Società Italiana di Ematologia

3rd MEETING ON T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

CAR T-cell therapy for mantle cell lymphoma

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BOLOGNA, ROYAL HOTEL CARLTON
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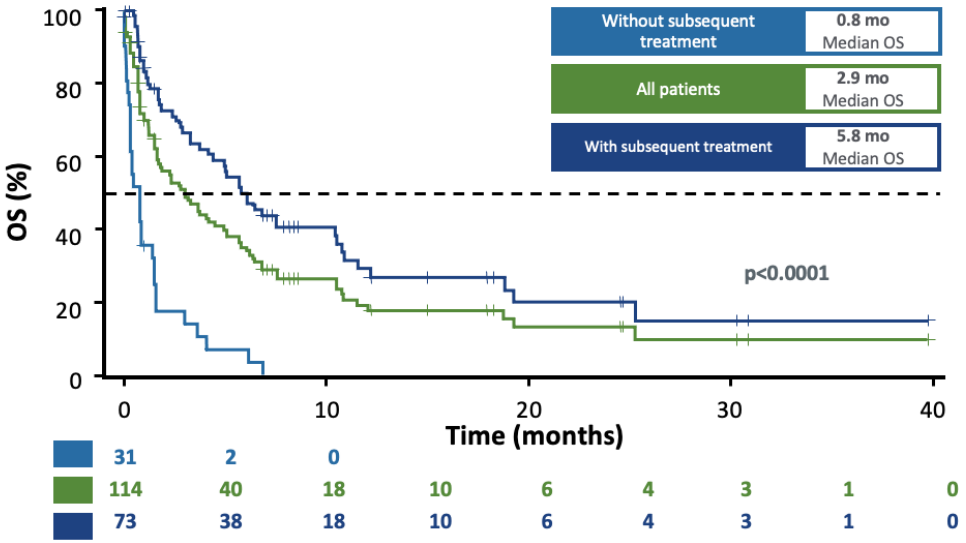
Disclosures of Gloria Iacoboni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite/Gilead						x	x
Novartis						x	x
BMS							x
Abbvie							x
AstraZeneca							x
Miltenyi						x	x
Autolus						x	
Sandoz							x

Outcomes for patients with MCL after BTKi therapy

Overall survival of patients with MCL after ibrutinib cessation (± subsequent therapy; N=114)[2]



Despite the efficacy of BTKi in R/R MCL:

- The main cause of discontinuation is **disease progression,**[1–4]
  - Acquired resistance appears to be universal[2]
  - Primary resistance to ibrutinib occurs in ~1/3 of patients[2]
- **Lower activity of ibrutinib** in **high-risk MCL** (blastoid,[3,4] *TP53*,[4] Ki-67>50%[4])

Key unmet needs in R/R MCL

BTK: Bruton's tyrosine kinase; BTKi: BTK inhibitor; ORR: overall response rate; OS: overall survival

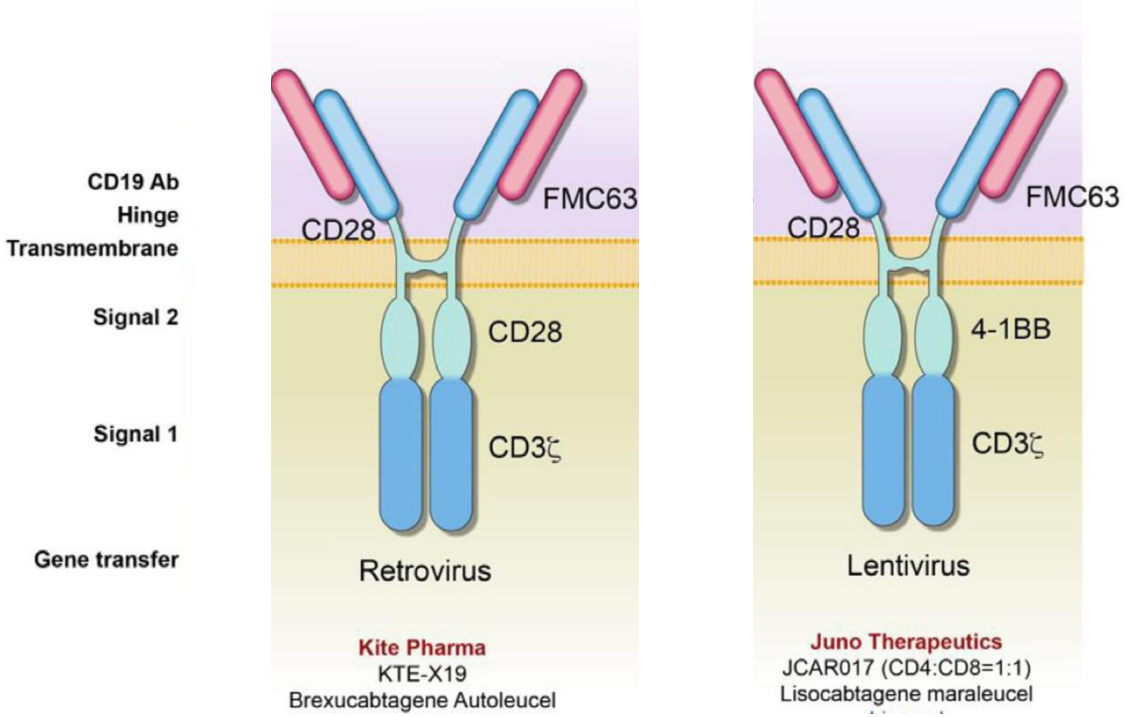
1. Wang M, *et al. Blood* 2015; 126:739–745. 2. Martin P, *et al. Blood* 2016; 127:1559–1563. 3. Rule S, *et al. Br J Haematol* 2017; 179:430–438.
4. Jain P, *et al. Br J Haematol* 2018; 182:404–411. 5. Cheah CY, *et al. Ann Oncol* 2015; 26:1175–1179.
6. Cencini E, *et al. Am J Blood Res* 2021; 11:373–383. 7. Rai S, *et al.* Pan Pacific Lymphoma Conference 2021 (Abstract MCL-041).

Available treatment options post-BTKi

Treatment	N	ORR	CR	DoR (m)	PFS (m)	OS (m)
R-CT[1]	31	32%	19%	5.8		8.4
CT/Lenalidomide[2]	73	26%	7%		1.9	5.8
R-BAC[3]	36	83%	60%	NR	10.1	12.5
Bortezomib	10	33%		3		7
Lenalidomide	12	50%		5.5		6
Bendamustine[4]	6	50%		2		4.5
Venetoclax[5]	20	53%	18%		3.2	9.4

1. Cheah CY, Ann Oncol 2015
2. Martin P, Blood 2016
3. McCulloch R, Br J Haematol 2020
4. Epperla N, Hematol Oncol 2017
5. Eyre TA, Haematologica 2019

Available CAR T-cells for R/R MCL



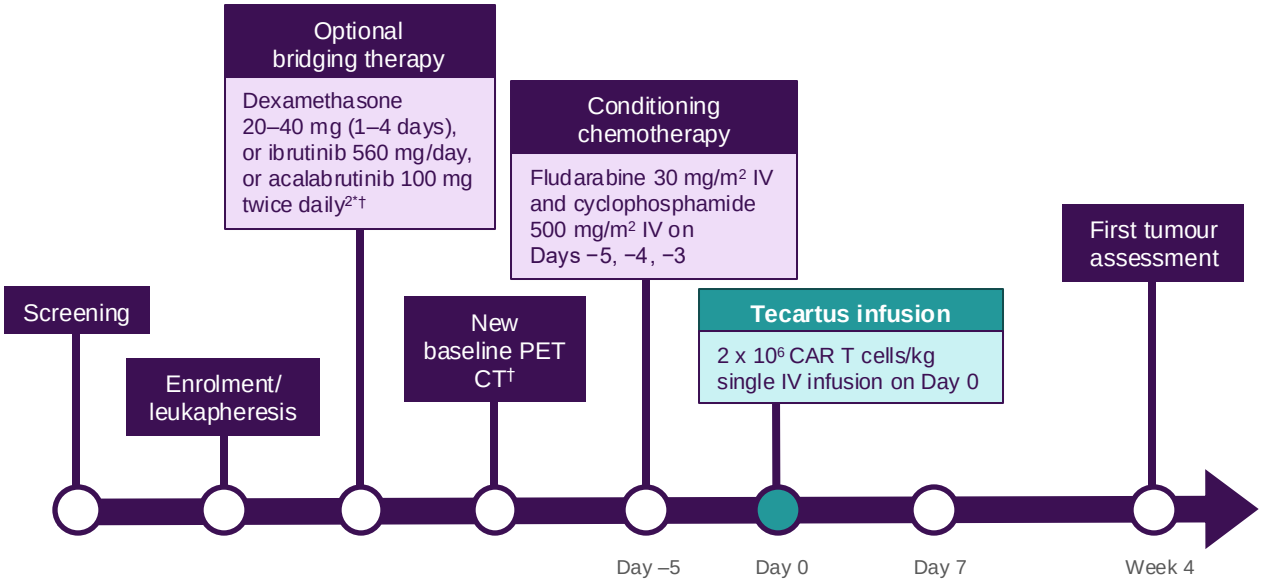
ZUMA-2

TRANSCEND NHL 001

Lu P, Journal of the National Cancer Center 2021

ZUMA-2: Pivotal, phase 2 study evaluating brexu-cel in 3L+ R/R MCL post-BTKi

Study design: International, single-arm, open-label trial (ITT N=74; n=68 treated)[1,2]



Primary endpoint[1]
- ORR (IRRC-assessed per the Lugano classification)[3]

Key secondary endpoints[1]
- DoR
- PFS
- OS
- AEs
- ORR (investigator-assessed per revised IWG criteria)[4]
- EQ-5D
- Levels of CAR T cells in blood and cytokines in serum

*Administered after leukapheresis and completed ≤5 days before initiating conditioning chemotherapy.
†PET CT required post-bridging.

1. Wang M, et al. N Engl J Med. 2020;382(14):1331–42; 2. Wang M, et al. ASH 2019 (Abstract 754; oral);
3. Cheson BD, et al. J Clin Oncol. 2014; 32:3059–68; 4. Cheson BD, et al. J Clin Oncol. 2007; 25:579–586.

ZUMA-2: Many patients had high-risk features and were heavily pre-treated

Characteristic	All-treated (N=68)
Median age, years (range)	65 (38–79)
Intermediate or high risk according to Simplified MIPI, n (%)*	38 (56)
Blastoid or pleomorphic morphological characteristics of MCL, n (%)	21 (31)
Ki-67 proliferation index ≥30%, n/N (%)*	40/49 (82)
TP53 mutation, n/N (%)	6/36 (17)
Positive CD19 status, n/N (%)	47/51 (92)
Median number of previous therapies (range)†	3 (1–5)
≥3 previous lines of therapy, n (%)	55 (81)
Previous autologous stem cell transplantation, n (%)	29 (43)
Refractory to most recent previous therapy, n (%)	27 (40)
Refractory to BTKi therapy, n‡ (%)	42 (62)

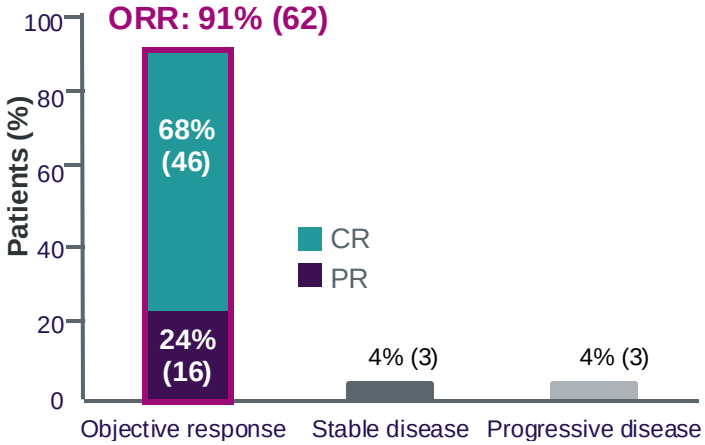
Wang M, et al. N Engl J Med. 2020;382(14):1331–42.

ZUMA-2: Tecartus shows durable long-term responses in patients with 3L+ R/R MCL post-BTKi

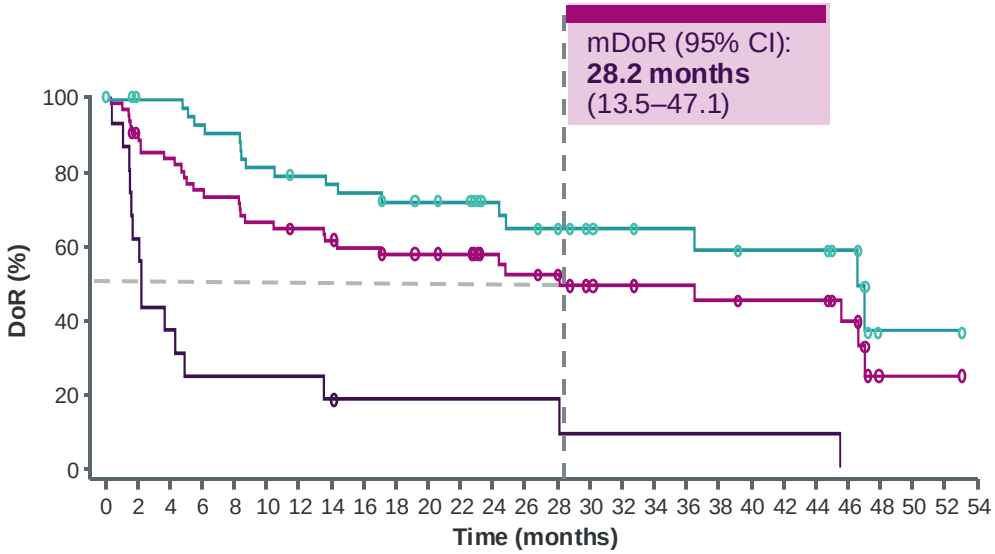
35.6 month
median follow-up
(range, 25.9–56.3)

Data cut off: July 2021

ZUMA-2 primary efficacy endpoint: Response rate (N=68)



DoR in all-treated population (N=68)



Number at risk

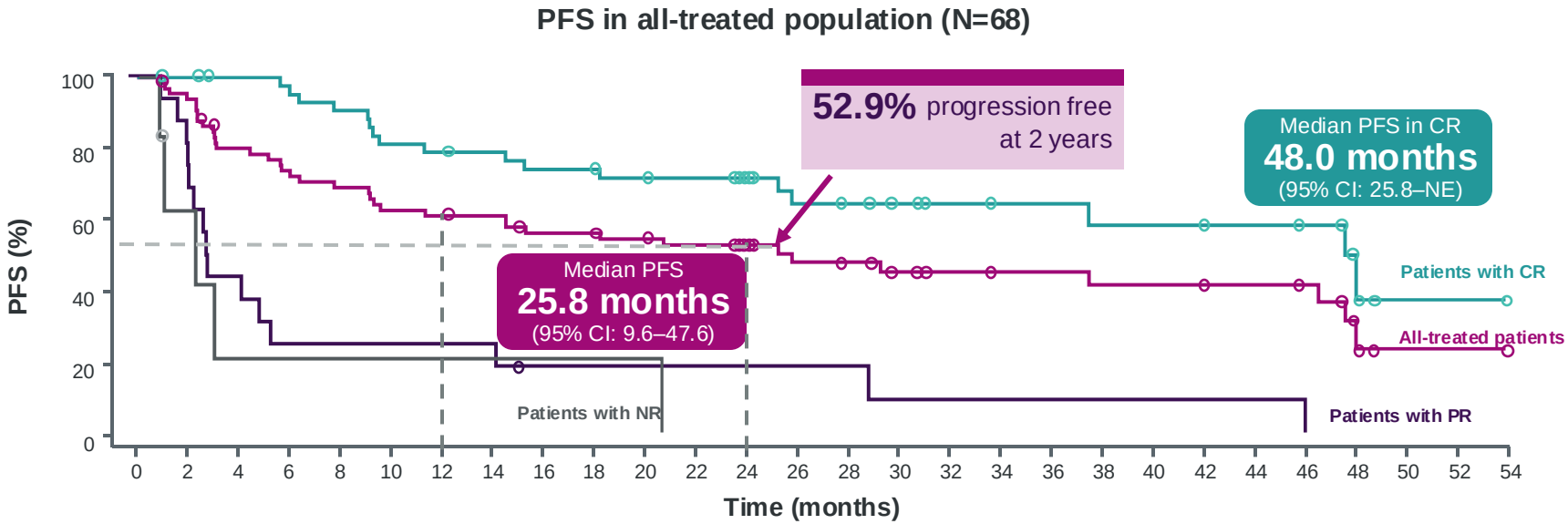
Patients with CR/PR	62	53	49	44	43	39	37	35	33	31	30	29	22	20	19	14	13	12	12	11	10	10	10	7	1	1	1	0
Patients with CR	46	43	43	40	39	35	33	32	31	29	28	27	20	18	17	13	12	11	11	10	9	9	9	7	1	1	1	0
Patients with PR	16	10	6	4	4	4	4	3	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	0	0	0	0	0

Figures adapted from Wang et al. 2023.

Wang M, et al. J Clin Oncol. 2023;41(3):555–67.

35.6 month median follow up

ZUMA-2: 53% of patients were progression free at 2 years



Number at risk																												
All-treated patients	68	62	51	47	44	40	39	38	34	34	32	30	24	20	19	15	13	12	12	11	11	10	10	9	4	1	1	0
Patients with CR	46	45	43	42	39	35	34	33	31	31	29	28	22	18	17	14	12	11	11	10	10	9	9	8	4	1	1	0
Patients with PR	16	14	7	4	4	4	4	4	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0	0	0	0
Patients with NR	6	3	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

In patients whose best response was CR, median PFS was 48.0 months[1]

1. Wang M, et al. J Clin Oncol. 2023;41(3):555-67.

35.6 month median follow up

ZUMA-2: delivered high rates of survival in patients with 3L+ R/R MCL post-BTKi, with ~ 58% of patients alive at 3 years

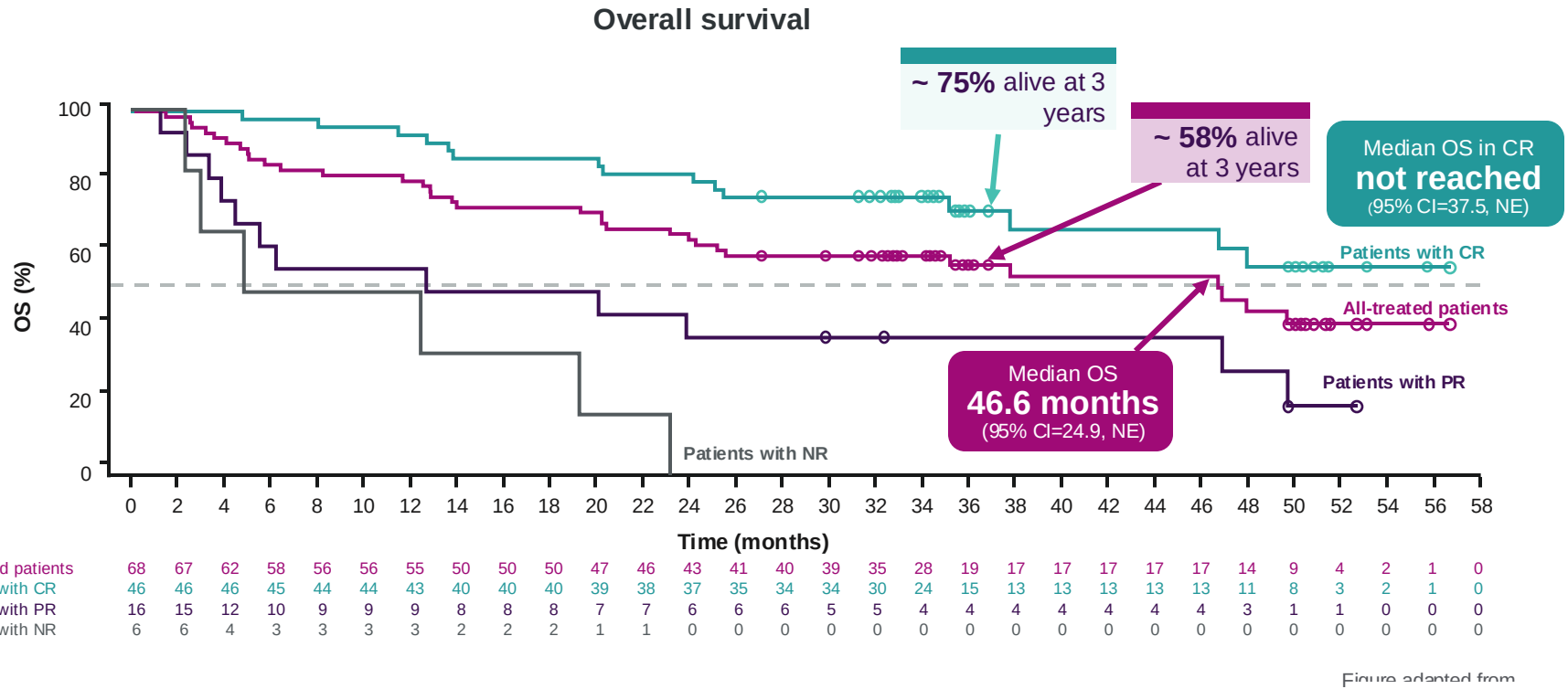
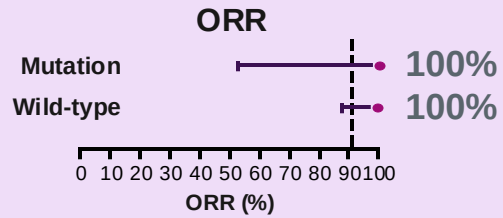


Figure adapted from

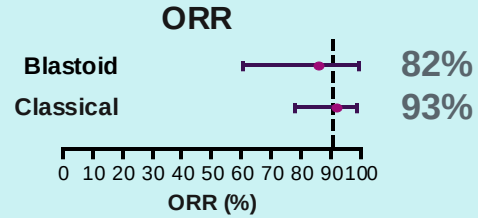
Wang M, et al. J Clin Oncol. 2023;41(3):555–67

ZUMA-2: has demonstrated clinical benefits in high-risk subgroups of patients with 3L+ R/R MCL post-BTKi

TP53 mutation
(Mutation, n=6 vs. wild-type, n=30)



Blastoid cytology
(Blastoid, n=17 vs. classical, n=40)



High Ki-67 index
(Ki-67 ≥30%, n=43 vs. Ki-67 <30%, n=9)

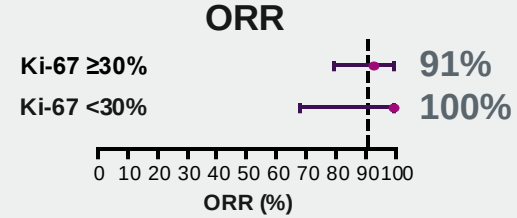


Figure adapted from Wang et al. 2023 (suppl).

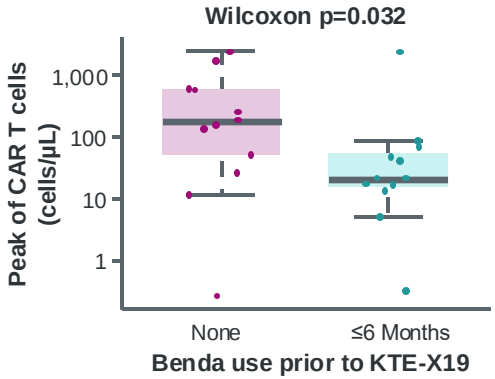
Outcomes in high-risk subgroups were generally comparable with the treated population

Wang M, et al. J Clin Oncol. 2023;41(3):555–67. Suppl.

Avoiding bendamustine prior to leukapheresis

Outcome or measure	Benda use ≤6 months vs No benda use*		Benda use >6 months vs no benda use†	
	Benda use ≤6 months (n=11)	No benda use (n=11)	Benda use >6 months (n=25)	No benda use (n=25)
Efficacy, No. (%)				
ORR	9 (81.8)	11 (100)	21 (84.0)	25 (100.0)
CR rate	6 (54.5)	9 (81.8)	15 (60.0)	20 (80.0)
Ongoing response at 18 months	2 (18.2)	4 (36.4)	8 (32.0)	13 (52.0)

Peak of CAR T pharmacokinetics in prior benda vs no benda



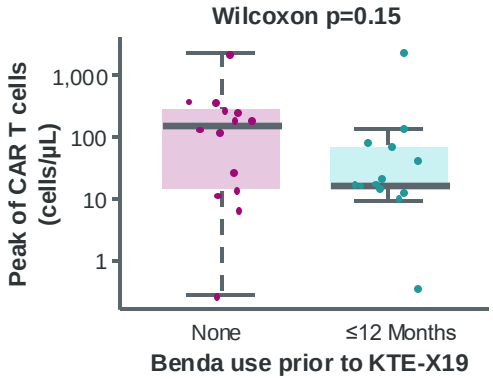


Figure adapted from Wang M, et al. J Clin Oncol. 2023.

ZUMA-2: CRS events occurred early, were reversible and were managed using established protocols

CRS*	N=68
Any grade, n (%)	62 (91)
Grade ≥3, n (%)	10 (15)
Most common symptoms, n (%) Pyrexia Hypotension Hypoxia	 62 (91) 35 (51) 23 (34)
Patients with resolved events, n/N (%)	62/62 (100)
Median time to onset (range), days	2 (1–13)
Median duration of events, days	11

CRS was managed with:

Tocilizumab (59%)	Corticosteroids (22%)	Vasopressors (16%)

There were no Grade 5 CRS events

*CRS was graded per Lee DW, et al. Blood 2014; Wang M, et al. N Engl J Med. 2020;382(14):1331–42.

ZUMA-2: Neurological events were mostly reversible and managed using established protocols[1,2]

Neurological events*	N=68[1,2]
Any grade, n (%)	43 (63)
Grade ≥3, n (%)	21 (31)
Most common symptoms, n (%) Tremor Encephalopathy Confused state	 24 (35) 21 (31) 14 (21)
Patients with resolved events, n (%)	37/43 (86)†
Median time to onset (range), days	7 (1–32)
Median duration of events, days	12

Neurological events were managed with:[1,2]

Corticosteroids (38%)

Tocilizumab (26%)

No Grade 5 neurological events occurred[1]

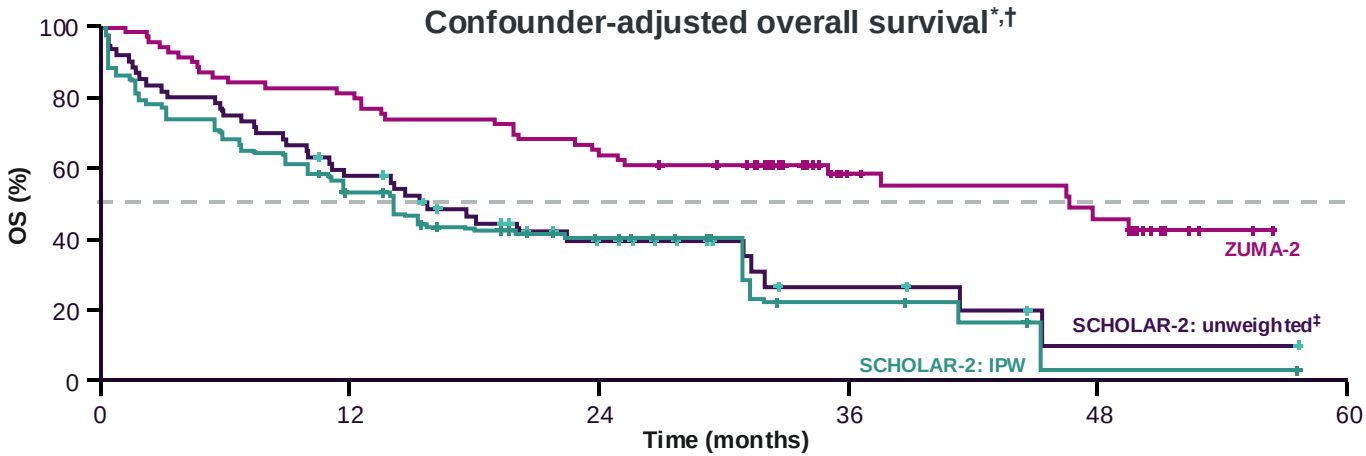
*Neurological events were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v4.03;[1] †Four patients had ongoing neurological events at data cutoff: Grade 1 tremor (n=3), Grade 2 concentration impairment (n=1) and Grade 1 dysaesthesia (n=1). Two patients died from unrelated AEs (organising pneumonia and staphylococcal bacteraemia) prior to the resolution of the neurological events[2]

CRS, cytokine release syndrome.

1. Wang M, et al. N Engl J Med. 2020;382(14):1331–42; 2. Wang M, et al. ASH 2019 (Abstract 754; oral).

improved survival rates compared with SoC in 3L+ R/R MCL post-BTKi based on an indirect comparison

Retrospective and comparative analysis of confounder-adjusted OS between ZUMA-2 (brexu-cel) (n=68) vs. SCHOLAR-2 (SoC) (n=59)



N at risk (N censored)						
ZUMA-2	68 (0)	55 (0)	43 (0)	19 (21)	14 (22)	0 (35)
SCHOLAR-2: unweighted	59 (0)	32 (2)	15 (10)	5 (17)	1 (19)	0 (20)
SCHOLAR-2: IPW	59 (0)	30 (1)	15 (9)	4 (16)	0 (18)	0 (10)

62%
reduction in risk of death with brexu-cel compared with SoC

HR 0.38
(95% CI: 0.23–0.63);
p<0.001

Figure adapted from Hess et al. 2022.

This analysis is based on an indirect retrospective comparative analysis of confounder-adjusted OS. Comparisons from this analysis should be made with caution as residual confounding may still exist.

*Hess G, et al. ASH 2022 (Abstract 4627; oral poster).

What about real-world data with brexu-cel?

Real-world European outcomes of brexu-cel

	Iacoboni 2022	Rejeski 2023	Herbaux 2024	O'Reilly 2024
Treatment sites	EAP - 11 sites (Germany, Italy, Netherlands, Spain)	8 sites (USA, Spain, Germany, France)	DESCAR-T French Registry (24 sites)	UK (12 sites)
Number of patients	33	103	152 (181)	83 (119)
mFU, months	10.1	15.4	12.2	13.3
ORR, %	91	93	85	87
CR, %	79	81	72	81
CRS (G≥3), %	91 (3)	89 (6)	88 (12)	93 (12)
ICANS (G≥3), %	64 (36)	62 (25)	55 (15)	55 (22)

Iacoboni G, et al. Blood Adv 2022; Rejeski K, et al. Am J Hematol 2023; Herbaux C, Haematologica 2024; O'Reilly MA, et al. Hemasphere 2024

Real-world European Outcomes of Brexu-cel

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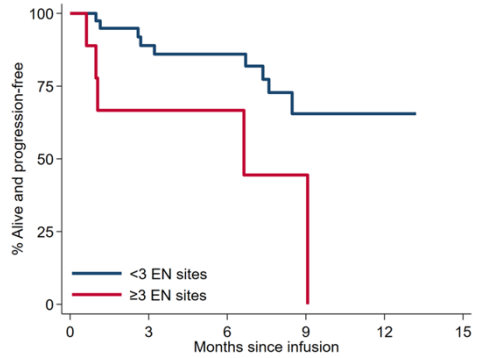
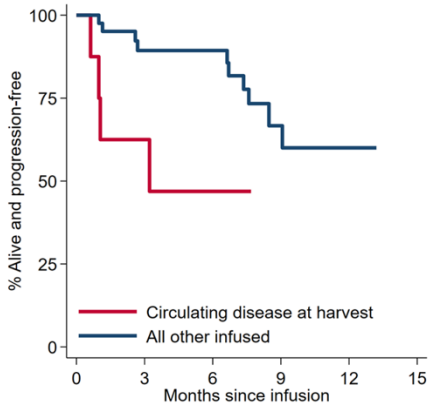
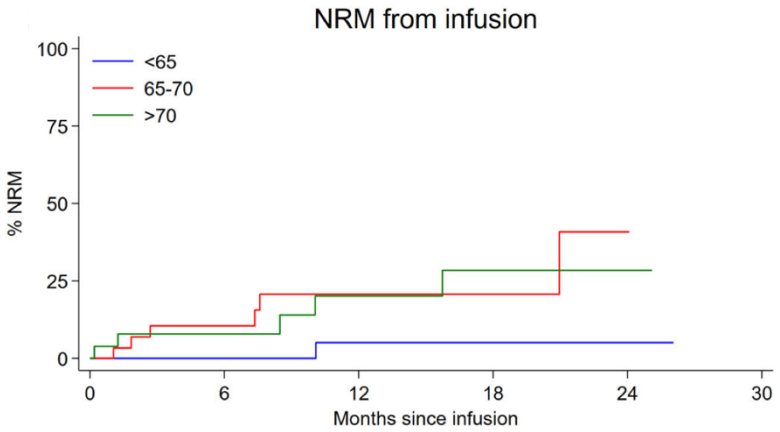
Iacoboni G, et al. Blood Adv 2022; Rejeski K, et al. Am J Hematol 2023; Herbaux C, Haematologica 2024; O'Reilly MA, et al. Hemasphere 2024

Real-World Outcomes of Brexu-cel in UK



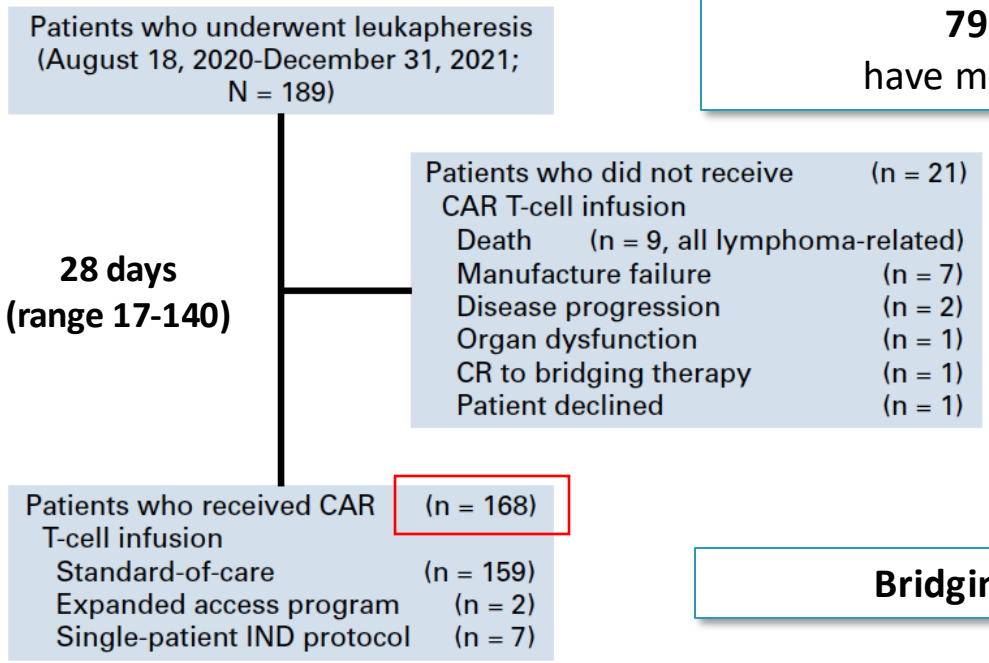




NRM was 6%, 15%, and 25% at 6, 12, and 24 months, mostly due to infection

O'Reilly M, Hemasphere 2024

Real-world Results From the US Lymphoma CAR T Consortium



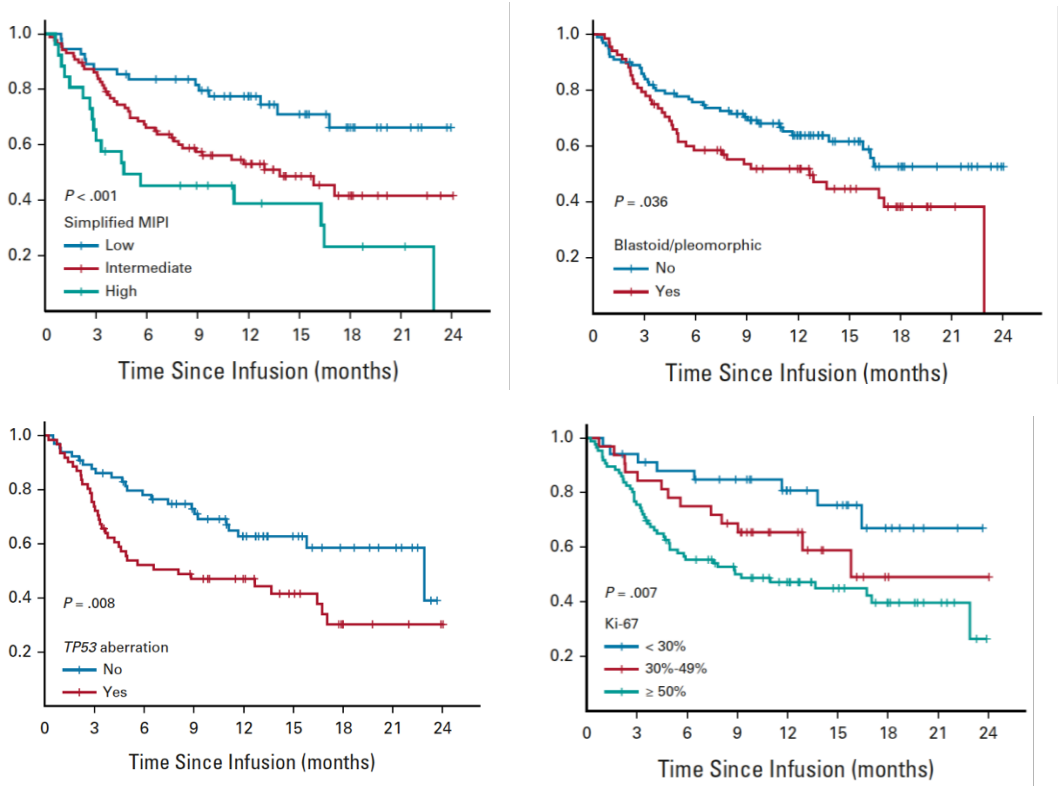
79% of patients would **not** have met **ZUMA-2 eligibility** criteria

82% CR
12-mo PFS 59%
12-mo OS 75%

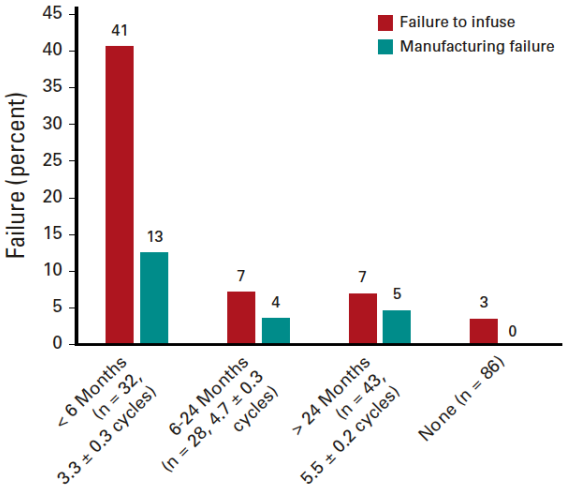
Bridging therapy was used in **68%**

Wang Y, JCO 2023

Inferior PFS in high-risk subgroups



mFU 14.3 mo



Wang Y, JCO 2023

Real-world Results From the US Lymphoma CAR T Consortium

CRS 90% (**8% G≥3**)
ICANS 61% (32% G≥3)

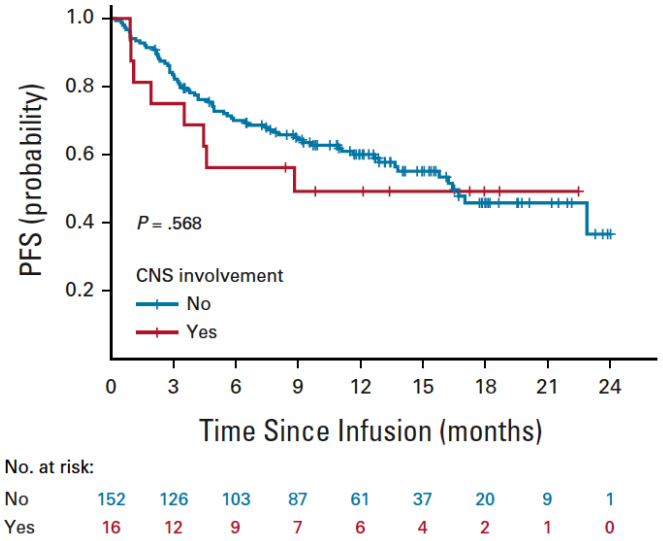
tocilizumab 77% - steroids 69%
anakinra 17% - siltuximab 3%

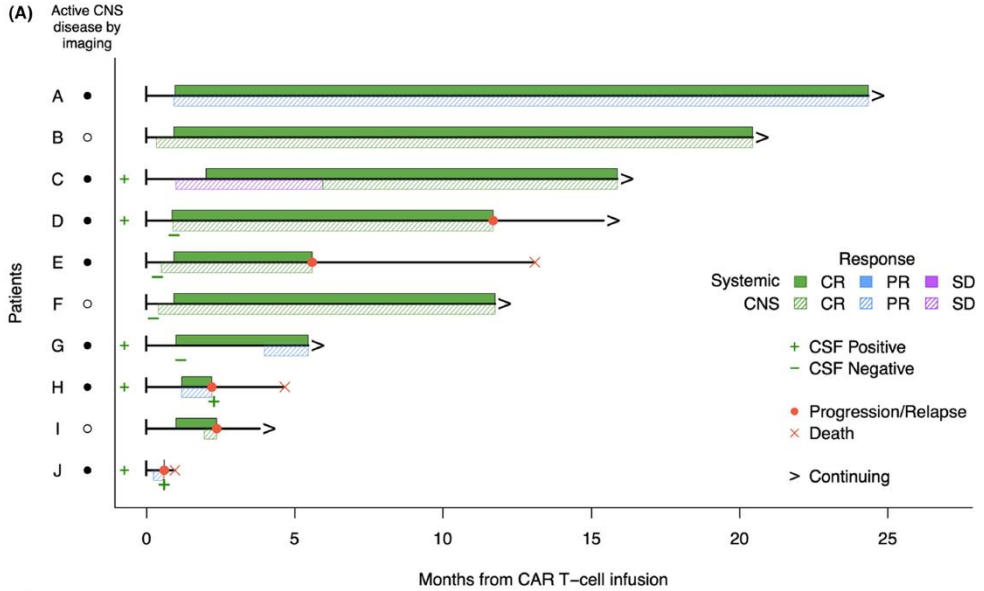
Age ≥65 years
ECOG PS ≥2
High-risk simplified MIPI
Blastoid variant
Bulky disease
Bridging therapy

Time of NRM	Events, No.	Cause of Death
< 1 month	4	Sepsis (n = 3)
		CRS (n = 1)
1-3 months	4	Sepsis (n = 1)
		Invasive aspergillosis and HHV6 encephalitis (n = 1)
		Alveolar rhabdomyosarcoma (n = 1)
		Unspecified (n = 1)[a]
3-6 months	6	Sepsis (n = 2)
		Stroke (n = 2)
		COVID-19 disease (n = 1)
		Unspecified (n = 1)[a]
6-12 months	2	Stroke (n = 1)
		COVID-19 disease (n = 1)
> 12 months	2	Recurrent pneumonia (n = 1)
		High-grade transitional cell cancer (n = 1)

Wang Y, JCO 2023

CNS infiltration yields similar results



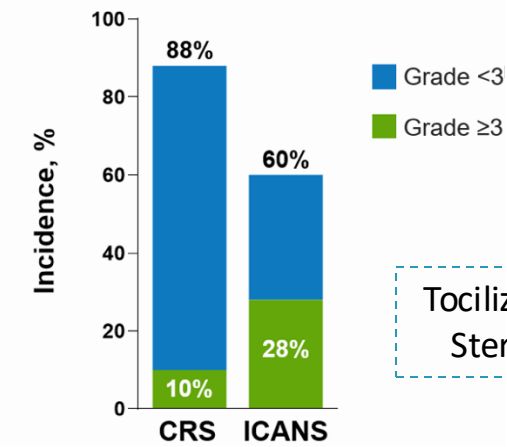


Wang Y, JCO 2023
Ryan CE, BJH 2023

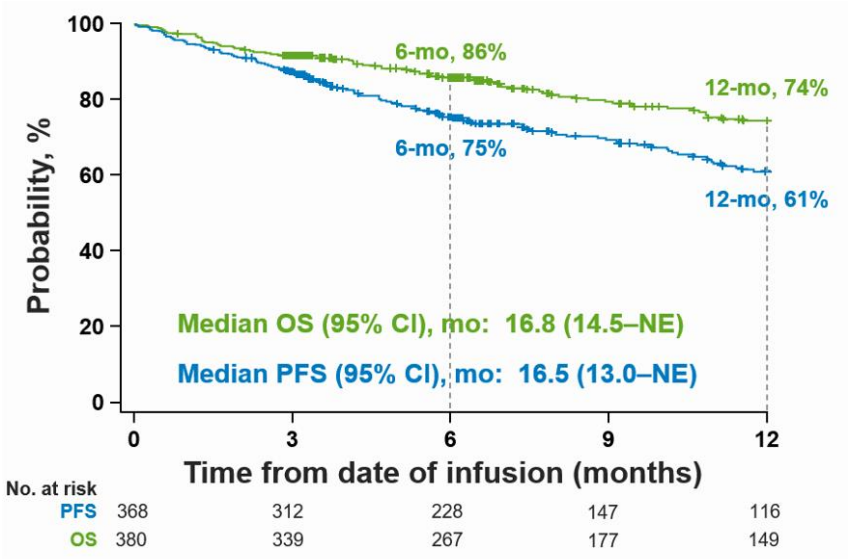
Real-World Outcomes of Brexu-cel

A CIBMTR Subgroup Analysis by Prior Treatment

July 2020–December 2022
Median FU 12 months
N=380



Tocilizumab 76%
Steroids 61%

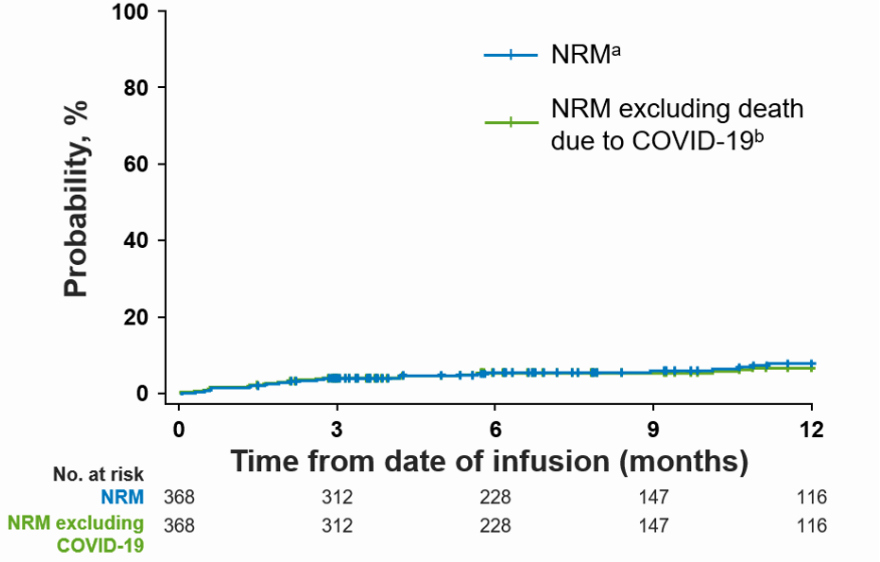


Cum Inc of Relapse/PD → 19% at 6-mo and 31% at 12-mo

Kambhampati S, #7507, ASCO 2023

Real-World Outcomes of Brexu-cel

Non-Relapse Mortality and Causes of Death



Causes, n (%)	Overall Population N=380
Total deaths	89 (23)
Primary disease	53 (14)
Malignancy	3 (<1)
CRS	2 (<1)
Neurotoxicity/ICANS	5 (1)
Chronic GVHD	1 (<1)
Infection	11 (3)
Bacterial infection	7 (2)
COVID-19	4 (1)
Organ failure[c]	5 (1)
Hemorrhage	2 (<1)
Other	6 (2)
Not reported	1 (<1)

NRM rate at Day 100 and **Year 1** were 4% and **8%**; most commonly due to **infections**

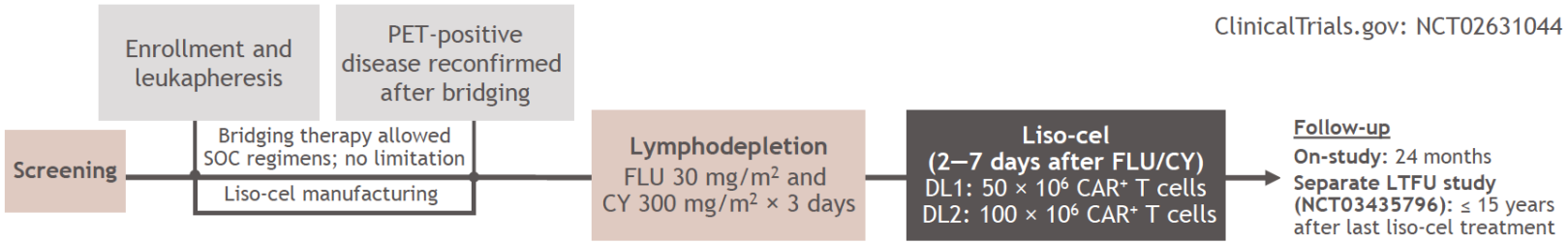
Kambhampati S, #7507, ASCO 2023

Mortality in CAR T-cell treatments

Meta-analysis	Non-relapse mortality	Cause of death
• N= 7,604 (18 trials, 28 RW studies)	• MCL: 10.6% • MM: 8% • LBCL: 6.1% • FL: 5.7%	• Infections: 50.9% • Other malignancies: 7.8% • Cardiovascular/respiratory: 7.3% • CRS + ICANS + HLH: 11.5%

Cordas do Santos DM. Et al., Nature Medicine July 2024

Lisocabtagene maraleucel in R/R MCL:
Primary analysis of the TRANSCEND NHL 001 study



Key eligibility criteria for MCL cohort

- Age ≥ 18 years
- PET-positive MCL with confirmed tissue diagnosis[a]
- ≥ 2 lines of therapy, including BTKi, alkylator, and CD20-targeted agent[b]
- ECOG PS 0–1[c]
- Secondary CNS lymphoma or prior autologous or allogeneic HSCT allowed
- Adequate bone marrow, organ, and cardiac function

Primary endpoint

- Safety
- ORR by IRC (Lugano 2014 criteria)

Secondary endpoints

- CR rate (key), DOR, PFS, OS
- Cellular kinetics
- Hospital resource utilization, HRQOL

Wang M et al, JCO 2023

Primary analysis of the TRANSCEND NHL 001 study
Demographics and baseline characteristics

	Liso-cel–treated set (n = 88)
Median (range) age, y	68.5 (36–86)
Median (range) prior lines of systemic therapy	3 (1–11)
≥ 5 prior lines of systemic therapy, n (%)	26 (30)
Prior autologous or allogeneic HSCT, n (%)	29 (33)
Prior BTKi, n (%)	83 (94)
Prior ibrutinib, n (%)	65 (74)
Refractory disease, n (%)[a]	61 (69)
Refractory to BTKi, n (%)[b]	47 (53)
Ki67 proliferation fraction ≥ 30%, n (%)	66 (75)
***TP53* mutation, n (%)**	20 (23)
Blastoid morphology, n (%)	27 (31)
LDH before LDC ≥ 500 U/L, n (%)	10 (11)
SPD before LDC ≥ 50 cm^2, n (%)[c]	7 (9)
Secondary CNS lymphoma at liso-cel infusion, n (%)	7 (8)
Received bridging therapy, n (%)	58 (66)

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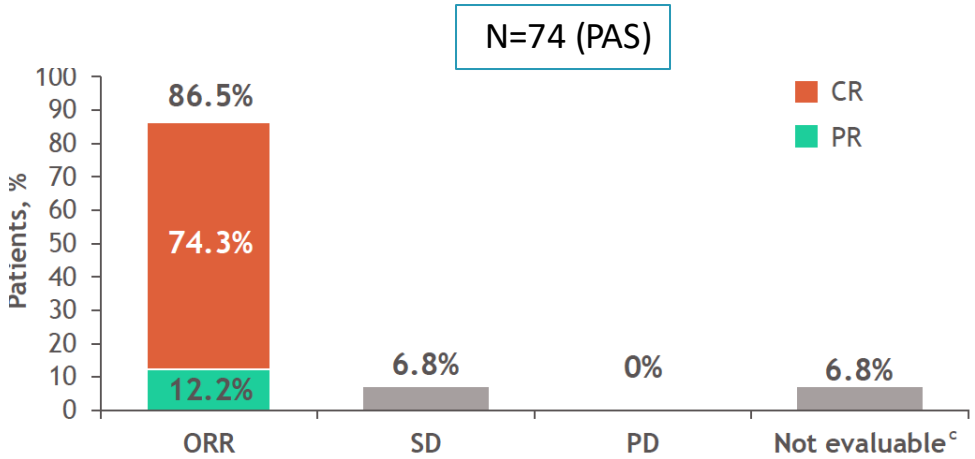
	N=88
CRS	54 (61%)
CRS ≥G3	1 (1%)
ICANS	27 (31%)
ICANS ≥G3	8 (9%)
Infections ≥G3	13 (15%)



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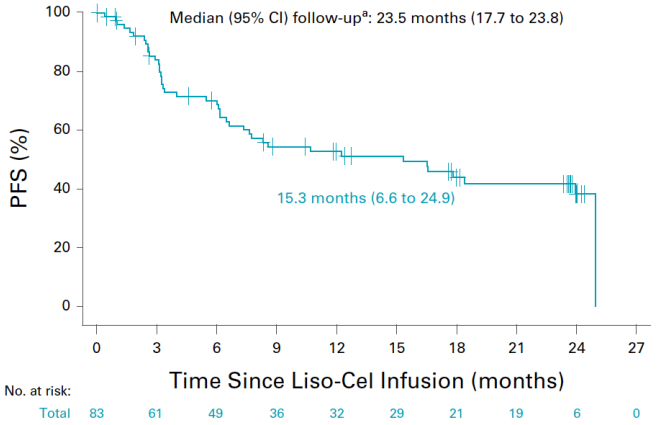

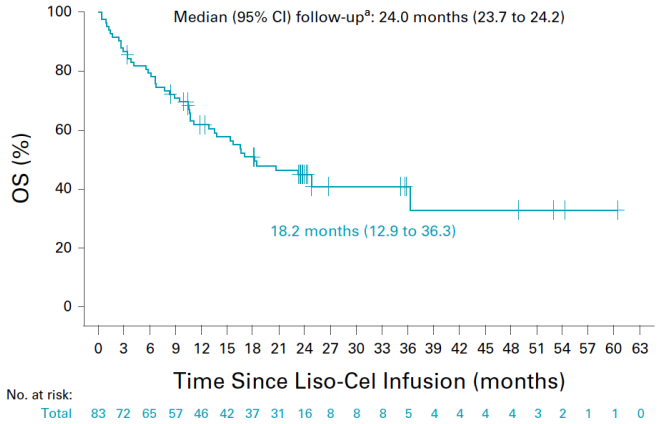

	PFS rate	
	Total (n = 83)	Patients with CR (n = 60)
12-mo rate (95% CI)[b]	52.8% (40.6–63.6)	59.8% (46.3–71.0)
18-mo rate (95% CI)[b]	43.9% (31.8–55.4)	49.4% (35.7–61.8)

	OS rate	
	Total (n = 83)	Patients with CR (n = 60)
12-mo rate (95% CI)[b]	61.8% (50.2–71.4)	72.9% (59.6–82.5)
18-mo rate (95% CI)[b]	50.8% (39.2–61.2)	59.8% (45.9–71.3)

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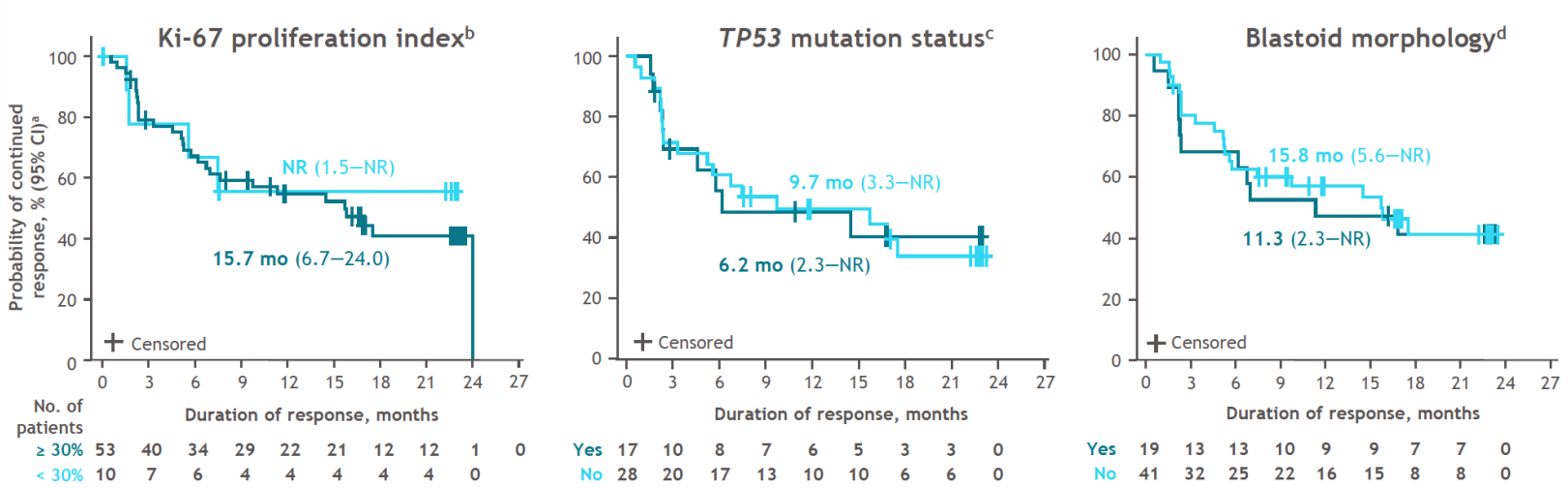
Lisocabtagene maraleucel in R/R MCL
DoR by high-risk disease feature subgroup



In the overall population, median DOR was 15.7 months; no clear differences across subgroups

Palomba ML, ASTCT 2024

Available treatment options post-BTKi

Treatment	N	ORR	CR	DoR	PFS	OS
R-CT[1]	31	32%	19%	5.8m		8.4 m
R-BAC[2]	36	83%	60%	NR	101m	12.5m
Bortezomib **Lenalidomide** **Bendamustine**[3]	10 12 6	30% 25% 50%		3 m		7m 6m 4.5m
Venetoclax[4]	20	53%	18%		3.2m	9.4m
Brexu-cel[5]	60	93%	67%	28.2	25.8	46.6
Liso-cel[6]	74	87%	74%	15.7	15.3	18.2
Glofitamab (Ib/II)[7]	29	81%	67%	NR	NA	NA
Pirtobrutinib (Ib/II)[8]	111	51%*	25%*	18m	NA	NA
Zilovertamab (Ph 1)[9]	15	46.7%	3/7	NA	NA	NA

*88% BTKi+

*90% BTKi+

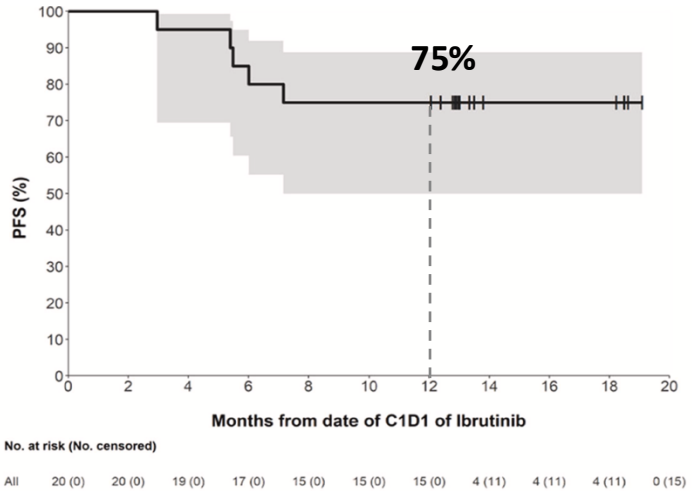
1. Cheah CY, Ann Oncol 2015
2. McCulloch R, Br J Haematol 2020
3. Epperla N, Hematol Oncol 2017
4. Eyre TA, Haematologica 2019
5. Wang M, JCO 2022
6. Wang M, ICML 2023, LBA3
7. Phillips T, Blood 2021; 136 (Suppl 1): abstract 130
8. Wang M, Blood 2021; 136 (Suppl 1): abstract 381
9. Wang M, NEJM Evidence 2022

Tisagenlecleucel + ibrutinib in R/R MCL

First report of the TARMAC trial

	N=20
Prior BTKi	50%
Bridging	20%
***TP53* mutation**	40%
Prior lines	2 (1-5)

	N=20
CRS (G≥3)	75% (20%)
ICANS (G≥3)	5% (0)
A-Fib	5%



ORR was 90% (CR 85%)

Similar RR and DoR irrespective of *TP53* status

Deep responses correlated with CAR-T expansion

Median FU was 13 months

Minson A, Blood 2024

CAR-T Trials in R/R MCL

Meeting Abstract: 2024 ASCO Annual Meeting I
FREE ACCESS | Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia | May 29, 2024

Combination of pirtobrutinib and lentiviral transduced bispecific anti-CD20/CD19 (LV20.19) CAR T-cell therapy to improve outcomes in patients with relapsed/refractory lymphoma.

Furqan F, ASCO 2024

CAR-T Trials in R/R MCL

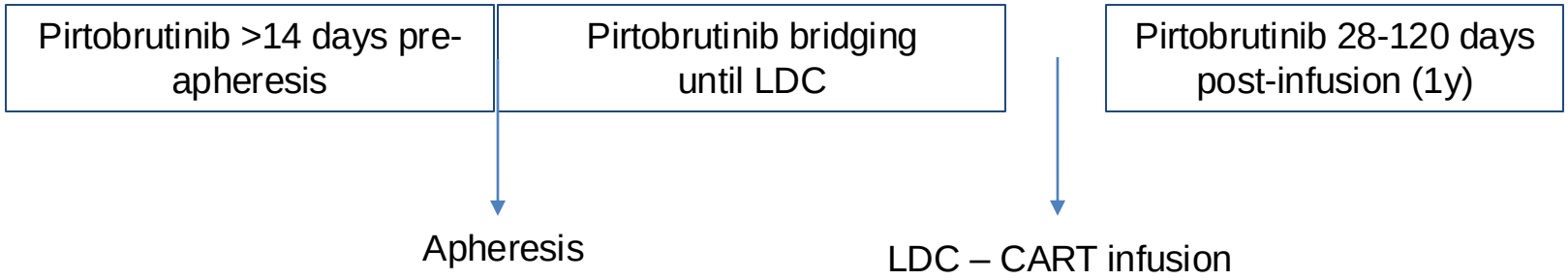
LV20.19 CAR T-Cells in Combination With Pirtobrutinib for Relapsed, Refractory B-cell Malignancies

ClinicalTrials.gov ID NCT05990465

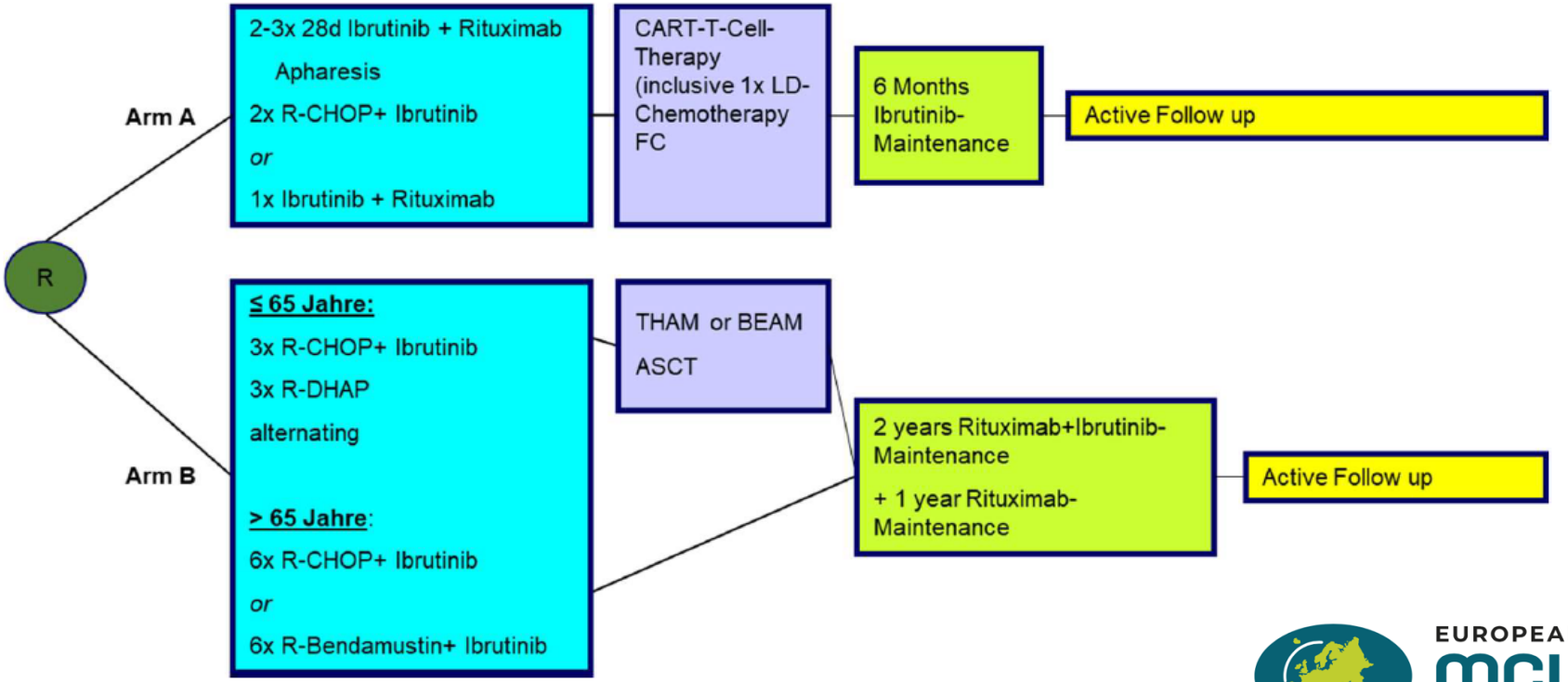
Sponsor Medical College of Wisconsin

Information provided by Nirav Shah, Medical College of Wisconsin (Responsible Party)

Last Update Posted 2024-08-16



CARMAN trial in front-line MCL



EUROPEAN mcl NETWORK

Conclusions in mantle cell lymphoma

- Timely referral for CAR-T is key in this patient population
- Efficacy and safety of RW brexu-cel is largely similar to the ZUMA-2 trial
- Liso-cel has a better safety profile than brexu-cel, but longer FU and RWE lacking – new standard of care?
- Do CAR-T have curative potential in MCL? Consolidation strategies?
- Future approval of bispecific antibodies? Other agents?

Thank you!