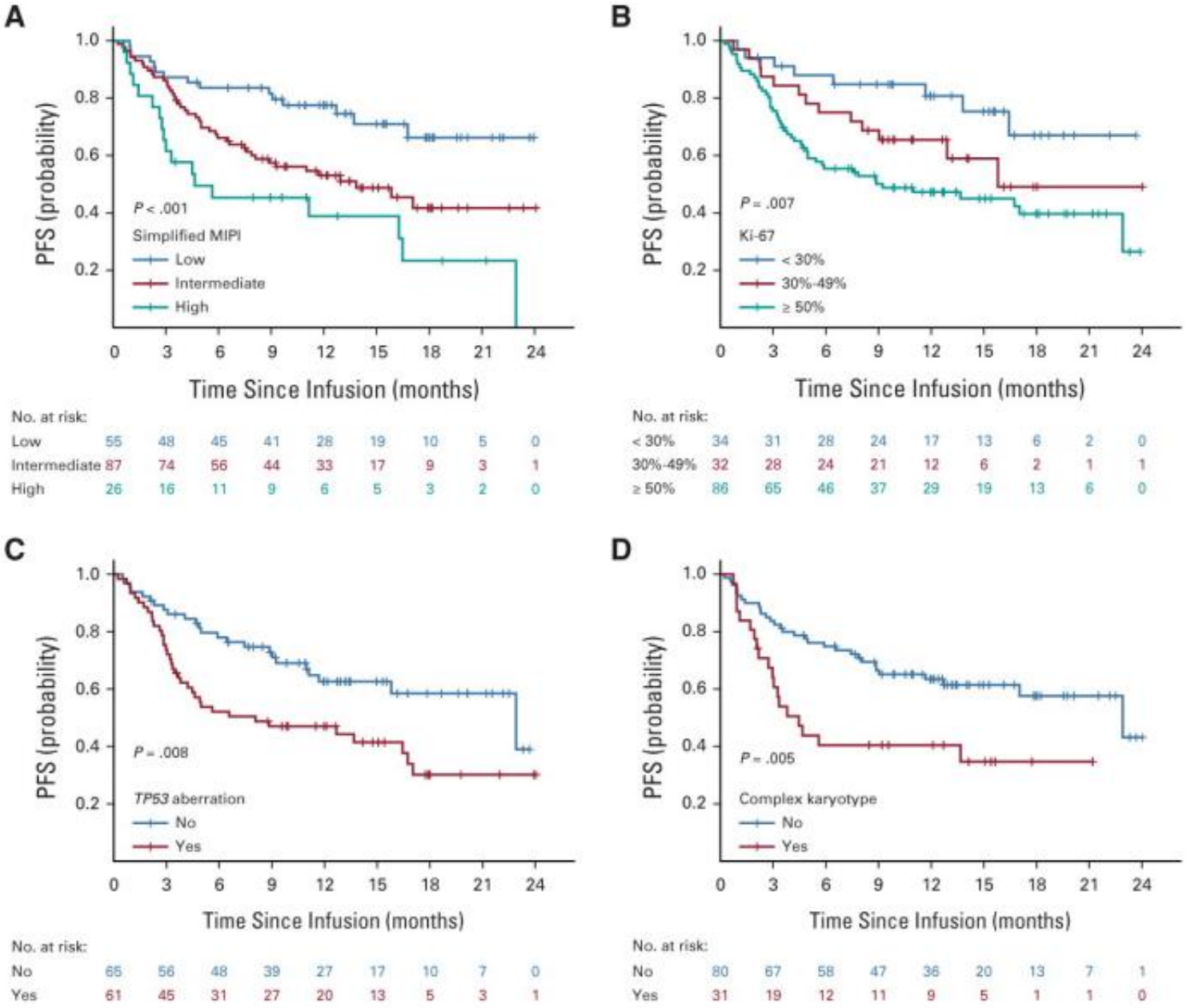
Wang Y et al, JCO 2023

Brexucabtagene Autoleucel for R/R MCL in Standard-of-Care Practice



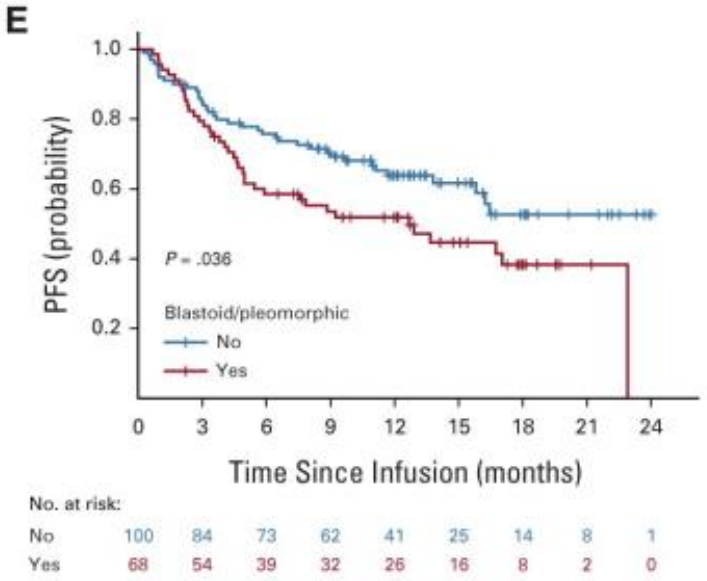
Wang Y et al, JCO 2023

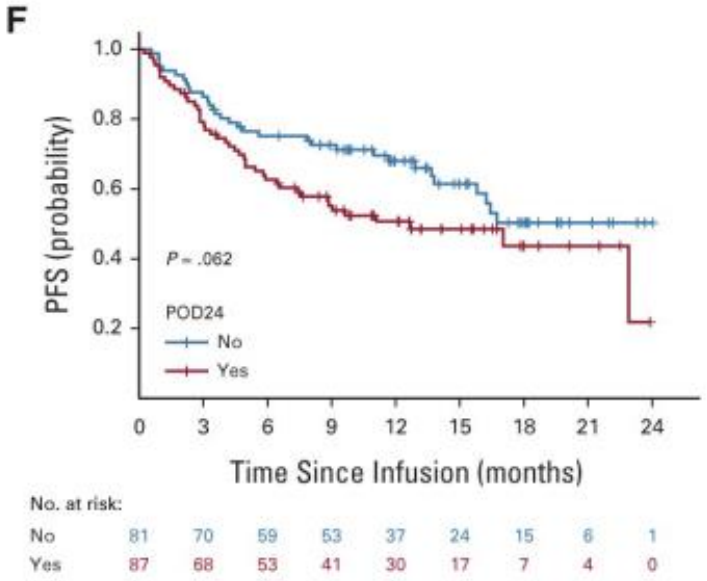
Brexu for R/R MCL in Standard-of-Care Practice

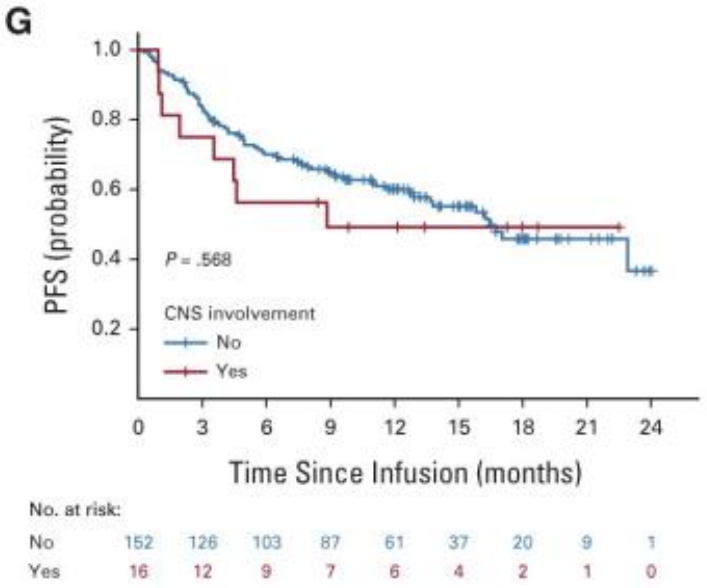


Wang Y et al, JCO 2023

Brexu for R/R MCL in Standard-of-Care Practice

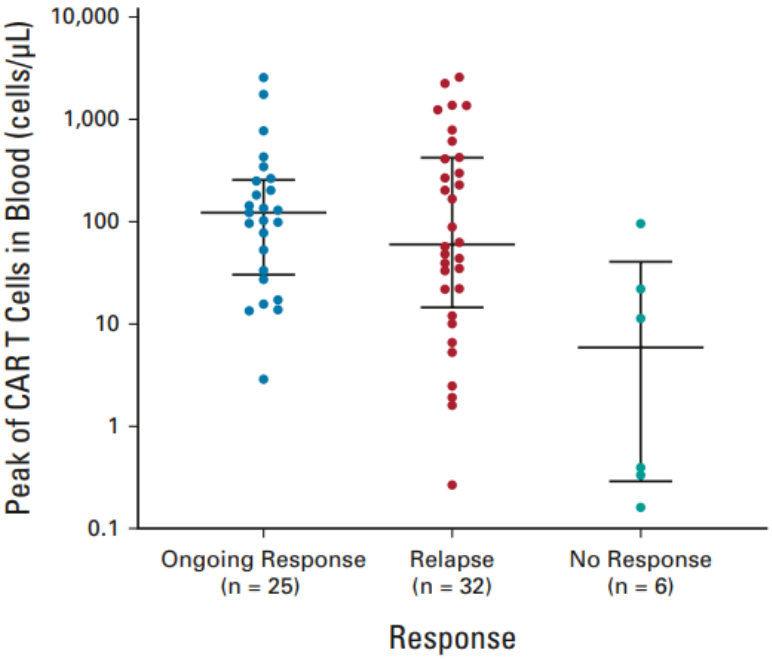




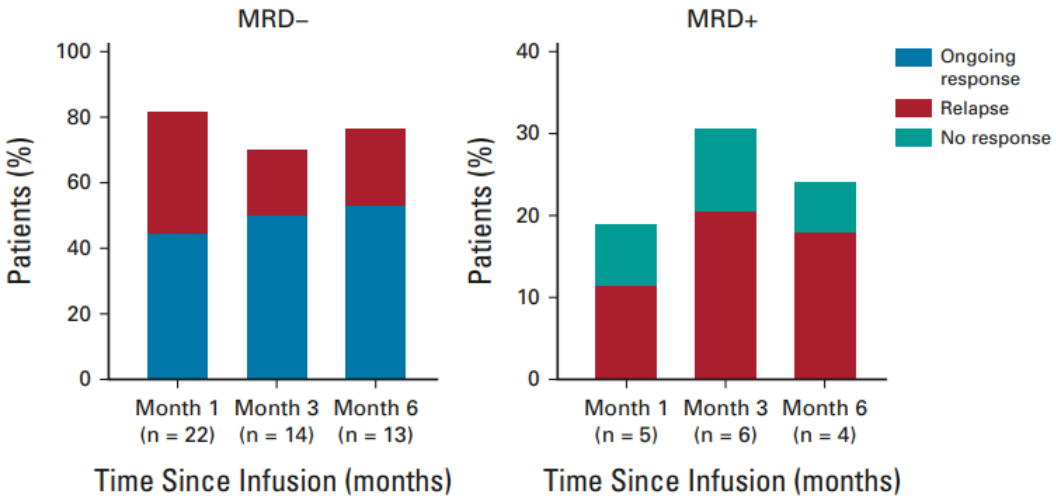


Wang Y et al, JCO 2023

Lessons from ZUMA-2 and real life studies



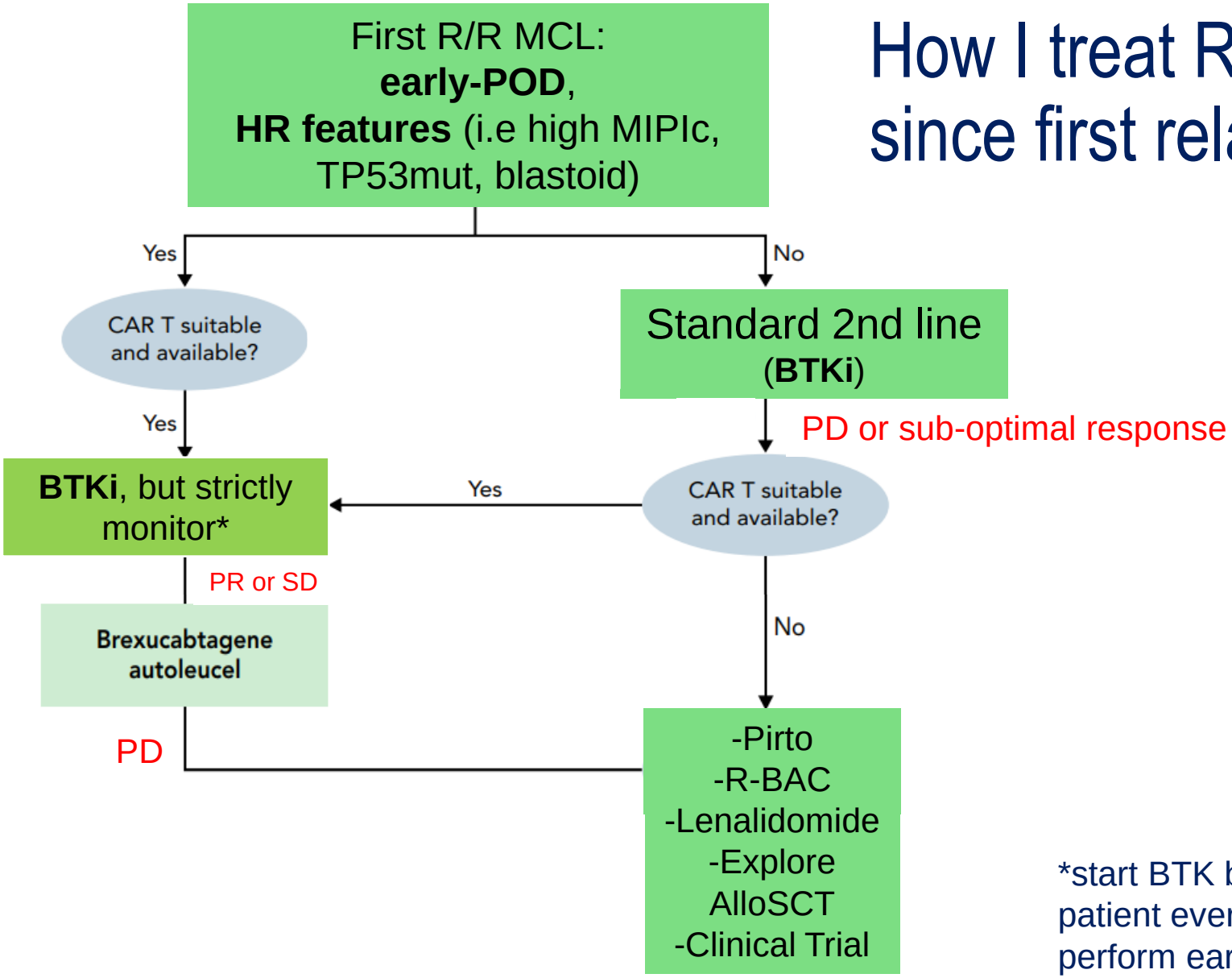
Peak CAR T-cell expansion was highest in patients with ongoing responses



MRD negativity at months 1, 3, and 6 was associated with durable response

Wang Y et al, JCO 2023

How I treat R/R MCL since first relapse



*start BTK but see the patient every month and perform early PET (8-12 weeks).

Visco C, personal view

3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

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Starhotels Majestic

Conclusions

- BTKi standard therapy at first relapse
- Time to first relapse and risk factors to module tumor assessment
- TP53 mutation still an unmet need in any line
- CarT-cells associated to excellent response rates, but room to improve in long term i.e. cells exhaustion, MRD, CD19 etc