Terapia de células CAR-T en el “mundo real”

Jose D. Sandoval Sus, MD FACP

Miembro Asociado

Departamento de hematologia maligna & terapia celular

H. Lee Moffitt Cancer Center at Memorial Health Care System

Profesor asociado, Florida Atlantic University (FAU)

Pembroke Pines, FL

@HemSandoval

GELL Grupo de Estudio Latinoamericano de Linfoproliferativos

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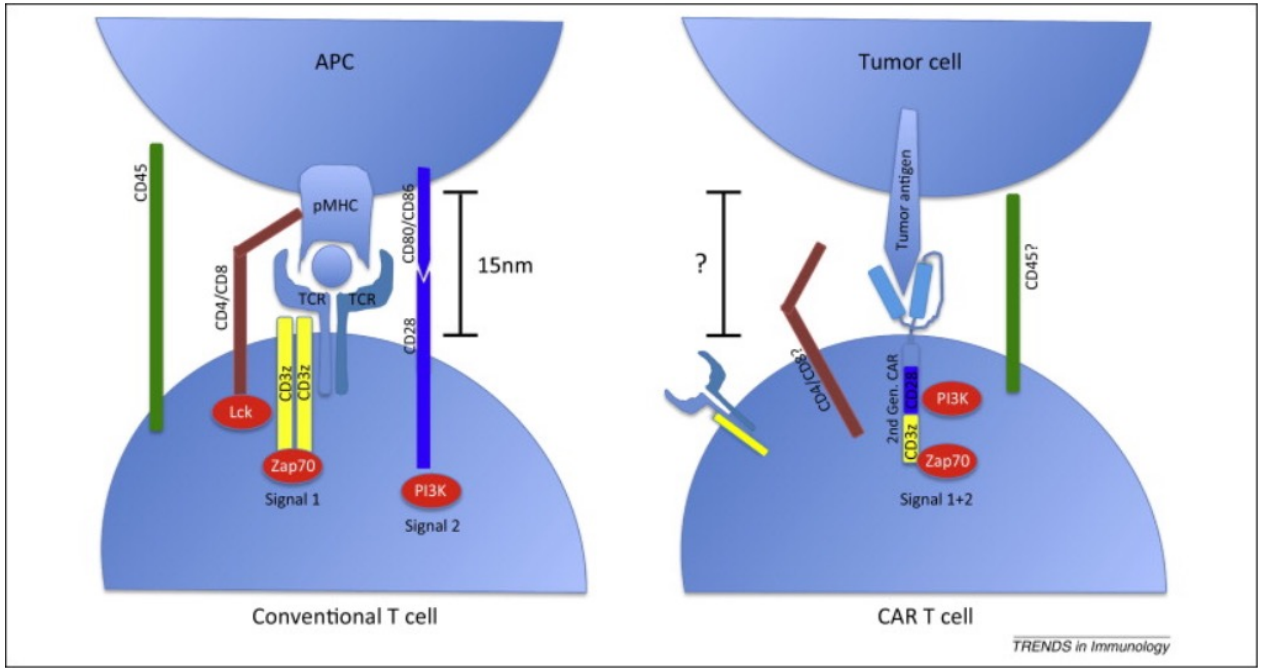
Conflictos of Interes

- **Speaker:** Pfizer
- **Advisory Board:** Janssen, MassiveBio, ADC therapeutics, Genmab, BeiGene, AbbVie, BMS, Genentech, Roche, Novartis, Acrotech.

Pero que es el ”mundo real” de la terapia CAR-T?

Chimeric Antigen Receptor (CAR) T- cell therapy in large B cell non-Hodgkin lymphoma



Jackson HJ, et al. Nat Rev Clin Oncol. 2016;13(6):370-383.
Sadelain M. Cell. 2017;171(7):1471.

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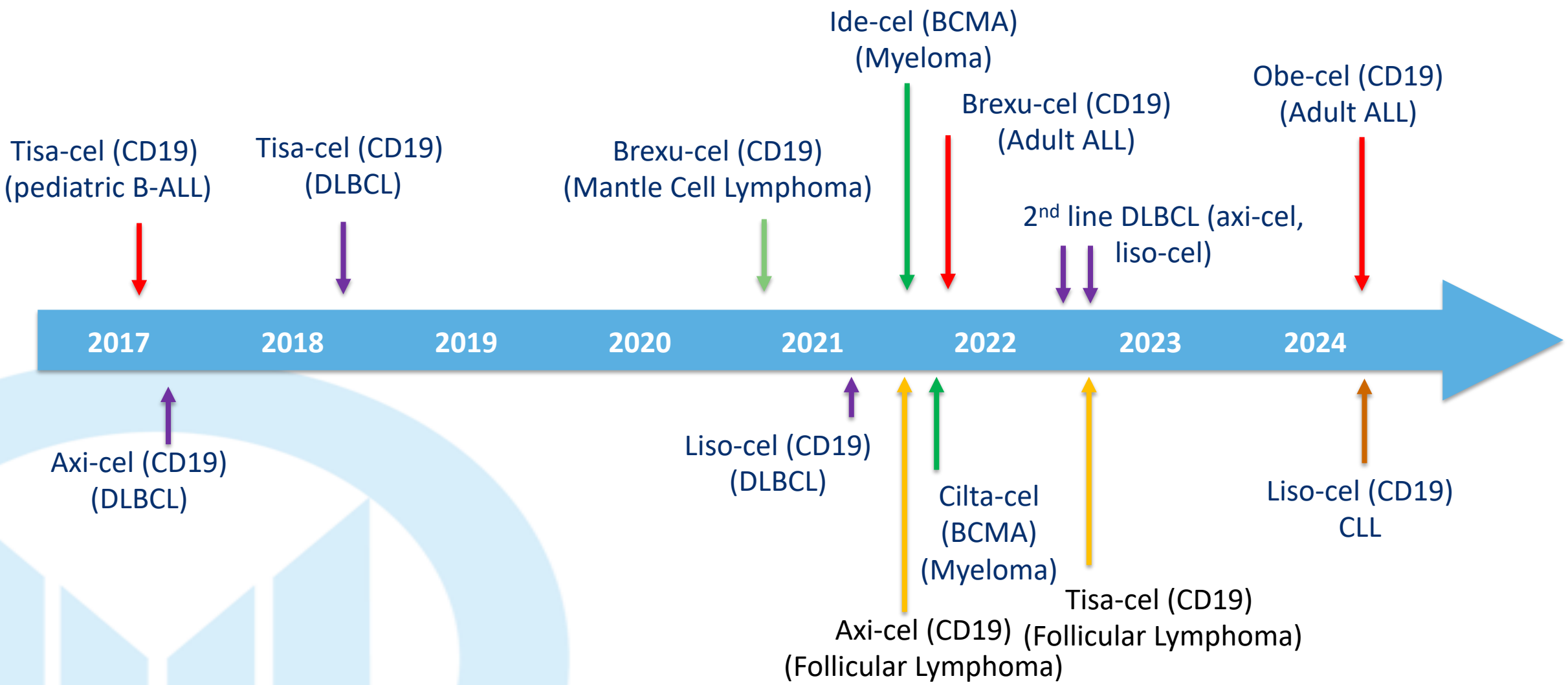
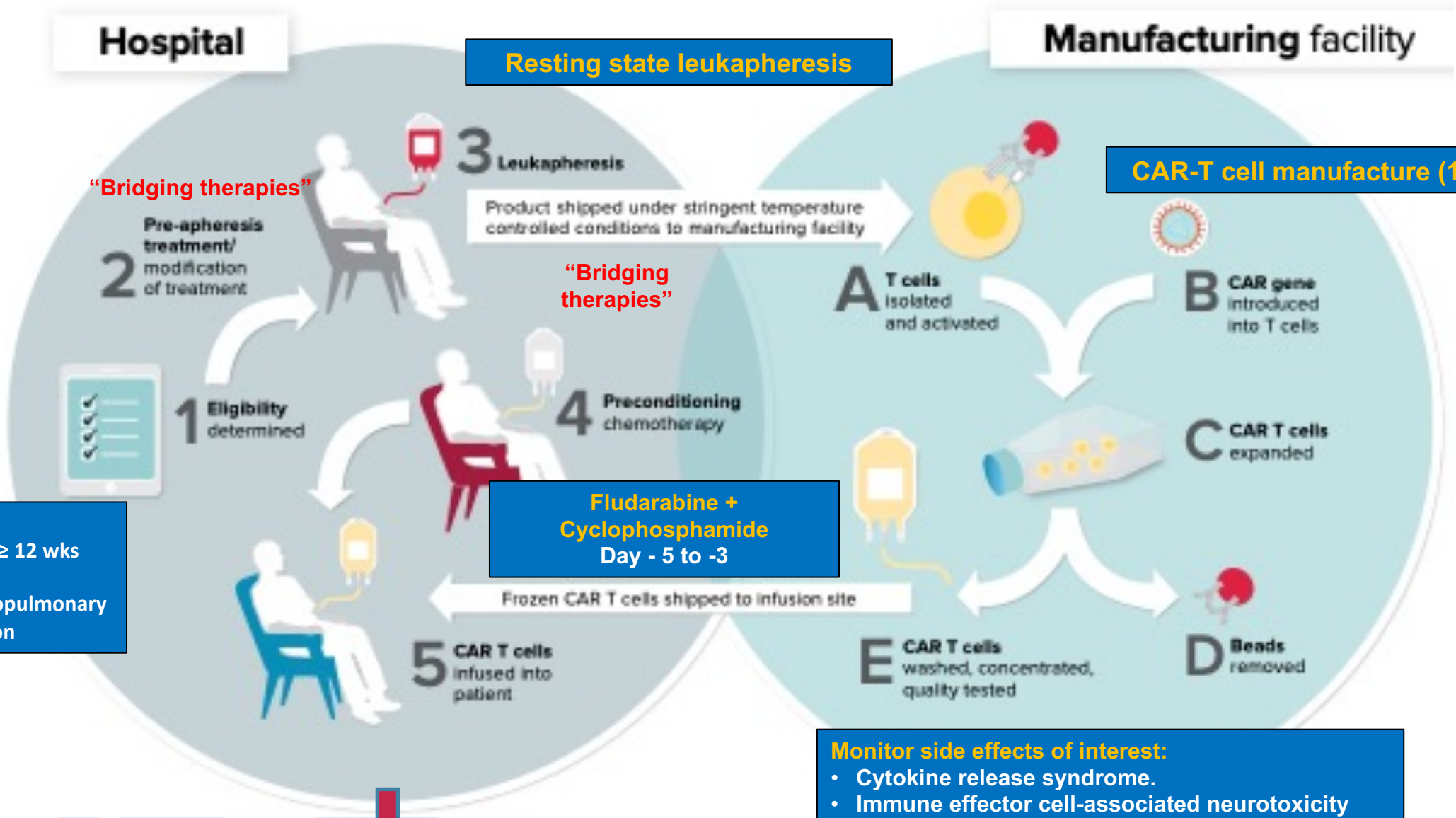
US FDA Approvals of CAR T-cell Therapy



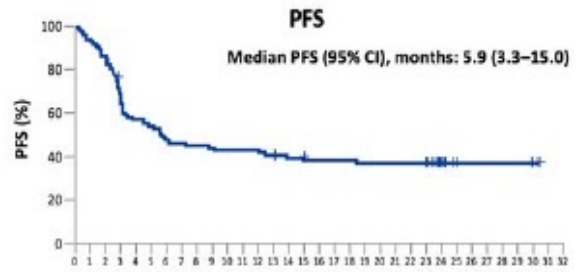


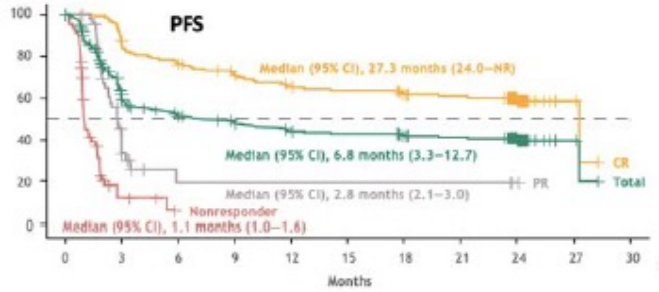
- Type of disease
- Life expectancy ≥ 12 wks
- ECOG PS = 0/1
- Adequate cardiopulmonary and organ function

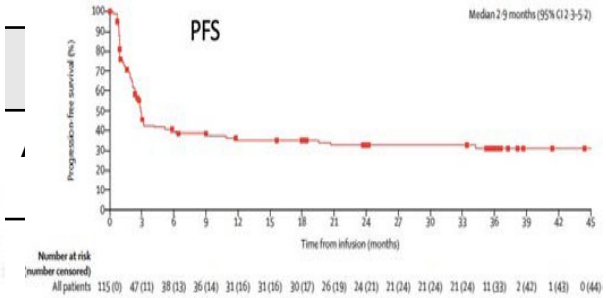
Monitor side effects of interest:

- Cytokine release syndrome.
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Infections, HLH, cytopenias, B cell aplasia, etc.

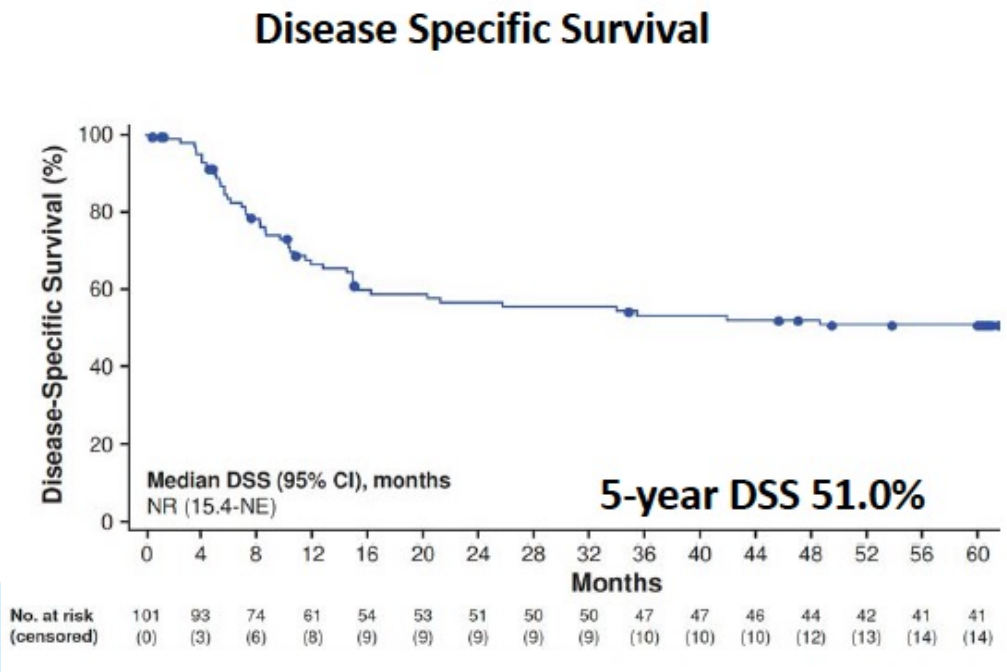
	Axicabtagene Ciloleucel (ZUMA-1)	Tisagenlecleucel (JULIETH)	Lisocabtagene Maraleucel (TRANSCEND)
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
Median age, y (range)	58 (23-76)	56 (22-76)	63 (18-86)
ORR/CR%	83/58	53/39	73/53
mPFS, mos (95%CI)	5.8 (3.3-15)	2.9 (2.3-5.2)	6.8 (3.3-12.7)
2-yr PFS %	50.5	40	41
mOS, mos (95%CI)	25.8 (12.8-NE)	11.1 (6.6-23)	27.3 (16.2-45.6)
5-yr OS %	46.6	11.1	38.1
Any CRS Median time to onset	93% 2 days	58% 3 days	42% 5 days
≥ Gr 3 CRS	11%	23%	2%
Any neurotoxicity	64%	21%	30%
≥ Gr 3 neurotoxicity			

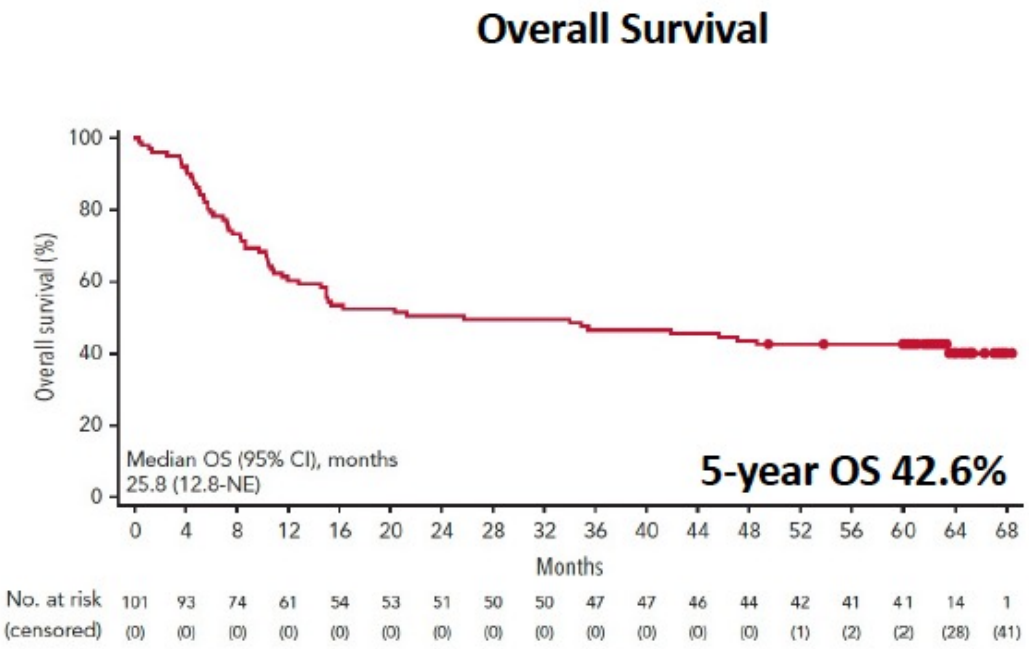






Axicabtagene ciloleucel (axi-cel) ZUMA-1, 5 year follow up





Lisocabtagene maraleucel (Liso-cel) TRANSCEND 5-year f/up

5-y DSS:	**52.0%**	**5-y OS:**	**38.1%**

Neelapu SS et al. Blood (2023) 141 (19): 2307–2315
Abramson J et al. Blood 2024

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Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

"Real World US Experience"

Baseline pt characteristics:

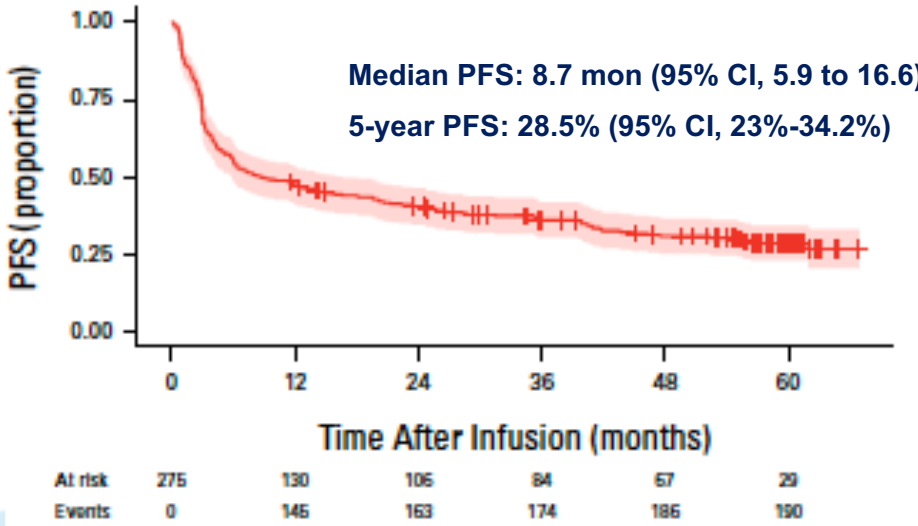
Characteristic	No. (%)
No. of patients	298
Age, years	
< 60	144 (48.3)
≥ 60	154 (51.7)
Median (range)	60 (21-83)
ECOG PS	
0	76 (25.5)
1	164 (55.0)
2	46 (15.4)
3	11 (3.7)
4	1 (< 1.0)
Disease stage	
I or II	52 (17.6)
III or IV	244 (82.4)
International Prognostic Index score[a]	
0-2	136 (45.6)
3-5	162 (54.4)
Disease type	
DLBCL	203 (68.1)
PMBCL	19 (6.4)
TFL	76 (25.5)
GCB-like[b]	158 (59.8)
Non-GCB[b]	106 (40.1)
Double/triple-hit[c]	64 (22.8)
Double expressor[c]	98 (37.4)
LDH > ULN at leukapheresis[e]	157 (60.6)
LDH > ULN at conditioning[e] chemotherapy	155 (59.4)
Bulky disease (≥ 10 cm)	68 (22.7)
Prior therapies	
≥ 3 prior lines of therapy	222 (74.5)
Median No. of prior lines (range)	3 (2-11)
History of primary refractory disease	101 (33.9)
Refractory to most recent therapy	125 (42.0)
Relapsed	72 (24.0)
Prior ASCT	98 (32.9)
Prior allogeneic SCT	7 (2.4)
Prior CD-19–directed therapy[f]	5 (1.7)

ZUMA-1 comorbidity exclusion criteria at the time of leukapheresis	
No. of patients with exclusion criteria	129 (43.0)
1 criterion	76 (58.9)
≥ 2 criteria	53 (41.1)
ECOG PS > 1	58 (19.0)
Platelets < 75,000/μL	34 (11.4)
DVT/PE within 6 months	31 (10.4)
History of CNS disease	21 (7.0)
Renal insufficiency (GFR < 60 mL/min/1.73 m^2)	21 (7.0)
Prior checkpoint inhibitor therapy	17 (5.7)
LVEF < 50%	10 (3.4)
Symptomatic pleural effusion	10 (3.4)
Bilirubin > 1.5 g/dL	7 (2.4)
Prior CD19-directed therapy	5 (1.7)

Nastoupil L, et al. J Clin Oncol. 2020;38(27):3119-3128
Jain MD J Clin Oncol. 2024; 42:3581-3592

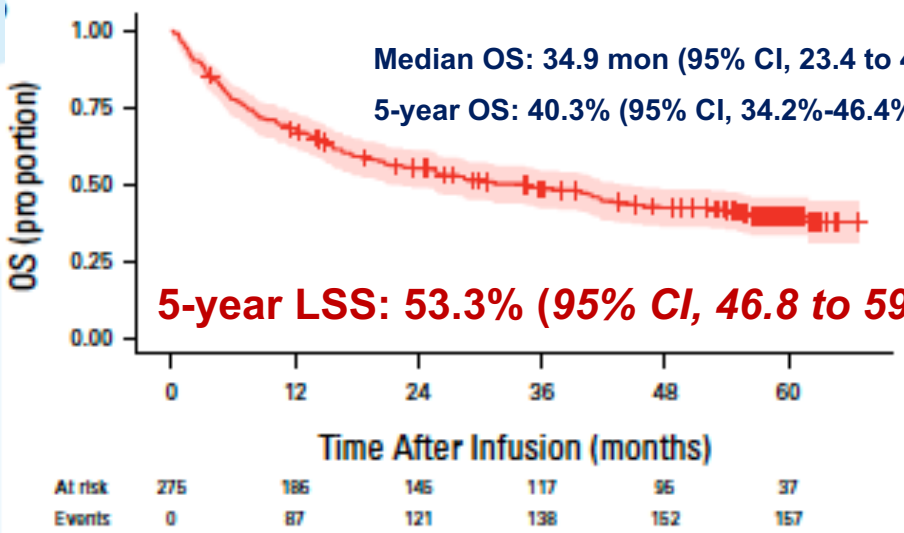
Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

”Real World US Experience”



Median PFS: 8.7 mon (95% CI, 5.9 to 16.6)

5-year PFS: 28.5% (95% CI, 23%-34.2%)



Median OS: 34.9 mon (95% CI, 23.4 to 44.8

5-year OS: 40.3% (95% CI, 34.2%-46.4%)

5-year LSS: 53.3% (*95% CI, 46.8 to 59.3*)

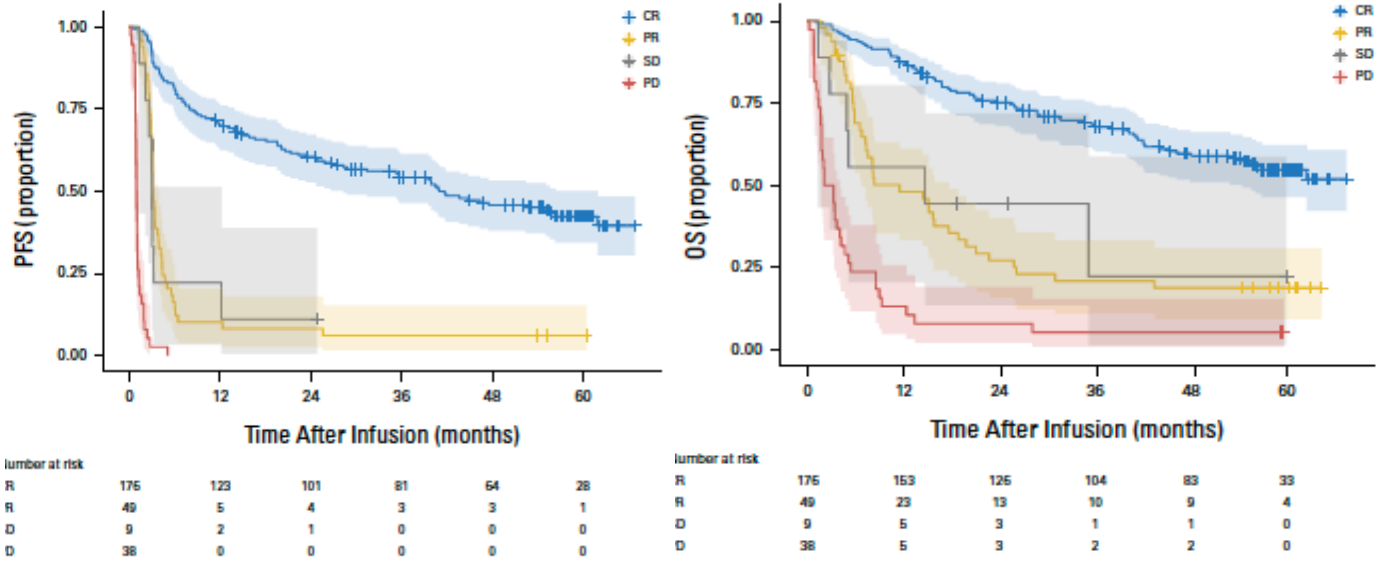


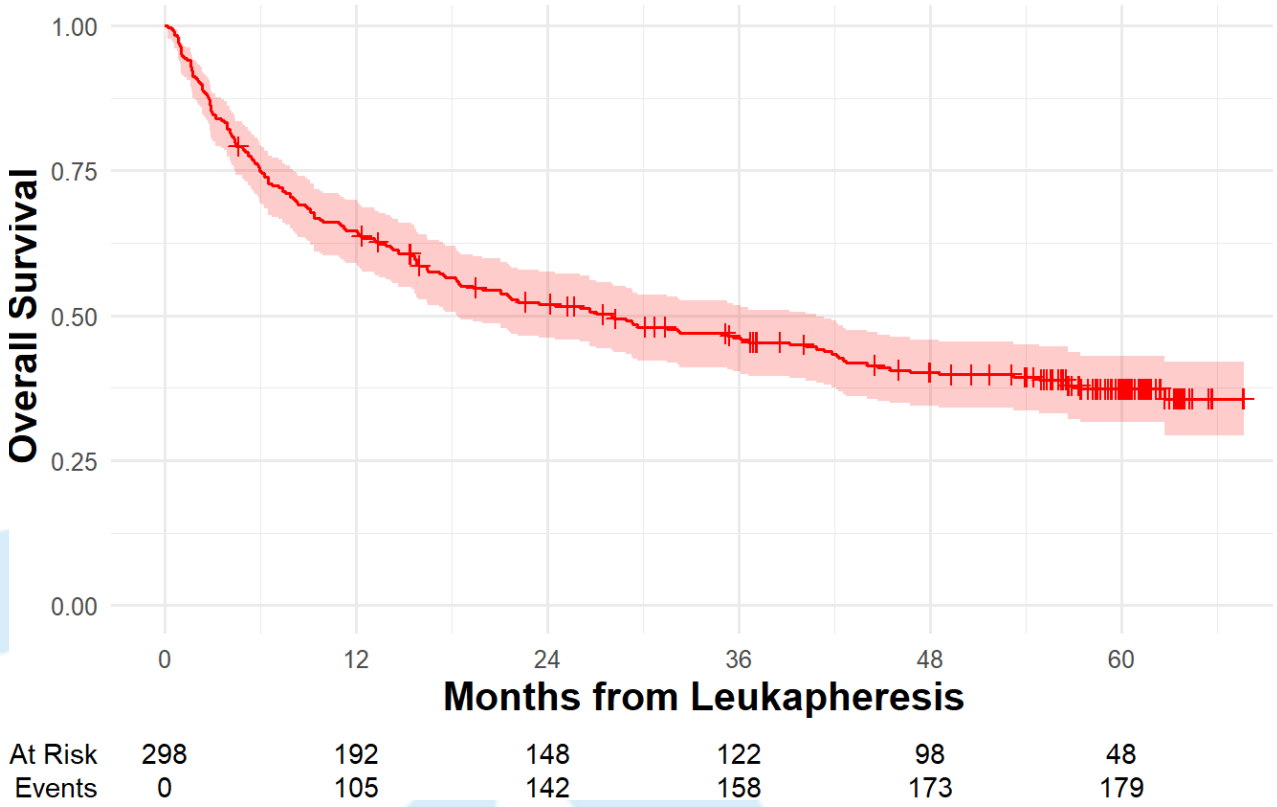
TABLE 1. Multivariable Analysis of PFS and OS

Characteristic	OS HR (95% CI)	OS *P*	PFS HR (95% CI)	PFS *P*
Age, years				
<60	–		–	
≥60	1.03 (0.74 to 1.43)	.9	0.87 (0.65 to 1.18)	.4
LDH ≥ ULN				
Below ULN	–		–	
Above ULN	1.57 (1.10 to 2.25)	.014	1.82 (1.31 to 2.53)	<.001
ECOG				
0-1	–		–	
2-4	2.00 (1.32 to 3.04)	.001	1.93 (1.30 to 2.86)	.001
Bridging therapy				
No	–		–	
Yes	1.25 (0.88 to 1.78)	.2	1.08 (0.78 to 1.49)	.6
Elevated bilirubin (≥1.5 g/dL)				
No	–		–	
Yes	5.61 (2.18 to 14.5)	<.001	3.68 (1.45 to 9.37)	.006
Previous lines of therapy				
<3	–		–	
≥3	1.43 (0.95 to 2.15)	.084	1.49 (1.03 to 2.13)	.032

Nastoupil L, et al. J Clin Oncol. 2020;38(27):3119-3128

Jain MD J Clin Oncol. 2024; 42:3581-3592

Standard of care: 5-year OS of all leukaphersed pts (ITT)



5-yr OS: 37% (31.5 – 43)

Leukapheresis for planned standard-of-care axi-cel CAR T-cell therapy as of 9/30/2018 (N = 298)

- Did not proceed to CAR T infusion (n = 23)
  - Lymphoma progression/death (n = 20)
  - Infection (n = 1)
  - Attained CR with bridging therapy (n = 1)
  - Renal failure (n = 1)

Axi-cel CAR T infusion (n = 275)
- Axi-cel standard of care (n = 268)
- Expanded access program ZUMA-9 (n = 7)

Evaluable for
- PFS/OS, leukapheresis (n = 298)
- infused (n = 275)
- CRS and neurotoxicity (n = 275)

Nastoupil L, et al. J Clin Oncol. 2020;38(27):3119-3128
Jain MD J Clin Oncol. 2024; 42:3581-3592

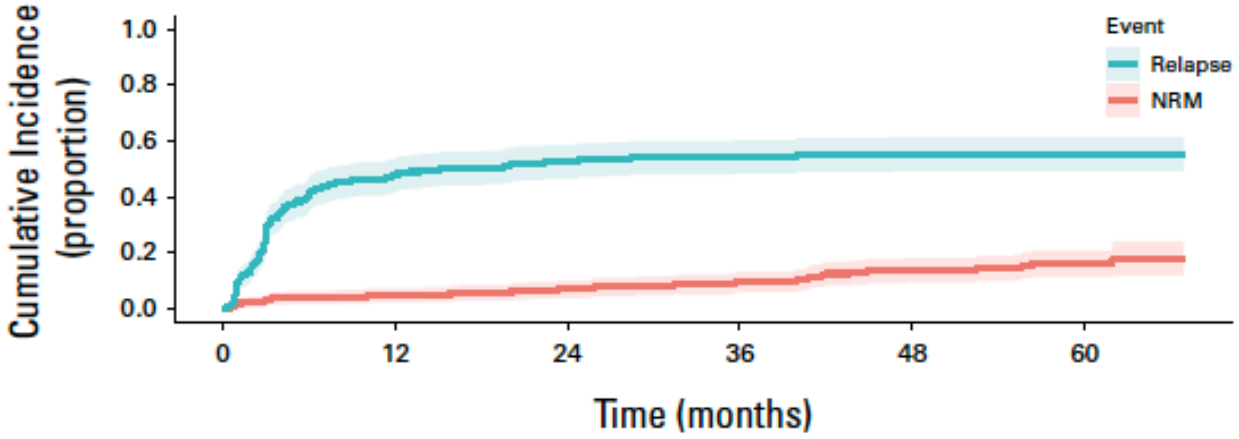
Relapse and Non-relapse mortality (NRM)

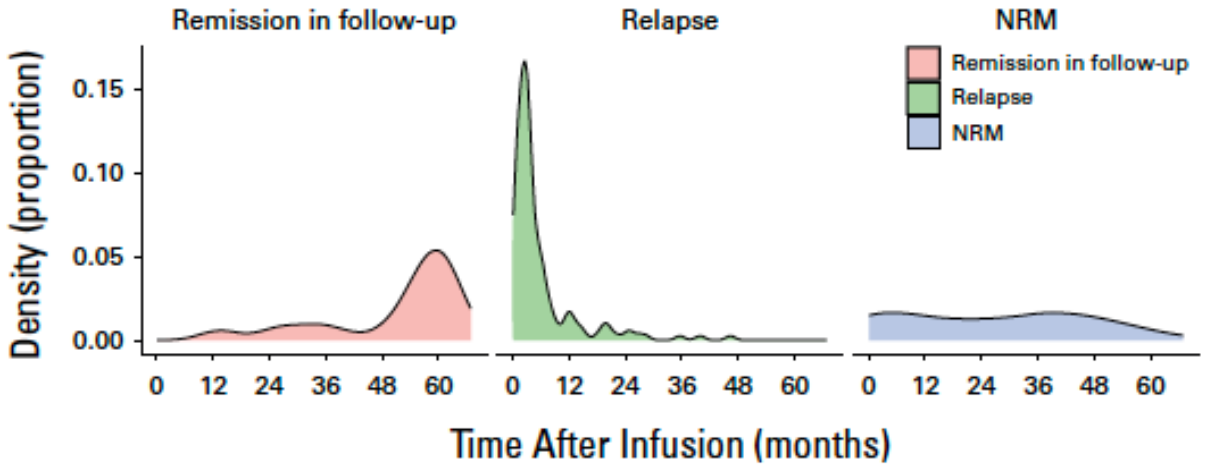
5-year cumulative risk of relapse: 55.2%

- ✓ 151 total progression events
- ✓ Latest progression at 46 months

5-year cumulative risk of NRM: 16.2%

- ✓ 40 NRM events





Jain MD J Clin Oncol. 2024; 42:3581-3592

Relapse and Non-relapse mortality (NRM):

Age could play important role in late NRM

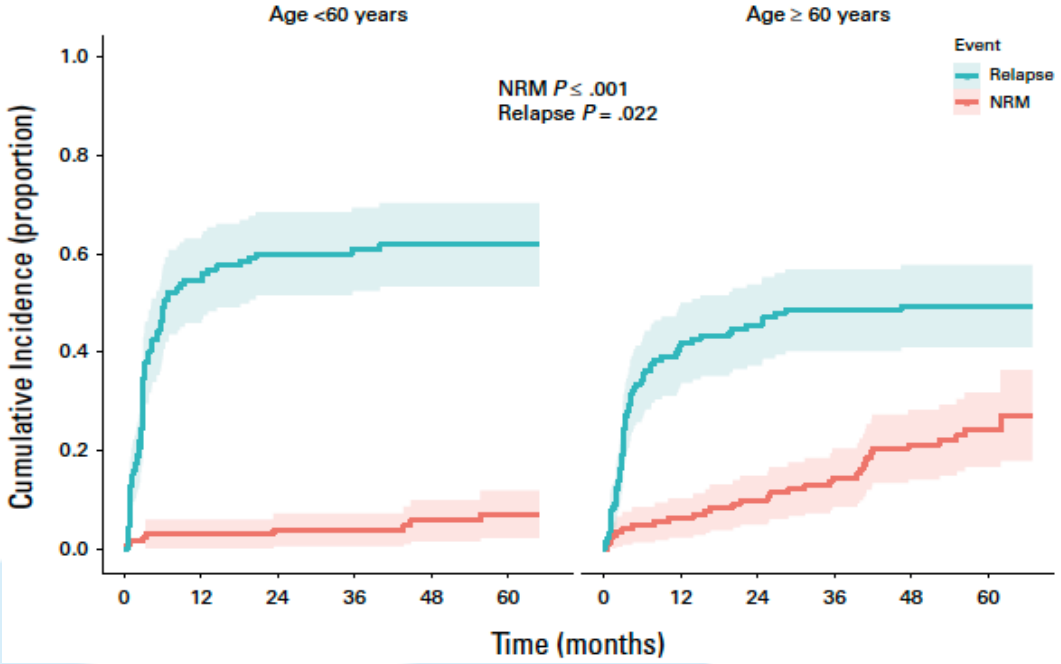


TABLE A2. Baseline Associations With NRM

Characteristic	Odds Ratio (95% CI)	P
NRM		
Sex		
Female	–	
Male	0.9 (0.4 to 1.8)	.67
Age, years		
<60	–	
≥60	4.5 (2.1 to 10.8)	<.001
Previous lines of therapy		
<3	–	
≥3	1.6 (0.7 to 3.8)	.29
Baseline LDH		
Below ULN	–	
Above ULN	1.0 (0.5 to 2.0)	.97
Bridging therapy		
No	–	
Yes	1.3 (0.7 to 2.6)	.45

Causes of death by year after Axi-cel infusion

Cause of Death	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6 or Later	Total
Progressive disease	74	28	11	4	1	0	118
Infection	8	2	4	6	1	0	21
Secondary malignancy	0	3	1	3	1	1	9
CAR-T toxicity[a]	3	0	0	0	0	0	3
Unknown/Other[b]	2	1	1	1	2	0	7

Cause of Death	Age < 60 (n=132)	Age ≥ 60 (n=143)
Lymphoma Progression	64 (48%)	54 (38%)
Infection	4 (3%)	17 (12%)
Secondary Malignancy	3 (2.3%)	6 (4.2%)
CAR T toxicity	1 (0.8%)	2 (1.4%)
Unknown/other	0 (0%)	7 (4.9%)

Jain MD J Clin Oncol. 2024; 42:3581-3592

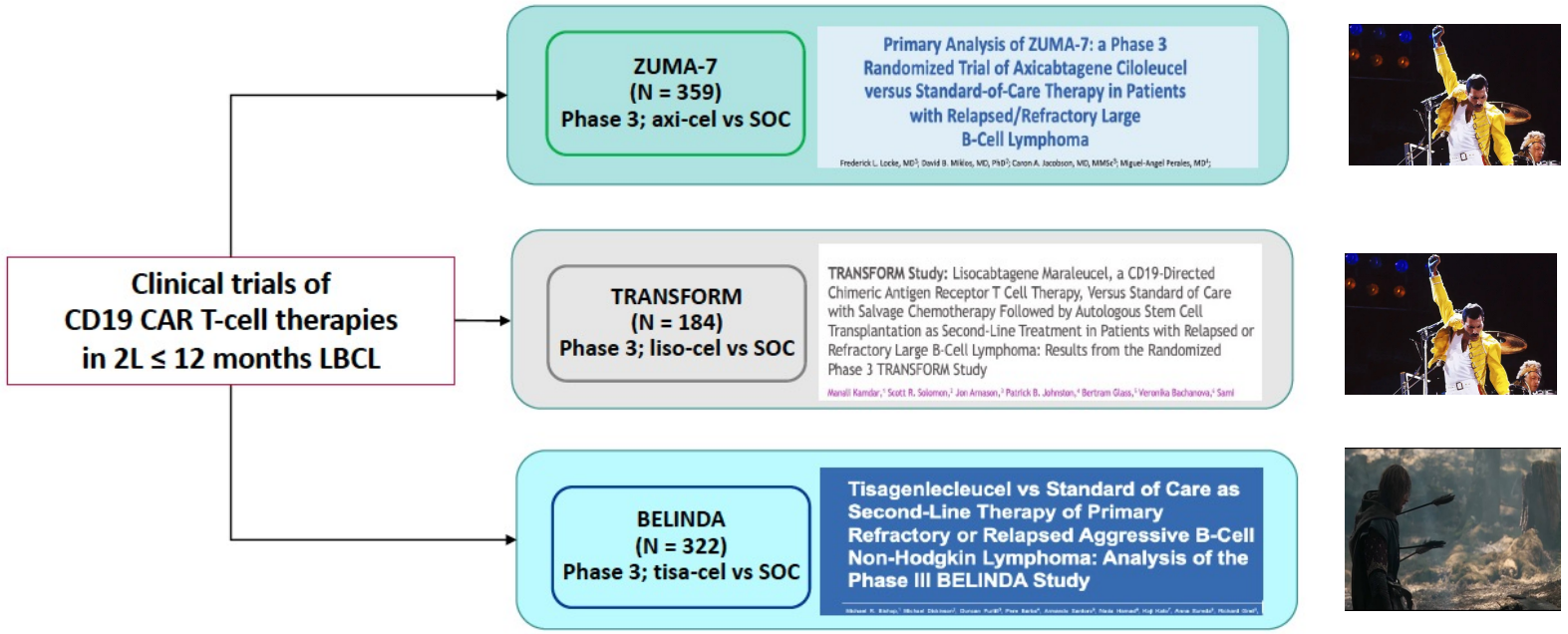


Table 1. Characteristics of the phase 3 trial comparing CAR-T vs SOC (salvage platinum-based immunochemotherapy and ASCT consolidation).

	ZUMA-7[13]	BELINDA[15]	TRANSFORM[17]
CAR-T product	Axi-cel	Tisa-cel	Liso-cel
Number of patients	359	322	184
ORR, %	83% vs. 50%	46.3% vs. 42.5%	87% vs. 49%
CRR, %	65% vs. 32%	28% vs. 28%	74% vs. 43%
EFS rate, %	41% vs. 16%	28% vs. 35%	53% vs. 21%
Median EFS, months	8.3 vs. 2 (HR 0.4, $p < 0001$)	3 vs. 3 (HR 1.07, $p = 0.61$)	NR vs. 2.4 (HR 0.34, $p < 0001$)
Median PFS, months	14.7 vs. 3.7	ND	NR vs. 6.2
OS rate, %	61% vs. 52%	ND	73% vs. 61%
Median OS, months (HR)	NR vs 35.2 (HR 0.73)	16.9 vs 15.3 (HR 0.99)	NR vs 29.9 (HR 0.7; $p = 0.098$)
Median follow-up, months	25	10	17.5
CRS, % (≥ grade 3, %)	92% (6%)	61% (5%)	49% (11%)
NE, % (≥ grade 3, %)	60% (21%)	10% (2%)	1% (4%)
Prolonged cytopenias grade ≥ 3, %	29% vs 19%	ND	37% vs 2%

Perez-Llamas L, Sandoval-Sus J, Chaves J. Expert Opin Biol Ther. 2025 Jan-Feb;25(2):139-148.

Second-Line Chimeric Antigen Receptor T Cell Therapy (CAR-T) As Standard of Care for Relapsed-Refractory Large B-Cell Lymphoma (LBCL)

Saurabh Dahiya[1], Jay Y. Spiegel, MDFRCPC[2], Dasom Lee, MD[3], Turab Mohammed, MD[4], Forat Lutfi, MD[5], Anmol Goyal, MD[6], Caroline Hana[7], Julio C Chavez, MD[8], Filip Ionescu, MD[9], Matthew J. Frank, MD PhD[1], Sushma Bharadwaj, MDMS[10], Jose Sandoval-Sus, MD[11], Amer M. Beitinjaneh, MD MS[12], Lazaros J. Lekakis[13], Joseph P McGuirk, DO[5], Frederick L. Locke, MD[14], David B. Miklos, MD PhD[1], Michael D. Jain, MD PhD[14]

65th ASH® Annual Meeting and Exposition
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Primary refractory LBCL: 59%

Leukapheresed pts: 112 (103 Axi-cel, 9 Liso-cel)

↓

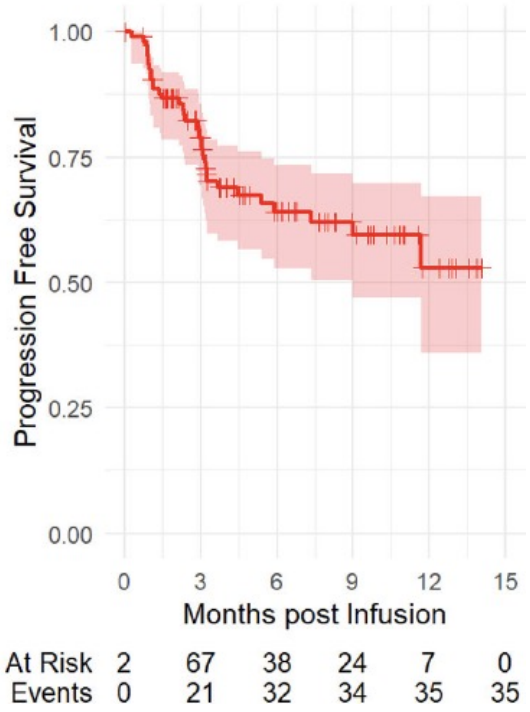
CAR-T cell treated pts: 110

↓

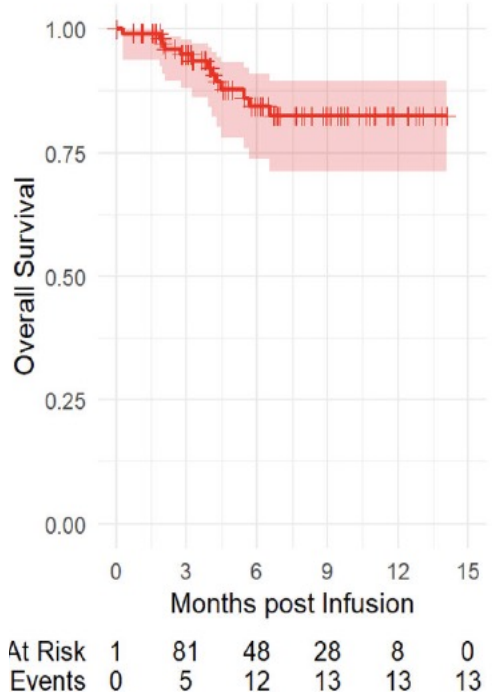
Outcomes	
ORR	82.7%
CR	61.8%
mPFS	NR
mOS	NR
CRS/G3-G4 CRS	88%/6.3%
ICANS/G3-G4 ICANS	59%/30%

Median f/up: 6.2 months (95% CI: 4.32 – 7.6 mo)

6-mo PFS: 64.1% (52.8% - 73.4%)



6-mo OS: 84.4% (73.8% - 90.9%)

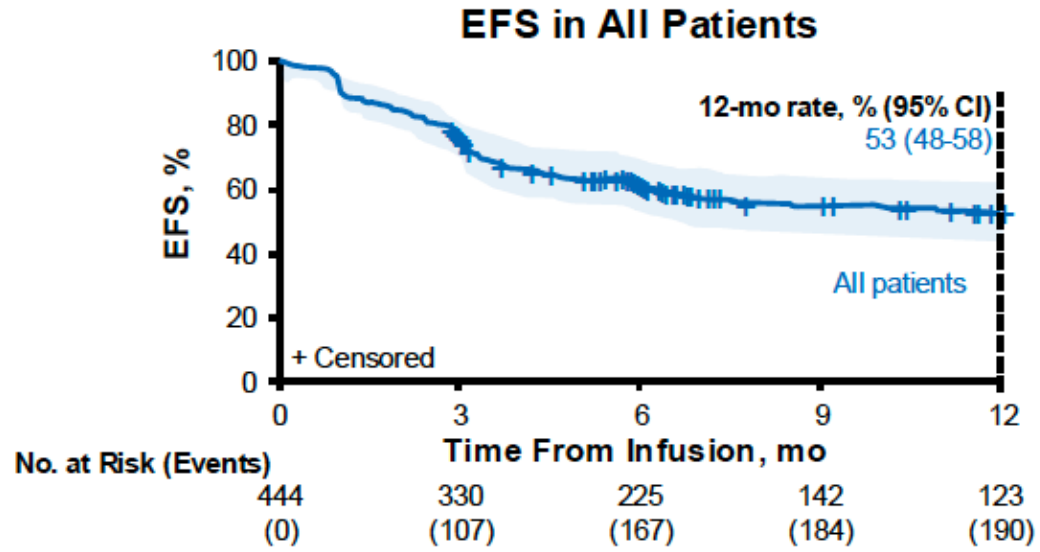


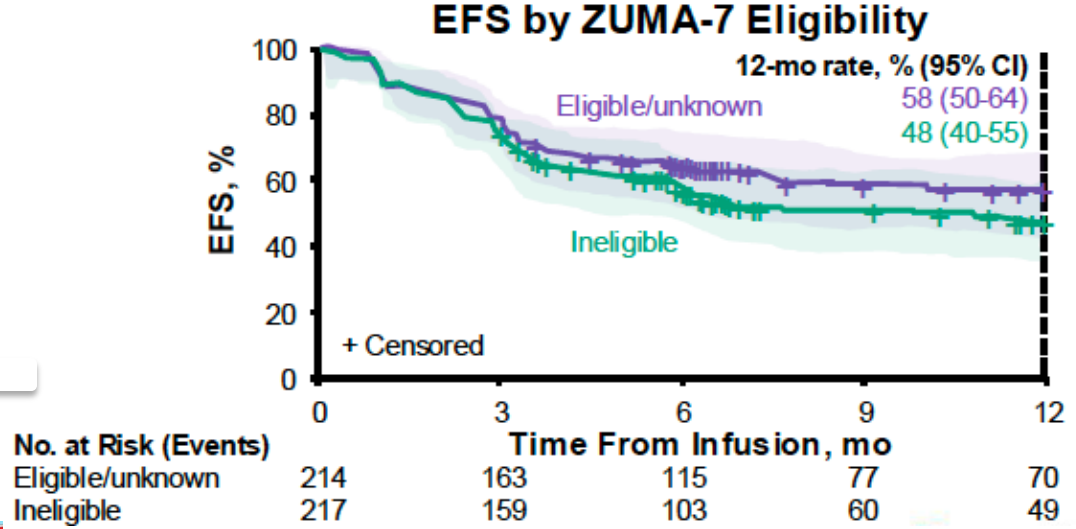
Real-World Early Outcomes of 2L Axi-Cel in Pts with R/R Large B-Cell Lymphoma (LBCL)

Large real-world analysis of patients with R/R LBCL receiving 2L axi-cel (only 48% eligible for ZUMA-7)[1]

Characteristic, n (%)	All Patients (N = 446)
ZUMA-7 eligibility	
Eligible	214 (48)
Not eligible	219 (49)
Organ impairment	150 (34)
Pulmonary (moderate/severe)	81 (18)
Cardiac	49 (11)
Bone marrow (platelets, ANC, and/or ALC)	37 (8)
Arrhythmia	26 (6)
Cerebrovascular disease	14 (3)
Renal (moderate/severe)	5 (1)
Heart valve disease	4 (<1)
Hepatic (moderate/severe)	1 (<1)
Prior malignancy	70 (16)
Other causes for ineligibility	48 (11)
PMBCL	13 (3)
Transplant ineligible	226 (52)

- After a median follow-up of 12 months, consistent efficacy (ORR, EFS, OS) outcomes were comparable with ZUMA-7 results **ORR: 79%, CR: 64%, 12 mon EFS: 53% and 12 mon OS: 71%.**
- Incidence of any-grade and grade ≥3 CRS was similar regardless of ZUMA-7 eligibility status





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Lee DC et al. ASH 2024. Abstract 526.

Multicenter, Real-World Study in pts with R/R LBCL who Received Liso-cel in the US (CIBMTR analysis)

US patients with R/R LBCL from the CIBMTR Cellular Therapy Registry between February 2021 and November 2022 after infusion with liso-cel (N = 323)[1]

Table. Baseline demographics and disease characteristics

Characteristic	All patients (N = 323)
Male, n (%)	204 (63)
Age, median (range), years	70 (24–91)
< 65, n (%)	107 (33)
≥ 65, n (%)	216 (67)
≥ 75, n (%)	89 (28)
Histology, n (%)	
DLBCL	270 (84)
DLBCL NOS	263 (81)
Transformed from CLL (Richter's)	22 (7)
Transformed from other lymphoma histology	66 (20)
PMBCL	2 (1)
FL3B	4 (1)
HGBCL	38 (12)
HGBCL with *c-MYC* and either *BCL2* and/or *BCL6* translocation at infusion	32 (10)
Other	9 (3)
ECOG PS, n (%)	
0–1 / ≥ 2	274 (85) / 18 (6)
Comorbidities, n (%)	
Pulmonary (moderate/severe)	82 (25)
Cardiac	80 (25)
Obesity	30 (9)
Renal (moderate/severe)	8 (2)
Hepatic (moderate/severe)	6 (2)
Other	32 (10)
Active CNS involvement, n (%)	18 (6)
IPI score, n (%)	
0–1 / 2	84 (26) / 121 (37.5)
3 / 4–5	92 (28.5) / 26 (8)
Number of prior lines of systemic therapy, median (range)	3 (0–11)
Received standard LDC (FLU/CY), n (%)	294 (91)

CY, cyclophosphamide; FL3B, follicular lymphoma grade 3B; FLU, fludarabine; LDC, lymphodepleting chemotherapy; PMBCL, primary mediastinal B-cell lymphoma.

Median f/up: 7.4 months

Outcome	Overall	Aged ≥65 y	TRANSCEND Noneligible
ORR, %	76	77	76
CR, %	63	62.5	64
Median DOR, mo	NR	NR	NR
1-y PFS, %	51	51	54
1-y OS, %	66	67.5	67.5

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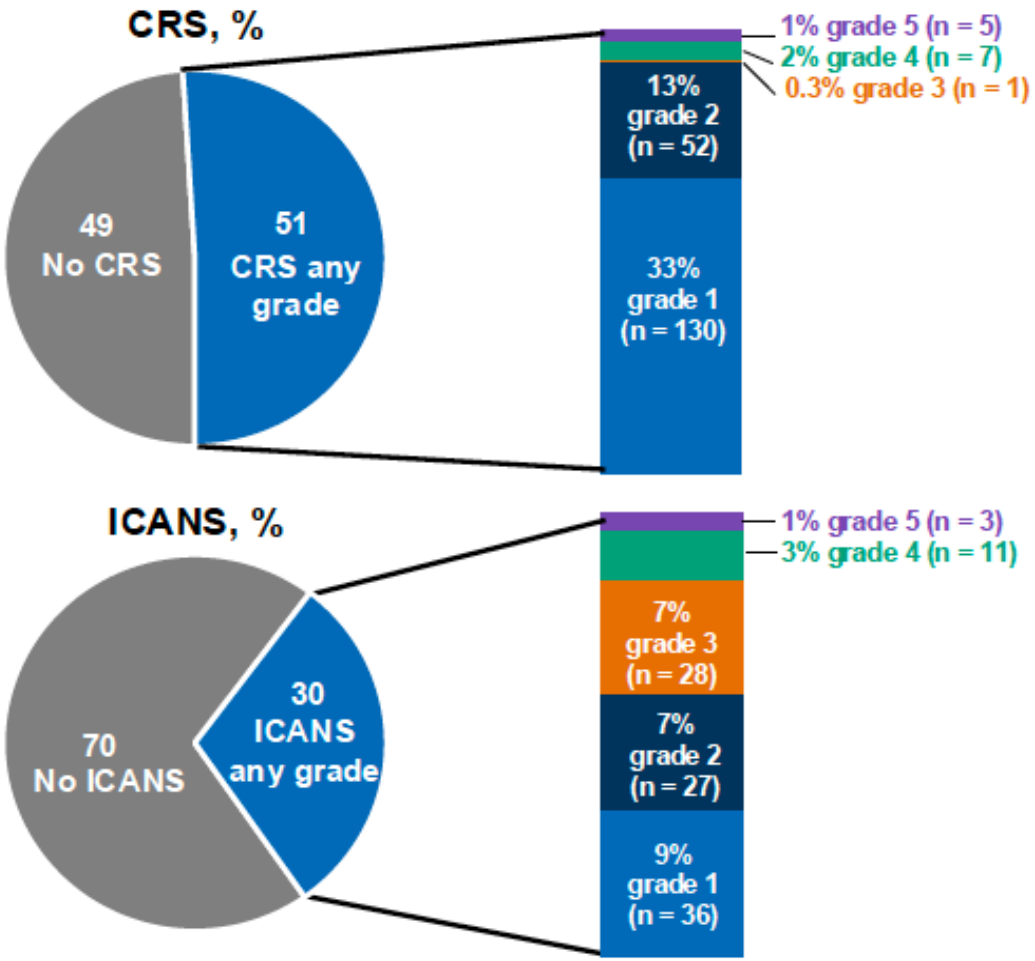
Crombie J et al. ASH 2023. Abstract 104.

Multicenter, Real-World Study in pts with R/R LBCL who Received Liso-cel in the US (CIBMTR analysis):
Safety with focus on CRS and ICANS

- N = 323; 84% of patients had DLBCL (81% with DLBCL NOS)
- Overall, safety outcomes were similar across all patient subgroups (age, TRANSCEND eligible vs noneligible) receiving a single infusion of liso-cel[1]
- Incidence of grade ≥3 CRS and ICANS was low
- 49% and 70% of patients did not experience CRS or ICANS, respectively



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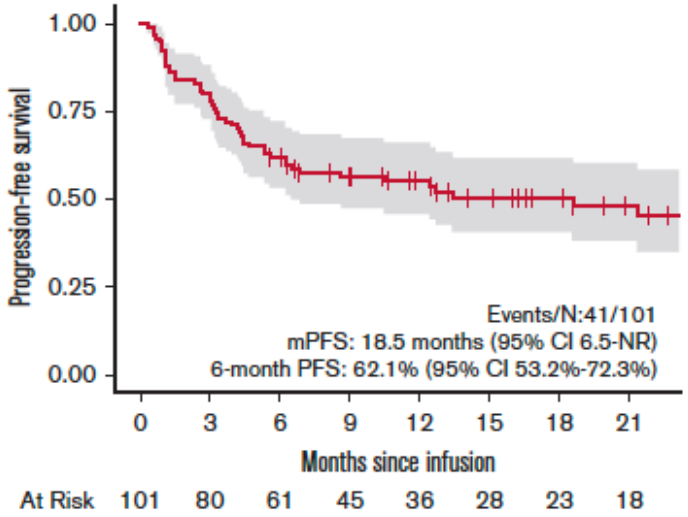
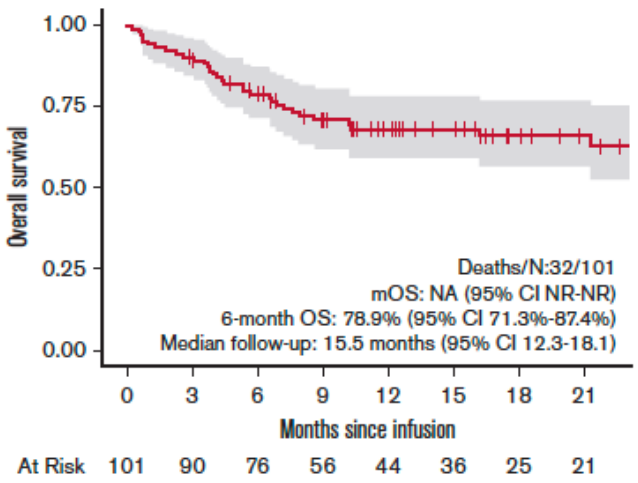
Crombie J et al. ASH 2023. Abstract 104.

Lisocabtagene maraleucel for relapsed/refractory large B-cell lymphoma: a cell therapy consortium real-world analysis

Table 1. Patient characteristics

Characteristic	N = 101
Age at apheresis, y	
Median (range)	71 (30-85)
<65, n (%)	28 (28%)
65-74, n (%)	38 (38%)
≥75, n (%)	35 (35%)
Male, n (%)	61 (60%)
Race	
Non-Hispanic White, n (%)	83 (86%)
Asian, n (%)	6 (6%)
Black, n (%)	5 (5%)
Hispanic, n (%)	2 (2%)
ECOG PS 0/1 at apheresis, n (%)	72 (84%)
Missing, n	15
Active secondary CNS lymphoma, n (%)	10 (10%)
Charlson comorbidity index	
0-1, n (%)	7 (7%)
2, n (%)	25 (25%)
≥3, n (%)	69 (68%)
Ineligible for TRANSCEND because of comorbidities‡, n (%)	30 (33%)
Missing, n	9
Bridging therapy, n (%)	61 (60%)
Lymphodepleting chemotherapy	
Fludarabine/cyclophosphamide, n (%)	75 (74%)
Bendamustine, n (%)	26 (26%)





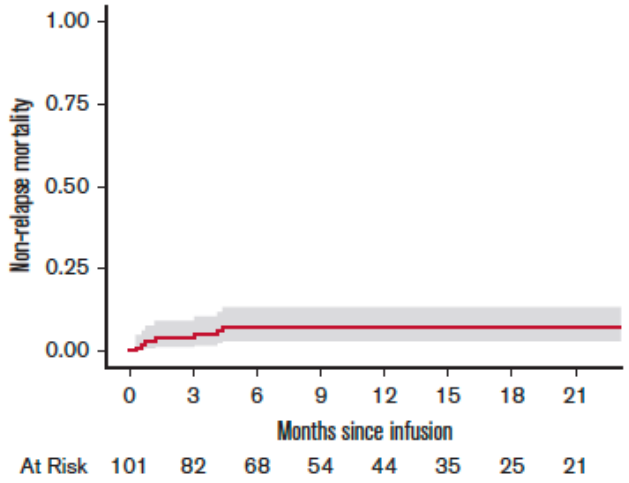


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Table 2. Main outcomes and multivariable regression analysis

Effect	*P* value	OR/HR estimate	95% CI
PFS			
Ineligible for TRANSCEND clinical trial	.008	2.64	1.29-5.40
Prelymphodepletion LDH equal to, or lower than, institutional ULN	<001	0.25	0.12-0.55
OS			
Bridging therapy and response: no bridging vs PR/CR to bridging	.60	1.39	0.40-4.81
Bridging therapy and response: no bridging vs SD/PD to bridging	<001	4.32	1.81-10.30
Prelymphodepletion LDH equal to, or lower than, institutional ULN	.004	0.30	0.13-0.68
Fludarabine and cyclophosphamide lymphodepletion	.033	3.76	1.11-12.70

OR, odds ratio; PD, progressive disease; SD, stable disease.

Table 3. Summary of safety

	N = 101
CRS, n (%)	
Any grade, n (%)	49 (49%)
Grade 3, n (%)	2 (2%)
Grade 4, n (%)	0 (0%)
Grade 5, n (%)	1 (1%)
ICANS, n (%)	
Any grade, n (%)	26 (26%)
Grade 3, n (%)	4 (4%)
Grade 4, n (%)	4 (4%)
Grade 5, n (%)	2 (2%)

Table 4. Resource use

	N = 101
Treatment setting, n (%)	
Inpatient, n (%)	86 (85%)
Outpatient, n (%)	15 (15%)
Unplanned hospitalization after outpatient administration, n (%)*	5 (33%)

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Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy Registry

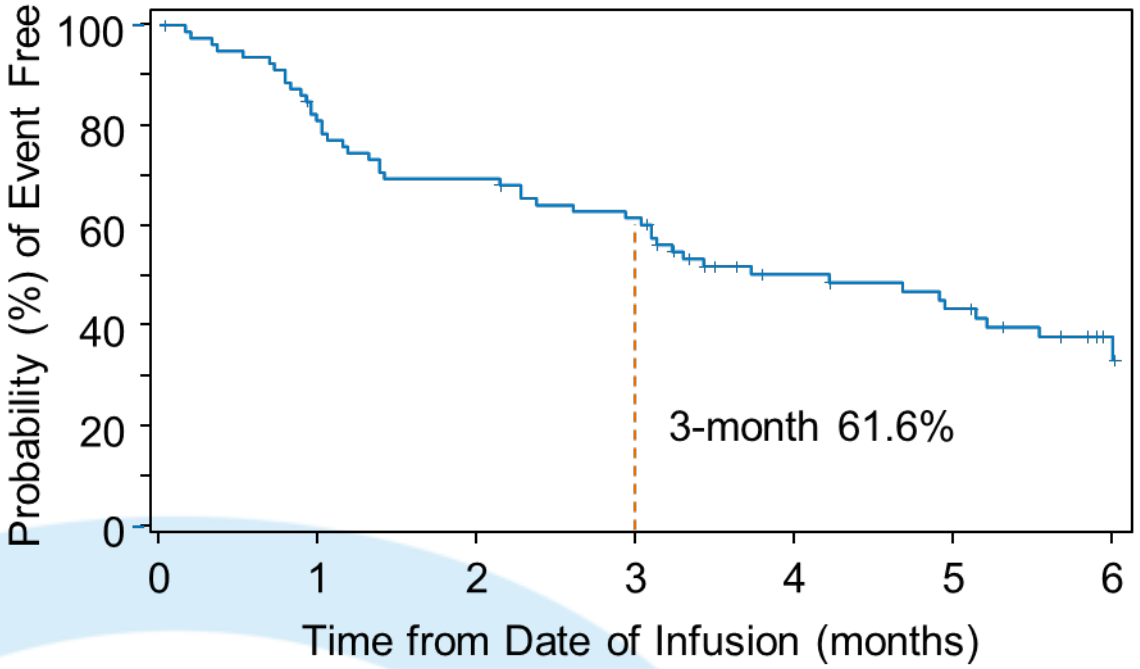
Samantha Jaglowski, Zhen-Huan, Yiyun Zhang, Hu, Manali Kamdar, Monalisa Ghosh, Premal D Lulla, Joshua P Sasine, Miguel-Angel Perales, Peiman Hematti, Sarah Nikiforow, Patricia Steinert, Lan Yi, Raghav Chawla, Lida Pacaud, Mary M Horowitz, Eric Bleickardt, Marcelo C. Pasquini

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW).

CIDR
CELLULAR IMMUNOTHERAPY DATA RESOURCE

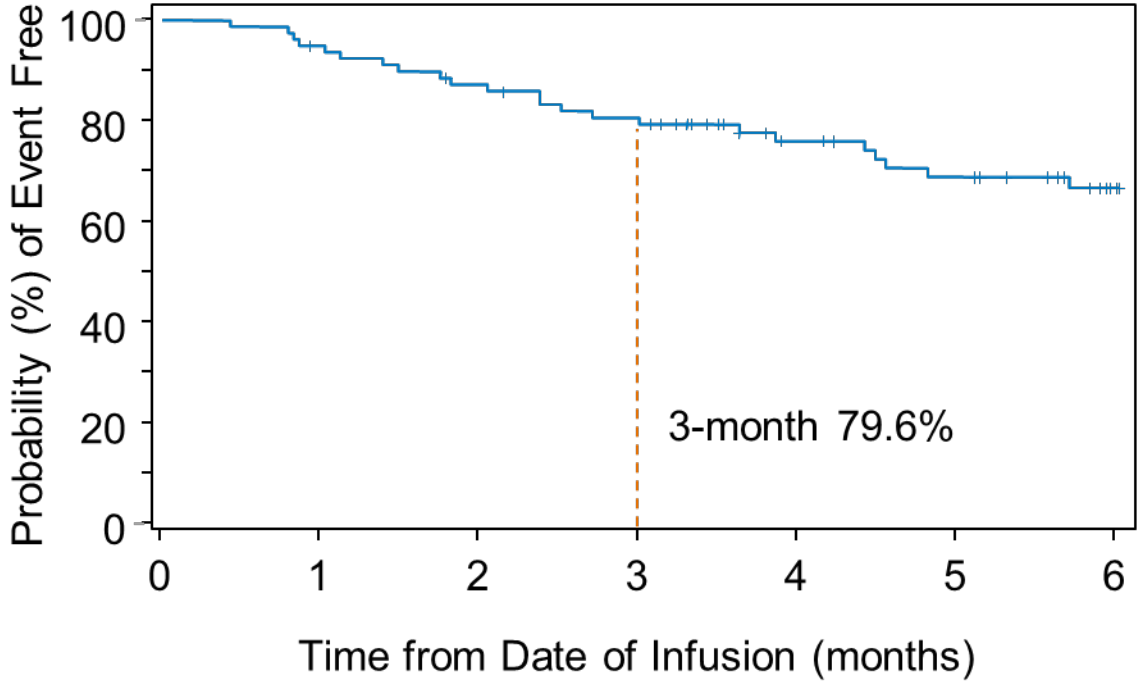
Progression Free Survival



N at Risk

All subjects	80	63	54	47	30	25	14

Overall Survival



N at Risk

All subjects	80	75	68	61	45	39	24

Courtesy of Dr. Krishna Komanduri

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CIDR
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Malignant Hematology & Cellular Therapy

Jaglowski S et al. Nov 2019 Blood 134(Supplement_1):766-766

Comparison to JULIET Pivotal Trial

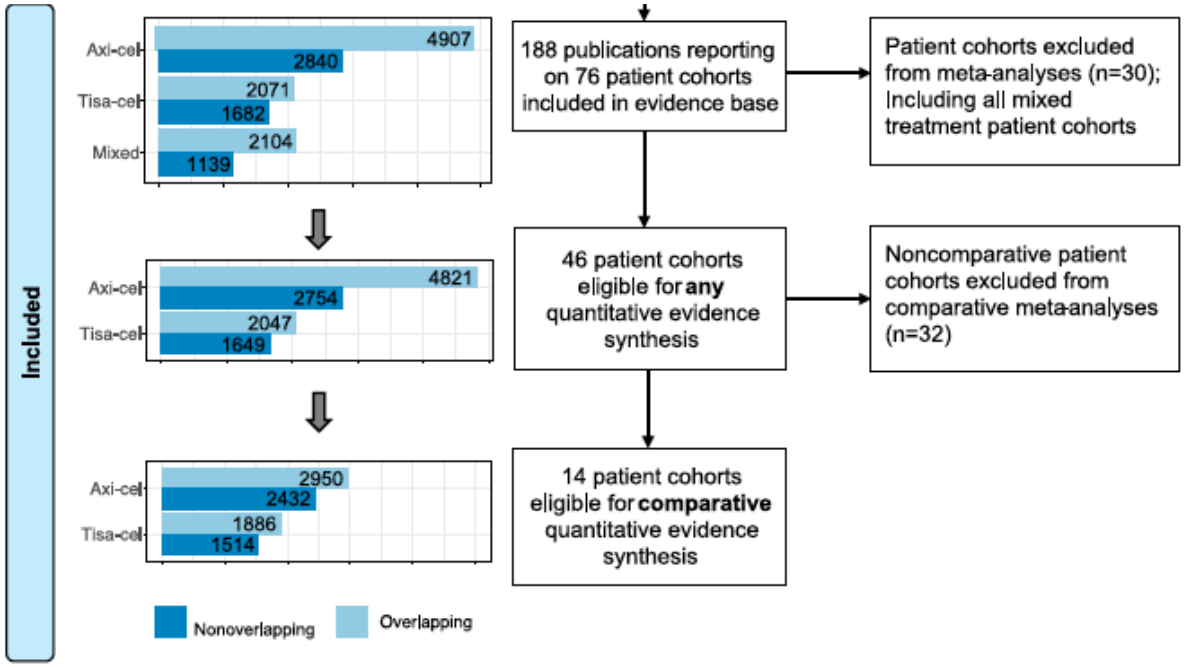
	CIBMTR Registry N=83[a] (%)	JULIET[b] N=115 (%)
ORR	58	52
CR	40	38
DOR at 3 months	75	76
PFS at 3 and 6 months	62 / 33	46 / 39
OS at 3 and 6 months	80 / 67	83 / 61
CRS (Gr. ≥ 3)	4[c]	23[e]
Neurotoxicity (Gr. ≥ 3)	5[d]	11[f]

Courtesy of Dr. Krishna Komanduri

[a]Efficacy set N=80; safety set N=83
[b]Bachanova V, et. al. Clin Lymphoma Myeloma Leuk 2019 Sep. Vol 19; (Suppl 1); S251-S252
[c] ASTCT grading
[d] ICANS Grading
[e] UPenn grading
[f] MedDRA SMQ: non-infectious encephalopathy/delirium

Jaglowski S et al. Nov 2019 Blood 134(Supplement_1):766-766

Real-World Outcomes with Chimeric Antigen Receptor T Cell Therapies in Large B Cell Lymphoma: A Systematic Review and Meta-Analysis



Variable	Axi-cel Cohorts				Tisa-cel Cohorts	
	RWE (95% CI)	ZUMA-1 Pivotal [39]	ZUMA-1 Cohort 4 [40]	ZUMA-1 Cohort 6 [41]	RWE (95% CI)	JULIET [34,42]
Objective response rate, %	73.4 (67.9-78.3)	83	73	95	57.7 (53.1-62.1)	53
Complete response rate, %	51.0 (44.5-57.4)	58	51	80	39.0 (34.6-43.7)	39
Median OS, mo	19.5 (16.9-25.8)	25.8	NR	NR	11.7 (10.2-13.0)	11.1
Median PFS, mo	7.3 (6.1-9.3)	5.9	NR	NR	3.3 (3.3-3.8)	2.9
ICANS any grade, %*	47.6 (41.6-53.7)	64	61	58	19.9 (17.7-22.3)	20
ICANS grade ≥3, %†	19.0 (15.0-23.8)	30	17	13	5.8 (4.3-7.9)	11
CRS any grade, %*	86.3 (82.0-89.7)	93	93	80	70.6 (59.1-80.0)	57
CRS grade ≥3, %†	8.2 (7.1-9.4)	11	2	0	8.9 (6.9-11.2)	17‡

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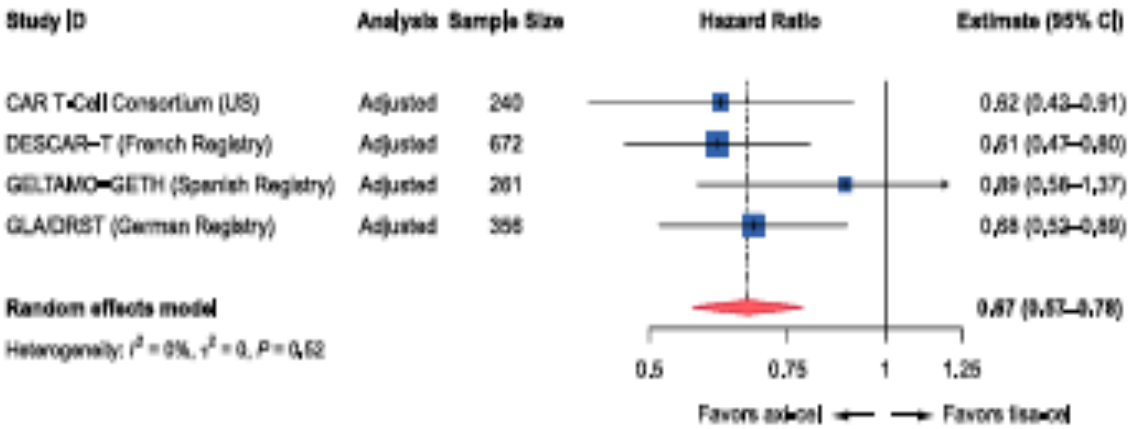
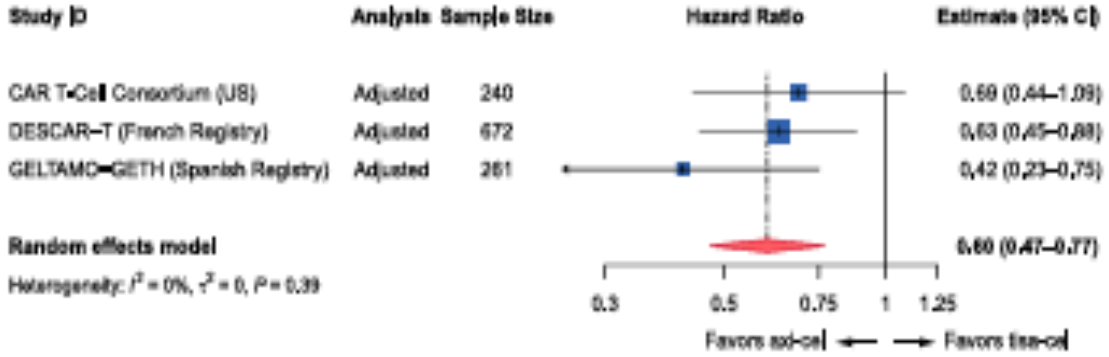
Jacobson C et al. TransplantationandCellularTherapy30(2024)77.e177.e15

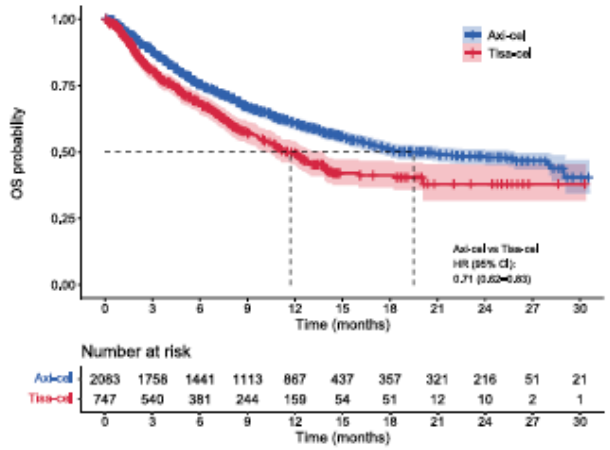
B. PFS – Adjusted hazard ratios



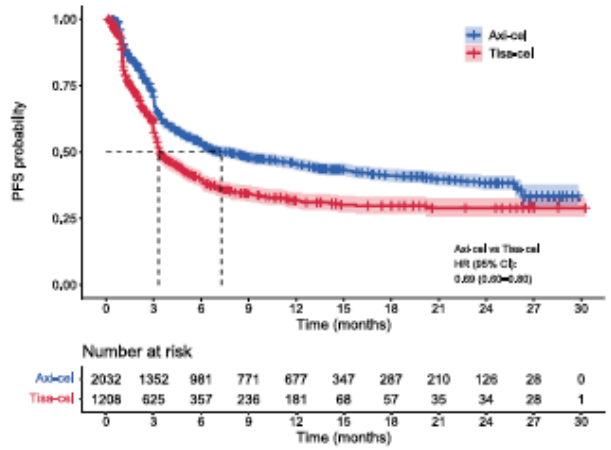
A. OS – Adjusted hazard ratios



E. OS – Kaplan–Meier curve



F. PFS – Kaplan–Meier curve



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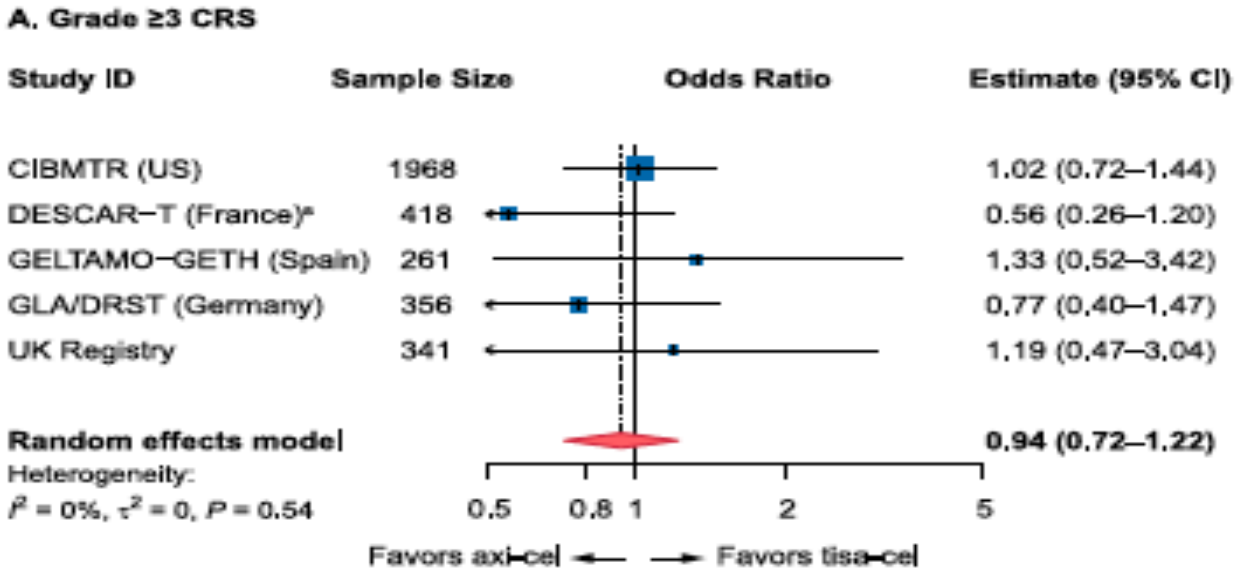

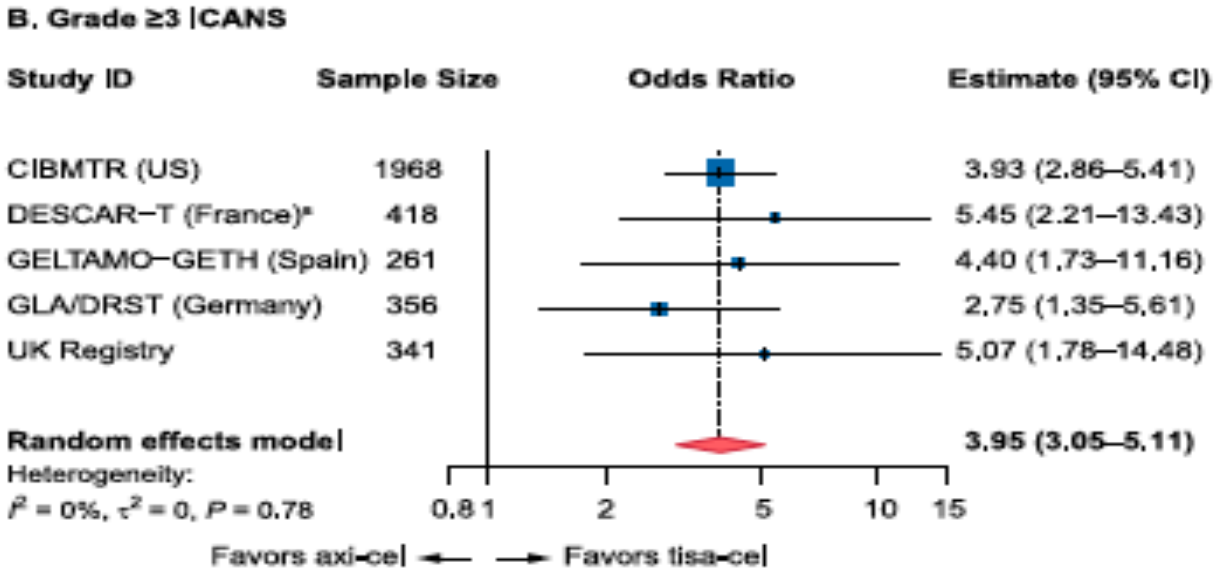

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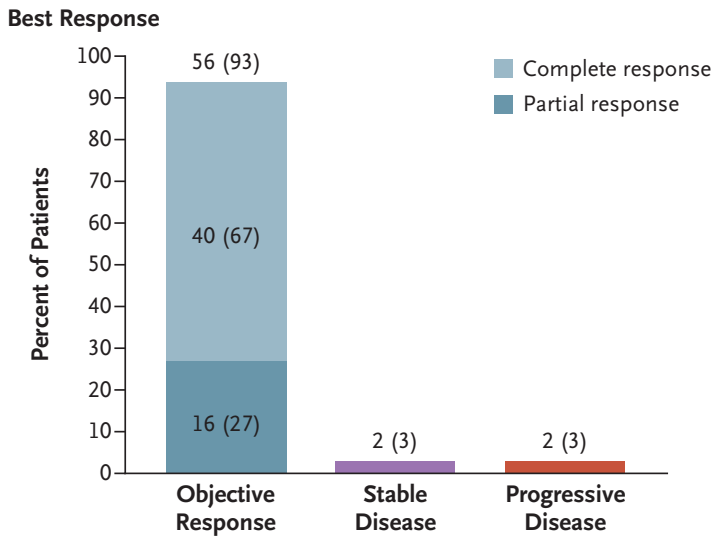
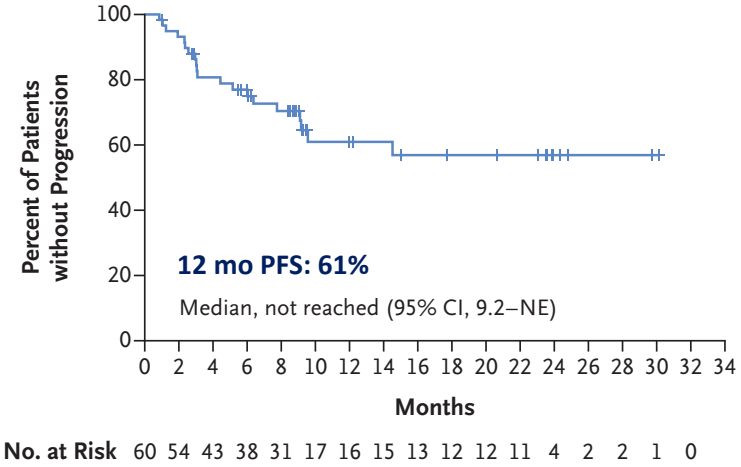
ZUMA-2: Brexucabtagene Autoleucel (KTE-X19) for Patients With R/R MCL

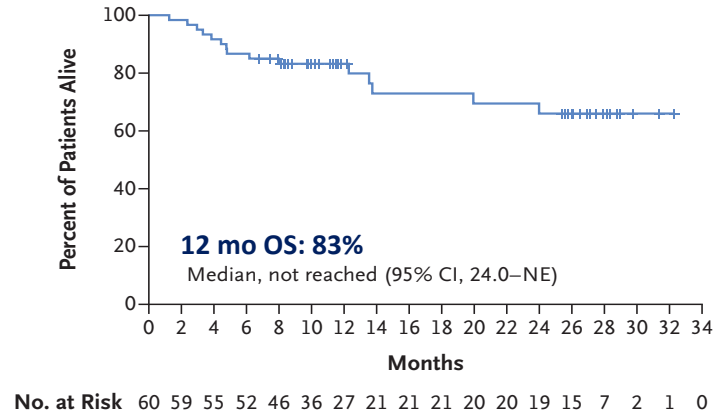
Patient baseline characteristics (N=68)

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)







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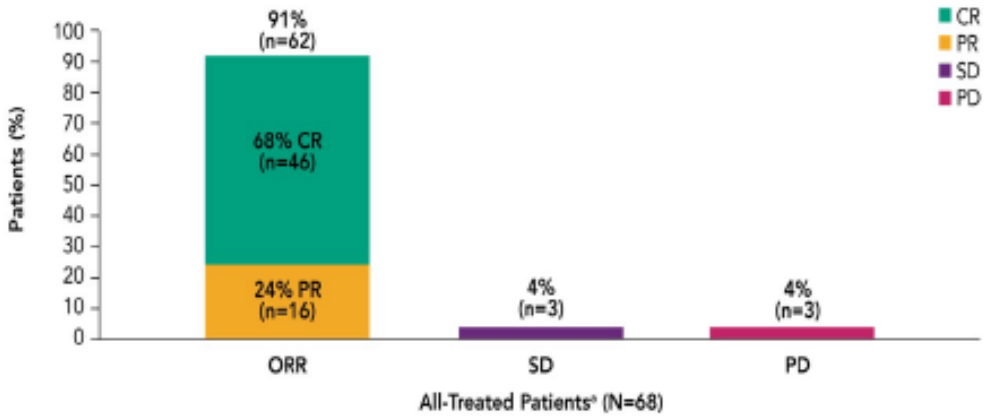
Wang M et al. N Engl J Med 2020;382:1331-42.

Relapsed/Refractory MCL (ZUMA-2):

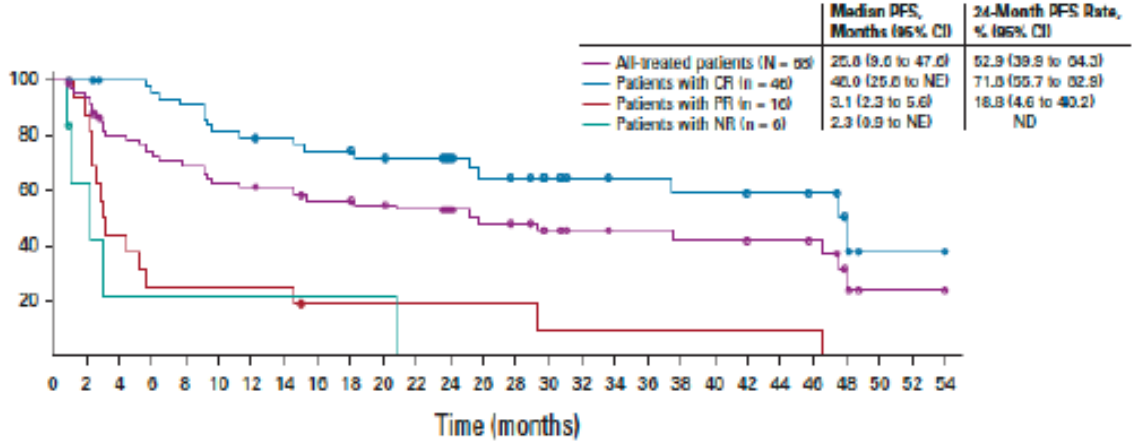
3-year follow-up of outcomes with Brexucabtagene autoleucel in R/R MCL



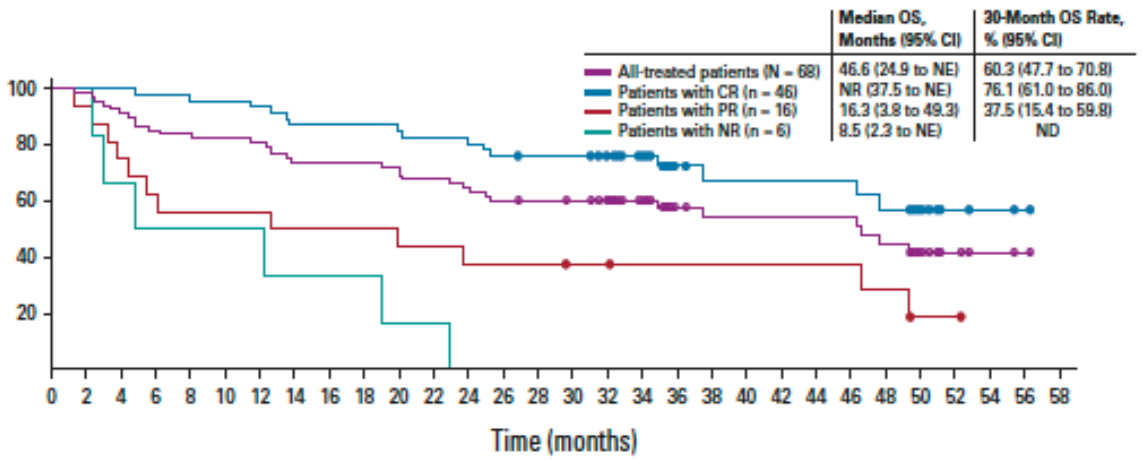
Adverse events	N (%)
≥ G3 CRS	10 (15)
≥ G3 NE	21 (31)
≥ G3 infections	13 (15)
≥ G3 neutropenia/ > 90 days, %	58 (85)/16
≥ G3 anemia/ > 90 days, %	34 (50)/12
≥ G3 thrombocytopenia/ > 90 d, %	35 (51)/16

NRM: 2 pts (3%)
(2 infections)

mPFS: 25.8 months (95% CI, 9.6 to 47.6)



mOS: 46.6 months (95% CI, 24.9 to not estimable)



Wang M et al. ASCO 2022;Abstract 7518; Wang M et al. *J Clin Oncol* 2023;41(3):555-67.

Relapsed/Refractory MCL:

Brexu-cel performance in R/R MCL outside clinical trial (still not “real life”)

- **189 pts underwent leukapheresis.**
- **168 (89%) received Brexu-cel.**
- **79% would not have met ZUMA-2 eligibility criteria.**

- ✓ **Prior # of Tx: 3 (1-10)**
- ✓ **cBTKi exposed/resistant: 100%/76%**
- ✓ **Blastoid/pleomorphic: 40%**
- ✓ **TP53 mut: 46%**
- ✓ **Ki67 > 30%: 78%**
- ✓ **CNS MCL/POD24: 10%/52%**

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)

1-year NRM: 9.1%
(10 from 18 deaths= infection)

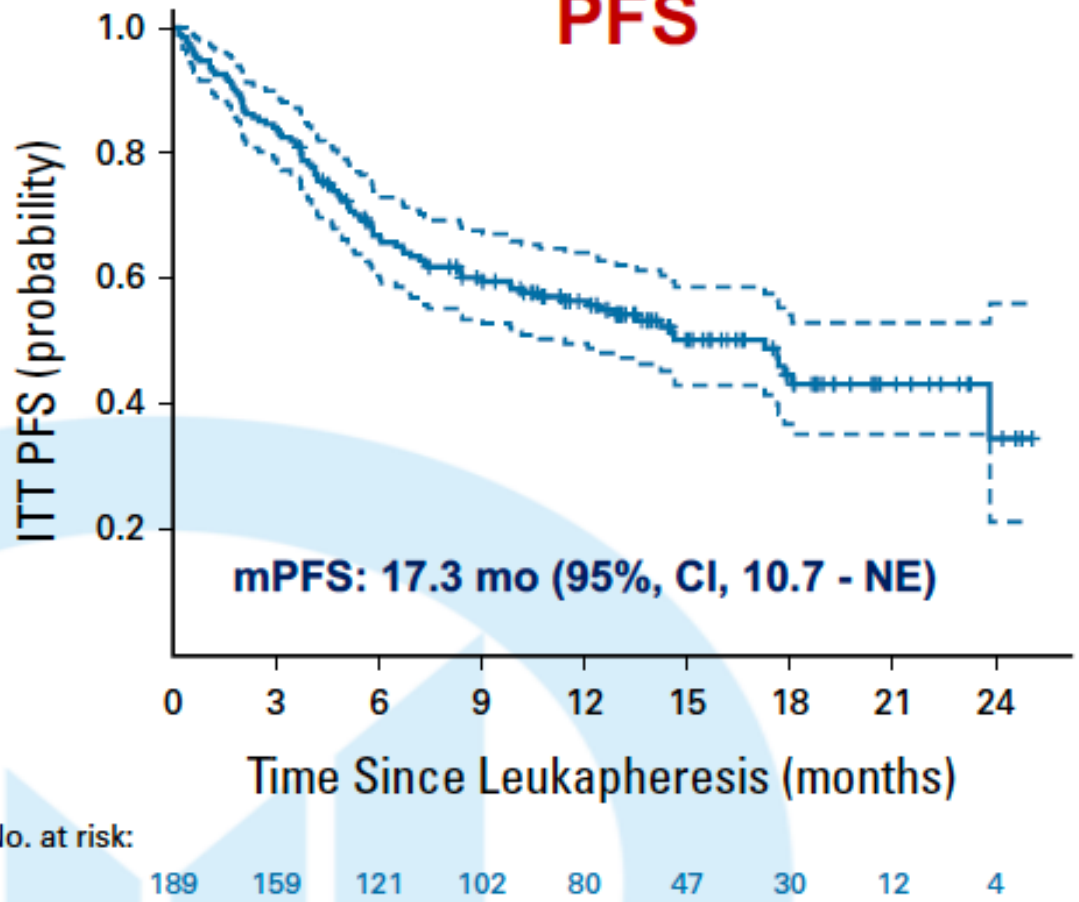
	Brexu-cel (n=168)
ORR, %	90%
CR, %	82%
6-mo PFS	69%
12-mo PFS	59%
≥ G3 CRS	8% (1 G5)
≥ G3 ICANS	32%

Wang Y, Jain P, Locke F, et at. JCO 2023

Relapsed/Refractory MCL:

Brexu-cel performance in R/R MCL outside clinical trial (still not “real life”)

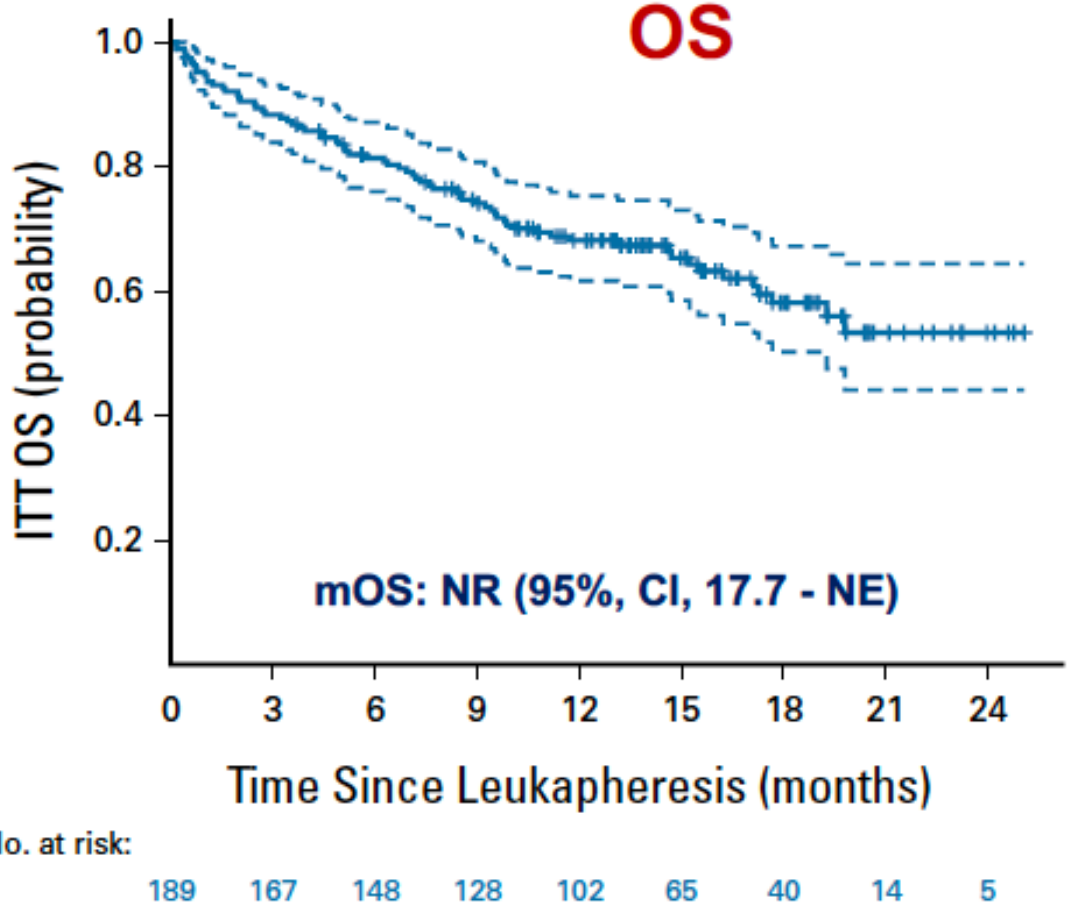
PFS



No. at risk:

189	159	121	102	80	47	30	12	4

OS



No. at risk:

189	167	148	128	102	65	40	14	5

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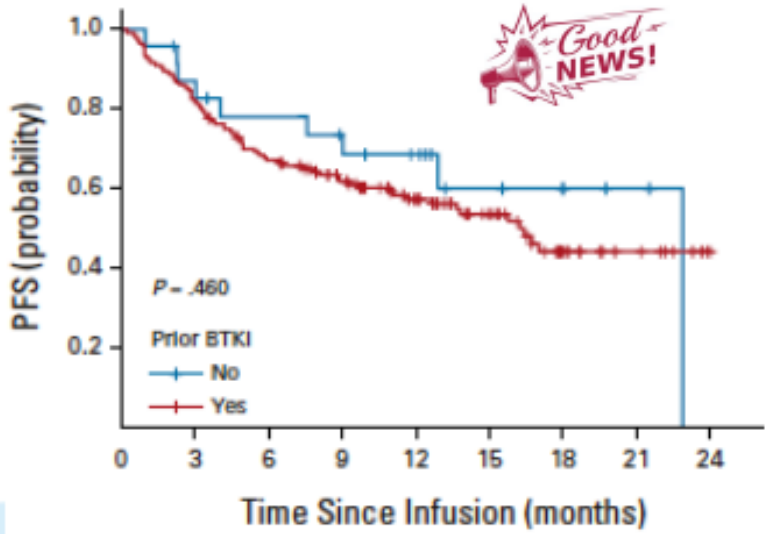
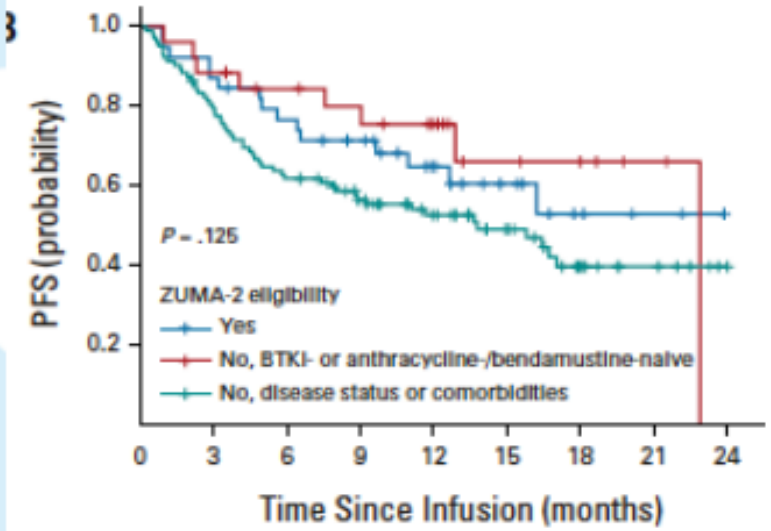
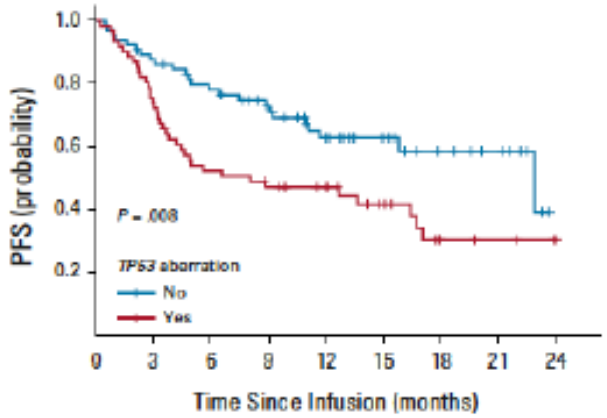
Relapsed/Refractory MCL:

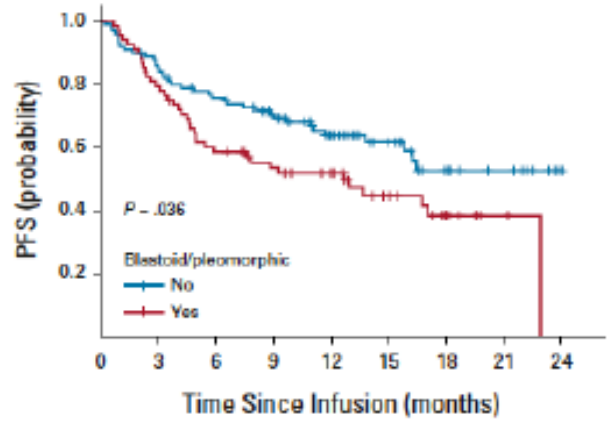
Brexu-cel performance in R/R MCL outside clinical trial (still not “real life”)

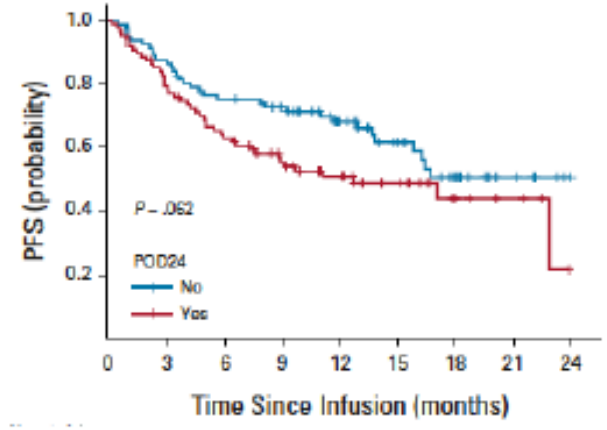


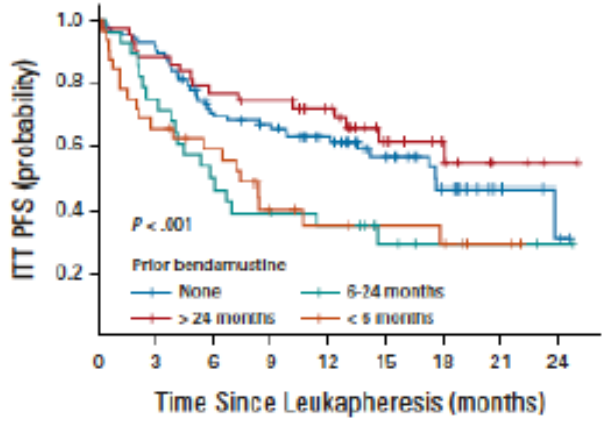


Bad players are still bad…









Wang Y, Jain P, Locke F, et at. JCO 2023

Brexu-cel performance outside clinical trials: safety

(CRS, ICANS, NRM and others)

	CRS	ICANS	ZUMA-2 CRS (%)	ZUMA-2 ICANS (%)
Total, No, (%)	151 (90)	103 (61)	**91**	**63**
Max Grade, No, (%)				
1-2	138 (82)	49 (29)	**76**	**32**
3-4	12 (7)	54 (32)	**15**	**31**
Days to onset	4 (0-13)	6 (1-8)	**2 (1-13)**	**7**
Days to max Grade	5 (0-30)	8 (1-18)	**-**	**-**
Duration	5 (1-33)	6 (1-144+)	**11**	**12**

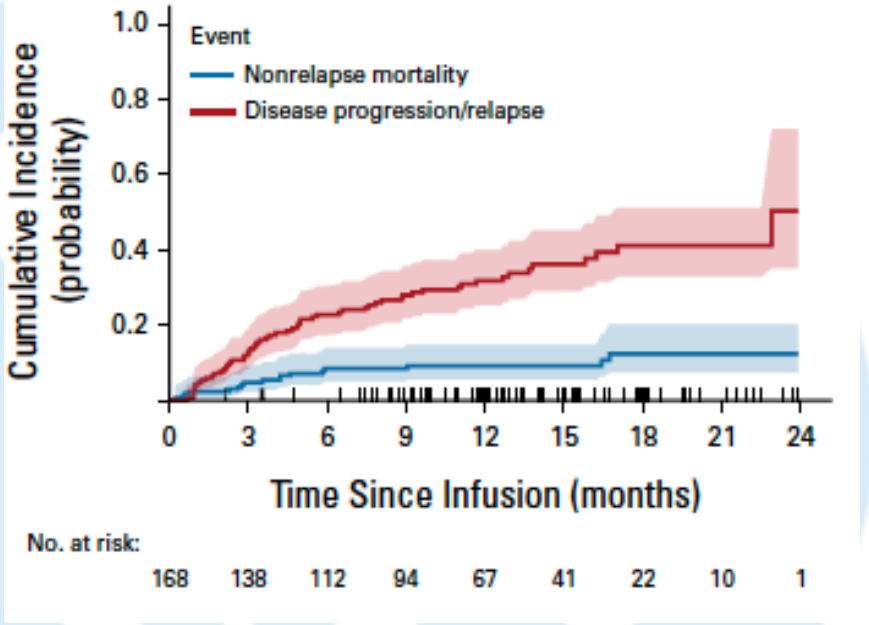


TABLE A5. Causes of Death in Cases with Nonrelapse Mortality

Time of NRM	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)
Total	18	Infections other than COVID-19 disease (n = 8)
		COVID-19 disease (n = 2)
		Stroke (n = 3)
		Subsequent solid tumor (n = 2)
		CRS (n = 1)
		Unspecified (n = 2)[a]

Management	Number	ZUMA-2 (%)
Tocilizumab	129 (77%)	**CRS: 59% ICANS: 26%**
Tocilizumab doses, median	2 (1-4)	
Steroids	116 (69%)	**CRS: 22% ICANS: 38%**
Anakinra	28 (17%)	
ICU admissions	34 (20%)	
ICU days, median	3 (1-12)	
Vasopressors	18 (11%)	**16%**
Mechanical ventilation	5 (3%)	
Dialysis	4 (2%)	

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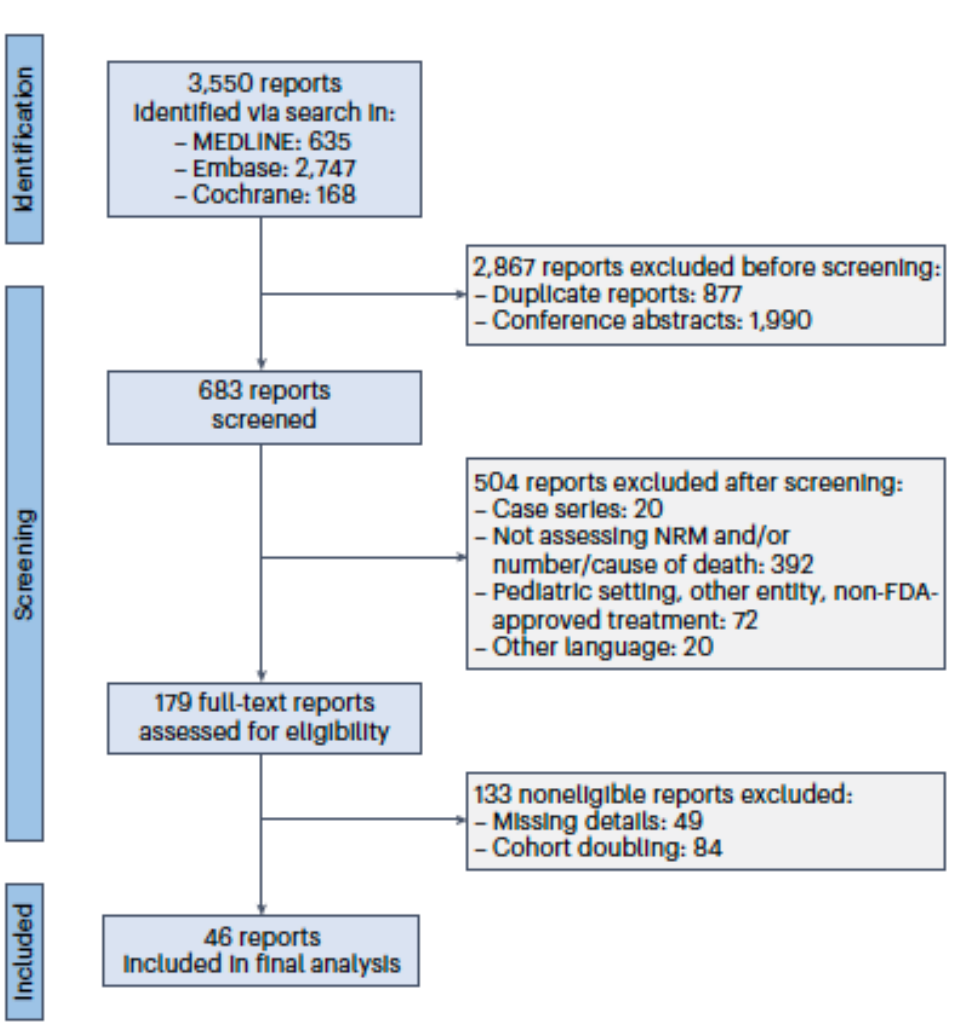
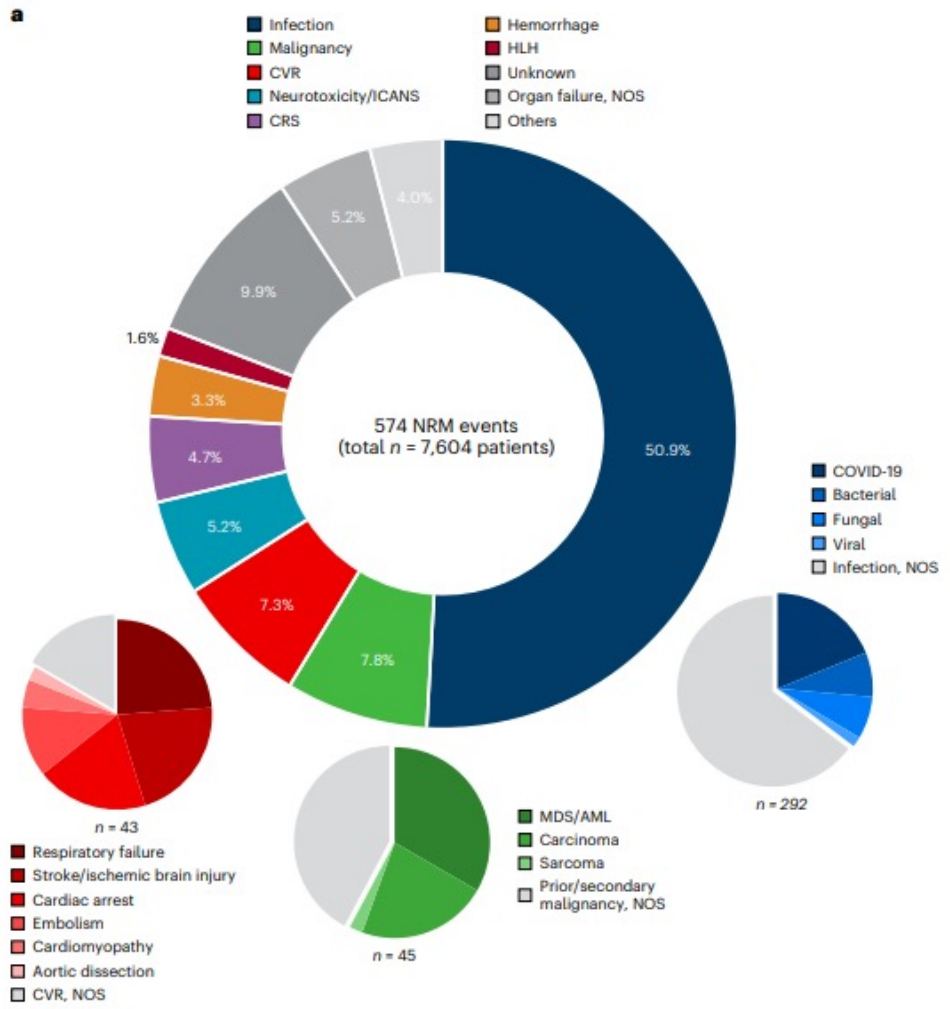
Non-relapse (NRM) mortality after CAR-T cell therapy

N= 7,604 pts
18 trials
28 RW studies





- **NRM point estimate = 6.8%**
- NRM point estimates varied across disease:
  - ✓ Indolent lymphomas= 5.7% (3.4–9.2%),
  - ✓ LBCL= 6.1%, (4.9–7.6%),
  - ✓ **MCL= 10.6% (7.7–14.3%, P = 0.026)**

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Malignant Hematology & Cellular Therapy

Cordas dos Santos DM et al. Nat. Med. 2024

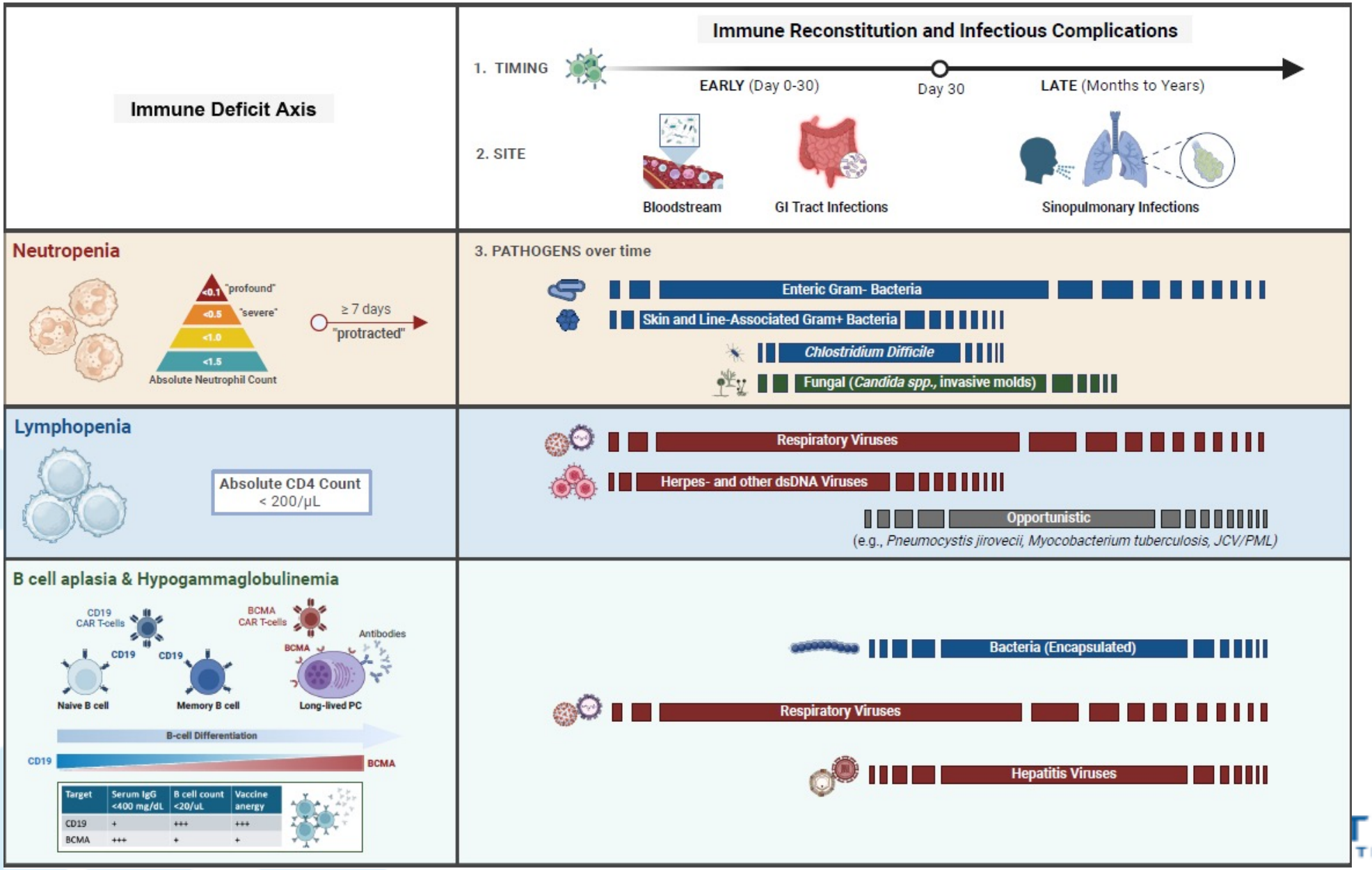
Infections in CAR-T therapy

- **Patients treated with anti-CD19 CAR-T cell therapy diagnosed with infections:**
  - ✓ 18 to 56% in prospective clinical trials (G≥3: 5%-32% of pts in CT).
  - ✓ 20 to 60% in retrospective cohorts.
  - ✓ Leading cause of NRM: 1%-12% with median f/up 10-16 mon.

- **Risk factors for infectious complications:**
  - ✓ **Pre-CART factors**: disease type, # of prior therapies, prior alloHCT, need for systemic bridging tx, high CAR-HEMATOTOX score, etc.
  - ✓ **CAR-T related factors**: CD4+ T cell lymphopenia, B cell aplasia, immunosuppressive therapy for management of complications (steroids, anti-IL6, etc), prolonged neutropenia, etc.

Brudno JN, Kochenderfer J. Nat Rev Clin Oncol. 2024 Jul;21(7):501-521.
Wudhikarn K, Perales MA. Bone Marrow Transplantation (2022) 57:1477–1488

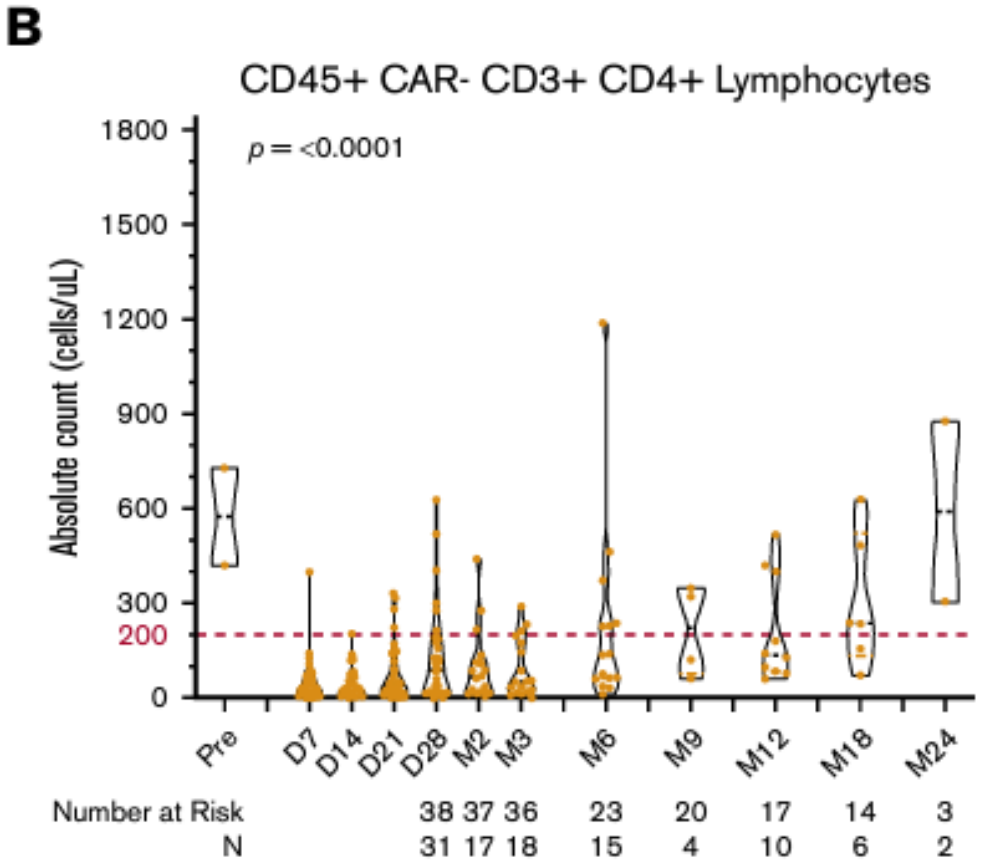
Infections after CAR-T cell therapy

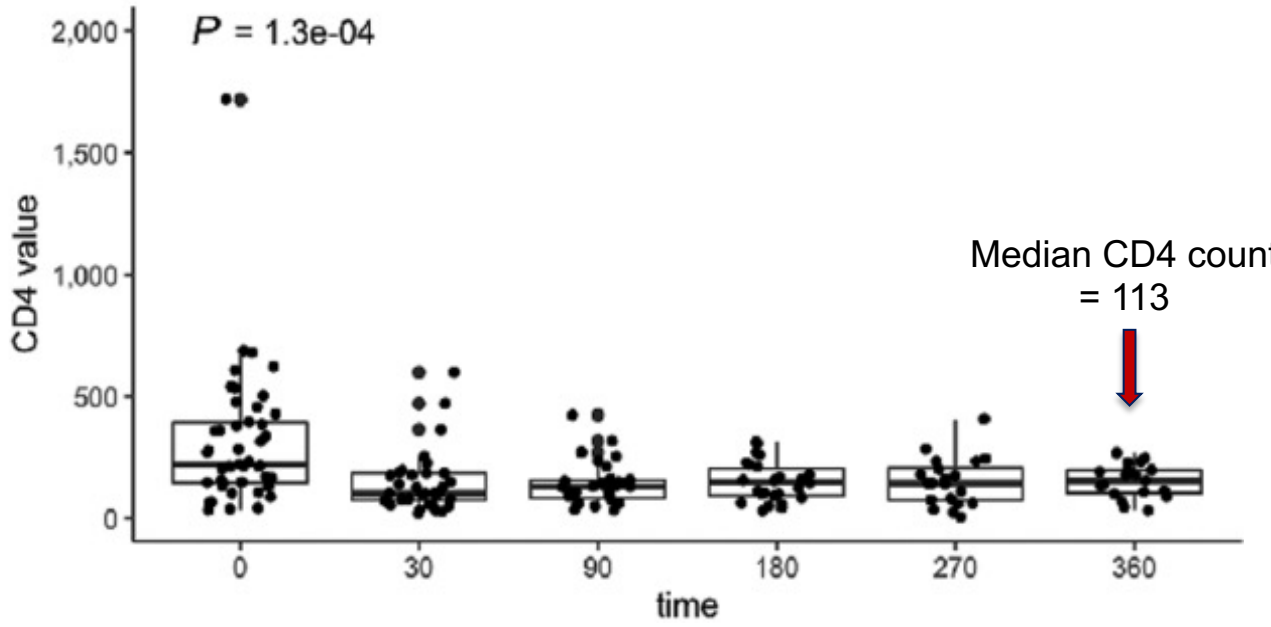


Courtesy of Michale Jain, MD PhD

Rejeski K et al. submitted

Prolonged CD4+ T cell lymphopenia s/p anti-CD19 CAR-T cell therapy





50% of pts had CD4⁺ T-cell count < 200 cells/mL
by 18 mon Axi-cel infusion

Baird JH et al. et al. Blood Adv. June 2021
Logue JM, et al. Haematologica April 2021

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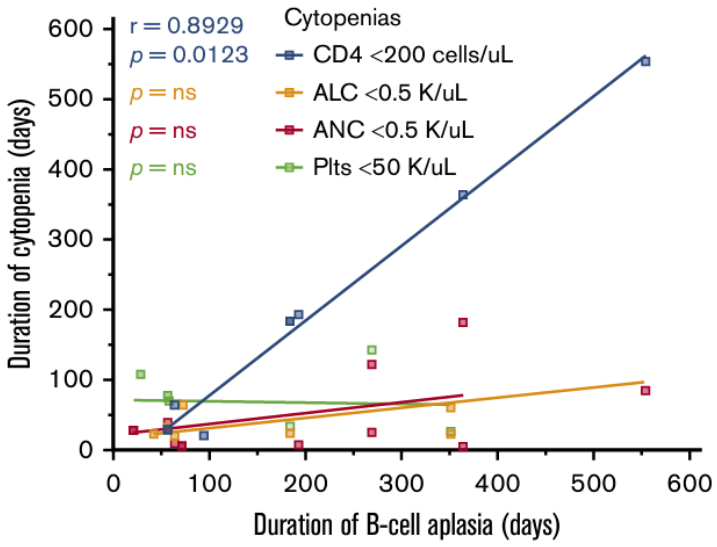
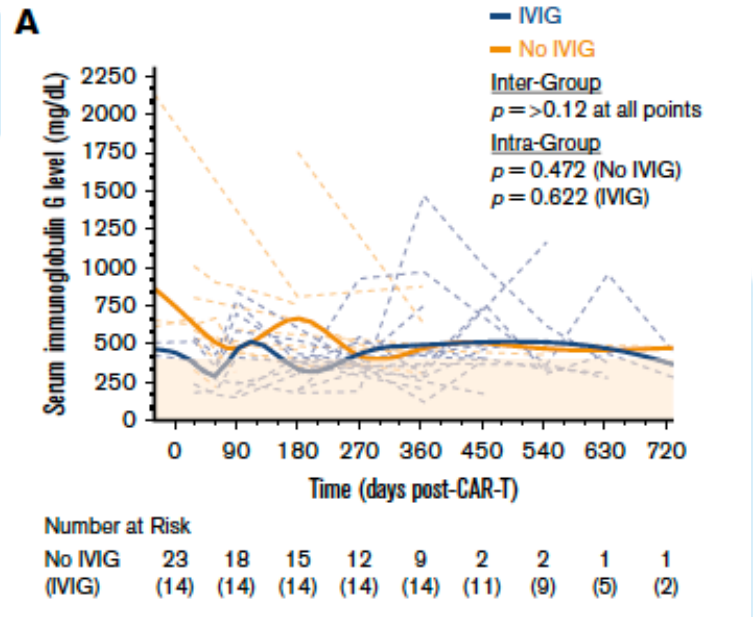
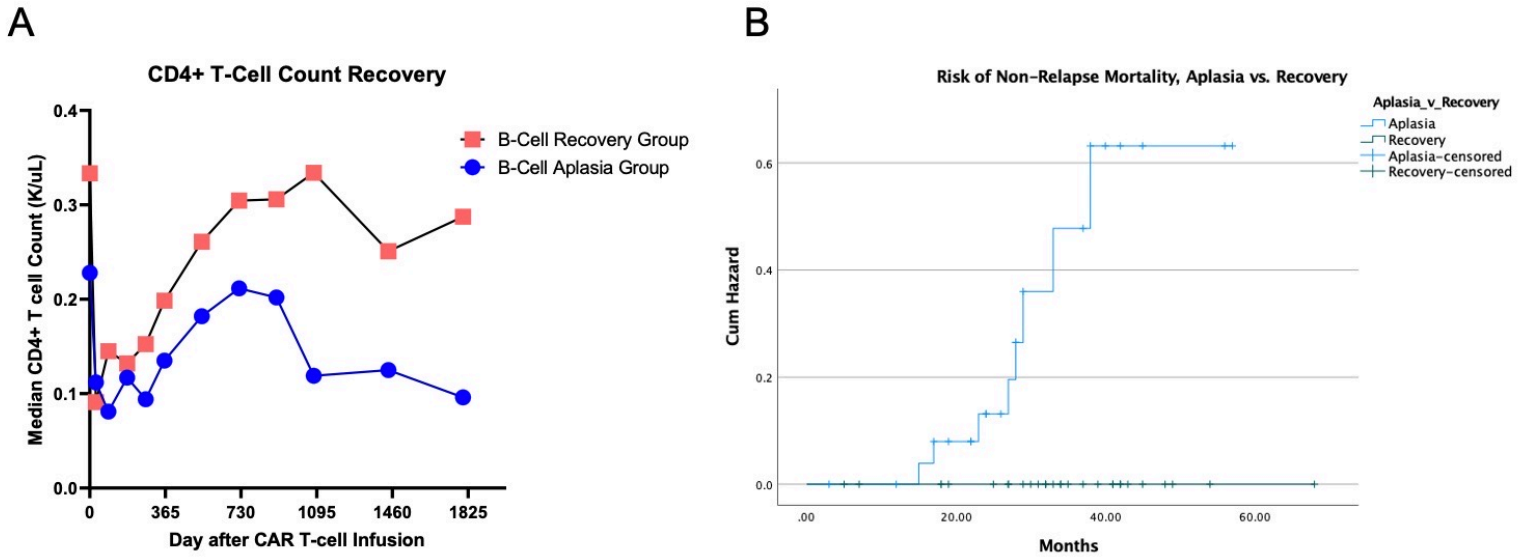
Long term B cell aplasia and hypogammaglobulinemia







A) Median peripheral blood CD4 T-cell counts after CAR T-cell therapy. B) Six-month landmarked cumulative risk of non-relapse mortality. Log-rank P-value <0.001.

Moffitt, CAR T in DLBCL, N=57 “survivors”
Johnson et al. ASH 2023

Baird JH et al. et al. Blood Adv. June 2021

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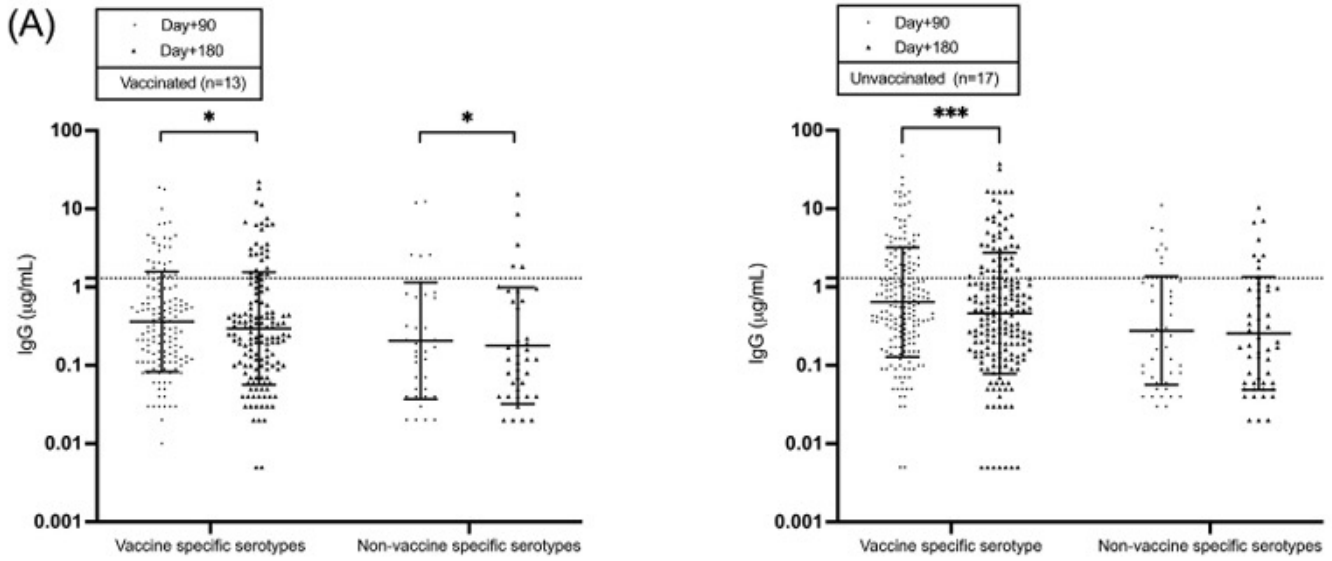
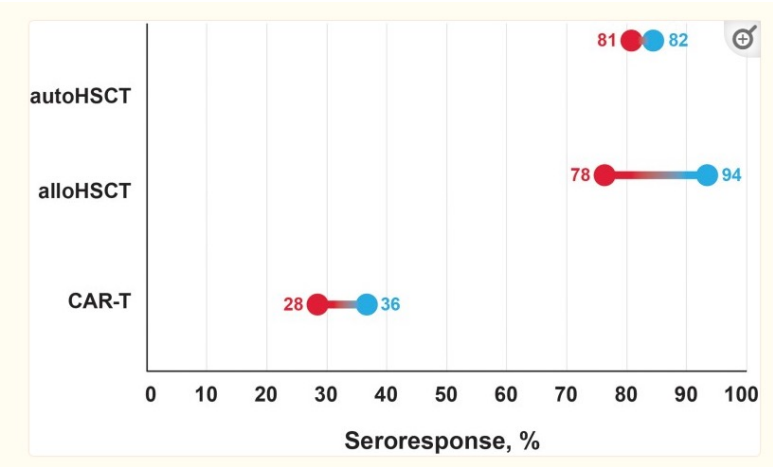
Vaccination after CAR-T

Pneumococcal Vaccine

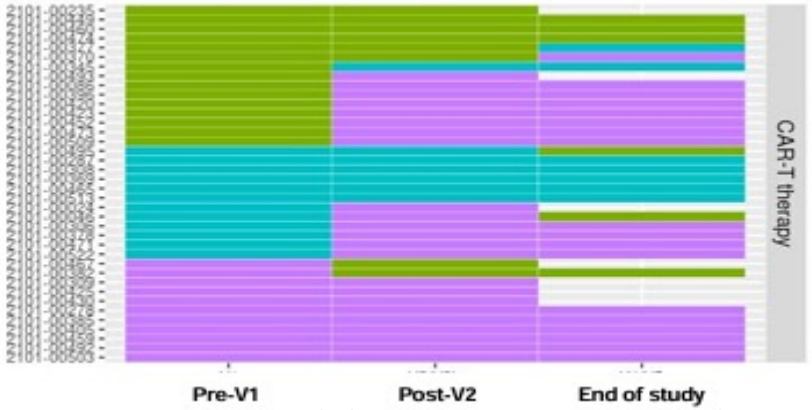


- Patients received PCV13 vaccine at day 90 (vs. unvaccinated).
- In both vaccinated and unvaccinated patients, vaccine-specific serotypes decreased between day 90 and day 180.

SARS-COV2 Vaccine



Pooled analysis of multiple studies.

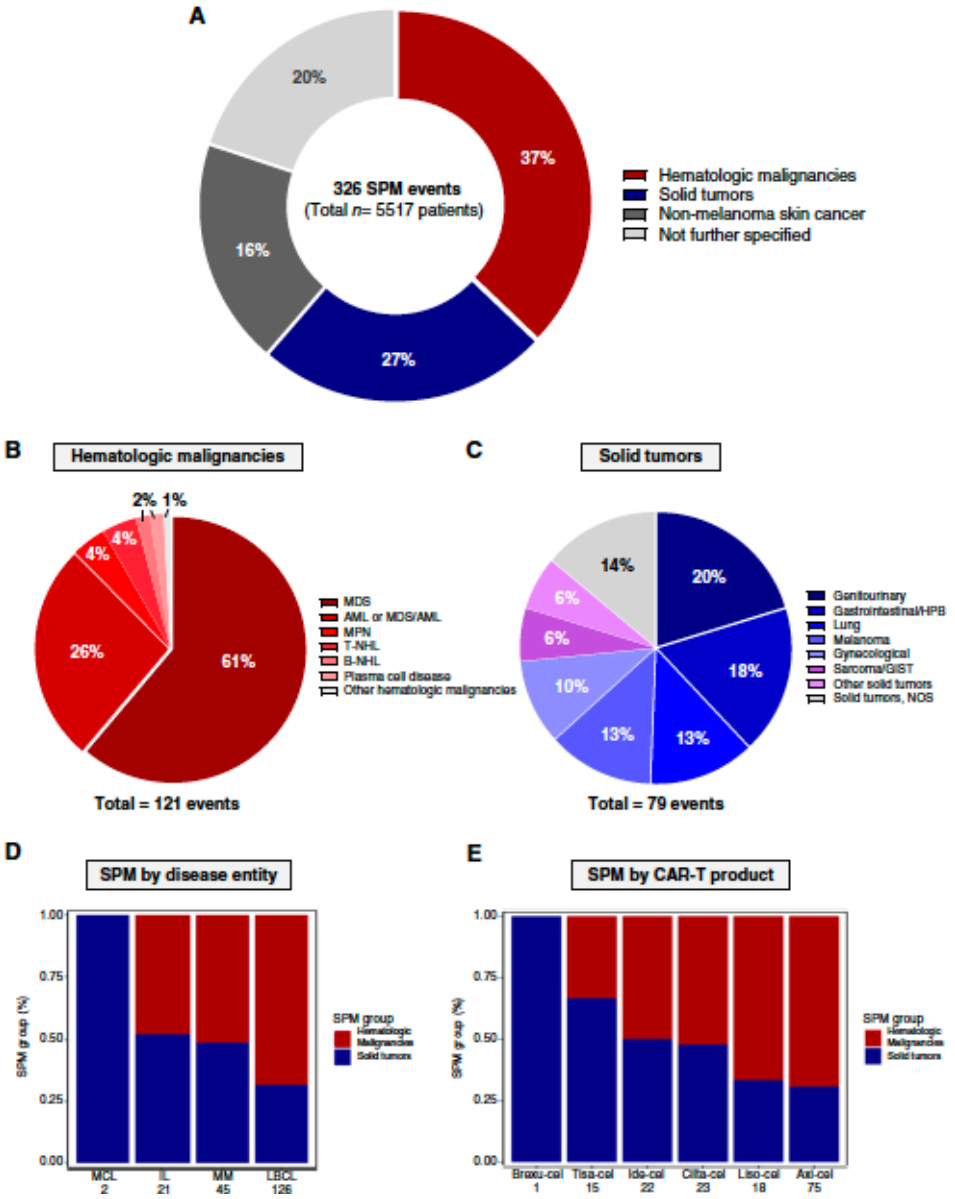


T cell responses to COVID vaccine post-CAR T.

1.Lee et al. JTCT 2022
2. Hall and Teh; J. Inf. Dis 2023.
3. Hill et al. CID 2024

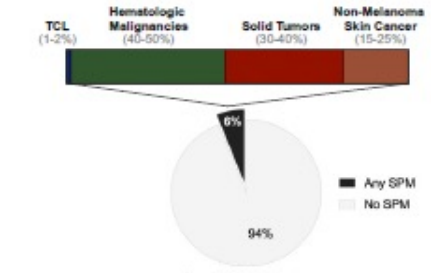
Secondary primary malignancies (SPM) after CAR-T cell therapy

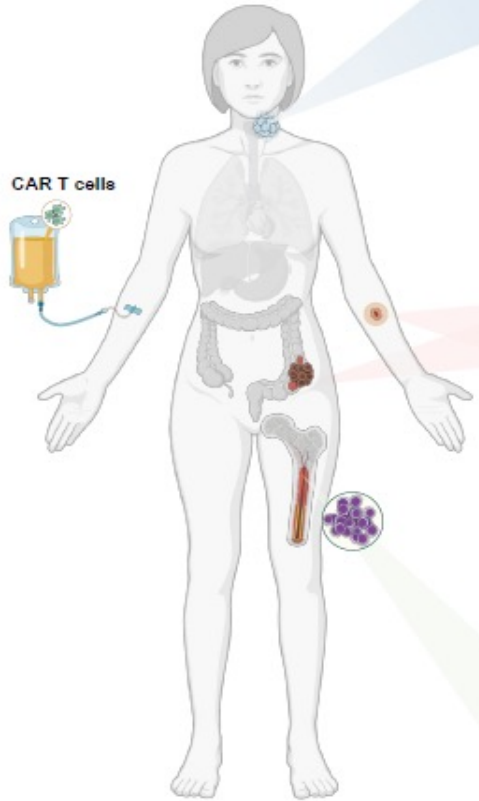
- N= 5,517 pts (18 CT and 7 RW studies)
- 326 SPM (media f/up: 21.7 mon)
- **SPM point estimate 6.0%(4.8%–7.4%).**
- SPM subtypes:
  - ✓ ***Hematologic malignancies: 37%.***
  - ✓ *Solid tumors: 27%*
  - ✓ *Non-melanoma skin cancers: 16%*
- ***<u>All</u>*** *T-cell malignancies: 1.5%.*

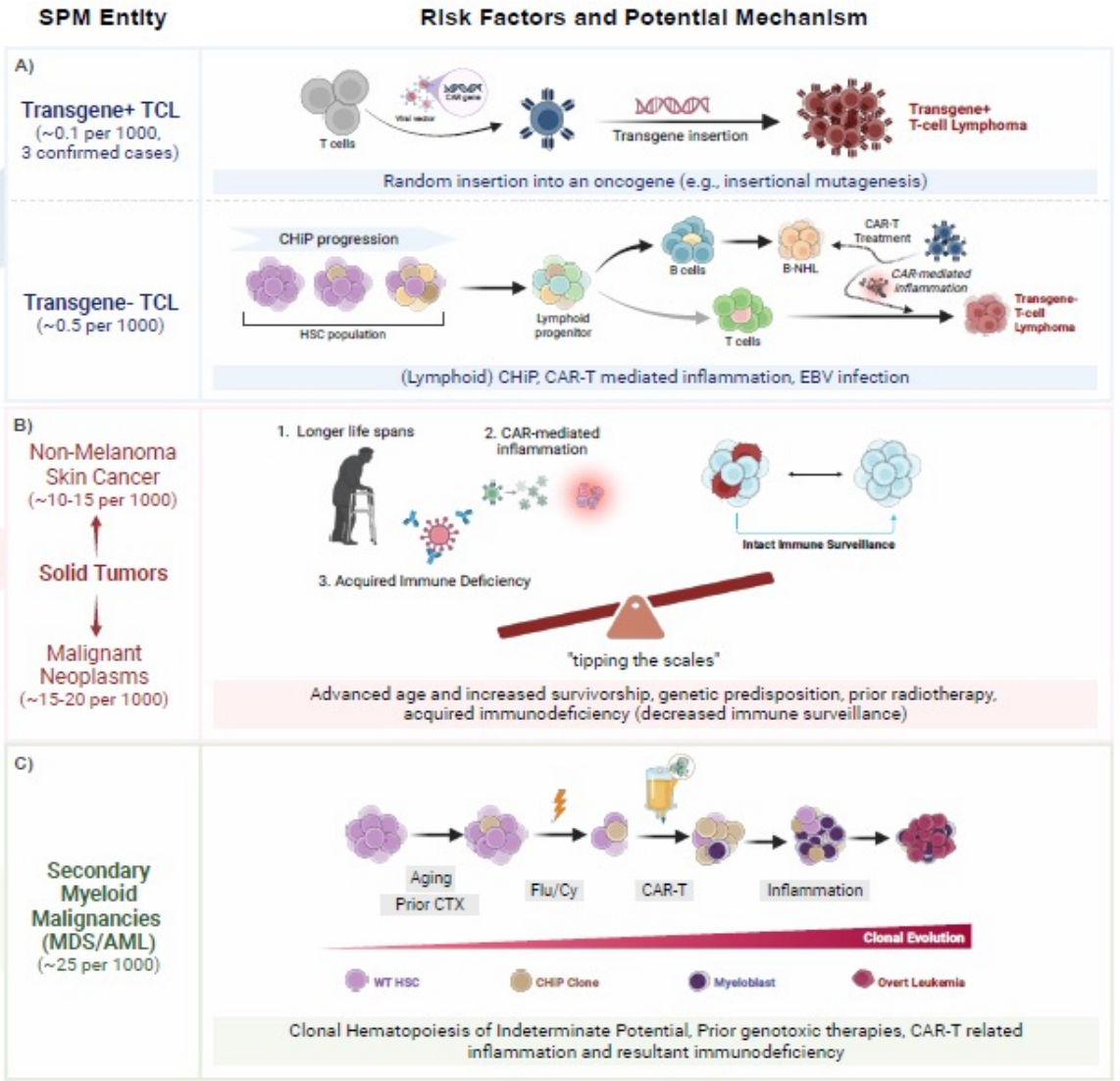


Tix T et al. Clin Cancer Res 2024;30:4690–700

Secondary Malignancies after CAR T cell Therapy







Surveillance & Reporting

1. Age-appropriate screening tests (e.g., rectal exam, mammogram, colonoscopy, low-dose CT in smokers).
2. Routine blood count monitoring.
3. In cases of T-cell malignancy, report to respective national authorities and rule out insertional mutagenesis with deep genomic integration site analysis.
4. CHiP mutation identification and post CAR-T infusion dynamics remains investigational and needs to be studied prospectively.

Rejeski K et al. submitted

Courtesy of Michale Jain, MD PhD

Therapy Related Myeloid Neoplasms Post Axi-cel

Patient	Diagnosis	Lymphoma Progression	Time to tMN diagnosis from Axi-Cel (months)	Mutations	Karyotype	Marrow Blasts (%)	Risk Stratification	Therapy for tMN	First tMN Regimen	Response to First tMN Regimen	HSCT	OS from tMN diagnosis (months)	Vital Status
1	CMML	Yes	29.7	KRAS, RUNX1	monosomy 7	3	High-risk (CPSS mol 5)	Yes	Azacitadine	HI	No	13.3	Dead
2	MDS	No	16.2	TP53, IDH2	Complex	1	6.5	Yes	Decitabine	SD	Yes	7.2	Dead
3	MDS	No	12.6	PPM1D, PM1D, BCOR	del 4q	0.5	2.5	No	Epoetin alfa	HI	No	47.9	Dead
4	MDS	No	8.7	KRAS, SRSF2, and PPM1D	NA	1.5	3	No	Sargramostim	NR	No	8.8	Dead
5	MDS	No	8.5	TP53	Complex	1	low risk (score=2)	Yes	Decitabine	SD	Yes	19.2	Dead
6	AML	No	11.5	KMT2A;STAG2;SF1	t(11:19); MLL2	88	Adverse risk per ELN	Yes	Decitabine + Venetoclax	CR	Yes	14.1	Dead
7	MDS-EB2	Yes	2.7	PPM1D	Deletion 7	10	very high	Yes	Decitabine	SD	No	5.5	Dead
8	MDS-MLD	No	1	NA	20q-	2	low risk (score=2)	No	NA	NA	No	34.3	Dead*
9	MDS	Yes	18.3	TP53	Complex	2	NA	Yes	Azacitadine	NA	No	1.9	Dead
10	MDS	No	20	NA	Monosomy 7	2	NA	Yes	Azacitadine	SD	No	58.9	Alive
11	MDS	Yes	4.2	NA	Complex	2	NA	Yes	Azacitdine + Venetoclax	SD	No	23.7	Dead
12	MDS	No	18.5	NA	Complex	2	NA	Yes	Azacitadine	CR	No	13	Dead
13	Mast cell neoplasm	No	64	c-KIT	Monosomy 7	9	NA	No	NA	NA	No	2	Alive**
14	MDS	No	41	NA	Complex	NA	NA	No	NA	NA	No	0.7	Dead
15	AML	No	61.1	NA	Monsomy 7	NA	Adverse risk per ELN	No	NA	NA	No	0.5	Dead

*died of trauma **in hospice at data cutoff

Jain MD J Clin Oncol. 2024; 42:3581-3592

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Cc

Secondary Myeloid Malignancies after CAR T

Assembled an international cohort of patients who had MDS/AML after CAR T

- US, UK, Germany, Spain: (CAR T n=53)

Compared to Moffitt database (Dr. Komrokji) of patients who developed MDS/AML after:

- Standard Chemotherapy/Radiation (STD n=244)
- Autologous stem cell transplant (AUTO n=96)

	All Patients	STD	AUTO	CAR T
Age, median, range,		67.5	65.2	64.1
Prior Treatment				
Chemotherapy only	278(70.7%)	174(71.3%)	64(66.7%)	40(75.5%)
Chemotherapy and radiation	109(27.7%)	64(26.2%)	32(33.3%)	13(24.5%)
Radiation only	6(1.53%)	6(2.46%)	0(0.00%)	0(0.00%)
Cellularity				
Hypercellular marrow	197 (53.0%)	135(58.7%)	41(43.6%)	21(43.8%)
Hypocellular marrow	81 (21.8%)	41 (17.8%)	26 (27.7%)	14(29.2%)
Normocellular marrow	94 (25.3%)	54 (23.5%)	27(28.7%)	13(27.1%)
R-IPSS				
Very good-good	128(34.0%)	96 (40.5%)	23(24.7%)	9(19.6%)
Intermediate	61 (16.2%)	37 (15.6%)	15 (16.1%)	9(19.6%)
Poor-very poor	187(49.7%)	104 (43.9%)	20(21.5%)	15 (29.4%)
AML transformation	97 (25.0%)	62 (25.4%)	9(18.0%)	15(29.4%)
Allo Transplant	92 (23.7%)	52 (21.3%)	28(30.4%)	12(22.6%)

No differences in terms of cytogenetic risk, or frequency of any specific mutation by NGS between the three groups.

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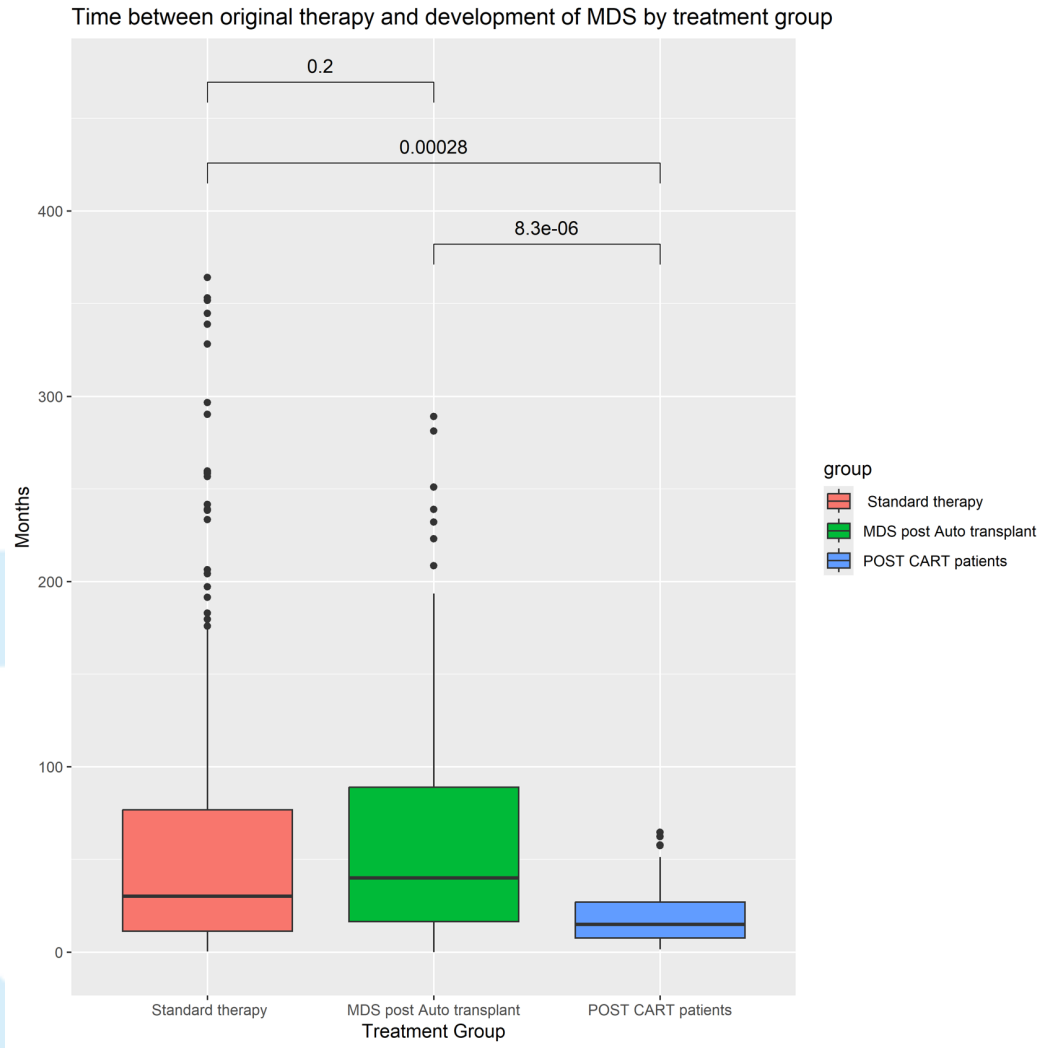
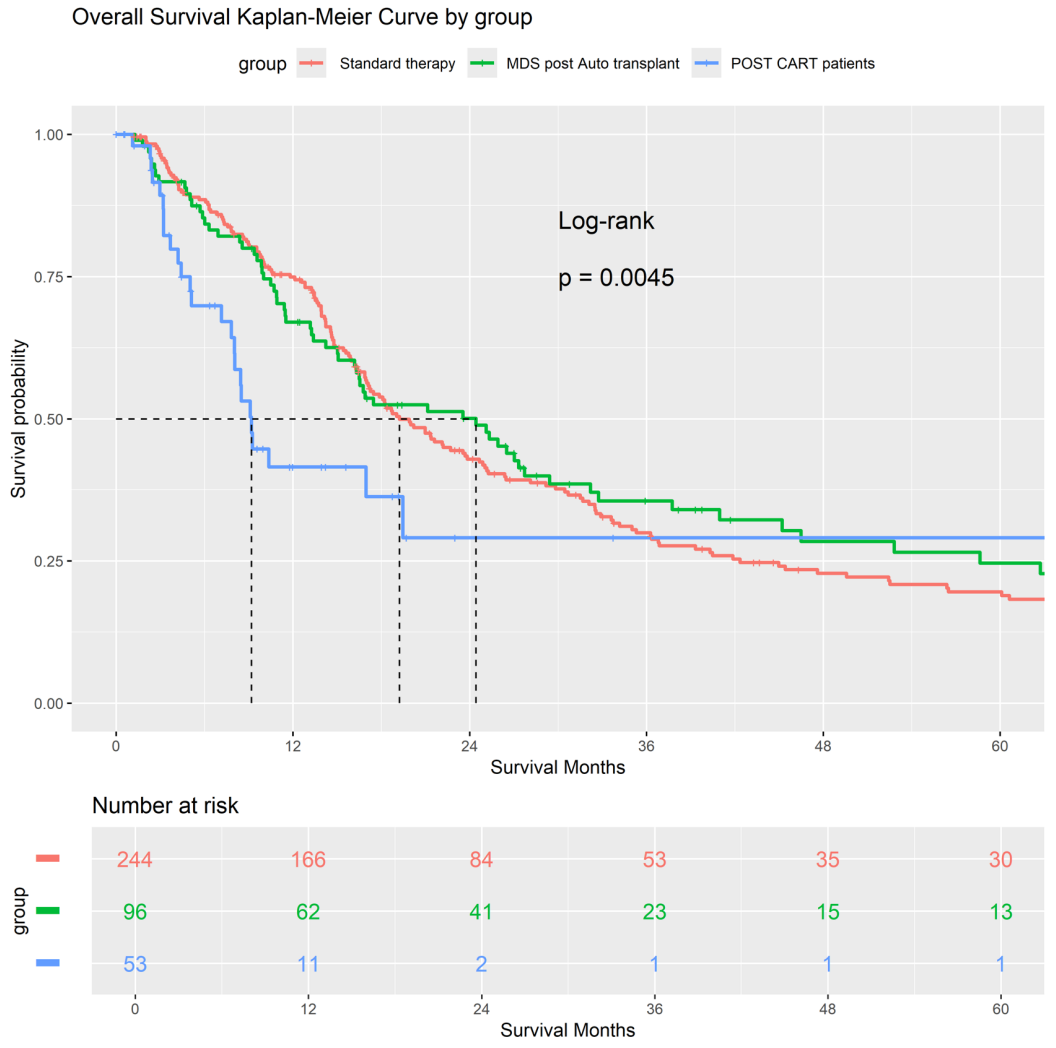
Roman Diaz et al. ASH 2024

Courtesy of Michale Jain, MD PhD

Secondary Myeloid Malignancies after CAR T





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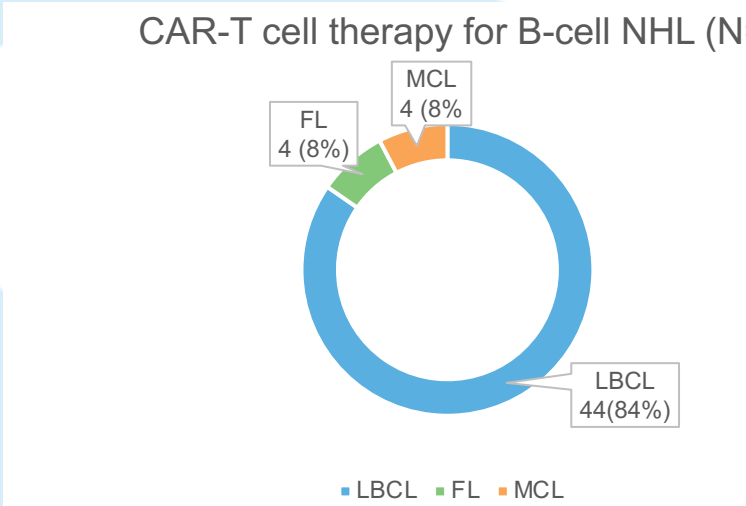
Roman Diaz et al. ASH 2024

Courtesy of Michale Jain, MD PhD

Our experience: MCC at MCI

- Q4 2021 to Q1 2025 = 52 pt with R/R B cell NHL
- All FDA CAR-T cell approved constructs are available.
- LBCL: 44 patients (42 Axi-cel/ 2 Tisa-cel).
- FL: 4 patients (2 Axi-cel/2 Tisa-cel).
- MCL: 4 patients (3 Brexu-cel/1 Liso-cel).
- All inpatient: median length of stay= 10 days.



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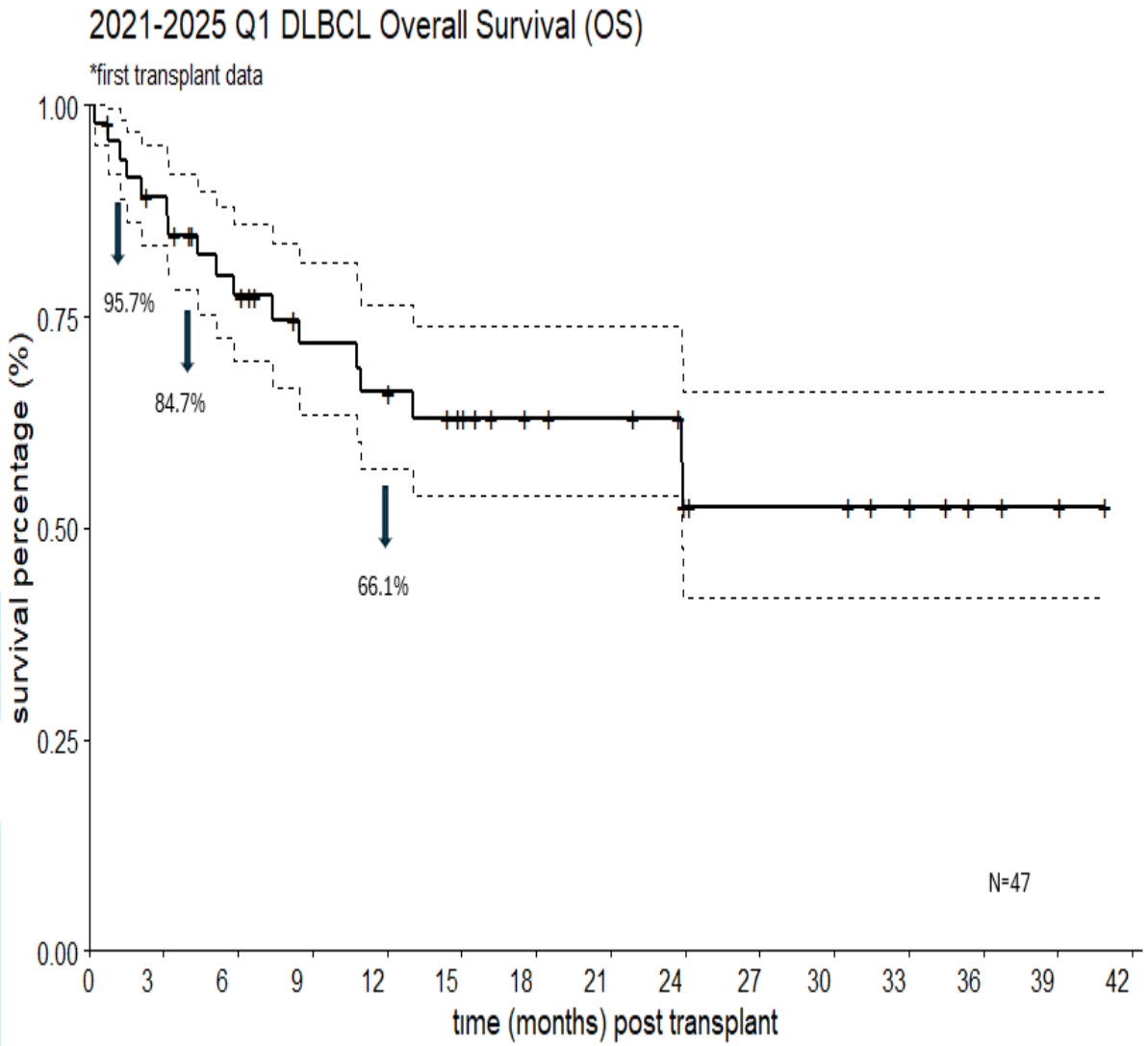
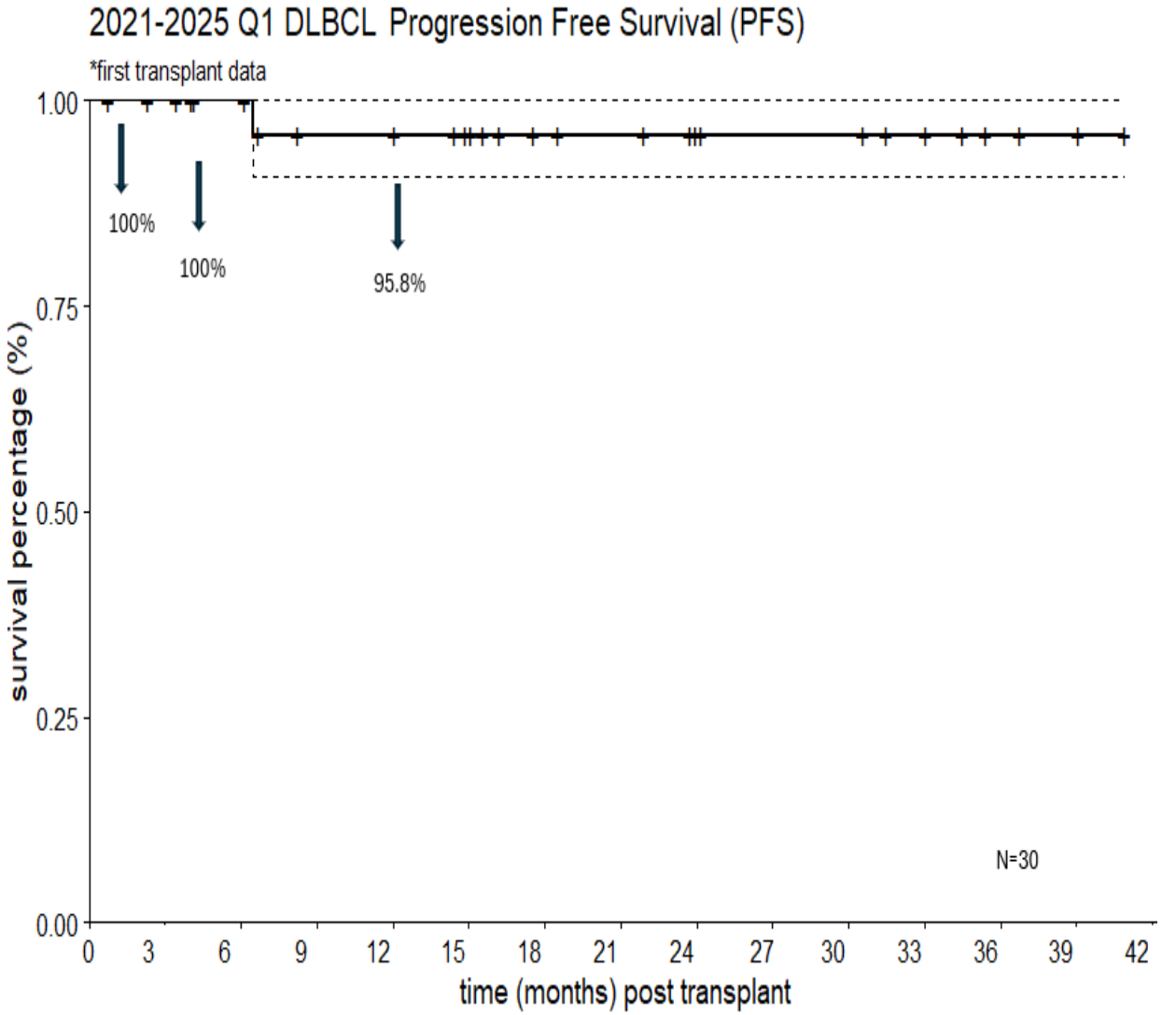
LBCL Survival Analysis 2021-2025 Q1





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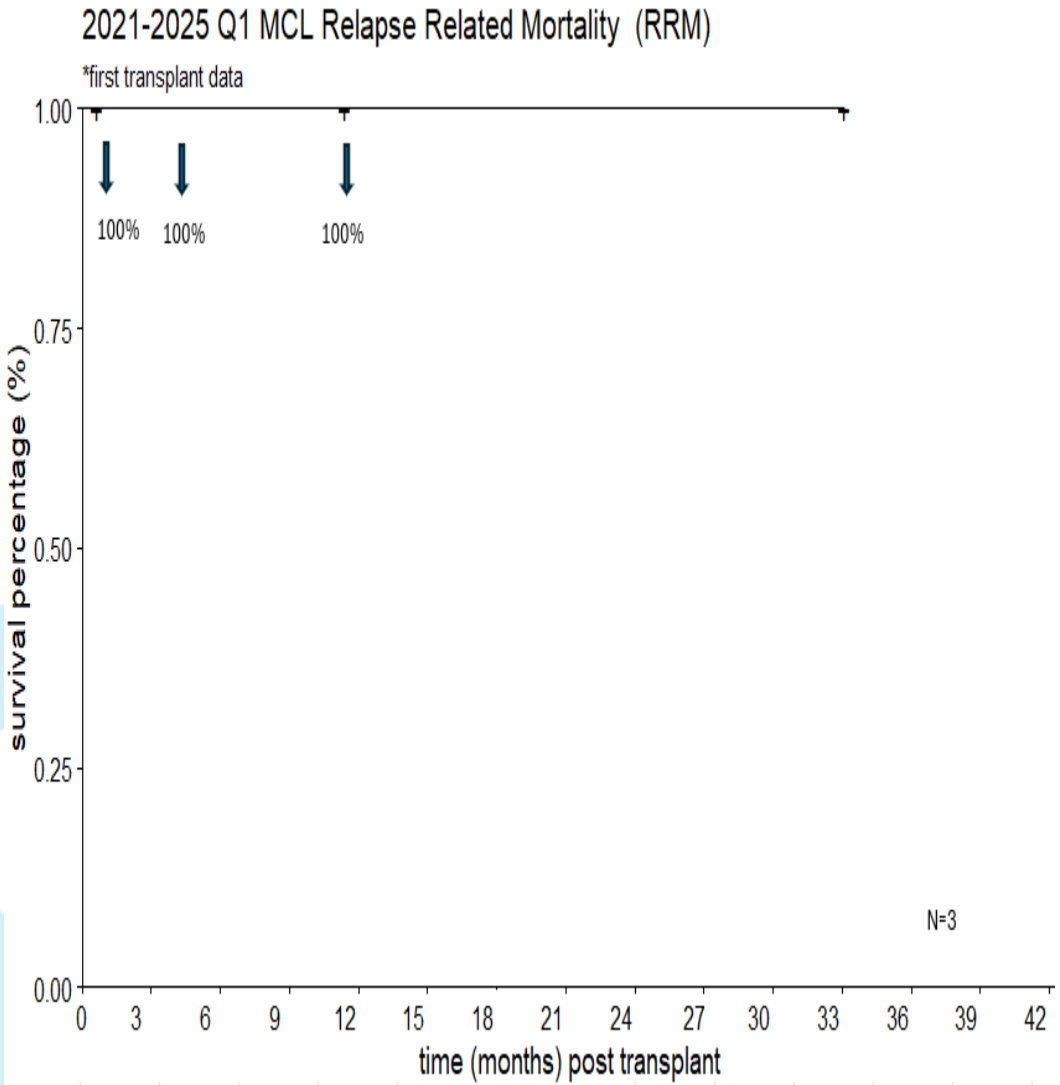
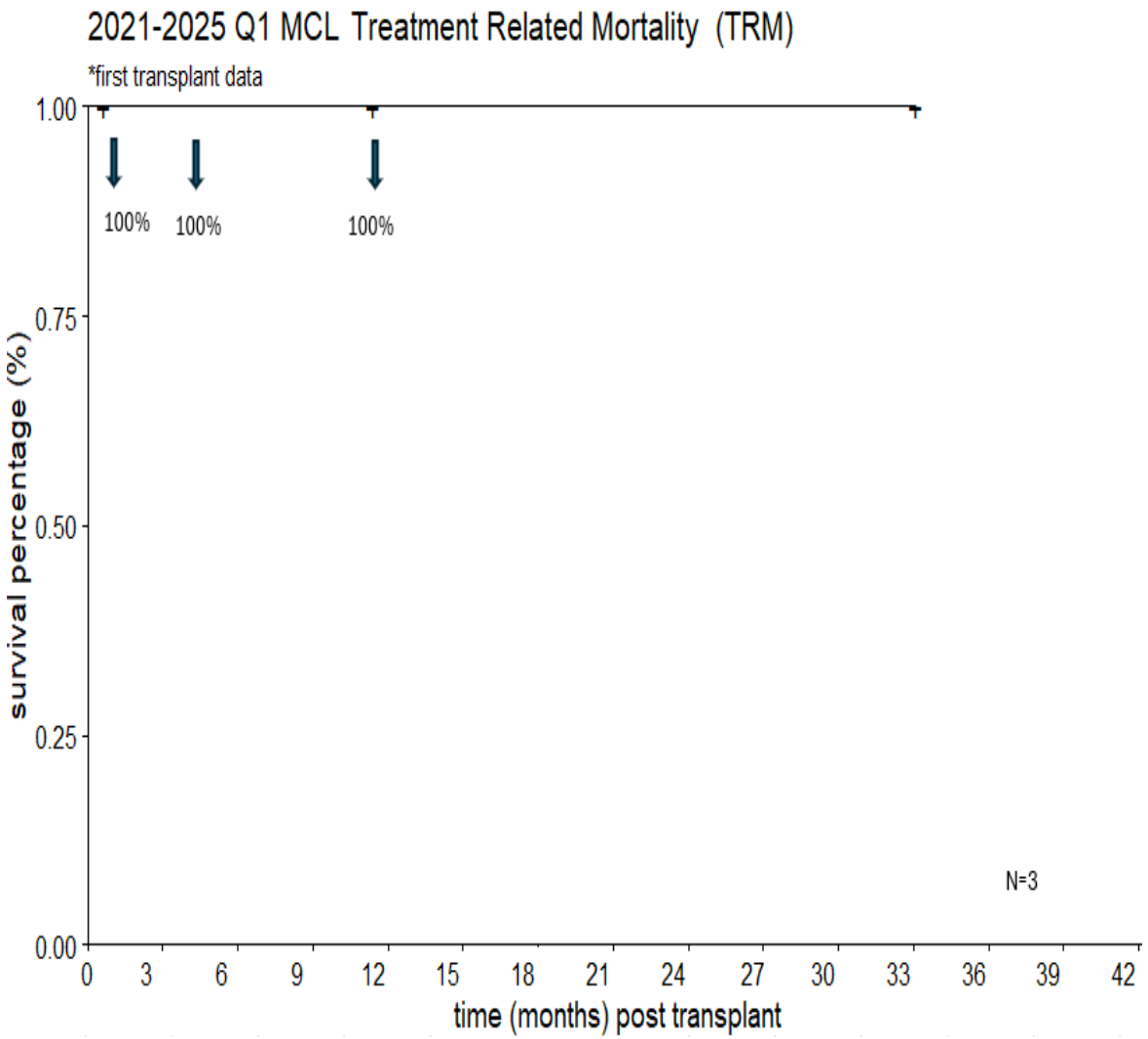
MCL Survival Analysis 2021-2025 Q1





Gracias por su atención

Barichara, Santander

Email:
jsandovalsus@mhs.net
jose.sandoval@moffitt.org

Cañon del chicamocha, Santander