Il suono DELL' INNOVAZIONE
Bologna Palazzo De' Toschi 27-28 novembre 2025

Trattamento del paziente R/R

Maurizio Martelli
Ematologia Policlinico Umberto 1
Università Sapienza Roma

Maurizio Martelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X		X	x	
Beigene					X	x	
Eli Lilly					X	x	
Recodati Rare disease					X	x	
Incyte			X		X	X	
Kite Gilead			X		X	x	
Novartis						X	
Janssen							
Roche			X		X	X	
SOBI						X	
Takeda						X	
BMS					X	x	

Current Treatment in Mantle Cell Lymphoma

Preferred First-line Treatment Options

Aggressive Chemotherapy
R-DHAP (cisplatin, or oxaliplatin)
R-CHOP/R-DHAP (alternating)
NORDIC (maxi-CHOP/R + HD cytarabine)

→ **Consolidation and Maintenance**
HDT + ASCT → R maint for 3 yr

Less Aggressive Chemotherapy
BR
R-CHOP
RBAC

→ **Maintenance**
After R-CHOP: R maint until Progression.

Preferred Second-line Treatment Options

BTK inhibitor
- **Ibrutinib**
- Pirtobrutinib (if previously treated with Ibrutinib)

Third-line Treatment

Brexucabtagene autoleucel (after chemoimmunotherapy and BTK inhibitor)

Pirtobrutinib

Adattato da NCCN guidelines version 1.0 2024.

ARTICLE

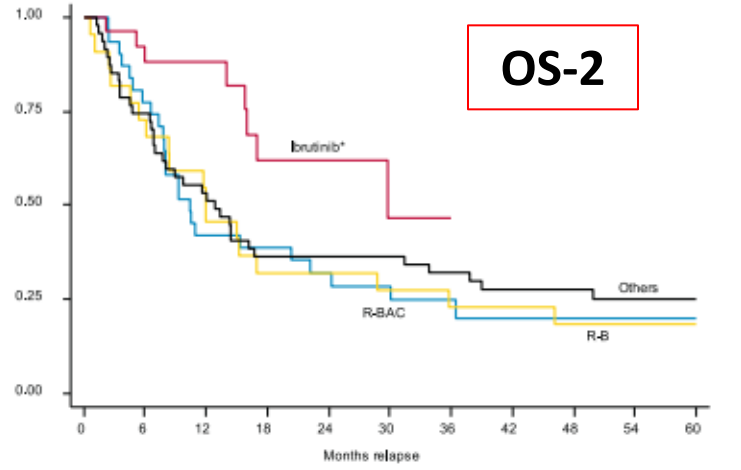
Lymphoma

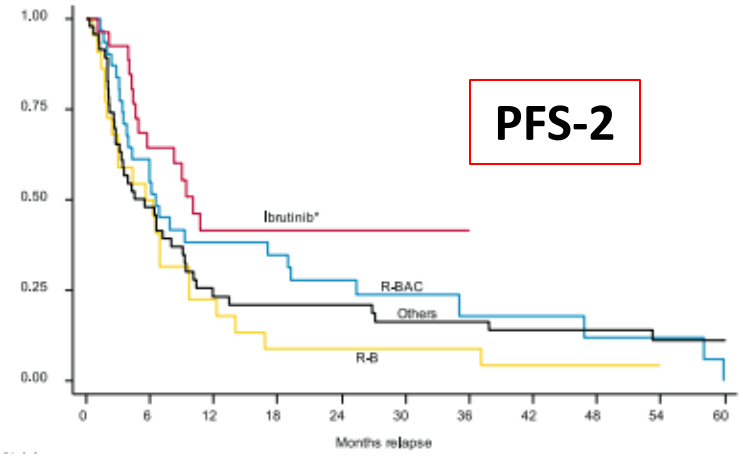
Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: results from the MANTLE-FIRST study

Carlo Visco[1] · Alice Di Rocco[2] · Andrea Evangelista[3] · Francesca Maria Quaglia[1] · Maria Chiara Tisi[4] · Lucia Morello[5] · Vittorio Ruggero Zilioli[6] · Chiara Rusconi[6,7] · Stefan Hohaus[8] · Roberta Sciarra[9] · Alessandro Re[10] · Cristina Tecchio[1] · Annalisa Chiappella[7,11] · Ana Marin-Niebla[12] · Rory McCulloch[13] · Guido Gini[14] · Tommasina Perrone[15] · Luca Nassi[16] · Elsa Pennese[17] · Piero Maria Stefani[18] · Maria Christina Cox[19] · Valentina Bozzoli[20] · Alberto Fabbri[21] · Valentina Polli[22] · Simone Ferrero[23] · Maria Isabel Alvarez De Celis[24] · Antonello Sica[25] · Luca Petrucci[2] · Luca Arcaini[9] · Simon Rule[13] · Mauro Krampera[1] · Umberto Vitolo[26] · Monica Balzarotti[5]

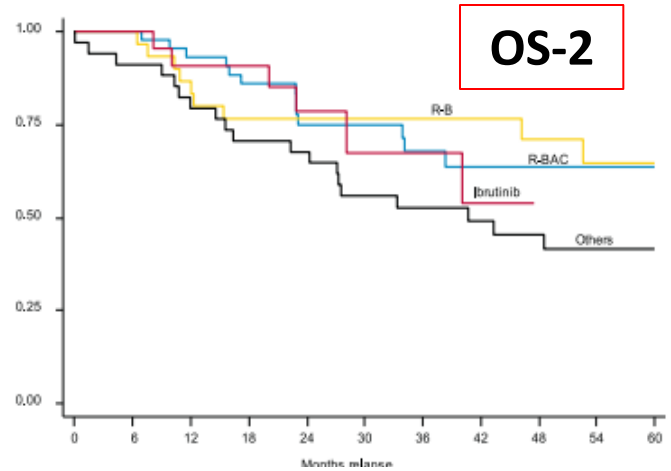
- R-BAC was associated with similar PFS-2 to ibrutinib.
- **Ibrutinib was the best performer in early-POD patients.**
- Bendamustine-based regimens demonstrated similar activity to ibrutinib

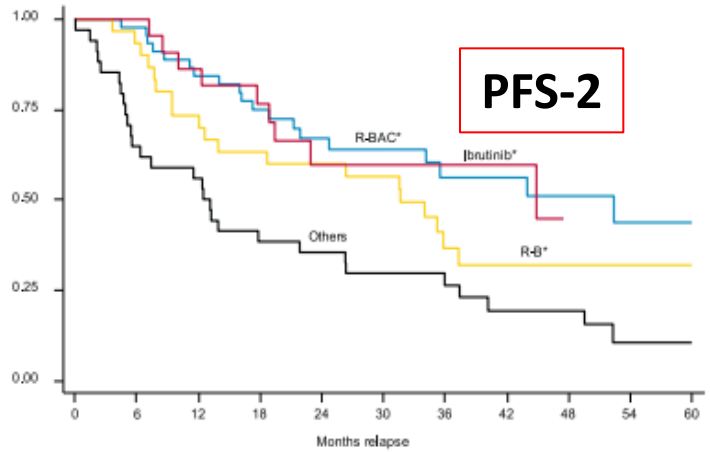
EARLY POD





LATE POD



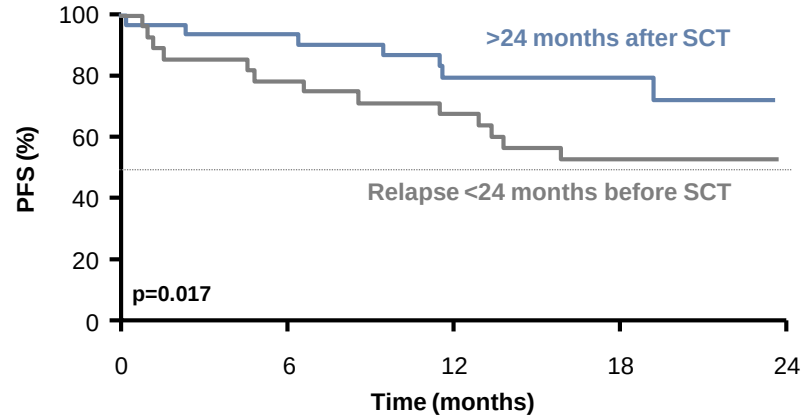


Visco C. et al. Leukemia. 2021 Mar;35(3):787-795

Ibrutinib Therapy Does Not Overcome Poor Outcomes in Patients With POD24 After First-line Chemotherapy and ASCT

Retrospective analysis of patients with MCL who received ibrutinib after first-line chemotherapy and ASCT (N=66; EBMT registry)

PFS after start of ibrutinib

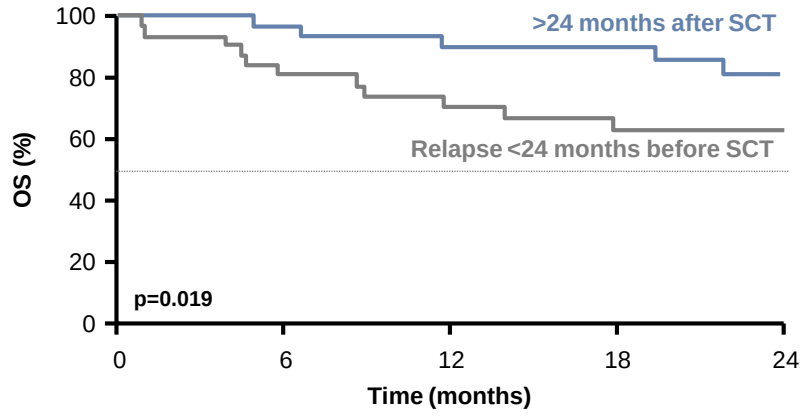


No. at risk					
<24 mo	28	22	18	13	7
>24 mo	32	29	22	21	14

	POD24	POD≥24	All patients
2-year PFS, %	53	72	62

Adapted from Figure 1 in Ref. Burney C, *et al. Blood* 2019

OS after start of ibrutinib



No. at risk					
<24 mo	32	24	20	16	9
>24 mo	34	31	25	23	15

	POD24	POD≥24	All patients
2-year OS, %	68	80	72

Adapted from Figure 2 in Ref. Burney C, *et al. Blood* 2019

A high ORR of 74% (CR 48%; PR 27%) was observed following ibrutinib therapy; however, the median duration of response was 10.1 months

Burney C, et al. Blood. 2019; 134:701

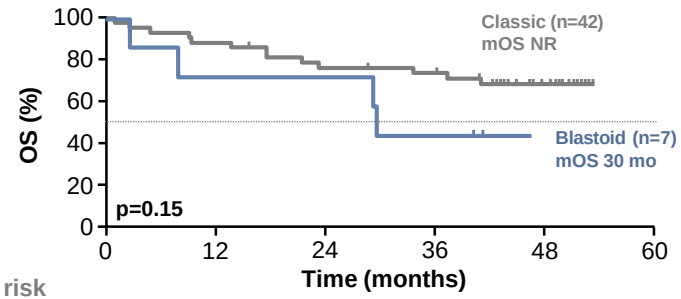
Outcomes Are Poor in Patients With R/R MCL and High-Risk Features After Treatment With Ibrutinib

Phase 2 open-label study of ibrutinib plus rituximab *(N=50; median 3 [range 1–6] prior lines of therapy)*

High-risk feature

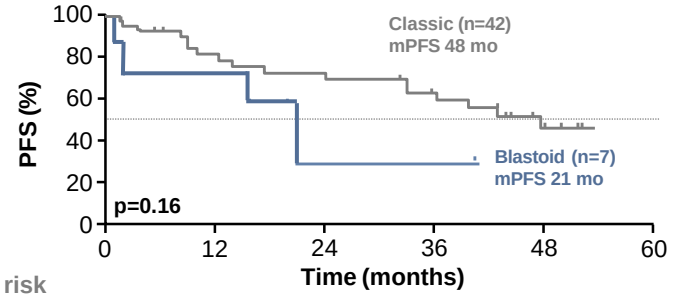
OS | **PFS**

MCL morphology (classic vs. blastoid)



No. at risk						
Blastoid	7	6	5	4	1	0
Classic	42	37	32	29	15	0

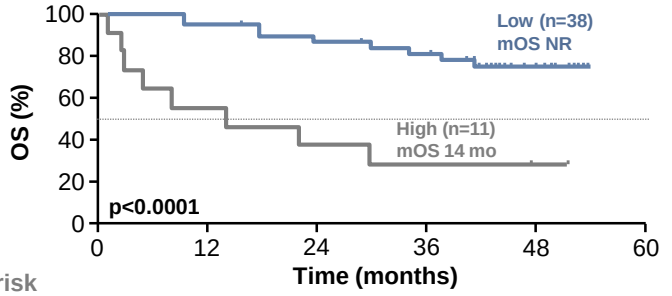
Adapted from Figure 2D in Ref. Jain P, *et al. Br J Haematol* 2018



No. at risk						
Blastoid	7	6	2	1	1	0
Classic	42	27	23	18	8	0

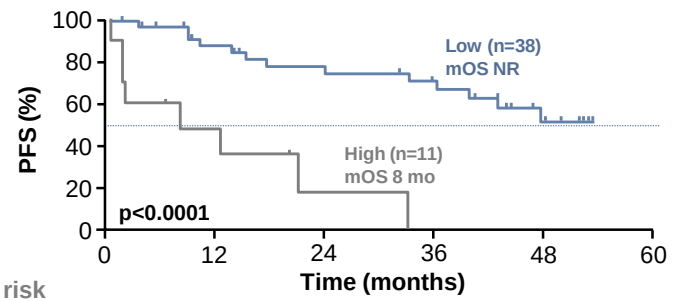
Adapted from Figure 2A in Ref. Jain P, *et al. Br J Haematol* 2018

Ki-67 index (low <50% vs. high ≥50%)



No. at risk						
Low	38	37	33	29	14	0
High	11	6	5	4	2	0

Adapted from Figure 2F in Ref. Jain P, *et al. Br J Haematol* 2018



No. at risk						
Low	38	29	23	18	8	0
High	11	4	2	1	1	0

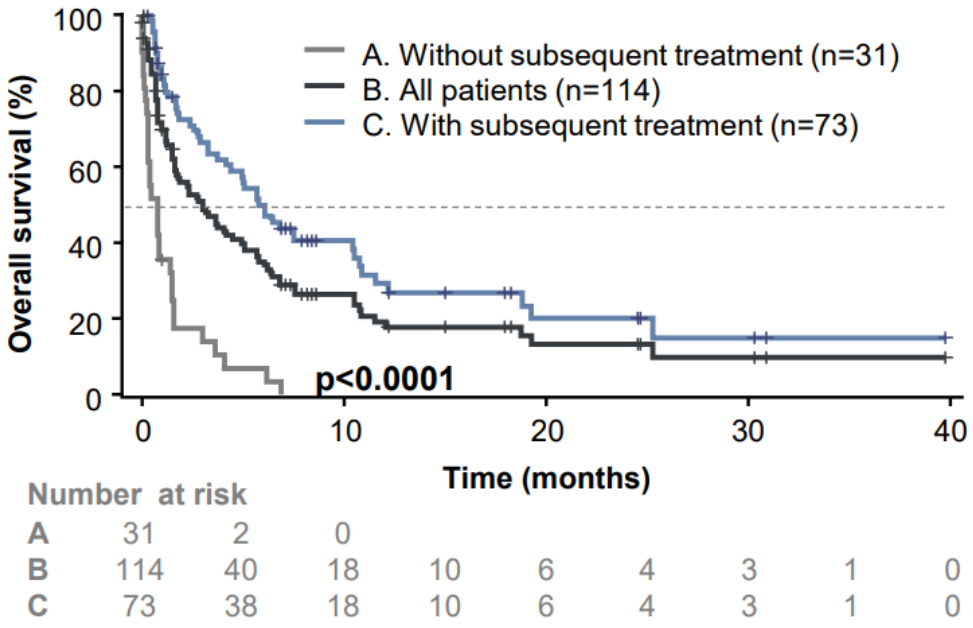
Adapted from Figure 2C in Ref. Jain P, *et al. Br J Haematol* 2018

Median OS and PFS were lower in patients with vs. without high-risk features

Jain P, et al. Br J Haematol 2018; 182:404–411

Outcome in MCL is Poor Following Covalent BTK Inhibitor Progression

OS of patients with MCL after ibrutinib cessation (± subsequent therapy) (N=114)



Adapted from Figure 1 in Ref. Martin P, et al. Blood 2016

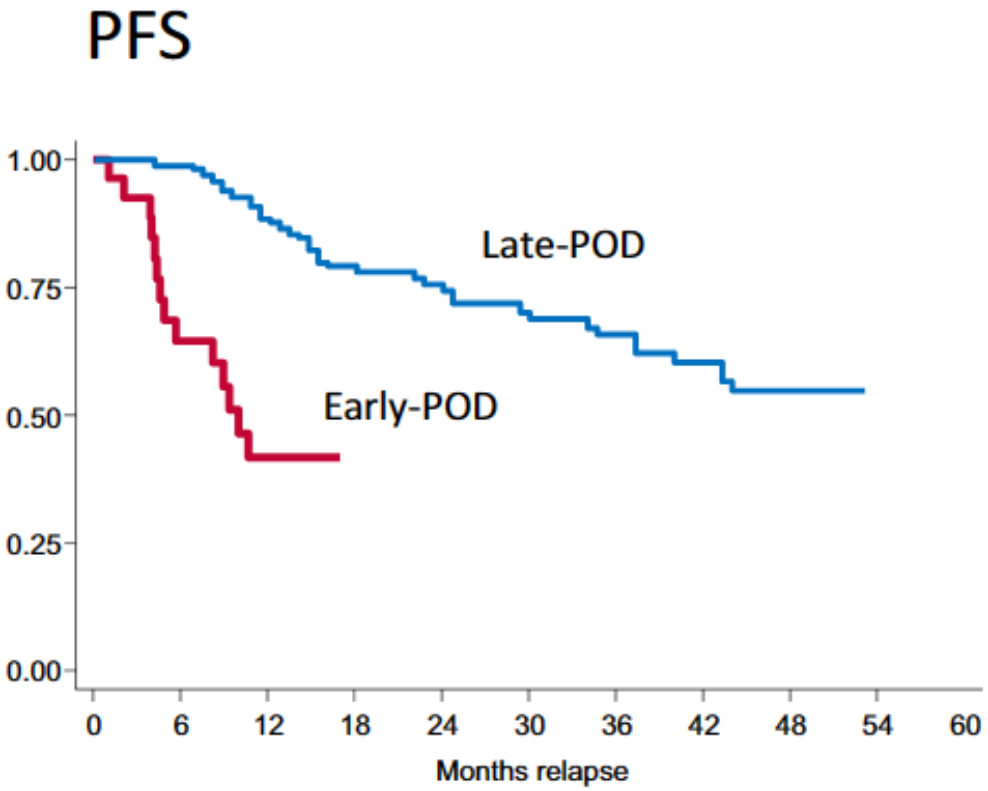
Median OS all patients: 2.9 months[1]

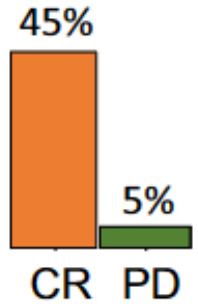
- The main cause of discontinuation is **disease progression***
  - Acquired resistance appeares to be universal[1]
  - Primary resistance to ibrutinib occurs in 1/3 patients[1]
- **Lower activity of ibrutinib in high-risk MCL (**Blastoid, TP53, ki67≥ 50%)*,[2]

Unmet medical needs[1]

Martin P, et al. Blood 2016; 127:1559-1563; 2. Jain P, et al. Br J Haematol 2018; 182:404–411

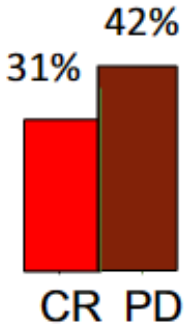
Ibrutinib at first relapse and CAR-T





Late-POD

Standard approach during BTKi
Refer to CAR-T centre if suboptimal response or high-risk features (i.e. TP53 mutation)



Early-POD

Refer to CAR-T centre at start of therapy
Close clinical monitoring
Restage 8-12 weeks

Patient identification at first relapse (before starting 2L): High risk patients

- Blastoid/pleomorfic morphology
- TP53 mut (including high expression of p53 with immunohistochemistry)
- Ki 67 > 50%
- Bulky > 5 cm
- POD24
- sMIPI high score

Visco, BJH 2023; Eyre BJH 2023

Current Treatment in Mantle Cell Lymphoma

Preferred First-line Treatment Options

Aggressive Chemotherapy
R-DHAP (cisplatin, or oxaliplatin)
R-CHOP/R-DHAP (alternating)
NORDIC (maxi-CHOP/R + HD cytarabine)

→ **Consolidation and Maintenance**
HDT + ASCT → R maint for 3 yr

Less Aggressive Chemotherapy
BR
R-CHOP
RBAC

→ **Maintenance**
After R-CHOP: R maint until Progression.

Preferred Second-line Treatment Options

BTK inhibitor
- Ibrutinib
- Pirtobrutinib (if previously treated with Ibrutinib)

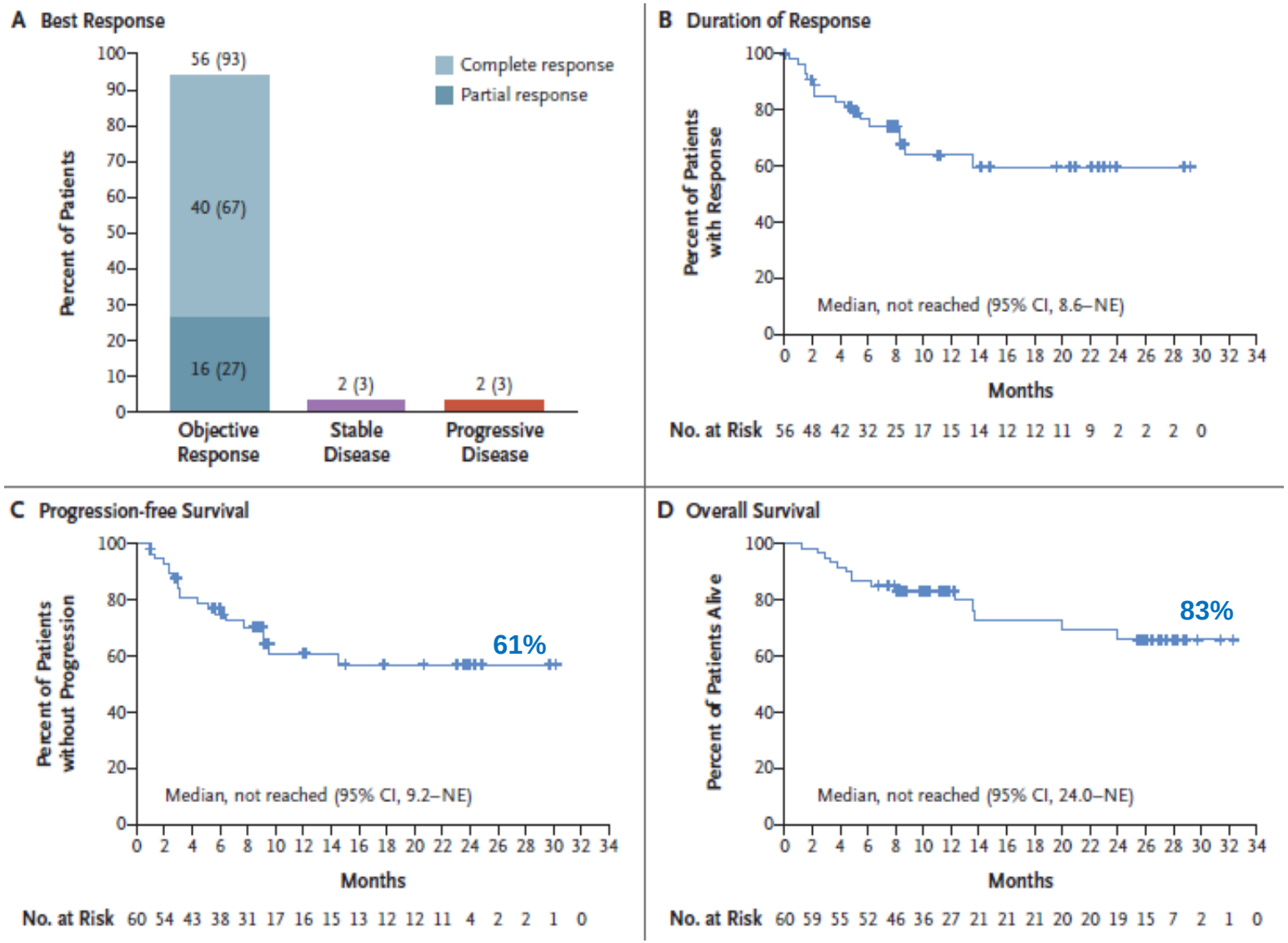
Third-line Treatment

Brexucabtagene autoleucel (after chemoimmunotherapy and BTK inhibitor)

Pirtobrutinib

Adattato da NCCN guidelines version 1.0 2024.

MCL ZUMA 2: phase 2 study



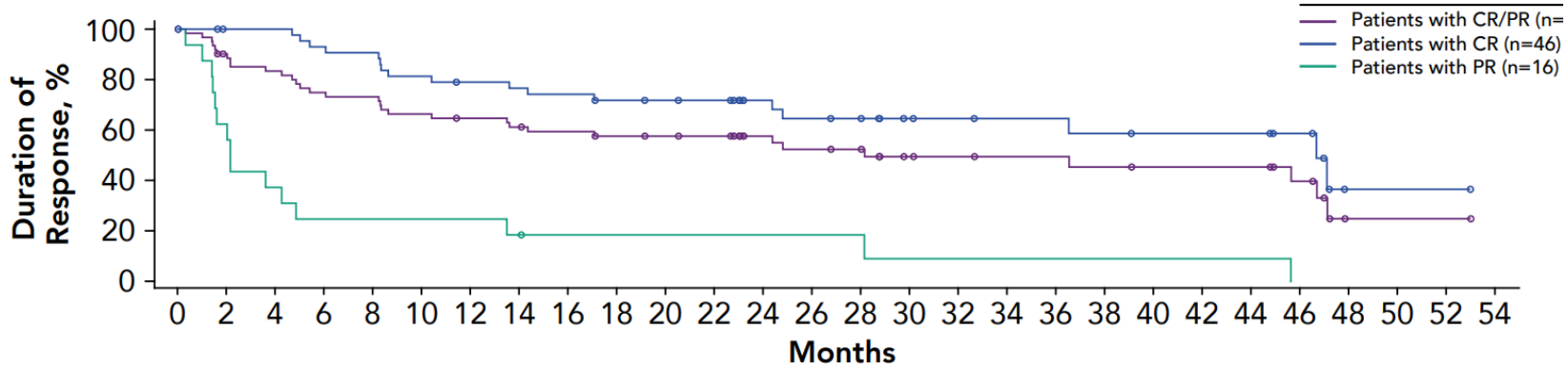
Median follow up: 12.3 months

74 patients enrolled

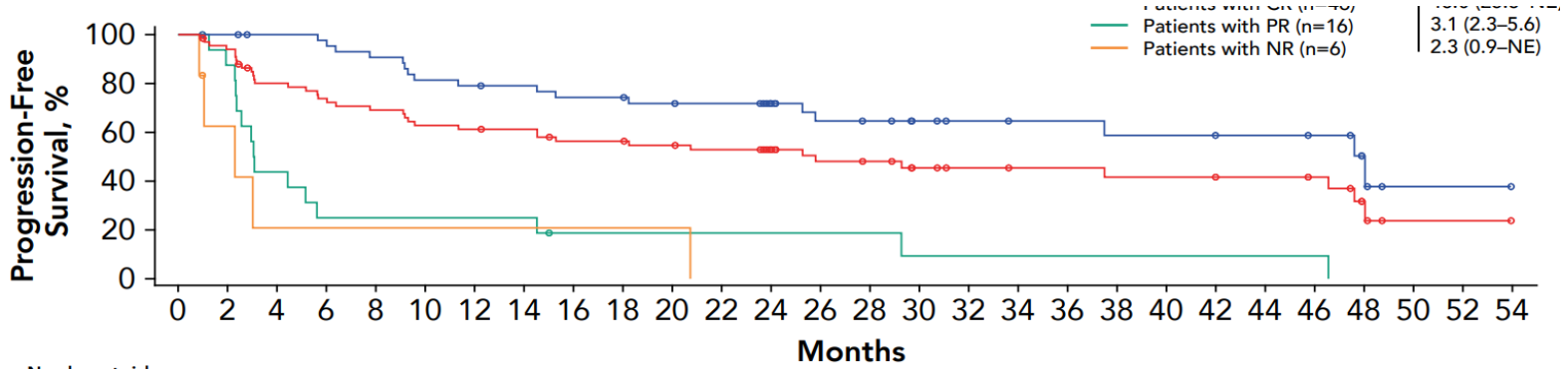
Wang M, et al. N Engl J Med 2020

Three-Year Follow-up of Outcomes With KTE-X19 in R/R MCL

DOR

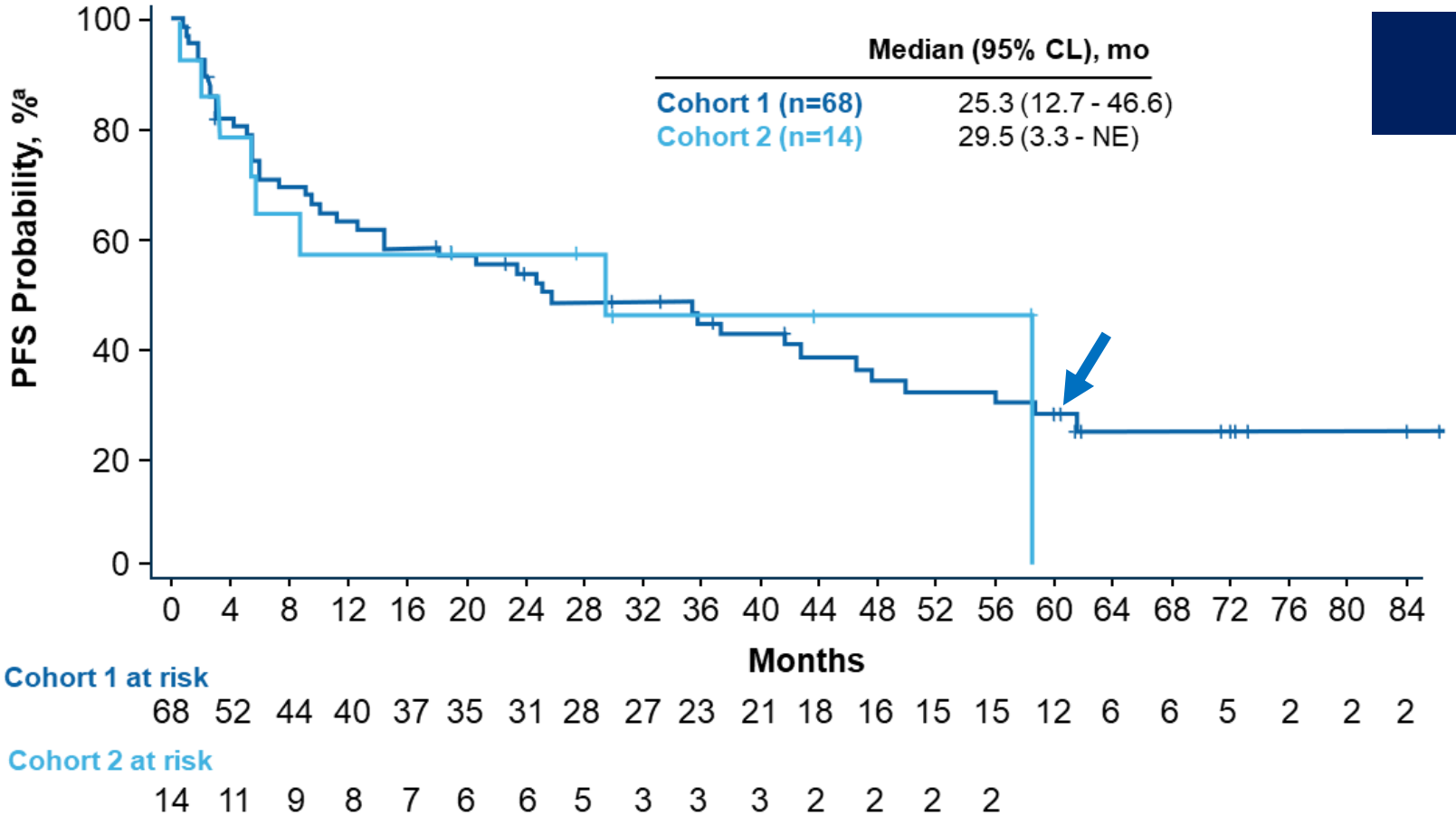


PFS



. *Wang M, et al. J Clin Oncol 2022;*

Patient disposition for ZUMA-2 Cohorts 1 and 2: follow up 5-years



ORR 93%
CR rate 64%

Median age 65
(38-79)

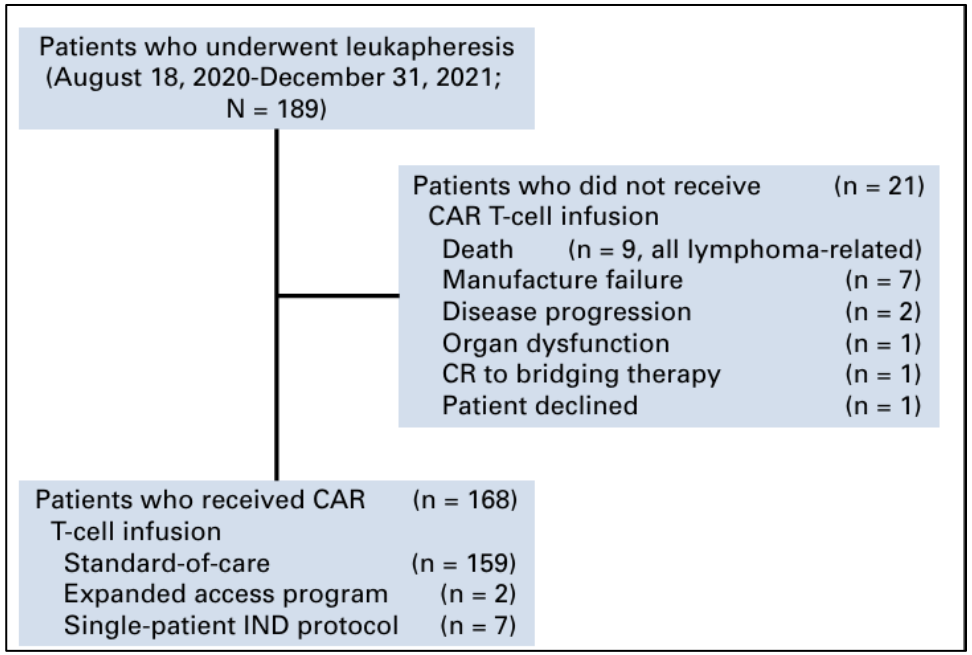
Median follow-up of 5 years

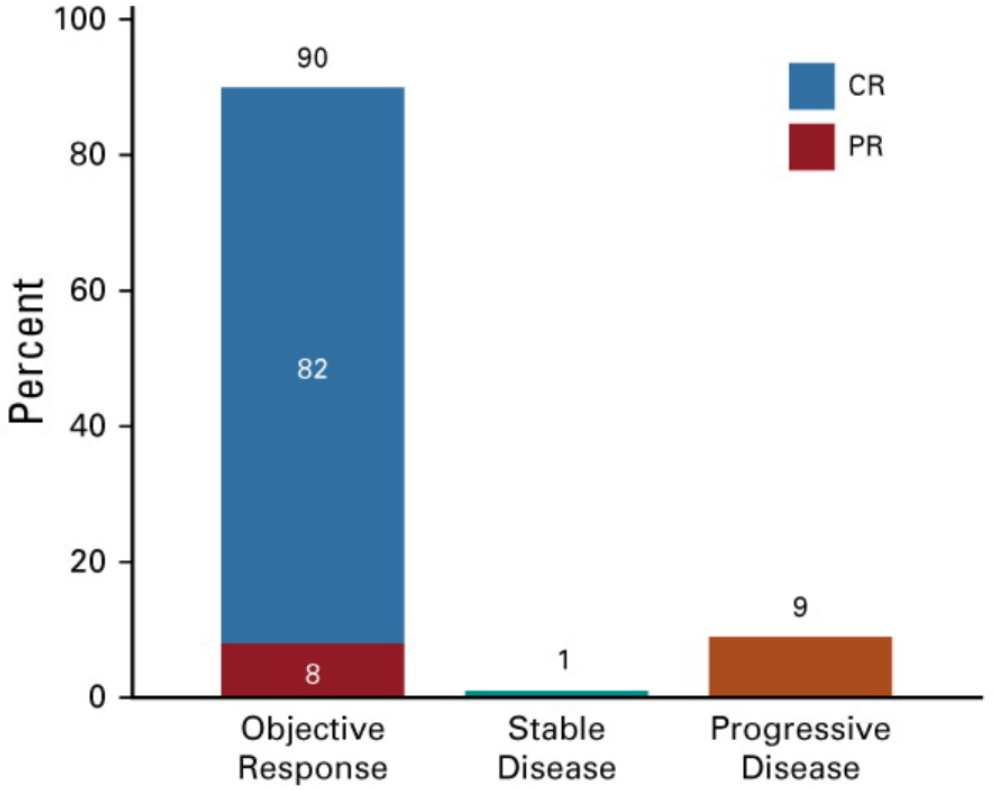
Late-onset toxicities were infrequent; only 3% of treatment-emergent adverse events of interest in ZUMA-2 occurred during this longer follow-up.

Wang M et al, ASH 2024

Brexu-cel for R/R MCL in Standard of Care Practice: results from the US consortium

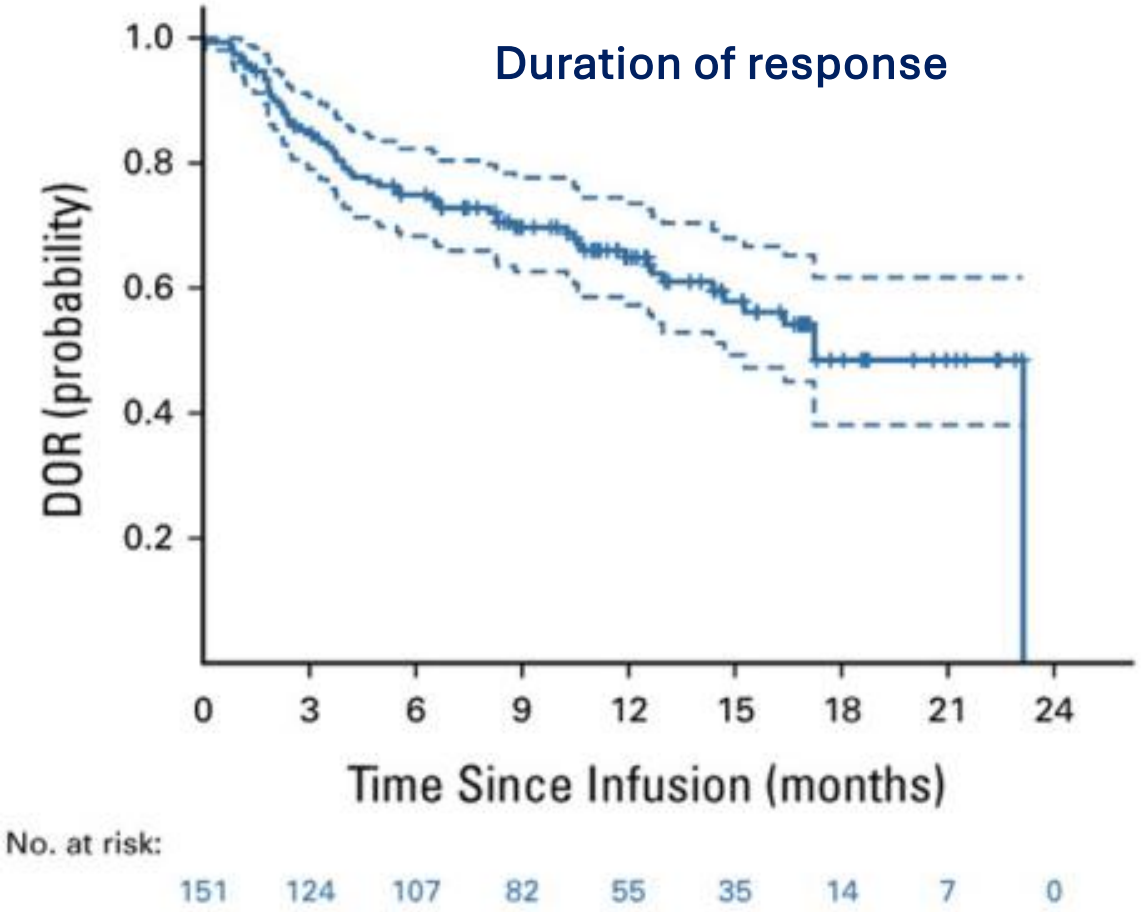
US Lymphoma CAR T Consortium: retrospective, multicenter study in patients receiving KTE-X19 (n= 189)

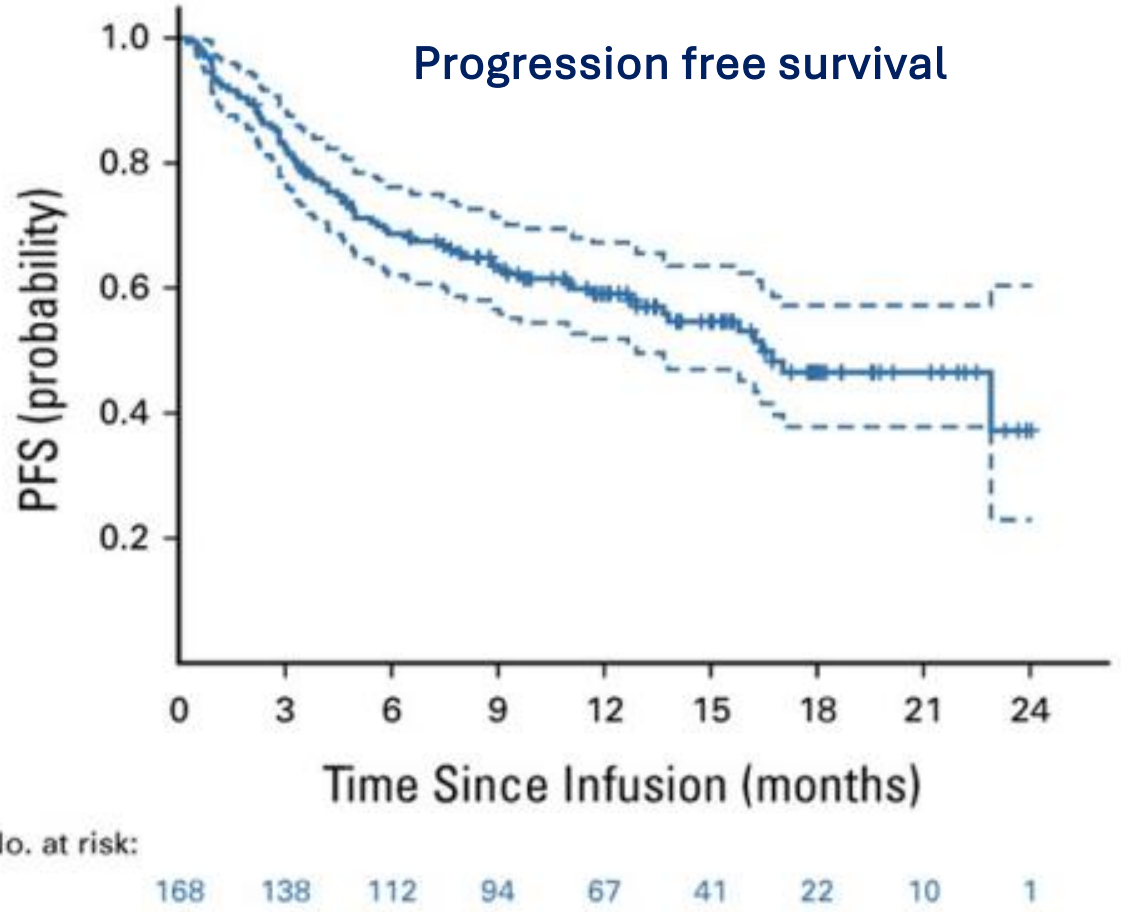




Wang Y, et al. JCO 2023

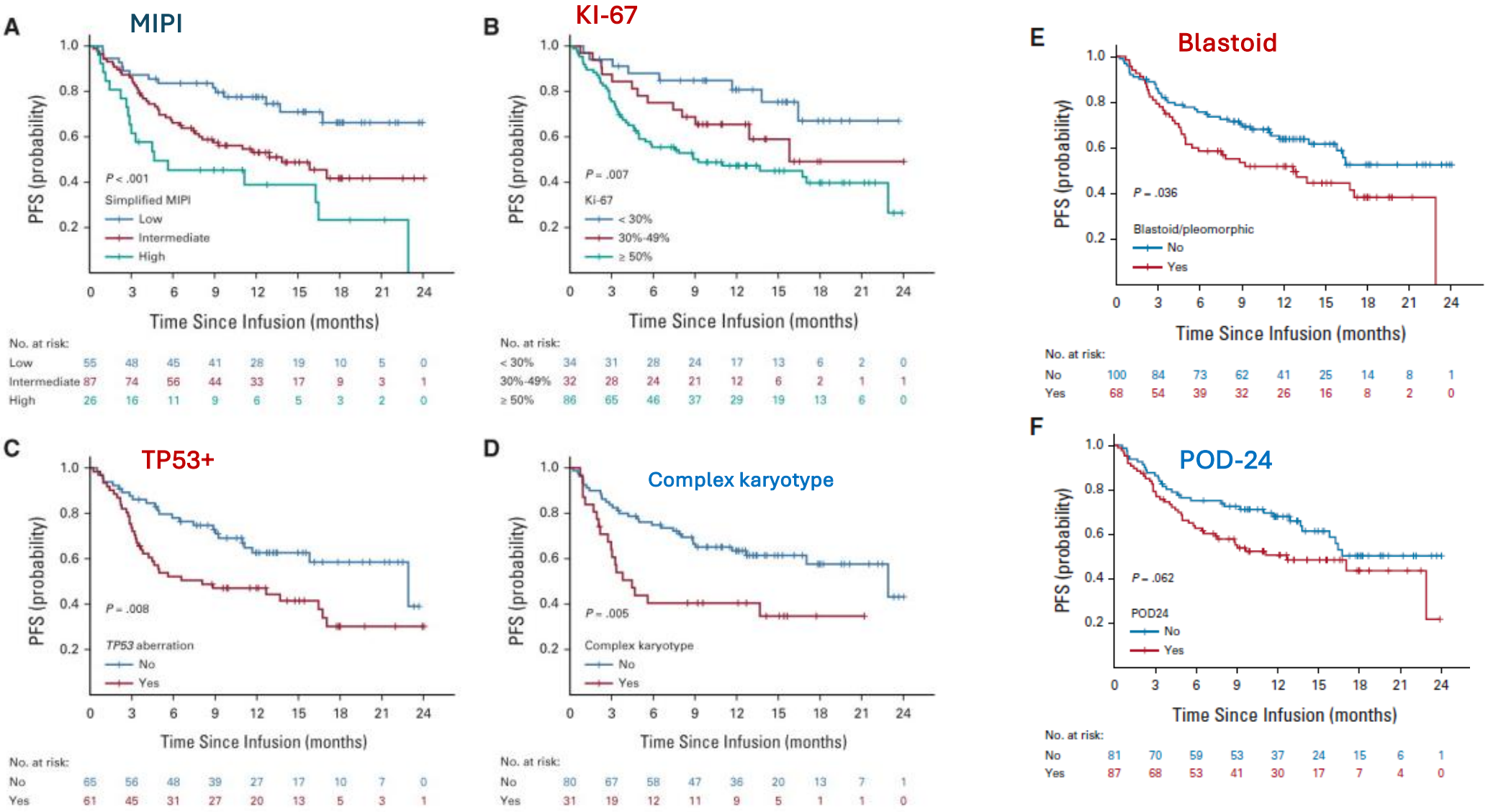
Brexu-cel for R/R MCL in Standard of Care Practice





Wang Y, et al. JCO 2023

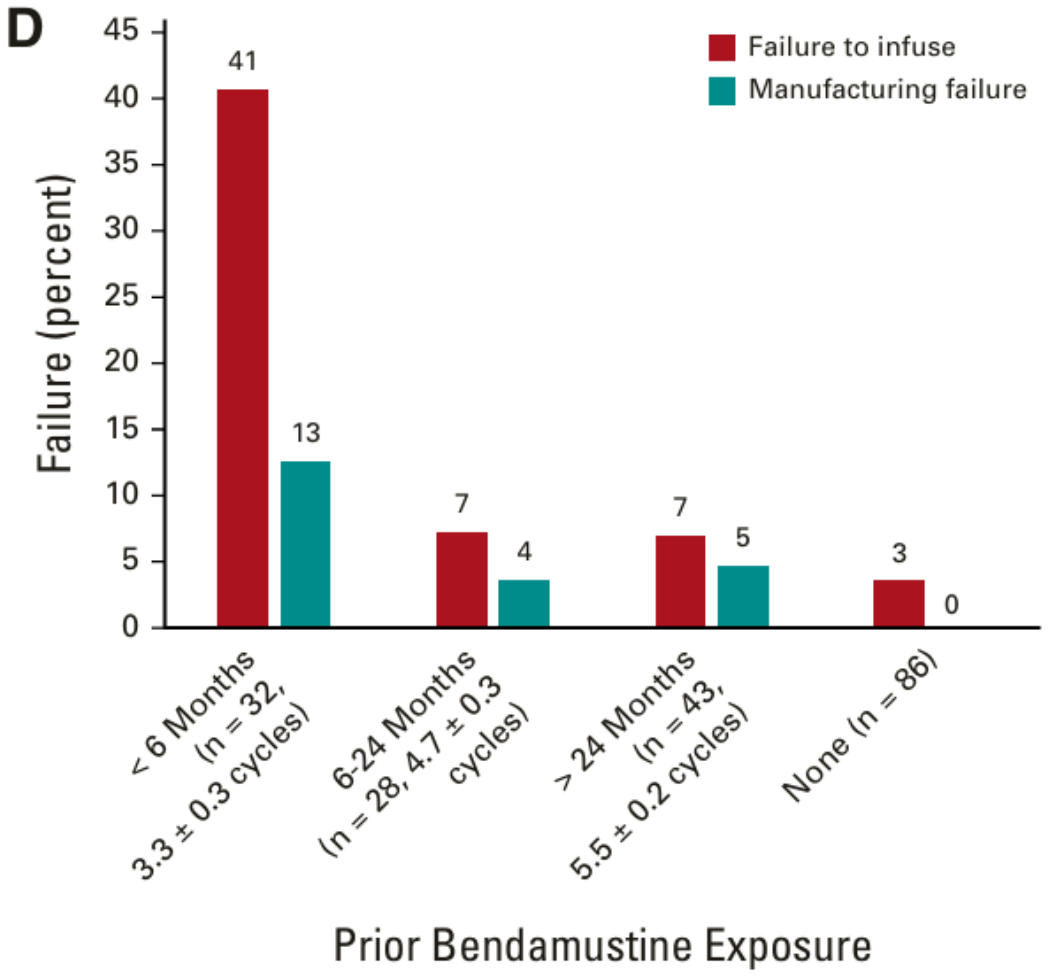
Brexu-cel for R/R MCL in Standard-of-Care Practice

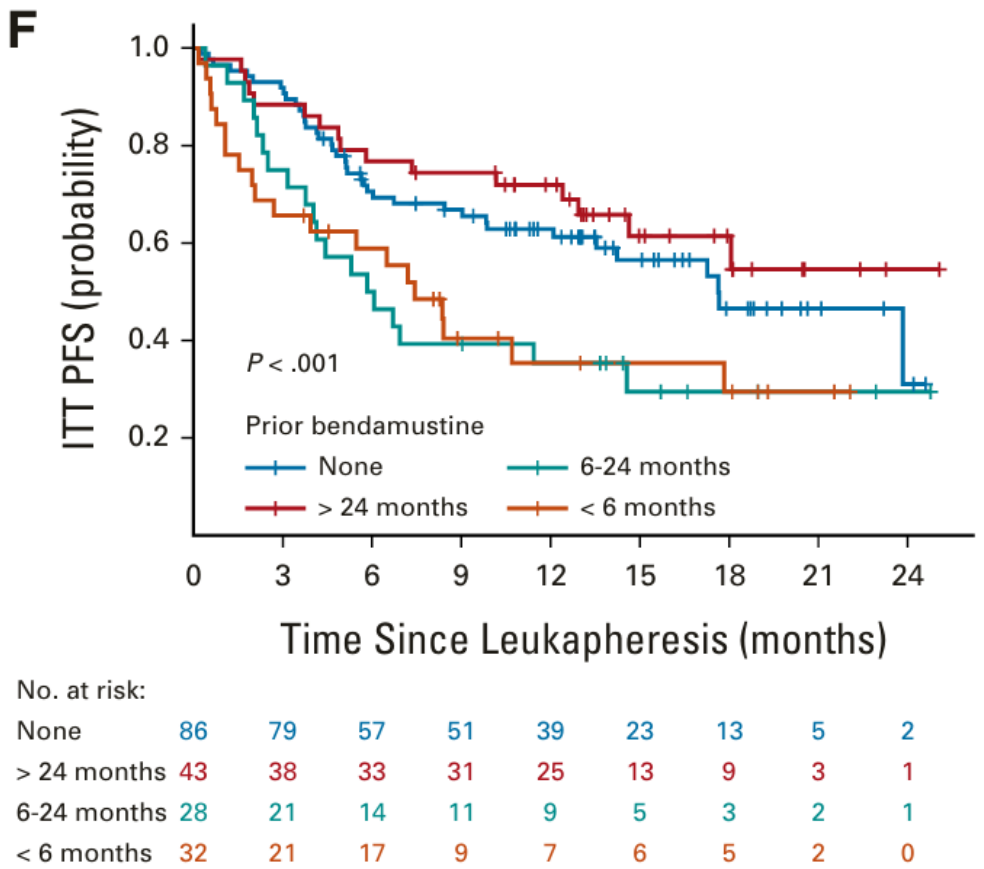


Wang Y, et al. JCO 2023

Prior Bendamustine exposure and outcomes

103/189 patients received prior bendamustine





No. at risk:

None	86	79	57	51	39	23	13	5	2
> 24 months	43	38	33	31	25	13	9	3	1
6-24 months	28	21	14	11	9	5	3	2	1
< 6 months	32	21	17	9	7	6	5	2	0

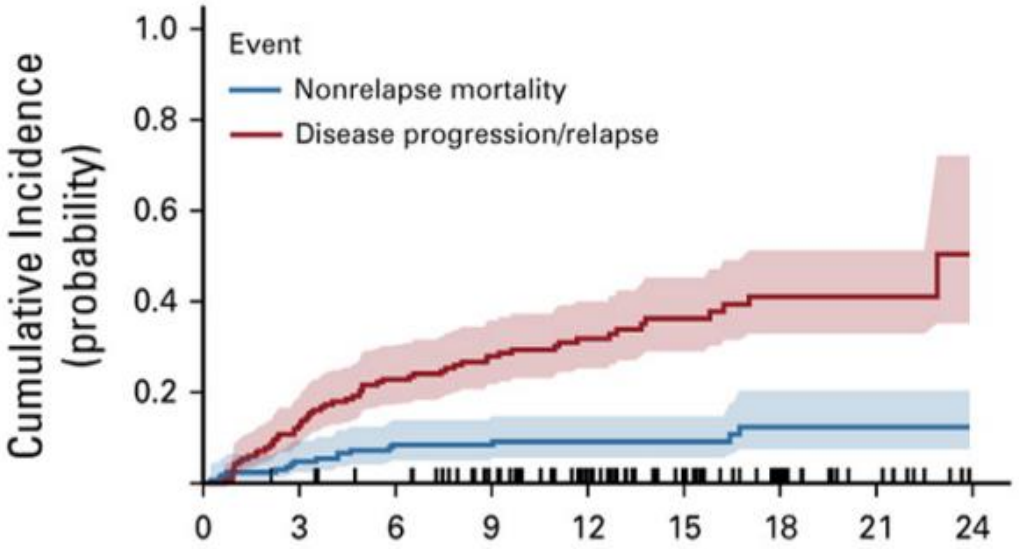
Wang Y, et al. JCO 2023

Short term and long term toxicity

- The incidences of CRS and ICANS were comparable to those reported in ZUMA-2.
- Tocilizumab and corticosteroids use appeared to be more frequent in this Consortium study cohort

	CRS, n (%)	ICANS, n (%)	ZUMA-2 CRS (%)	ZUMA-2 NE (%)
Total	86 (91%)	57 (60%)	91%	63%
Max Grade*				
1-2	78 (82%)	24 (25%)	76%	32%
3-4	8 (8%)	33 (35%)	15%	31%
Days to onset	4 (0-11)	6 (1-15)	2 (1-13)	7
Days to max Grade	5 (0-7)	7 (3-15)	-	-
Duration	5 (1-33+)	6 (2-144+)	11	12

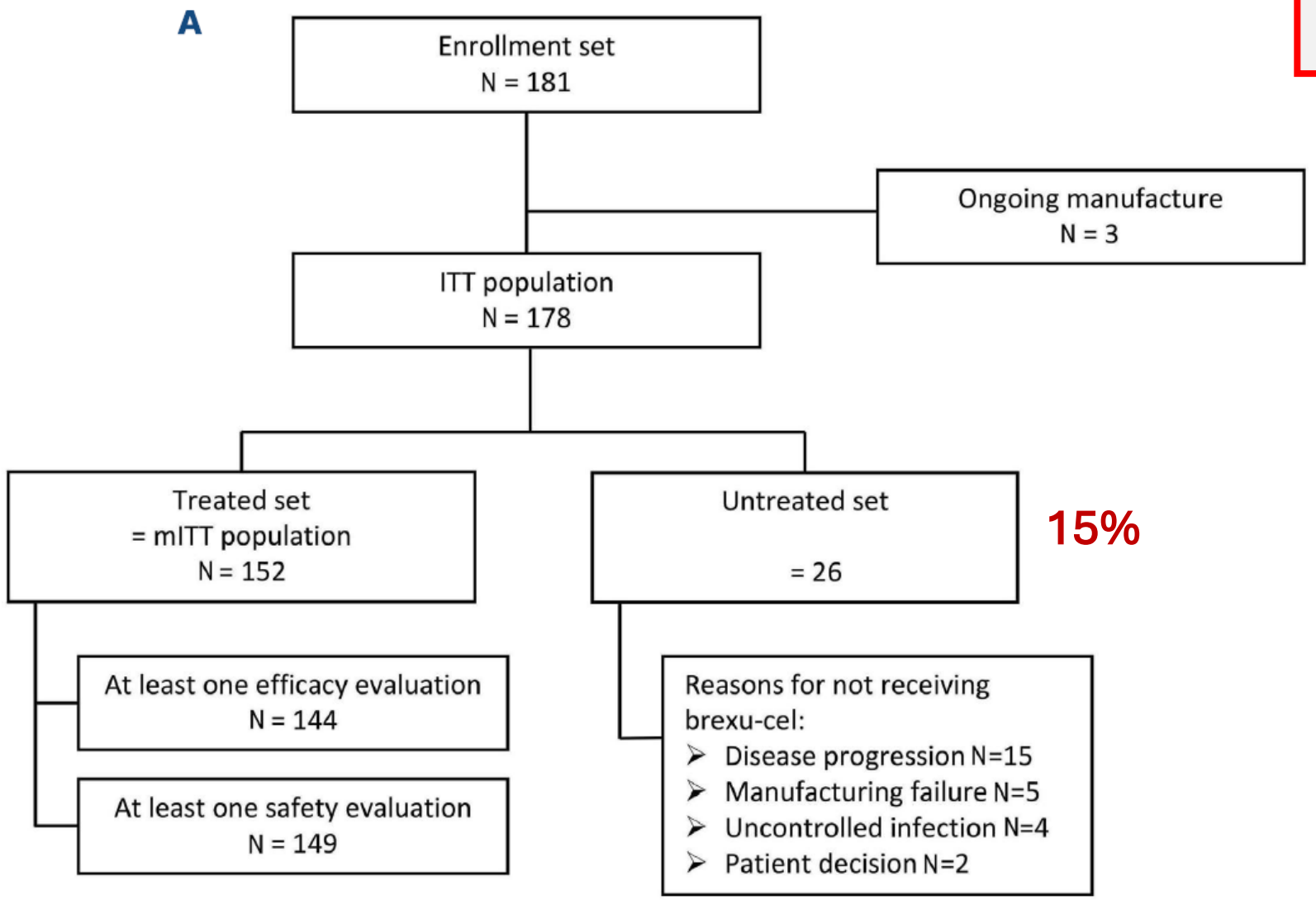
- **The non relapse mortality was 9.1% at 1 year**, primarily because of infections.



Wang Y, et al. JCO 2023

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

DESCART

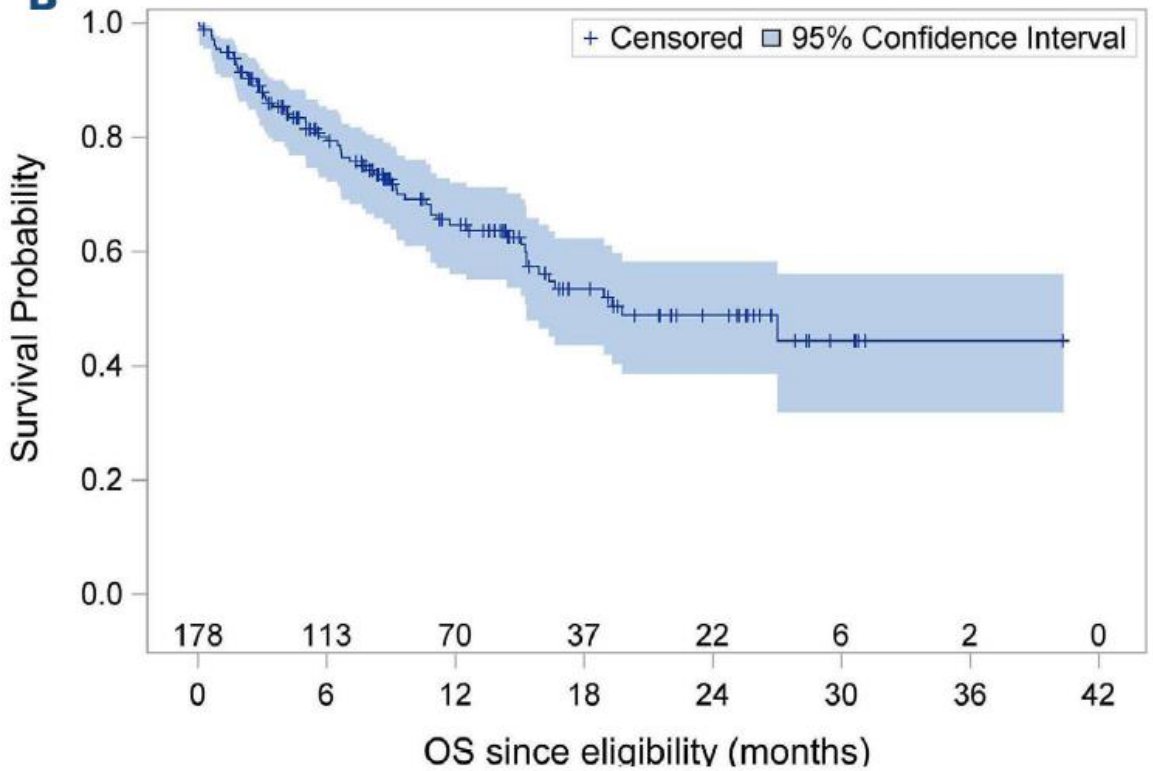


Herbaux C et al, Haematologica 2024

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

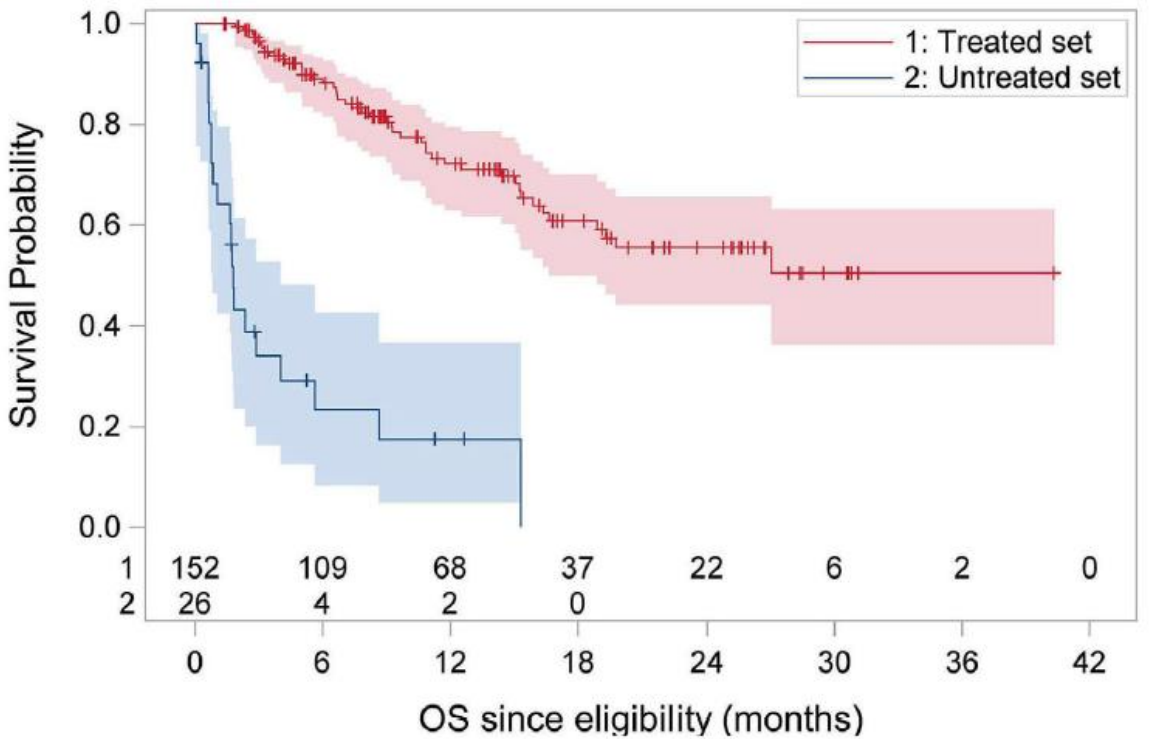
DESCART

B



Subjects	Event	Censored	Median Survival (95%CI)
178	36.5 % (65)	63.5 % (113)	19.8 (15.3 - NA)

C



	Subjects	Event	Censored	Median Survival (95% CI)
Treated set	152	29.6 % (45)	70.4 % (107)	Not reached (18.9 - NA)
Untreated set	26	76.9 % (20)	23.1 % (6)	1.8 (0.9 - 4)

Herbaux C et al, Haematologica 2024

DOI: 10.1111/bjh.19961

ORIGINAL PAPER
Transplantation and Cellular Therapy

Brexucabtagene autoleucel in-vivo expansion and BTKi refractoriness have a negative influence on progression-free survival in mantle cell lymphoma: Results from CART-SIE study

Federico Stella[1,2] | Annalisa Chiappella[2] | Martina Magni[2] | Francesca Bonifazi[3] | Chiara De Philippis[4] | Maurizio Musso[5] | Ilaria Cutini[6] | Silva Ljevar[7] | Anna Maria Barbui[8] | Mirko Farina[9] | Massimo Martino[10] | Massimo Massaia[11] | Giovanni Grillo[12] | Piera Angelillo[13] | Barbara Botto[14] | Francesca Patriarca[15] | Mauro Krampera[16] | Luca Arcaini[17,18] | Maria Chiara Tisi[19] | Pierluigi Zinzani[3] | Federica Sorà[20] | Stefania Bramanti[4] | Martina Pennisi[2] | Cristiana Carniti[2] | Paolo Corradini[1,2]

Società Italiana di Ematologia

CART-SIE

PI: Prof Paolo Corradini

Participants: all Italian qualified centers for CAR-T treatment

Aim of this analysis was to evaluate efficacy and safety outcomes of patients with R/R MCL treated with brexu-cel

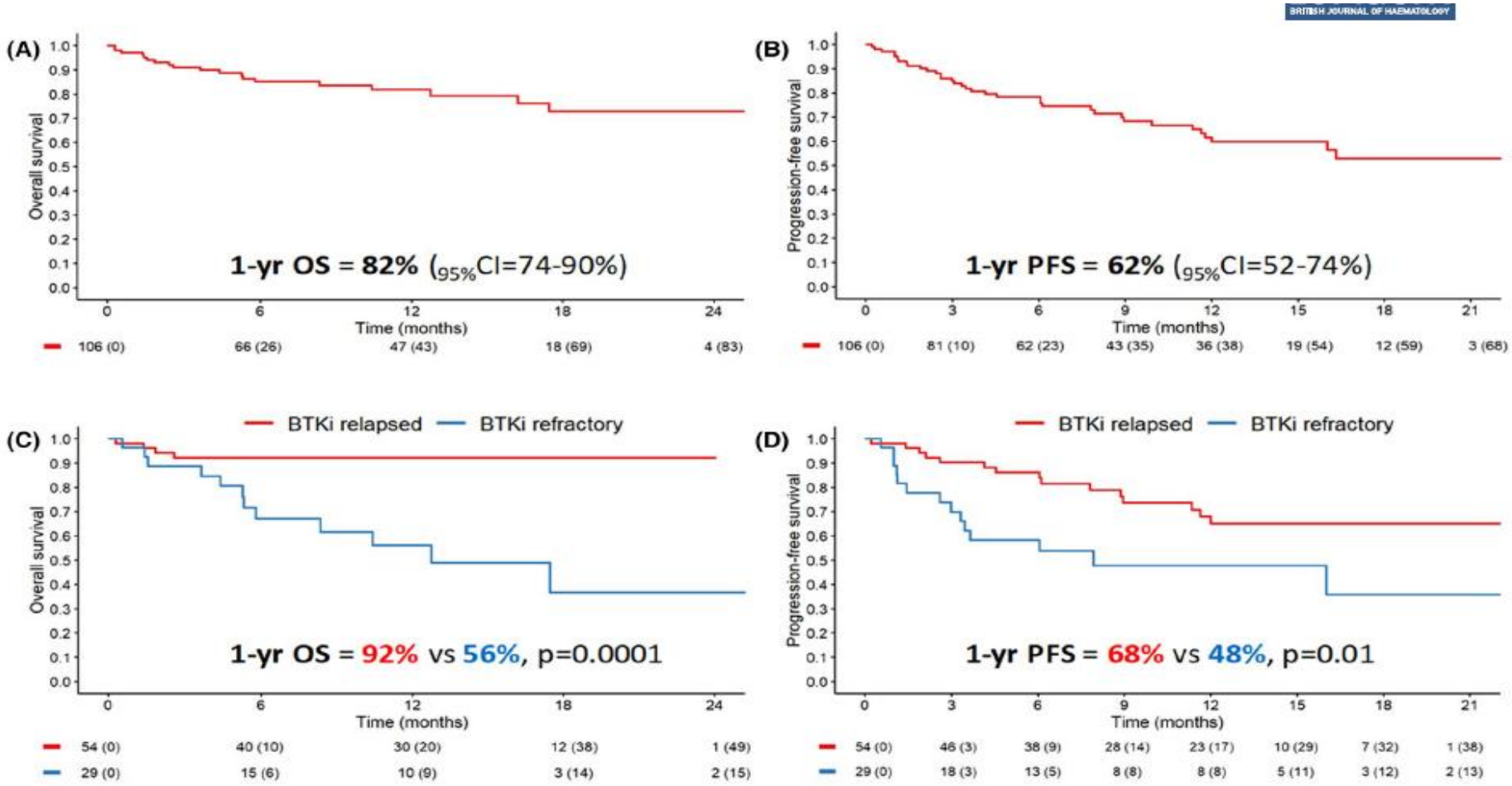
March 2019 – July 2024: 106 MCL

Stella F. et al, B.J.Hematology 2024

Brexucabtagene autocell in real word : PFS and OS

CART-SIE

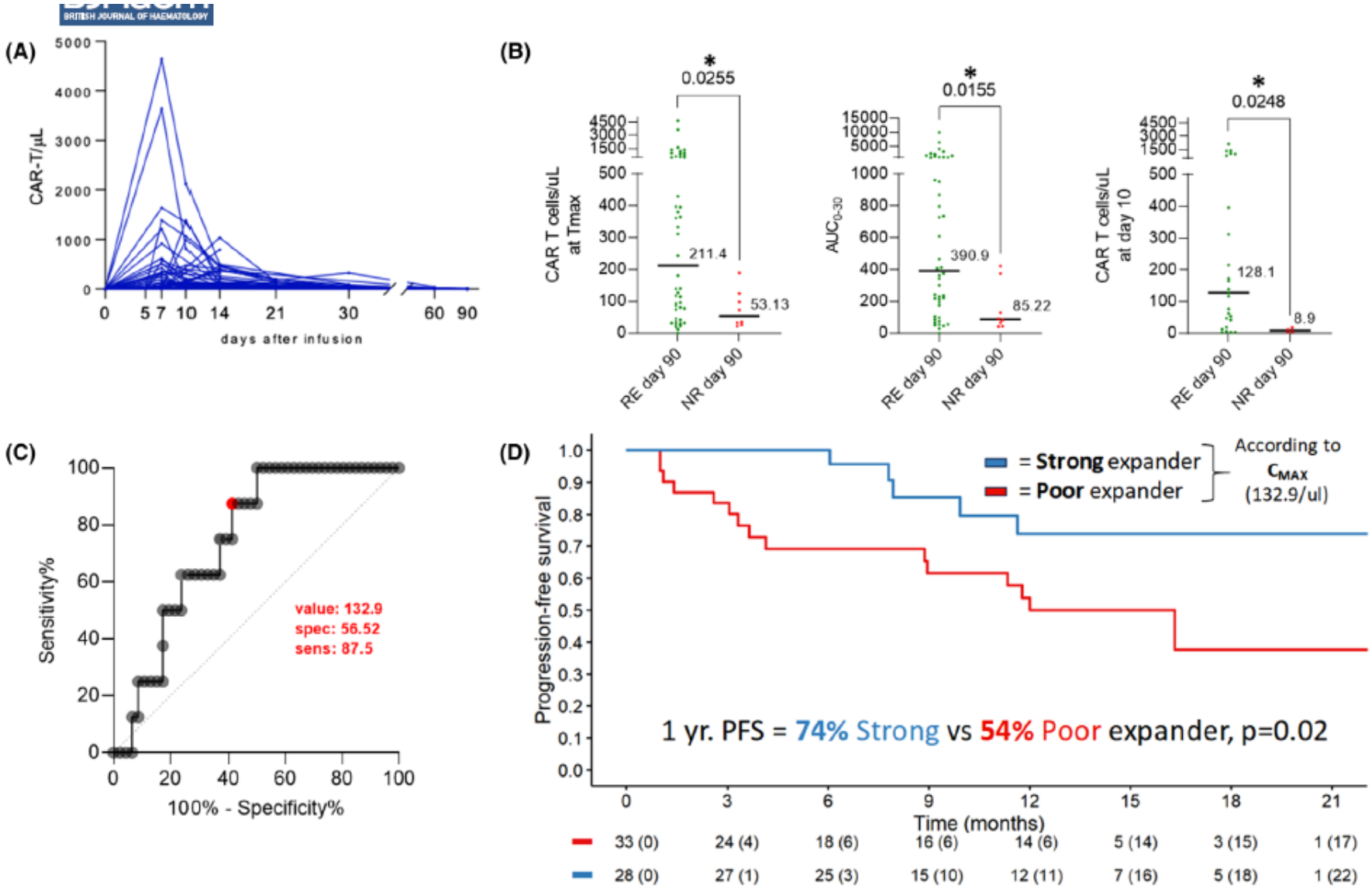
Responser day + 90: ORR 77%, CR 70%



Median follow-up: 12.07 months (IQR: 5.95, 17.86

Stella F. et al, B.J.Hematology 2024

In vivo Brexu-cell exspansion



Stella F. et al, B.J.Hematology 2024

Current Treatment in Mantle Cell Lymphoma

Preferred First-line Treatment Options

Aggressive Chemotherapy
R-DHAP (cisplatin, or oxaliplatin)
R-CHOP/R-DHAP (alternating)
NORDIC (maxi-CHOP/R + HD cytarabine)

→ **Consolidation and Maintenance**
HDT + ASCT → R maint for 3 yr

Less Aggressive Chemotherapy
BR
R-CHOP
RBAC

→ **Maintenance**
After R-CHOP: R maint until Progression.

Preferred Second-line Treatment Options

BTK inhibitor
- Ibrutinib
- Pirtobrutinib (if previously treated with Ibrutinib)

Third-line Treatment

Brexucabtagene autoleucel (after chemoimmunotherapy and BTK inhibitor)

Pirtobrutinib

Adattato da NCCN guidelines version 1.0 2024.

Glofitamab RR-MCL : baseline characteristics by prior BTKi

n (%) of patients unless stated		Prior BTKi (n=31)*	BTKi naïve (n=29)*	All patients (N=60)*
Median age, years (range)		70.0 (41–84)	72.0 (52–86)	72.0 (41–86)
Male		23 (74.2)	21 (72.4)	44 (73.3)
Ann Arbor stage III/IV		28 (90.3)	24 (82.8)	52 (86.7)
MCL IPI score ≥6		7 (22.6)	8 (27.5)	15 (25.0)
Median no. of prior lines (range)		3.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Median time since last prior therapy to first study treatment, months (range)		1.3 (0.1–53.2)	7.4 (1.1–132.5)	2.4 (0.1–132.5)
Median time since last anti-CD20 therapy to first study treatment, months (range)		15.1 (0.7–159.0)	25.1 (1.4–132.5)	16.3 (0.7–159.0)
Refractory status	Refractory to any prior therapy	30 (96.8)	20 (69.0)	50 (83.3)
	Refractory to 1L therapy	17 (54.8)	14 (48.3)	31 (51.7)
	Refractory to last prior therapy	27 (87.1)	17 (58.6)	44 (73.3)

A higher proportion of patients with prior BTKi therapy were refractory to their last prior therapy compared with BTKi-naïve patients

1. Philips T, et al. ASH 2021; oral presentation (abstract #130).
2. Philips T, et al. ASH 2022; oral presentation (abstract #74).

Glofitamab in RR-MCL: step up dosing

Phase I dose escalation in R/R MCL[1,2]

Glofitamab IV administration

- **Fixed-duration treatment: maximum 12 cycles**
  - Fixed dosing: 0.6mg, 16mg or 25mg Q3W*[1]
  - Step-up dosing: target dose 30mg Q3W†

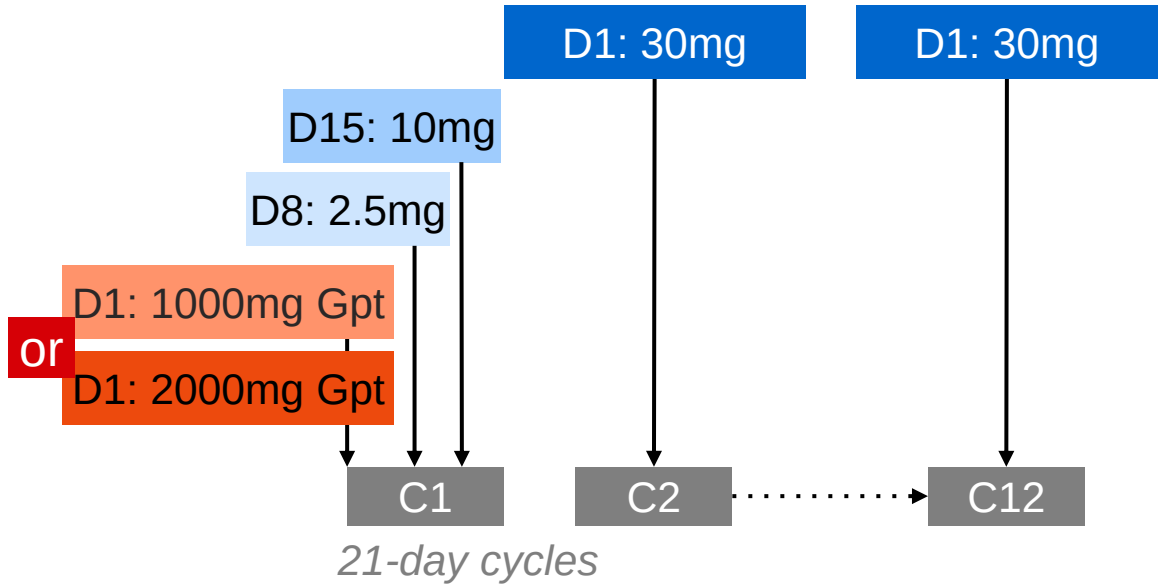
CRS mitigation

- Obinutuzumab pretreatment: 1 x 1000mg or 1 x 2000mg (2000mg option with step-up dosing only)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)

Population characteristics:

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS ≤1

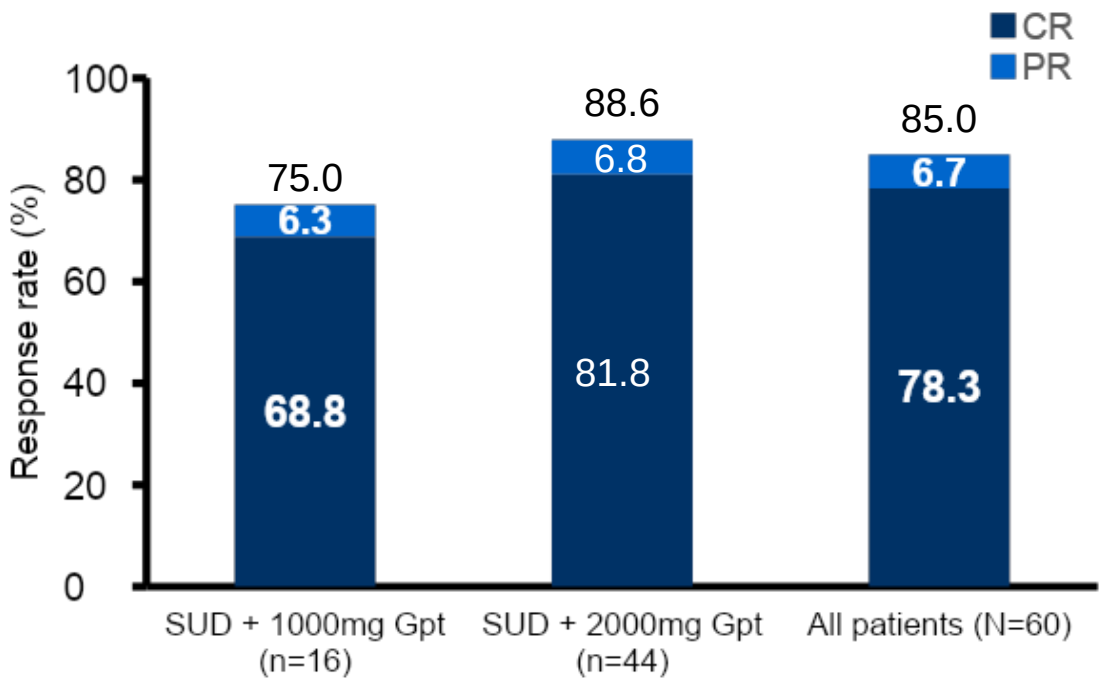
Glofitamab step-up dosing schedule[2]



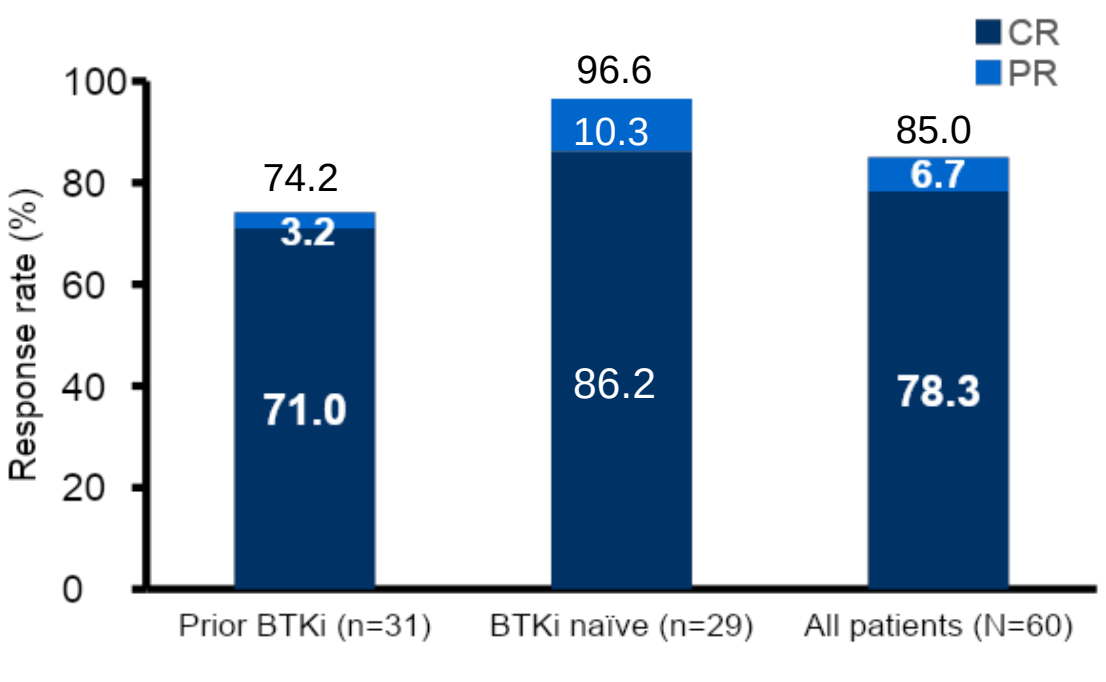
1. Philips T, et al. ASH 2021; oral presentation (abstract #130).
2. Philips T, et al. ASH 2022; oral presentation (abstract #74).

Glofitamab : Response rates by regimen and prior BTKi

All patients



Patients with prior BTKi

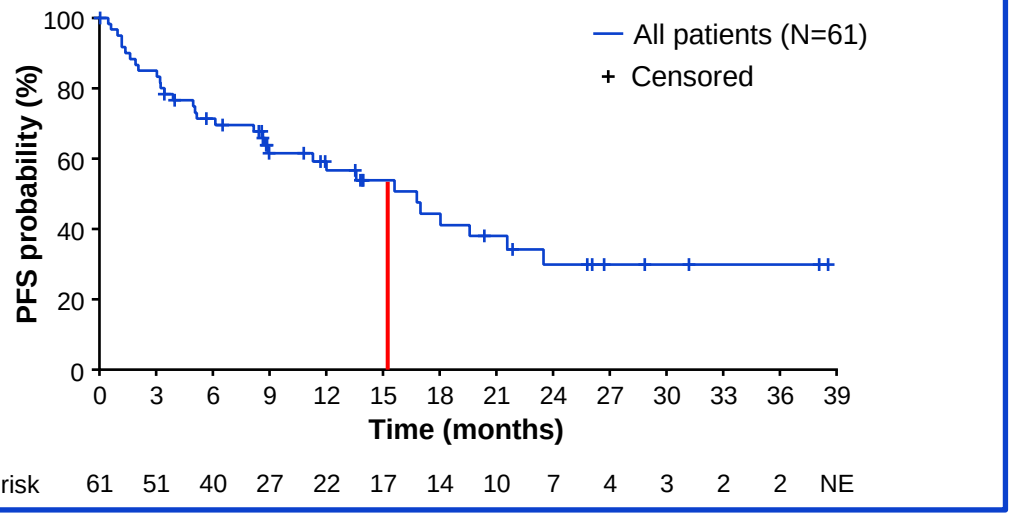


- **Median time to first response among responders (n=51): 42 days (95% CI: 42.0–45.0)**
- **High response rates in the overall population and in both BTKi-naïve patients and those with prior BKTi therapy**

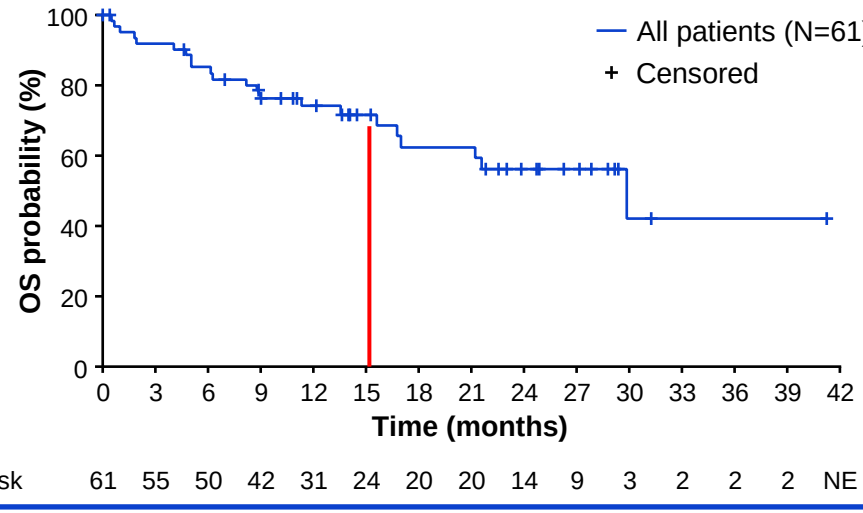
Philips T, et al. J Clin Oncol October 4, 2024

Glofitamab : Time-to-event endpoints

PFS



OS†



	Prior BTKi n=32*	All patients N=61*
Median PFS follow-up, months (95% CI)	26.1 (13.5–31.2)	19.6 (11.9–26.1)
Median PFS, months (95% CI)	8.6 (3.4–15.6)	**16.8 (8.9–21.6)**
15-month PFS rate, % (95% CI)	33.0 (14.8–51.1)	54.0 (40.1–67.8)

	Prior BTKi n=32*	All patients N=61*
Median OS follow-up, months (95% CI)	24.7 (13.6–28.8)	21.8 (14.0–24.9)
Median OS, months (95% CI)	21.2 (9.0–NE)	**29.9 (17.0–NE)**
15-month OS rate, % (95% CI)	55.0 (36.5–73.6)	71.4 (59.3–83.5)

- **Clinically significant PFS and OS at 15 months were achieved with fixed-duration glofitamab**

Philips T, et al. J Clin Oncol October 4, 2024

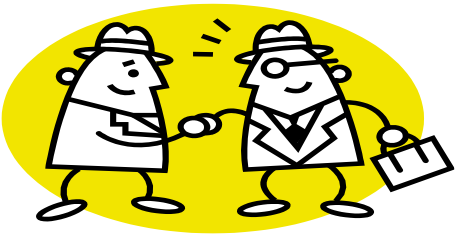
Glofitamab : AEs of interest CRS and ICANS

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
Any grade CRS*	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)
Grade 4	2 (12.5)	0	2 (3.3)
Serious AE of CRS†	11 (68.8)	12 (27.3)	23 (38.3)

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
Infections			
Any grade	12 (75.0)	32 (72.7)	44 (73.3)
Grade 3/4	4 (25.0)	9 (20.5)	13 (21.7)
Grade 5	2 (12.5)	6 (13.6)	8 (13.3)
ICANS (derived) related to glofitamab			
Any grade	2 (12.5)	1 (2.3)	3 (5.0)
Grade 1	1 (6.3)*	1 (2.3)‡	2 (3.3)
Grade 2	1 (6.3)†	0	1 (1.7)

- **The majority of CRS events were Grade 1/2, and a lower incidence of CRS was observed in the 2000mg versus 1000mg cohort**

Philips T, et al. J Clin Oncol October 4, 2024



SAPIENZA
UNIVERSITÀ DI ROMA

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERO-UNIVERSITARIA
POLICLINICO UMBERTO I

FONDAZIONE
ITALIANA
LINFOMI

Gruppo per la terapia dei linfomi non Hodgkin
Ematologia Sapienza Roma

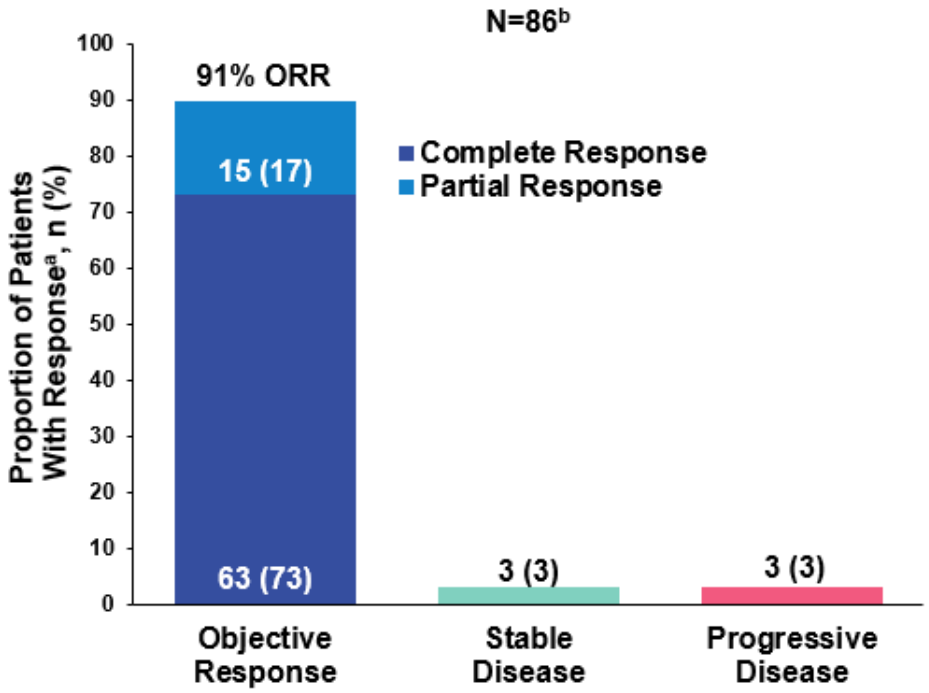
Grazie!

… a voi tutti per l'attenzione

Patient disposition and response for ZUMA-2 Cohorts 3

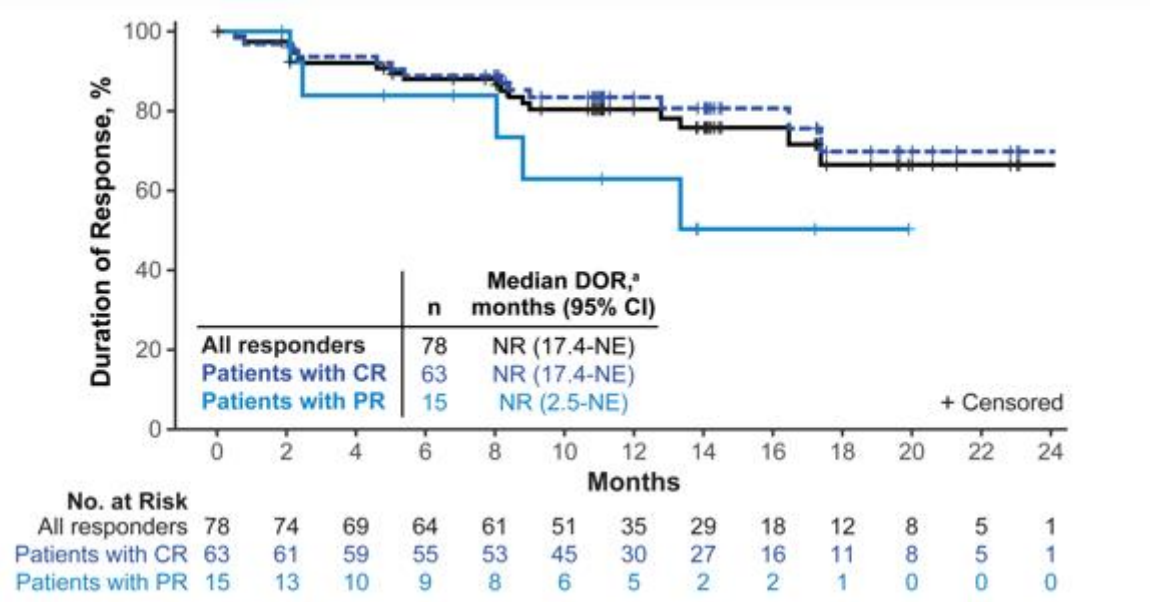
BTKI naive

Characteristic[a]	Cohort 3 (N=86)
Median age (range), years	64 (40-82)
Male, n (%)	67 (78)
ECOG PS of 1, n (%)	27 (31)
Intermediate and high simplified MIPI, n (%)	63 (73)
TP53 IHC by central laboratory performed,[b] n (%)	59 (69)
TP53 ≥50%, n (%)	7 (8)
TP53 mutation status by local laboratory performed,[c] n (%)	33 (38)
Yes	15 (17)
No	18 (21)
Ki-67 IHC by central laboratory performed,[b] n (%)	59 (69)
Ki-67 ≥30%	40 (47)
Ki-67 ≥50%	18 (21)
LDH relative to upper limit, n (%)	
LDH >ULN	49 (57)
Median tumor burden (SPD) by central read (mm^2),[d] (range)	1734 (204-31,212)
Extranodal disease, n (%)	45 (52)
Bone marrow involvement from diagnosis history, n (%)	34 (40)

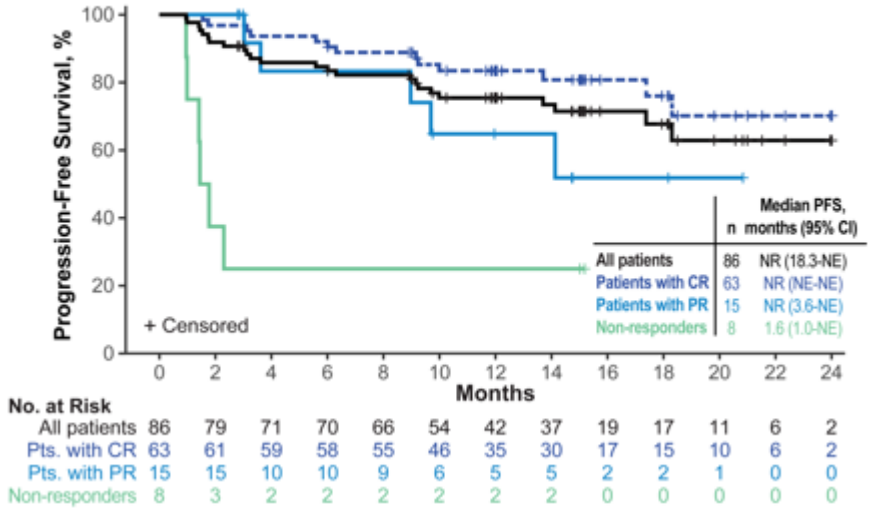


Wang M et al, ASH 2024

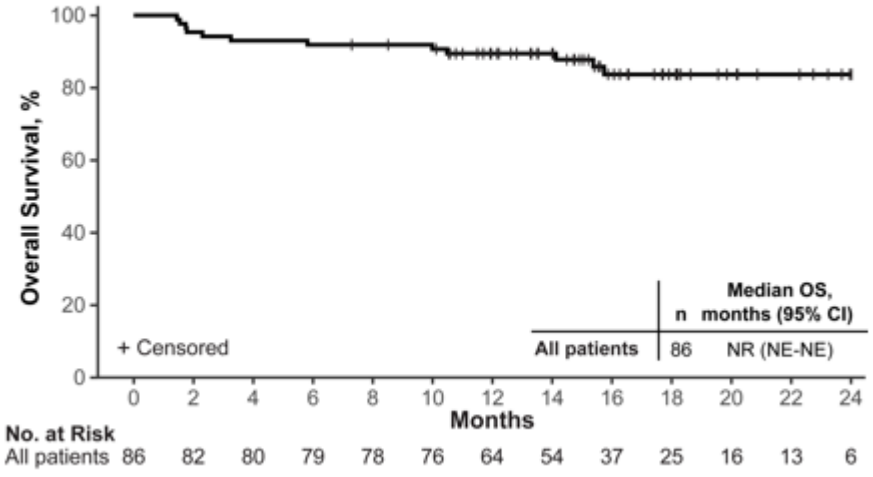
Patient disposition for ZUMA-2 Cohorts 3: survival curves



Progression-Free Survival[a]



Overall Survival



Wang M et al, ASH 2024