CAR-T in second or subsequent relapse of B-cell lymphomas: results from italian RWE

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UNIVERSITÀ DEGLI STUDI
DI MILANO

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Sistema Sanitario Regione Lombardia

Conflict of Interest Declaration

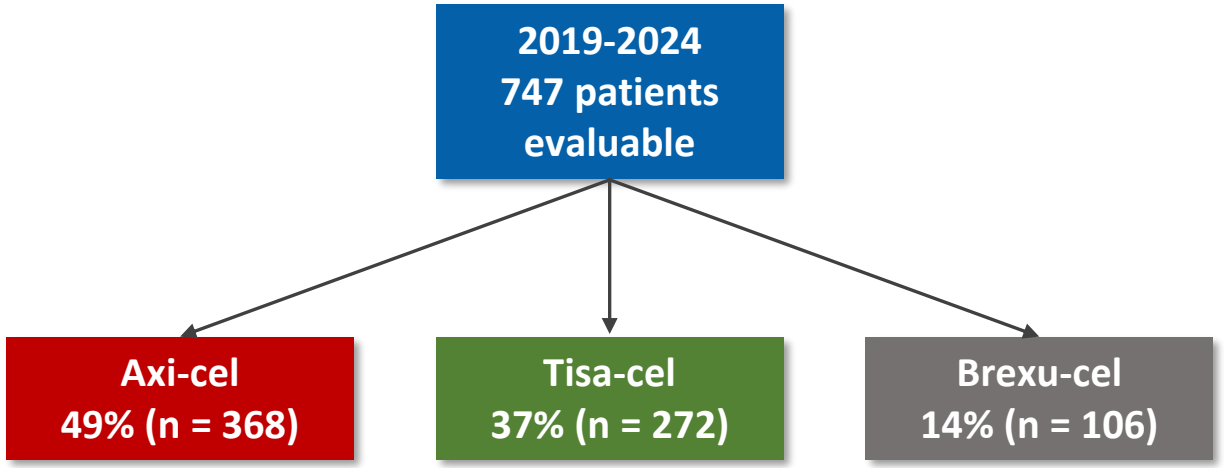
Prof. Paolo Corradini

- No employment for any for-profit health care company (public or private) to disclose
- No leadership role (officer or board of directors) in any for-profit health care company (public or private) to disclose
- No stock or other ownership interest in any for-profit health care company (public or private) to disclose
- No activity as speakers' bureau for any for-profit health care company (public or private) to disclose
- I had honoraria paid by for-profit health care companies during the past 2 years: Abbvie, Janssen, Kite-Gilead, Lilly, Novartis, Roche, Takeda, SOBI (Consulting, Advisory role or Lecturer)
- I had travel and accommodations paid by for-profit health care companies during the past 2 years: Novartis, Janssen, BMS, Takeda, Kite-Gilead, Roche,

CAR-T SIE prospective observational trial, as of August 2024

1002 pts recorded

747 infused patients with e-crf evaluable



	N = 1002
Median age	59.0 [IQR 49.0, 65.0]
Histology	
DLBCL/HGBCL*	745 (75%)
MCL	135 (13%)
PMBCL	92 (9%)
FL	17 (2%)
missing	13 (1%)

*40/745 (5%) axi-cel @ second line

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In Italy CAR-T for second relapse were reimboursed starting november 2019 (for first relapse nov 2023); 21 of 38 centers are enrolling.

QUESTIONS ADDRESSED IN A REAL LIFE SETTING:

- Role of histologies (PMBCL, DLBCL, HGBCL, MCL)
- Bridging therapy
- Activity of different CAR-T products
- Prognostic scores
- Second primary malignancies

Axicabtagene ciloleucel treatment is more effective in primary mediastinal large B-cell lymphomas than in diffuse large B-cell lymphomas: the Italian CART-SIE study

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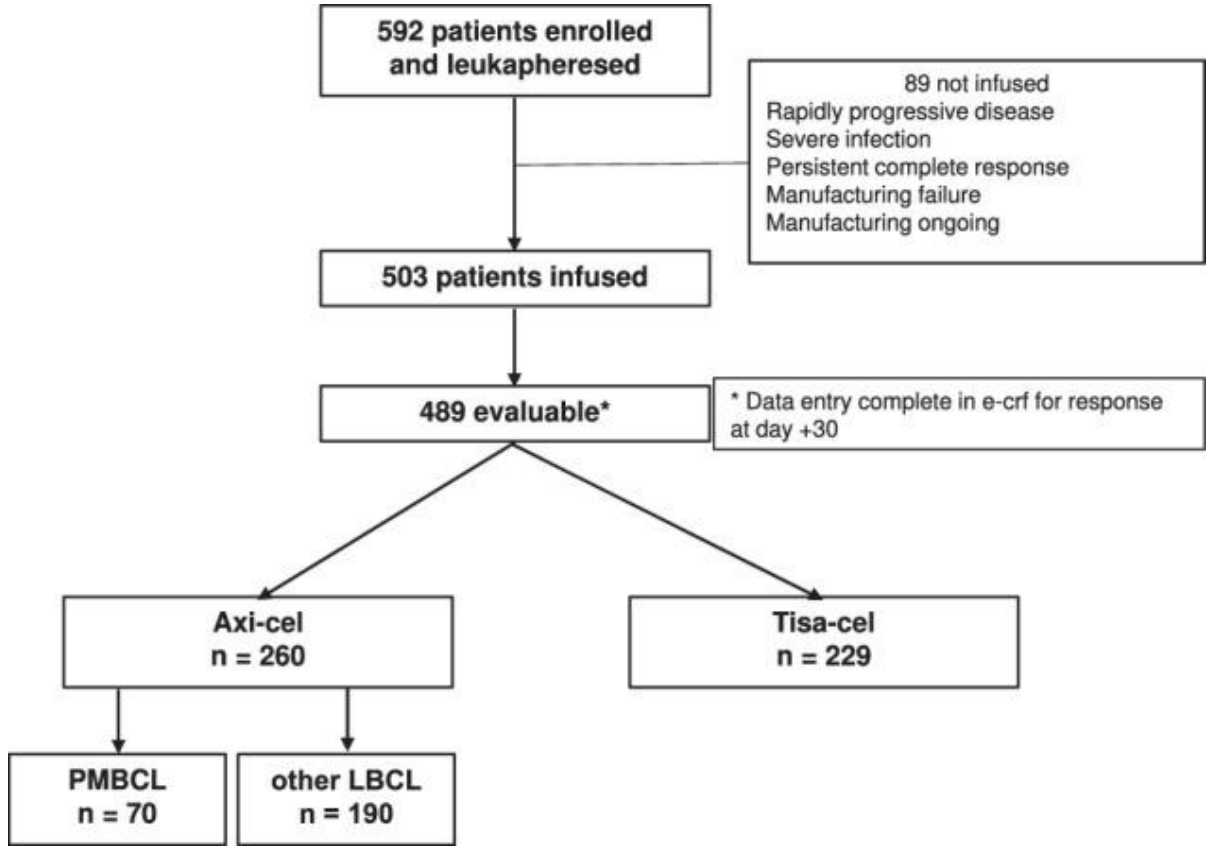

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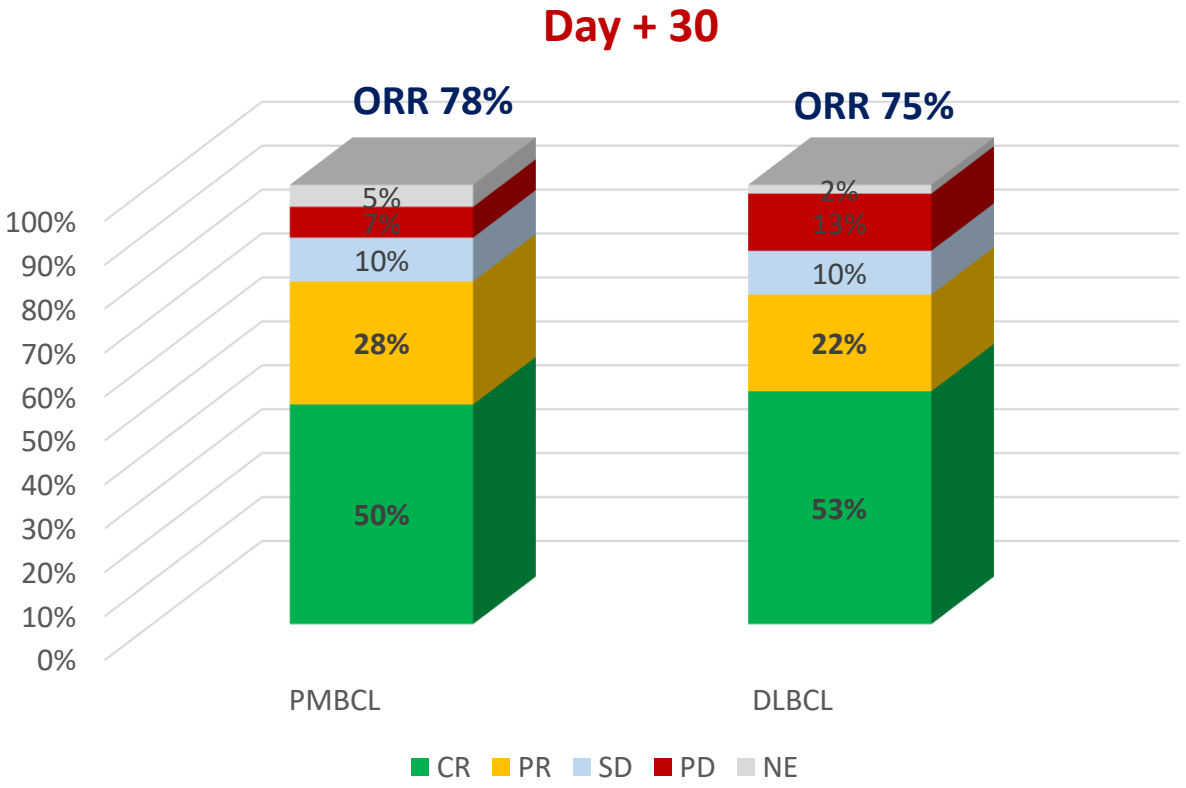
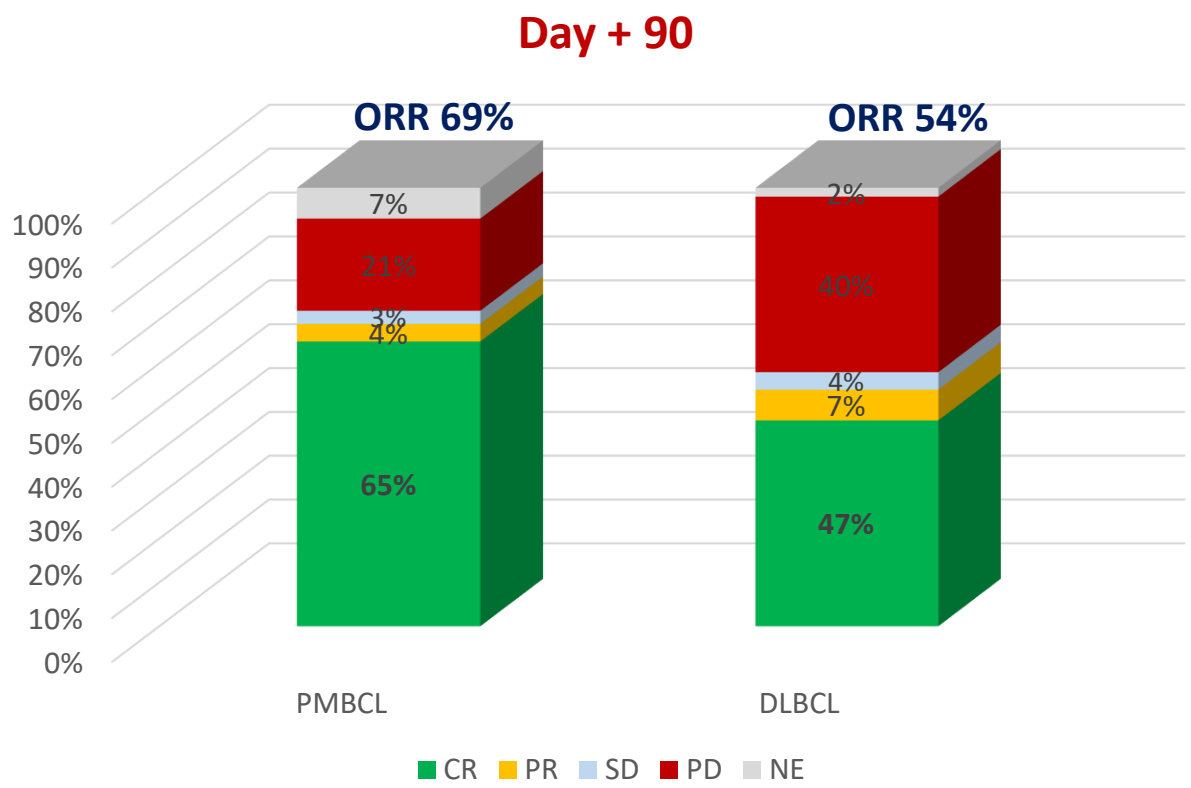
Response after CAR-T infusion, days +30 and +90



p 0.5457



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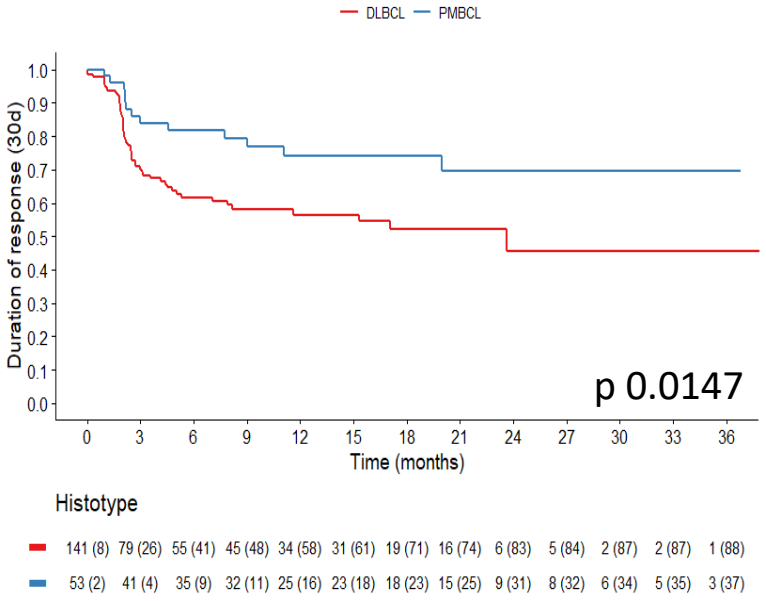
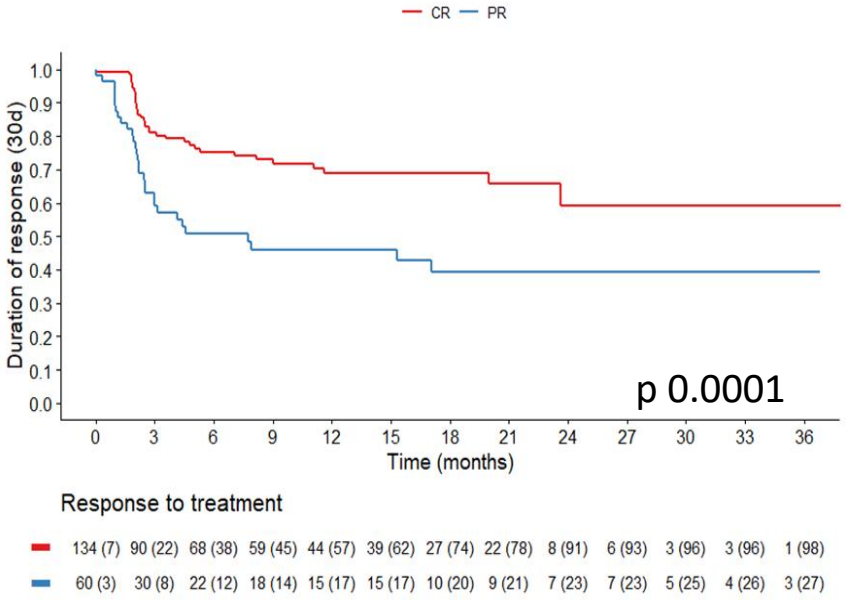
Duration of response (DoR) and Non relapse mortality (NRM)

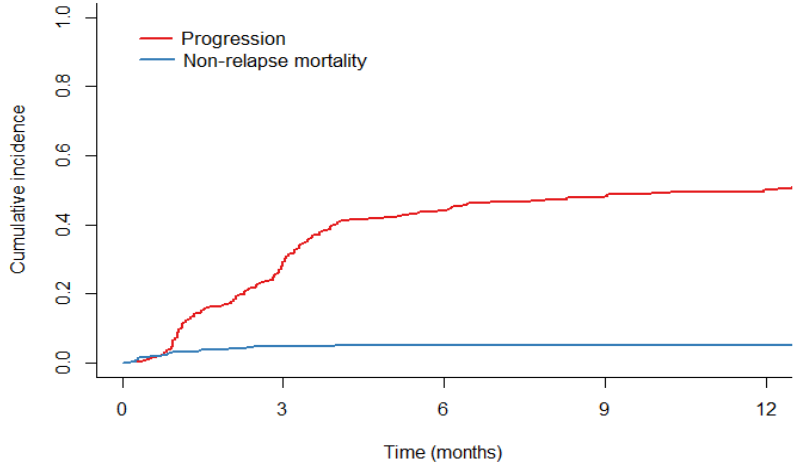
DoR: PMBCL vs DLBCL



DoR: CR vs PR (all)



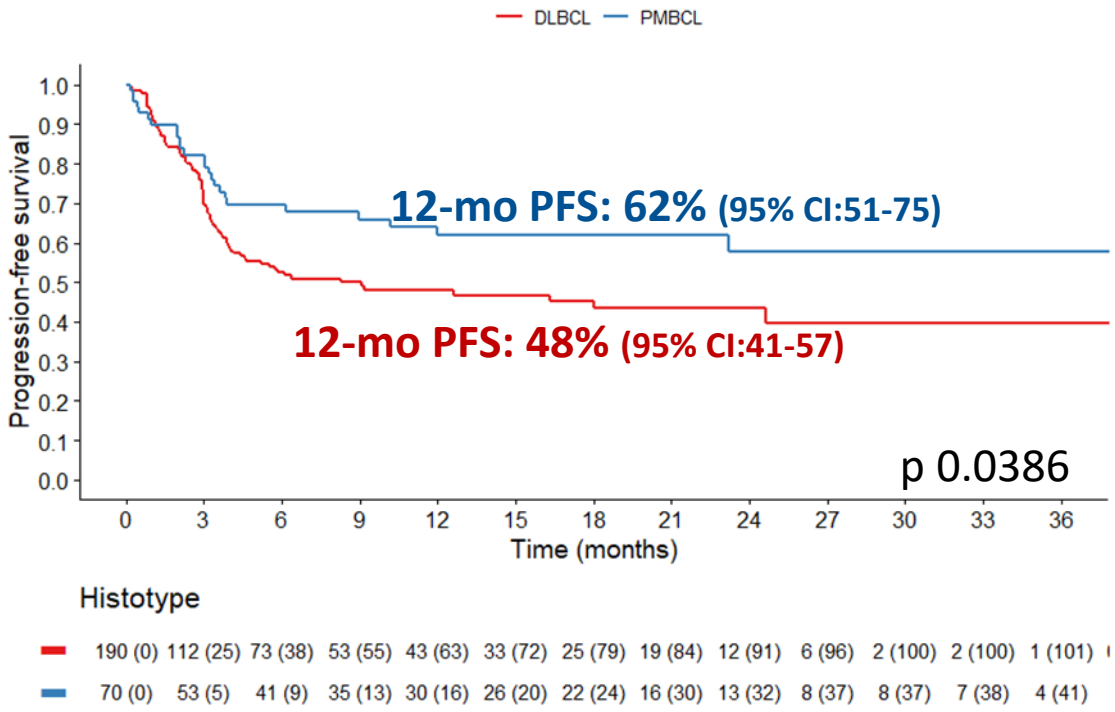
NRM at 12 months (all): 5.25% (95% CI: 3.52-7.83%)



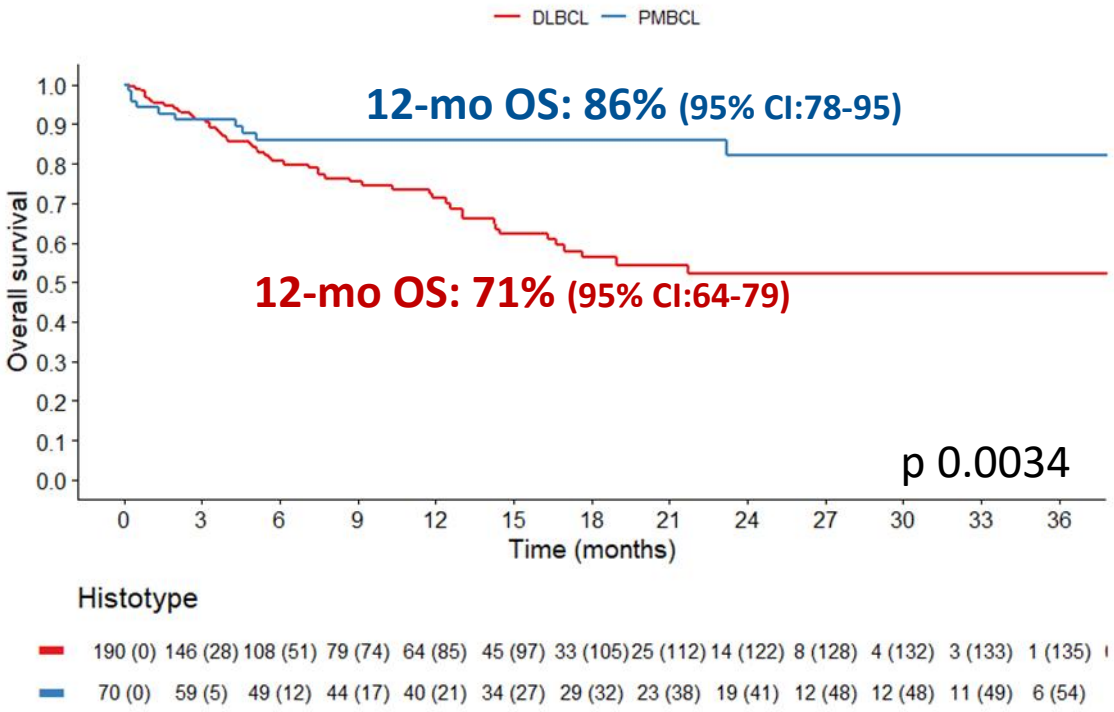
Progression-free and Overall Survival

median follow up 12.17 months

PFS
PMBCL vs DLBCL



OS
PMBCL vs DLBCL



Safety

	PMBCL (N=70)	DLBCL (N=190)	p value
CRS			0.5310
No	14%	12%	
Yes	**86%**	**88%**	
Grade 1	41%	50%	
Grade 2	31%	30%	
Grade 3	**10%**	**7%**	
Grade 4	**3%**	**1%**	
ICANS			0.3758
No	61%	68%	
Yes	**39%**	**32%**	
Grade 1	11%	12%	
Grade 2	7%	10%	
Grade 3	**9%**	**7%**	
Grade 4	**6%**	**3%**	
Grade 5	6%	0	

Tocilizumab was administered in 73% PMBCL and 73% DLBCL, steroids in 34% PMBCL and 30% DLBCL.

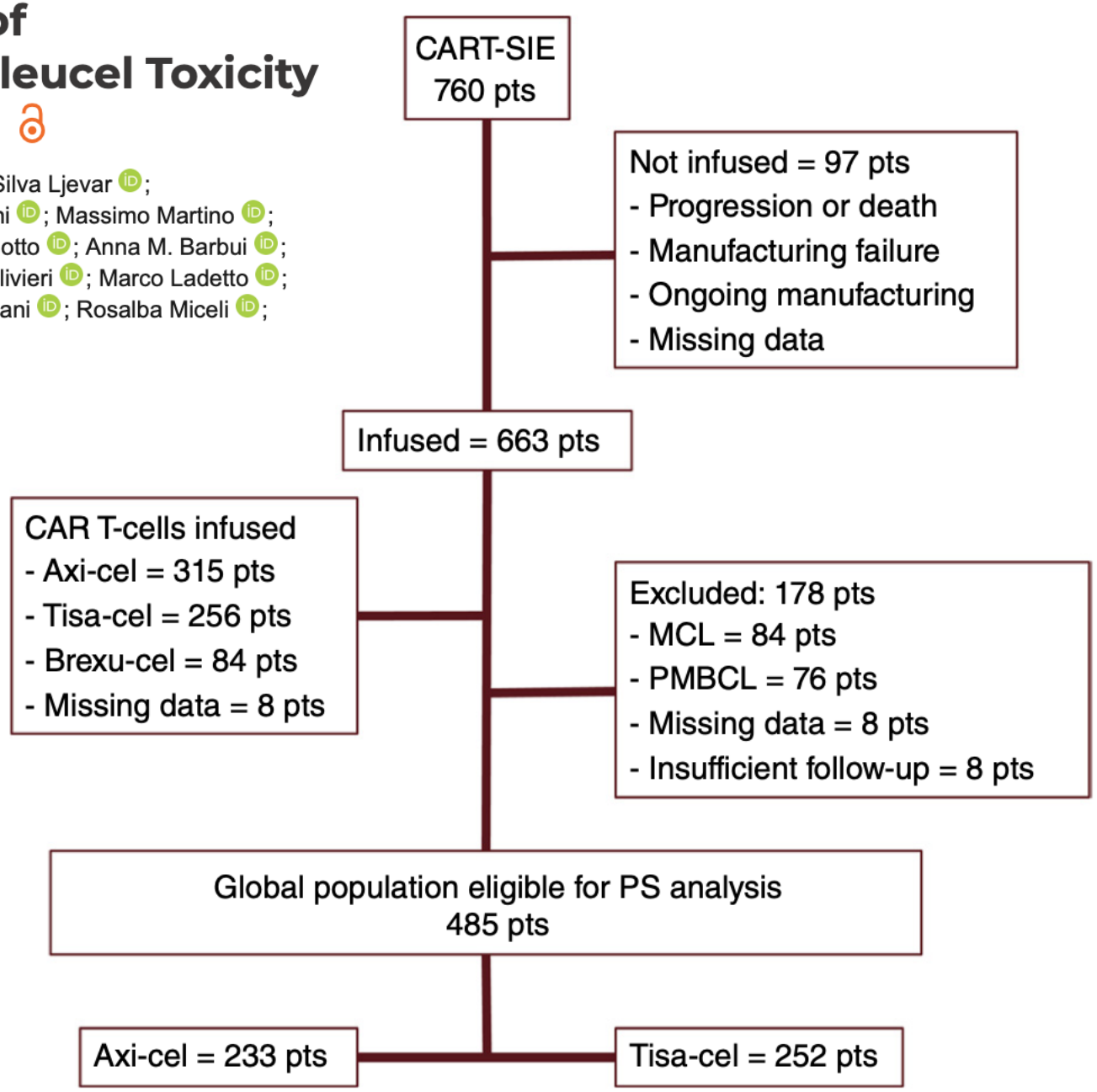
	PMBCL (N=70)	DLBCL (N=190)	p value
Anemia			**0.0236**
No	43%	27%	
Yes	57%	73%	
Grade 3-4	19%	23%	
Neutropenia			0.7242
No	17%	20%	
Yes	83%	80%	
Grade 3-4	74%	72%	
Thrombocytopenia			0.2532
No	44%	36%	
Yes	56%	64%	
Grade 3-4	23%	39%	
Febrile Neutropenia			0.0984
No	77%	66%	
Yes	23%	34%	
Grade 3-4	17%	27%	
Cardiac			0.2416
No	91%	95%	
Yes	9%	5%	
Grade 3-4	5%	2%	

A Multicenter Real-life Prospective Study of Axicabtagene Ciloleucel versus Tisagenlecleucel Toxicity and Outcomes in Large B-cell Lymphomas

Federico Stella; Annalisa Chiappella; Beatrice Casadei; Stefania Bramanti; Silva Ljevar; Patrizia Chiusolo; Alice Di Rocco; Maria C. Tisi; Matteo G. Carrabba; Ilaria Cutini; Massimo Martino; Anna Dodero; Francesca Bonifazi; Armando Santoro; Federica Sorà; Barbara Botto; Anna M. Barbui; Domenico Russo; Maurizio Musso; Giovanni Grillo; Mauro Krampera; Jacopo Olivieri; Marco Ladetto; Federica Cavallo; Massimo Massaia; Luca Arcaini; Martina Pennisi; Pier L. Zinzani; Rosalba Miceli; Paolo Corradini

Blood Cancer Discovery 2024

***Variables used for the propensity score model:**
histology, age, sex, disease status (relapse vs. refractory), Ann Arbor (I-II vs. III-IV), IPI (≥3 vs. <3), LDH, CPR, bulky disease, number of previous treatments, ASCT, bridging therapy (No vs. Yes with response vs. Yes without response), time since last treatment and center size (≥25 vs. <25 patients contributed).



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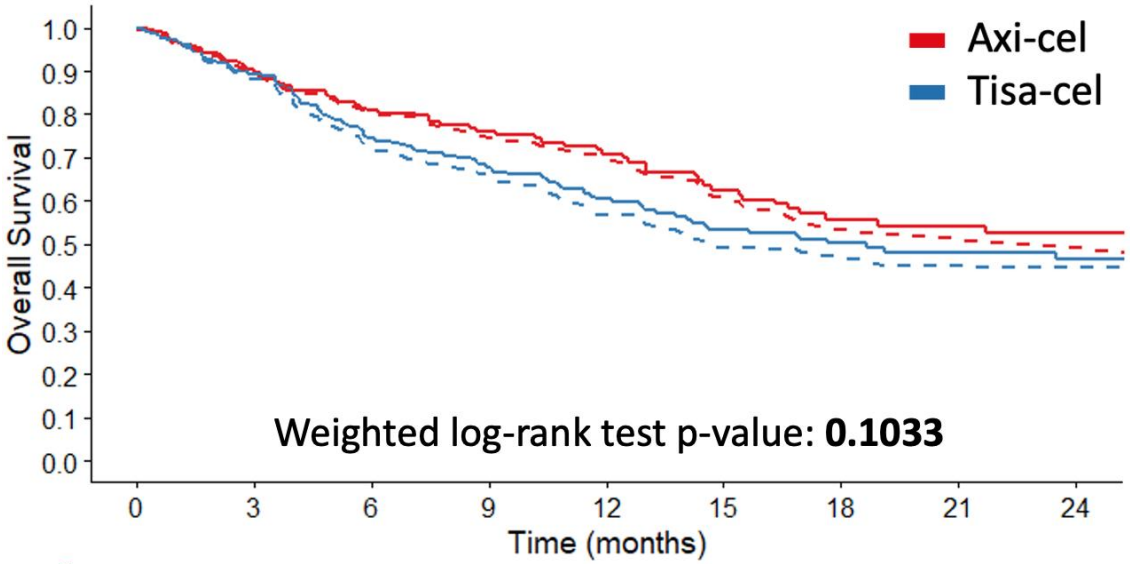
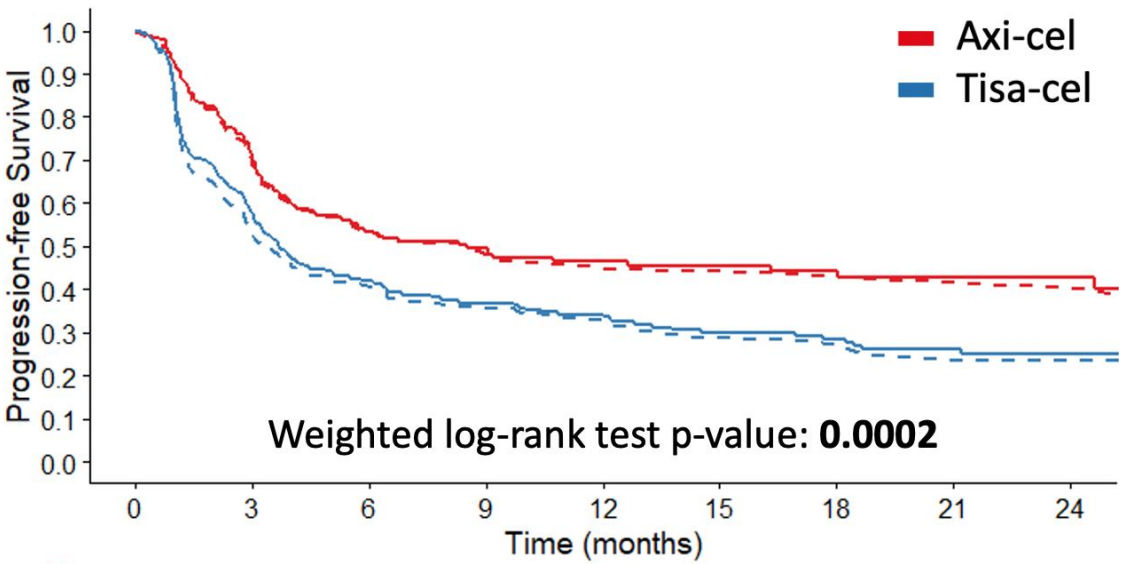
Overall Survival and Progression-Free Survival : Axi-cel vs Tisa-cel Propensity Score Analysis



A

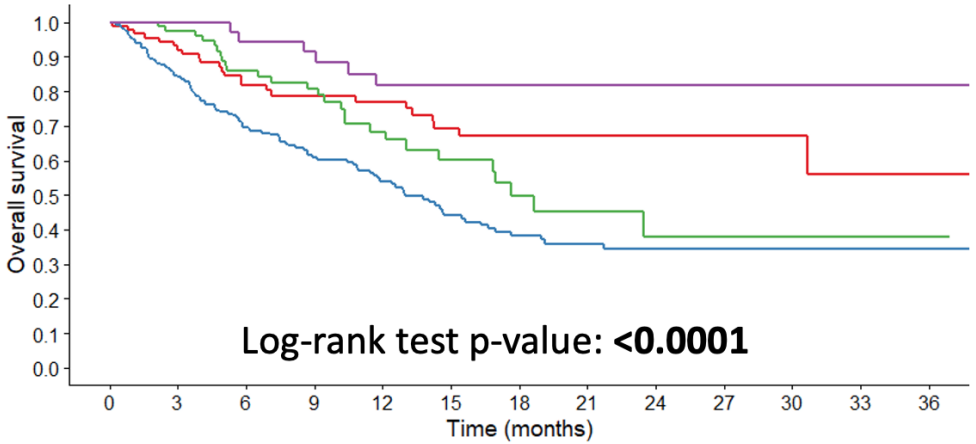
233 (0)	188 (22)	139 (55)	100 (87)	78 (103)	57 (116)	44 (123)	32 (134)	23 (142)
252 (0)	206 (20)	161 (32)	127 (53)	101 (66)	72 (85)	56 (97)	42 (109)	26 (124)



B

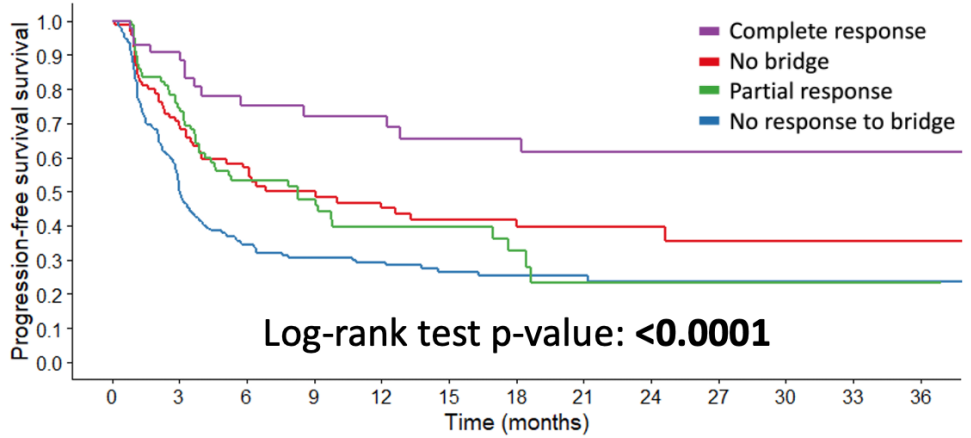
233 (0)	148 (18)	97 (37)	67 (61)	50 (74)	40 (83)	32 (90)	23 (98)	17 (104)
252 (0)	134 (14)	92 (21)	72 (30)	61 (36)	44 (46)	38 (50)	27 (58)	18 (66)

The role of bridging treatment



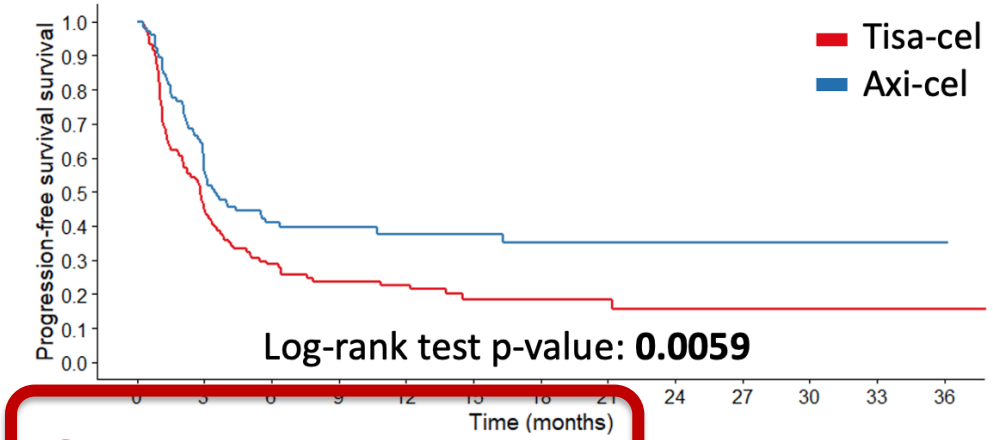
A Response to bridging therapy

	92 (0)	78 (7)	61 (16)	48 (27)	44 (30)	31 (39)	25 (44)	22 (47)	18 (51)	7 (62)	6 (63)	4 (64)	2 (66)
	225 (0)	172 (19)	129 (34)	88 (61)	68 (72)	47 (82)	38 (85)	27 (94)	17 (103)	11 (109)	6 (114)	6 (114)	3 (117)
	82 (0)	74 (6)	56 (16)	44 (25)	31 (32)	20 (40)	12 (45)	7 (49)	1 (54)	1 (54)	1 (54)	1 (54)	1 (54)
	44 (0)	42 (2)	34 (8)	30 (11)	25 (13)	22 (16)	19 (19)	13 (25)	10 (28)	5 (33)	4 (34)	3 (35)	1 (37)



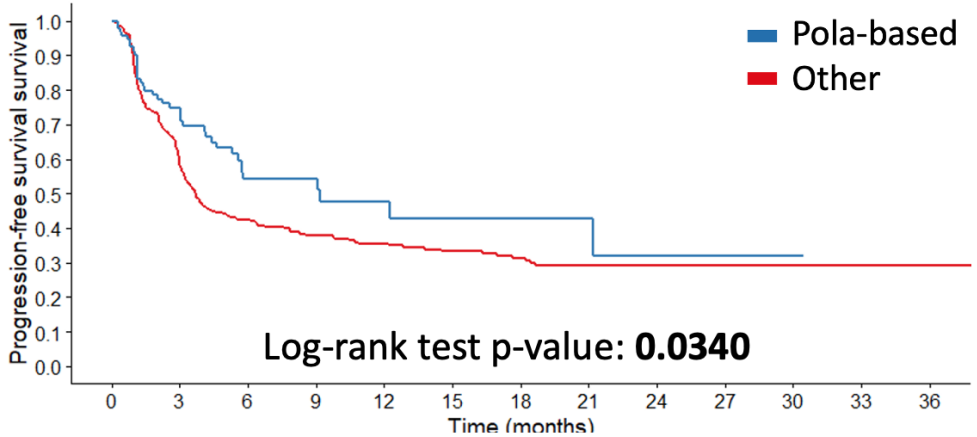
B Response to bridging therapy

	92 (0)	58 (7)	42 (13)	31 (19)	28 (20)	21 (24)	19 (26)	15 (29)	13 (31)	4 (39)	3 (40)	3 (40)	2 (41)
	225 (0)	105 (12)	67 (18)	46 (33)	36 (41)	26 (48)	22 (51)	15 (58)	9 (63)	6 (66)	4 (68)	4 (68)	2 (70)
	82 (0)	58 (4)	37 (9)	26 (17)	16 (23)	12 (27)	8 (29)	4 (31)	1 (34)	1 (34)	1 (34)	1 (34)	1 (34)
	44 (0)	38 (2)	26 (8)	24 (9)	22 (11)	18 (13)	16 (15)	12 (18)	9 (21)	4 (26)	3 (27)	2 (28)	1 (29)



C Axi-cel vs Tisa-cel in No response to bridge

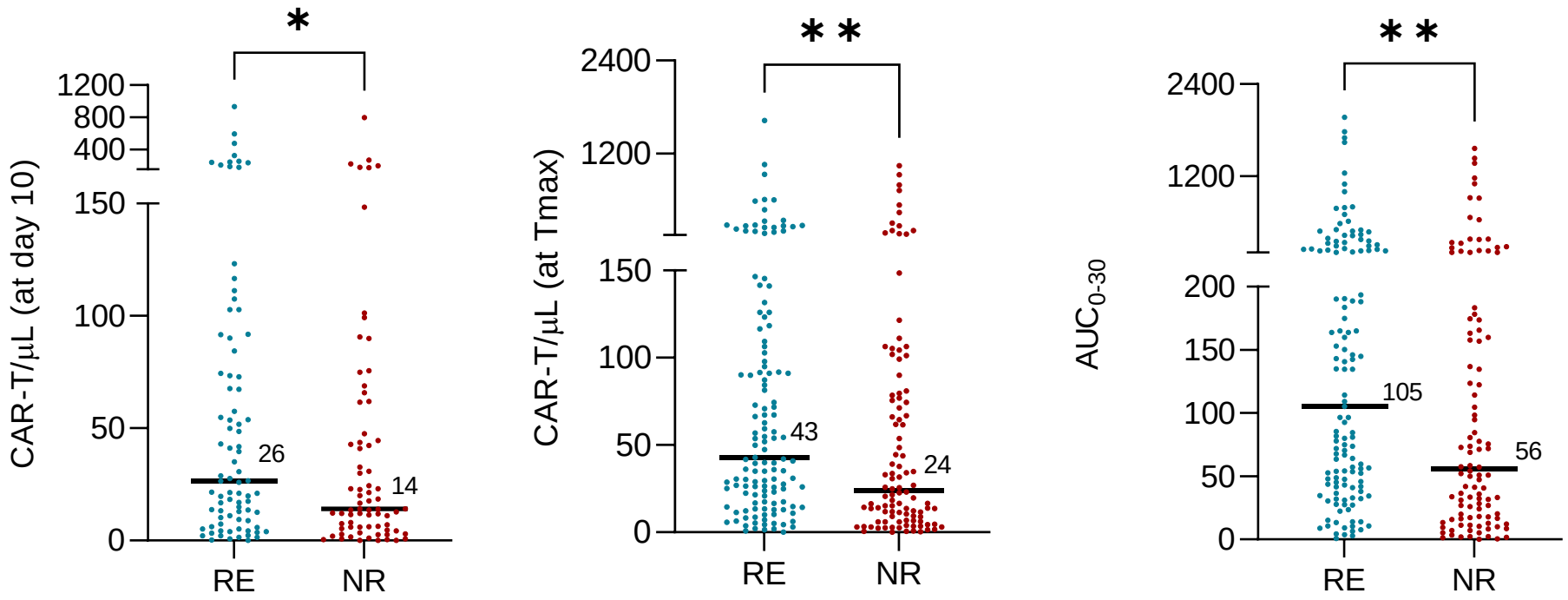
	119 (0)	51 (4)	32 (5)	22 (10)	19 (12)	11 (17)	10 (18)	7 (21)	4 (23)	3 (24)	2 (25)	2 (25)	1 (26)
	106 (0)	54 (8)	35 (13)	24 (23)	17 (29)	15 (31)	12 (33)	8 (37)	5 (40)	3 (42)	2 (43)	2 (43)	1 (44)



D Bridging therapy: Pola-based vs Other

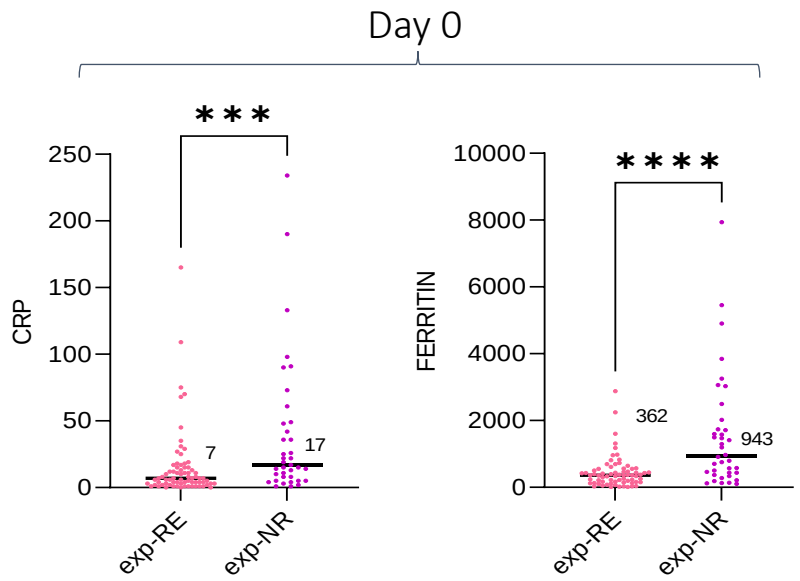
	298 (0)	166 (10)	117 (15)	91 (29)	72 (43)	57 (54)	45 (63)	31 (74)	20 (85)	11 (94)	8 (97)	8 (97)	5 (100)
	95 (0)	58 (15)	30 (30)	17 (43)	11 (47)	6 (51)	6 (51)	4 (53)	2 (54)	1 (55)	1 (55)	0 (56)	0 (56)

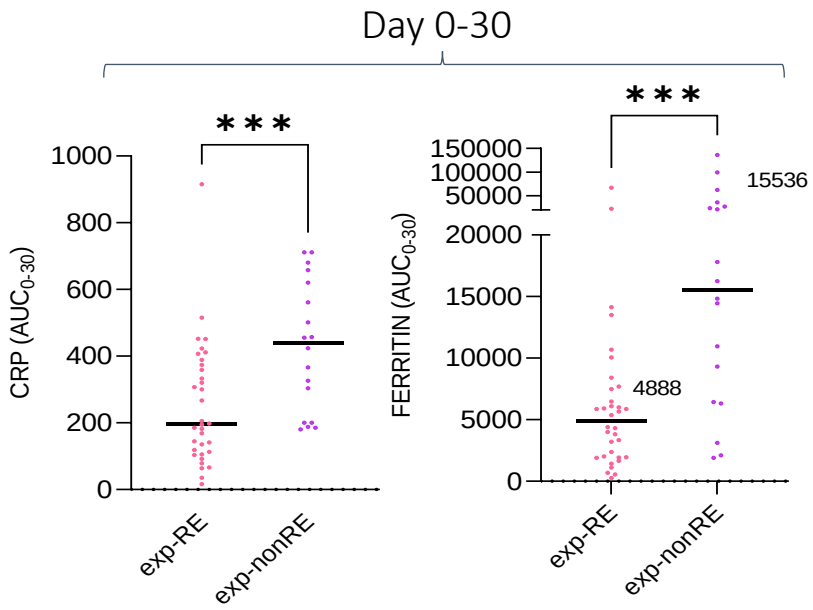
CAR-T *in vivo* expansion in LBCL is associated with response at day 90 (262 pts)

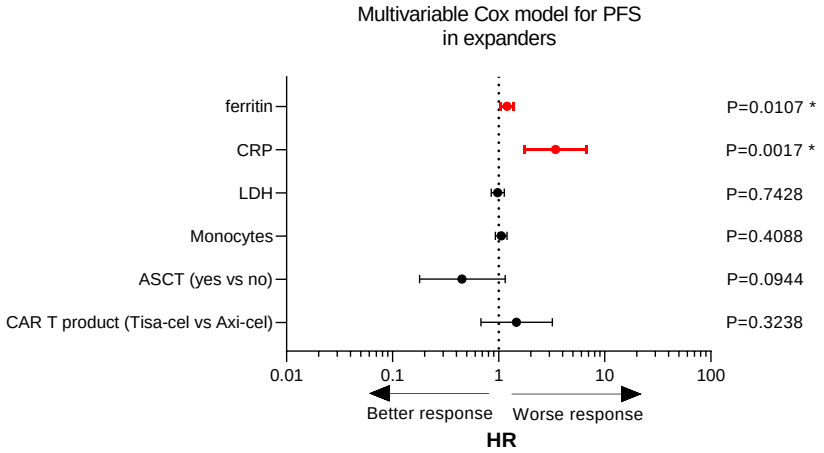


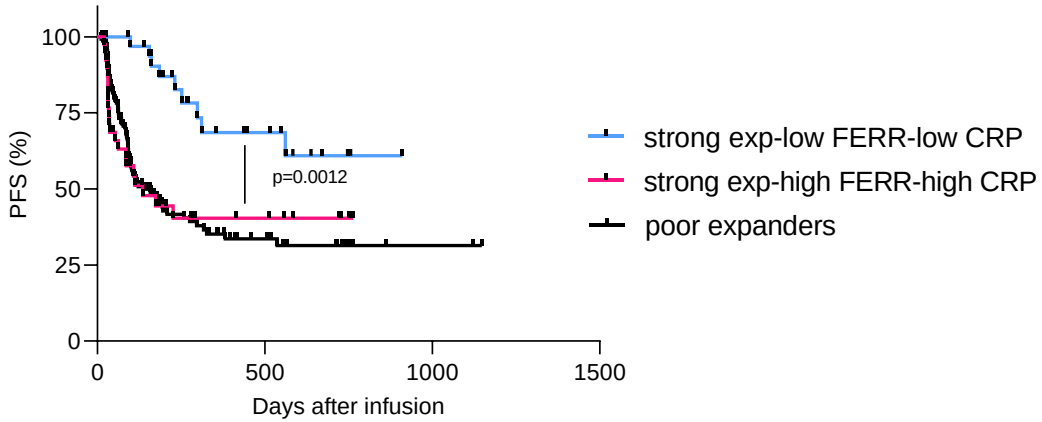
Magni M et al, ASH2024 do not post

High levels of inflammatory markers in pts expanding CAR T-cells but not responding









➡ These data support the role of inflammation in affecting the efficacy of CAR T cells despite expansion

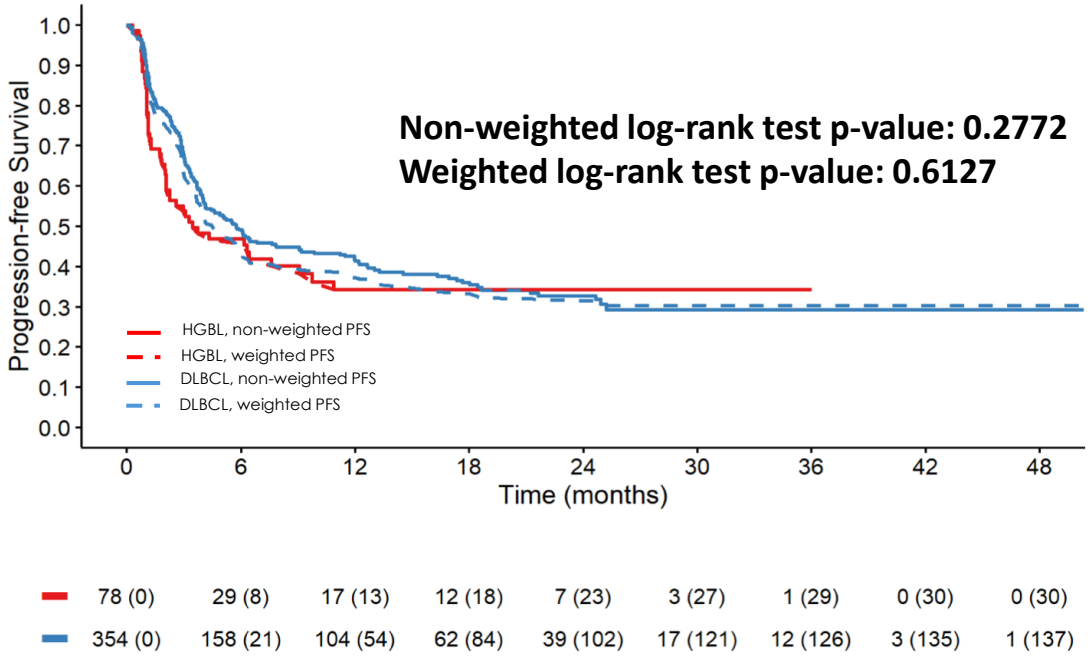
submitted

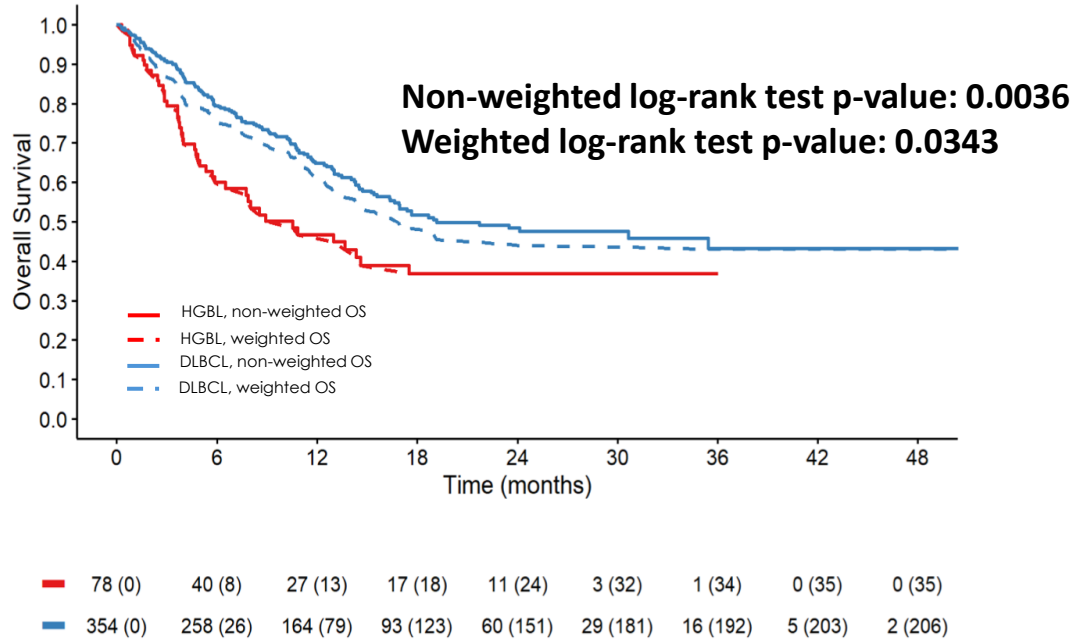
Patients Characteristic: HGBL vs DLBCL

	HGBL (n=78)	DLBCL (n=354)
Sex, n (%)		
Female	33 (42)	120 (34)
Male,	45 (58)	234 (66)
Age, median (range)	63 (55.5-68.0)	60 (52.0-67-0)
IPI, n (%)		
0-2	31 (40)	205 (58)
>2	47 (60)	149 (42)
LDH at infusion, n (%)		
normal	46 (59)	203 (57)
increased	18 (23)	90 (26)
missing	14 (18)	61 (17)
PCR at infusion, n (%)		
<10	39 (50)	176 (50)
>=10	39 (50)	178 (50)
ECOG, n (%)		
0	47 (60)	208 (59)
>=1	31 (40)	146 (41)
Disease status, n (%)		
Relapsed	18 (23)	108 (31)
Refractory	60 (77)	246 (69)
Bulky disease, n (%)		
Yes	33 (42)	110 (31)
No	45 (58)	244 (69)
CAR-T product, n (%)		
Axi-cel	38 (49)	172 (49)
Tisa-cel	40 (51)	182 (51)
CAR-HEMATOTOX score, n (%)		
Low (0-1)	29 (37)	144 (41)
High (>=2)	19 (24)	83 (23)
Missing	30 (39)	127 (36)

Dodero A et al, submitted do not post

PFS and OS in DLBCL and HGBCL: non-weighted and weighted analyses

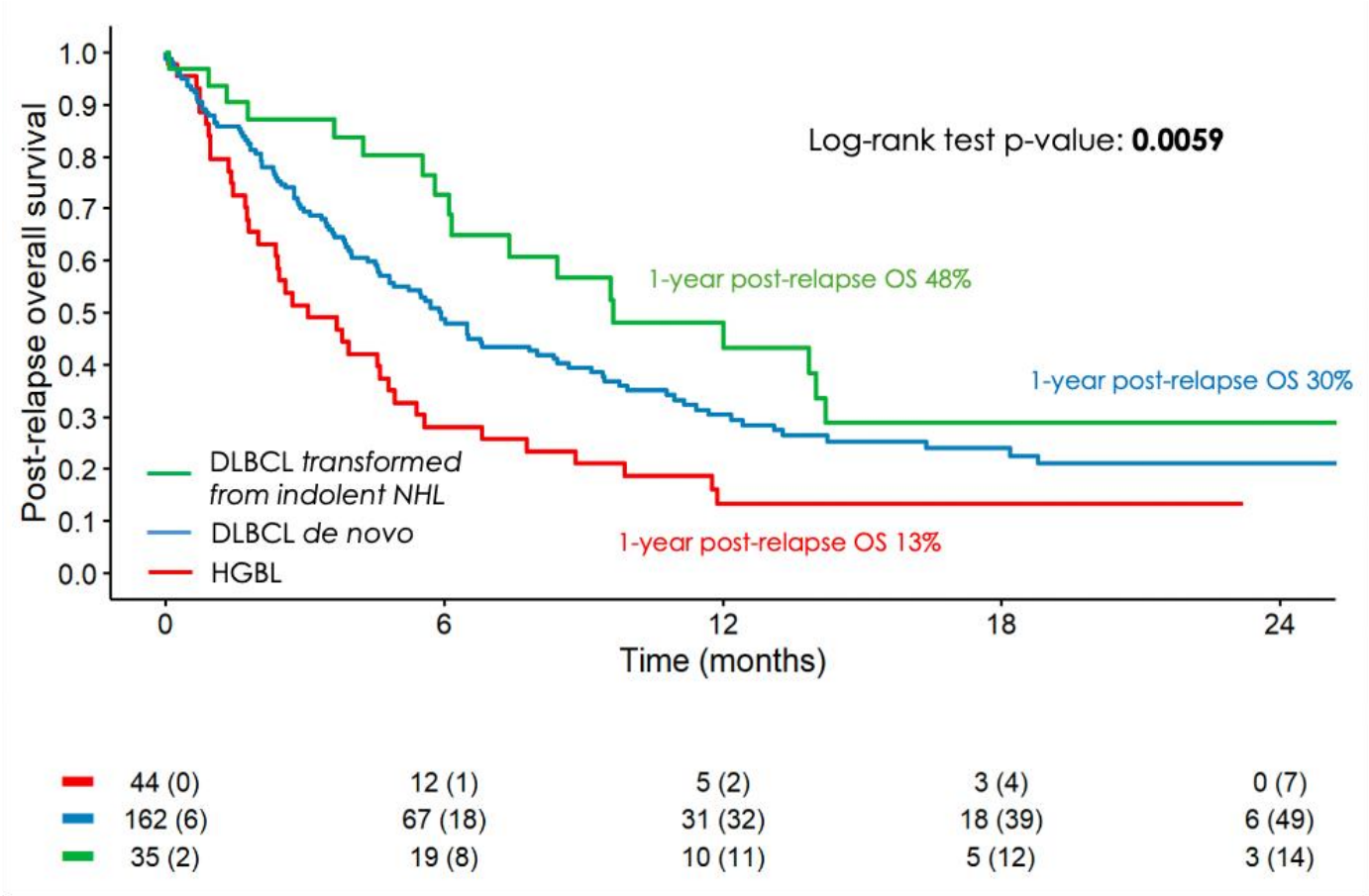




	Before IPW			After IPW		
Survival	**HGBL (*n*=78)**	**DLBCL (*n*=354)**	*p-value*	**HGBL (*n*=78)**	**DLBCL (*n*=77.8)**	*p-value*
2-y PFS, % (95% IC)	34.2 (24.4-47.9)	32.8 (27.5-39)	0.2772	34.2 (22.7-45.7)	31.6 (24.7-38.5)	0.6127
2-y OS, % (95% IC)	36.8 (26.5-51.2)	48.5 (42.5-55.3)	**0.0036**	36.8 (24.7-49)	44.3 (36.4-52.2)	**0.0343**
2-y DOR, % (95%IC)	46.9 (32.9-66.8)	43.3 (35.8-52.2)	0.7459	46.9 (30.3-63.5)	44.5 (34.3-54.8)	0.8252

Dodero A et al, submitted do not post

Not all LBCL are the same: outcome in different subtypes after CAR T-cells failure



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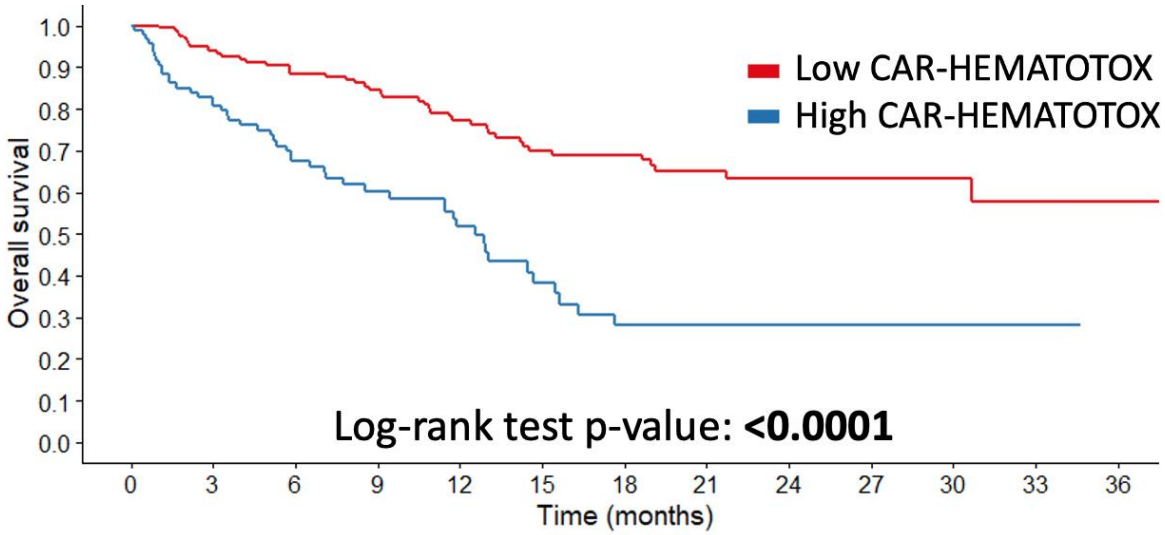
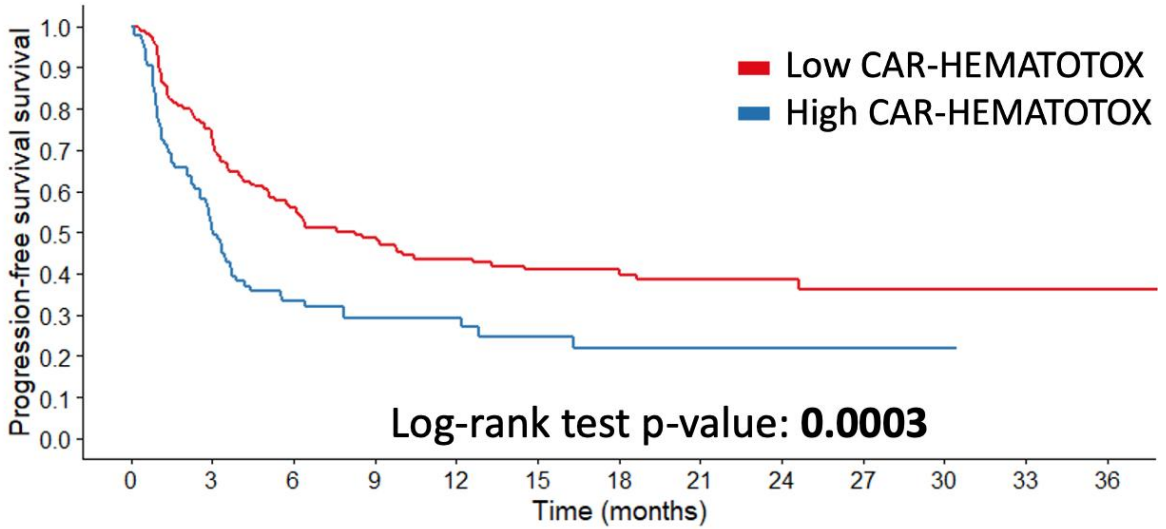
CAR – HEMATOTOX score in LBCL

Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1	High: ≥ 2		





A HEMATOTOX

	169 (0)	149 (10)	127 (24)	100 (46)	82 (56)	67 (64)	57 (73)	44 (83)	32 (94)	17 (109)	11 (115)	9 (116)	4 (121)
	94 (0)	74 (2)	54 (11)	38 (22)	29 (26)	15 (34)	10 (35)	7 (38)	3 (42)	2 (43)	2 (43)	1 (44)	0 (45)

B HEMATOTOX

	169 (0)	119 (5)	84 (13)	61 (26)	49 (32)	43 (35)	38 (40)	28 (48)	21 (55)	10 (65)	7 (68)	7 (68)	4 (71)
	94 (0)	46 (2)	27 (6)	18 (12)	16 (14)	8 (20)	7 (20)	5 (22)	2 (25)	1 (26)	1 (26)	0 (27)	0 (27)

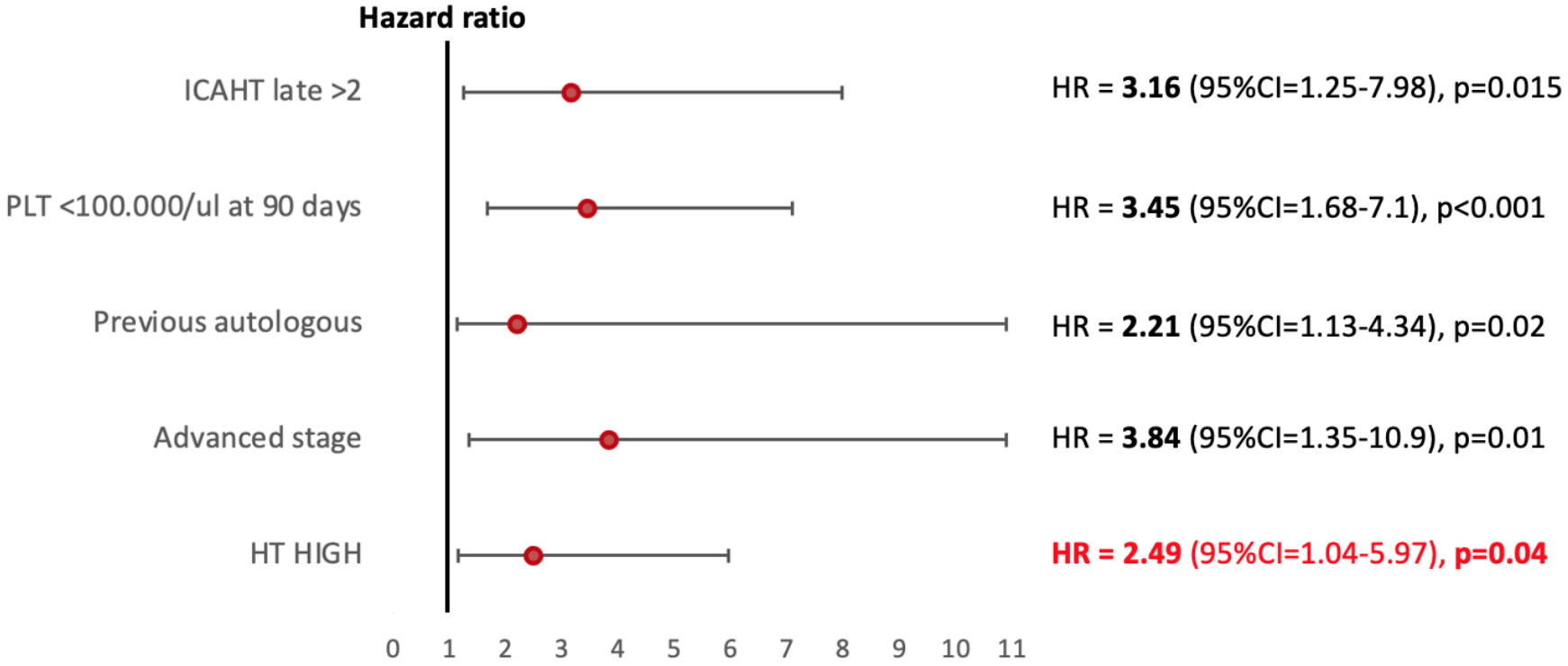
Stella F et al, in press JTCT

CAR HEMATOTOX and SPM

Rejeski K et al. Blood 2021

From univariable Fine and Gray models, a **high CAR HEMATOTOX score** was found to be associated with **higher risk** for occurrence of **SPM**.

The relative rarity of events prevented us from performing multivariate analyses.



SHORT REPORT

Haematological Malignancy – Clinical

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Società Italiana di Ematologia

Secondary primary malignancies after CD-19 directed CAR-T-cell therapy in lymphomas: A report from the Italian CART-SIE study

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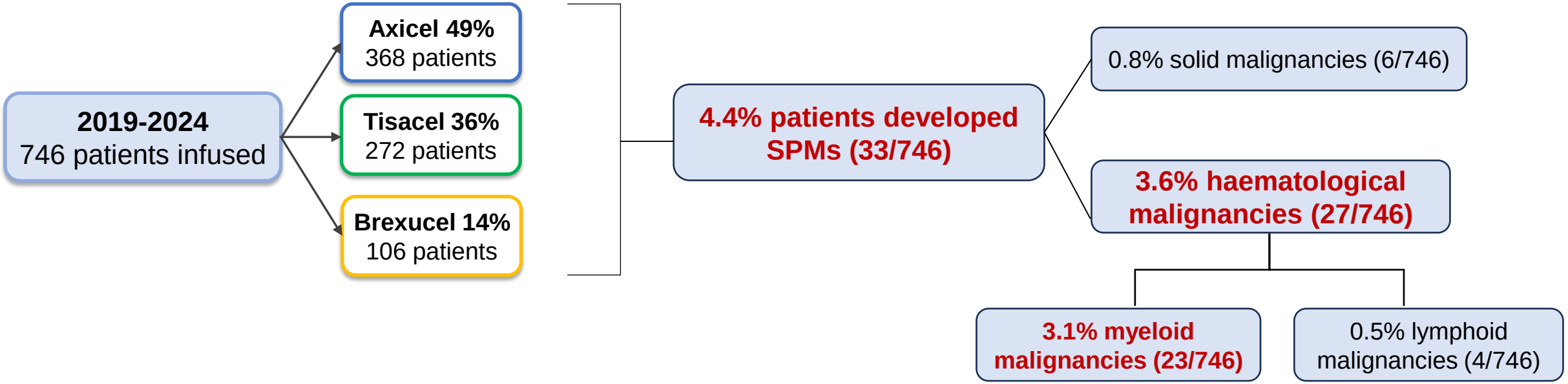
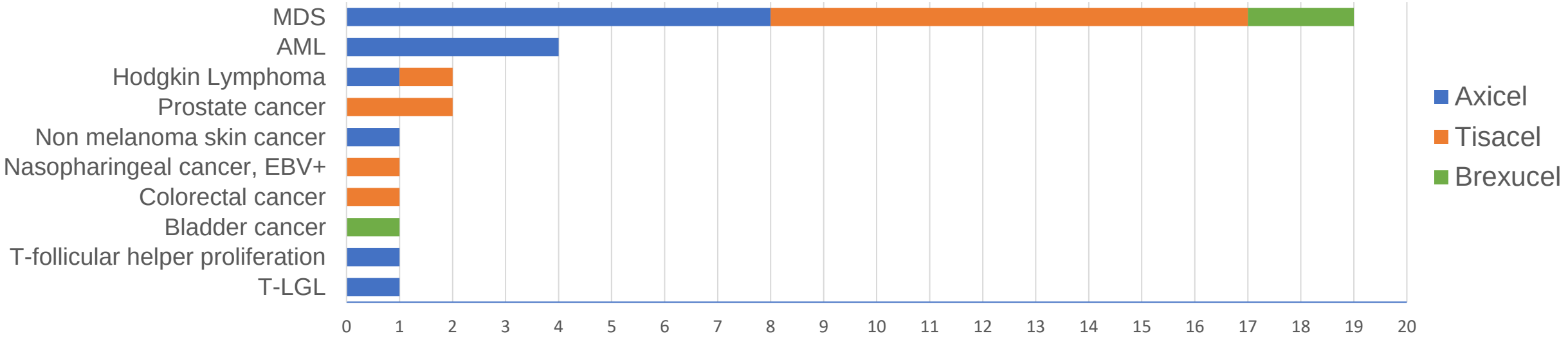


Secondary primary malignancies in CART-SIE NHL

- Median follow-up 14.9 months (IQR: 6.68-24.47)
- Median time to diagnosis: 12.6 months (range 1-40)
- **Very low incidence of T-NHL: 0.26%**
- **AML and MDS represented 70% of all SPMs (3.1%)**
- 12 deaths were observed, of which 7 were related to SPMs

Risk factors for occurrence of myeloid malignancies were Ann Arbor stage III-IV, previous ASCT, ICAHT, platelets count < 100.000/microliter at day 90 after infusion and neutrophils count < 500/microL before lymphodepletion.



2-year cumulative incidence of SPMs was 9.9% (95% CI: 6.5-14)
2-year cumulative incidence of myeloid malignancies was 6.7% (95% CI 4-10)

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Five-Year Follow-Up of Standard-of-Care Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

Michael D. Jain

Among axi-cel–infused patients, PFS at 5 years was 29% and OS at 5 years was 40%. The 5-year lymphoma-specific survival was 53% with infrequent late relapses. However, **the 5-year NRM was 16.2%, with over half of NRM events occurring beyond 2 years**. Patients who were 60 years and older had a lower risk of relapse, but a higher risk of NRM compared with patients younger than 60 years (NRM odds ratio, 4.5). **Late NRM was mainly due to infections and subsequent malignant neoplasms (SMNs).** In total, SMNs occurred in 24 patients (9%), including therapy-related myeloid neoplasms (n = 15), solid tumors (n = 7), and unrelated lymphoid malignancies (n = 2).

CART-SIE Mantle Cell Lymphoma - Clinical characteristics

	% (N=106)		% (N)
Median age	63 (IQR 55; 69)	**N prior therapies (median)**	3 (range 2-5)
Histology - Classic MCL - Blastoid MCL - Pleomorphic MCL	 70% (74) 19% (20) 11% (12)	**Previous BTKi** - BTKi relapsed - BTKi primary refractory - Missing	100% 51% (54) 28% (29) 21% (23)
Stage III/IV	91% (96)	**Previous ASCT**	58% (61)
Ki-67 >30%*	41% (43) *36% (38) missing	**POD24**	57% (60)
Tp53 - Wild type - Mutated - Not assessed	 26% (27) 12% (13) 62% (66)	**sMIPI** - High - Intermediate - Low - Missing	 39% (41) 17% (18) 30% (32) 14% (15)

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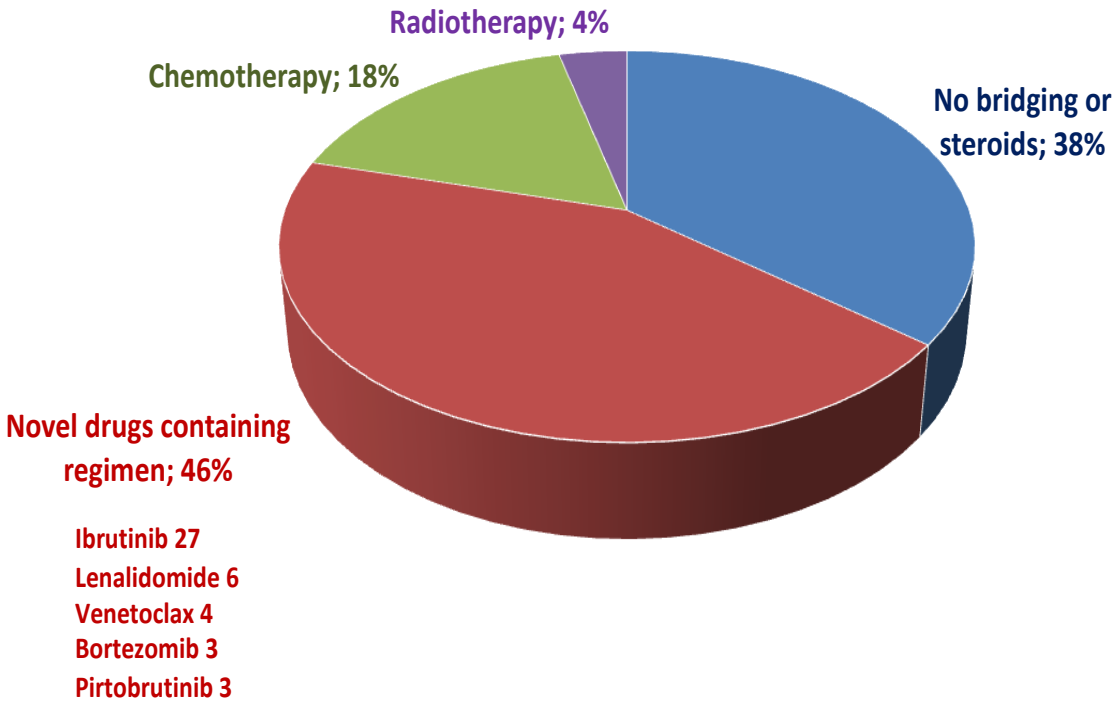
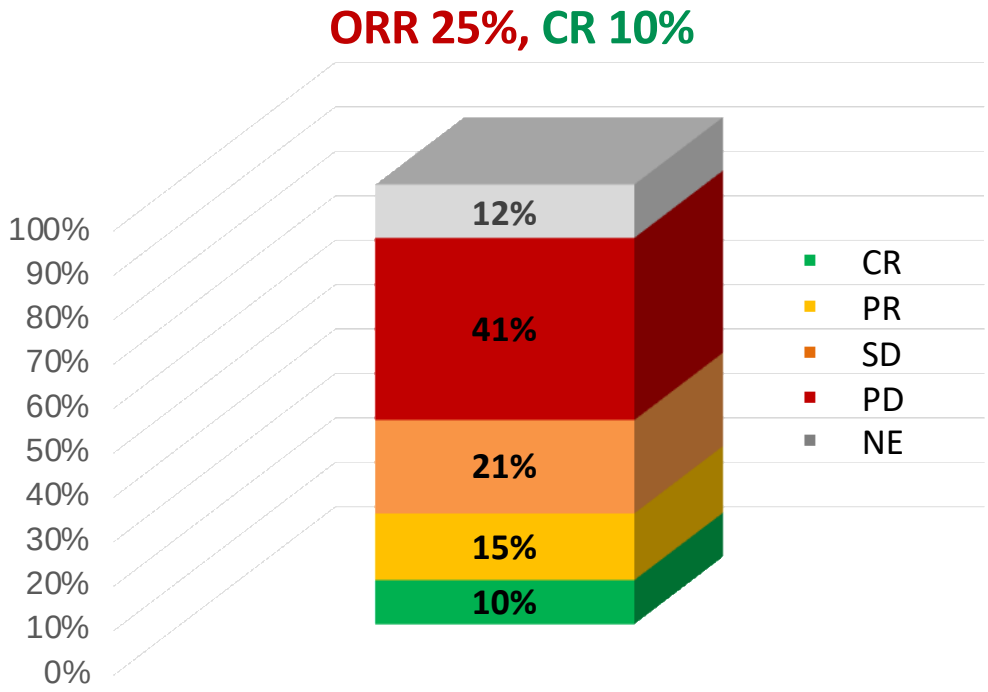
Bridging therapy



Response to bridging



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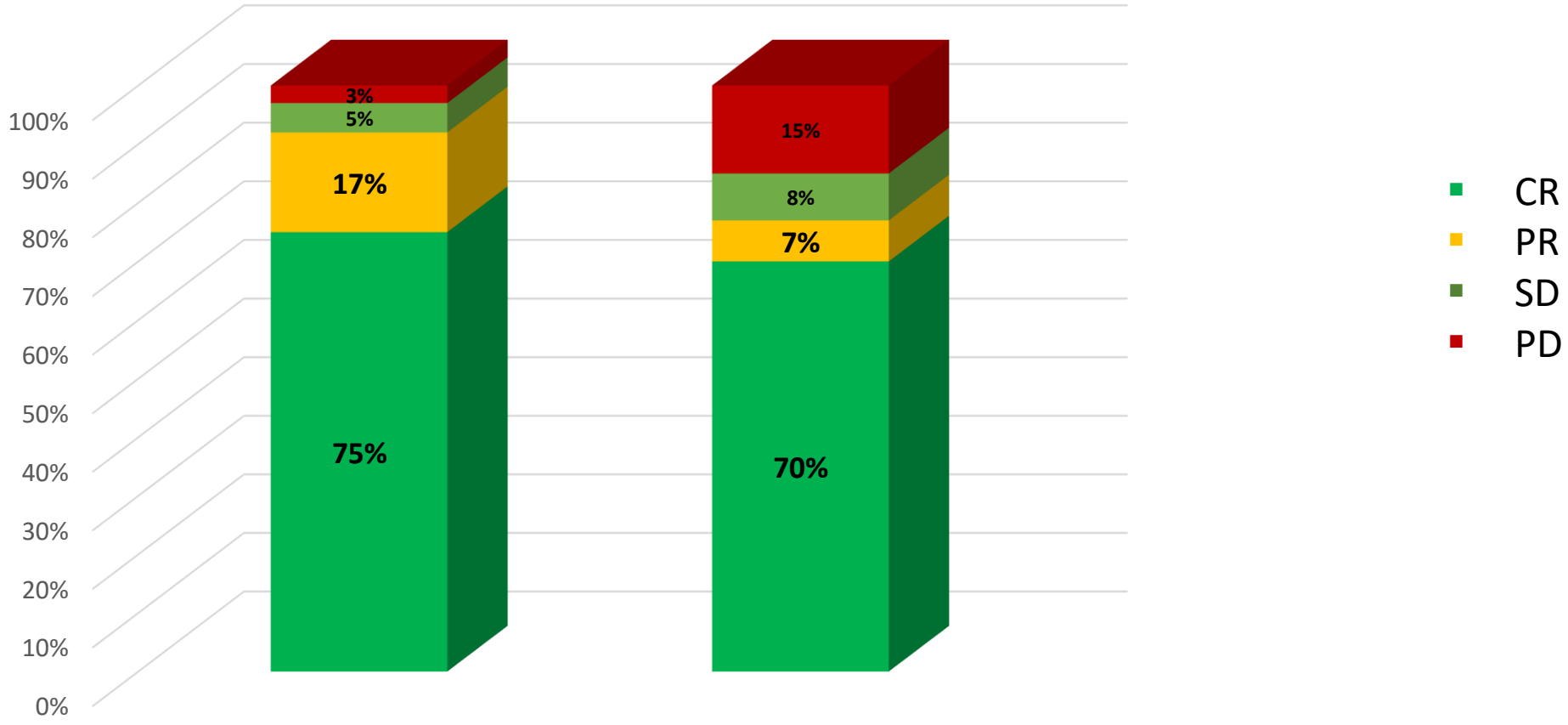
Response after CAR-T infusion

Day + 30:
ORR 92%, CR 75%

Day + 90:
ORR 77%, CR 70%



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Safety

	All grades	Grade ≥ 3
CRS	95%	22%
ICANS	48%	18%

Tocilizumab: 84%; Steroids: 54%

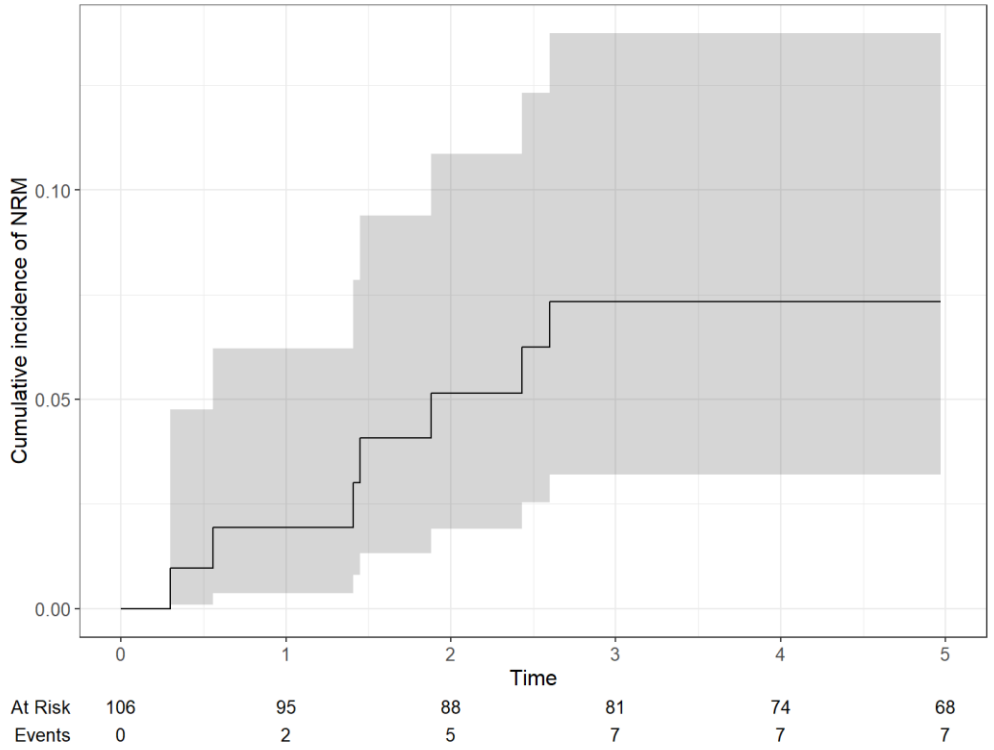
ICU admission: 18%

NRM: 7 patients

- **grade 5 CRS: 1**
- **grade 5 ICANS: 1**
- **infections: 2**
- **multi organ failure: 2**
- **stroke: 1**

Non relapse mortality (NRM)

NRM at 1 year = 7.3% (3.2%-14%).



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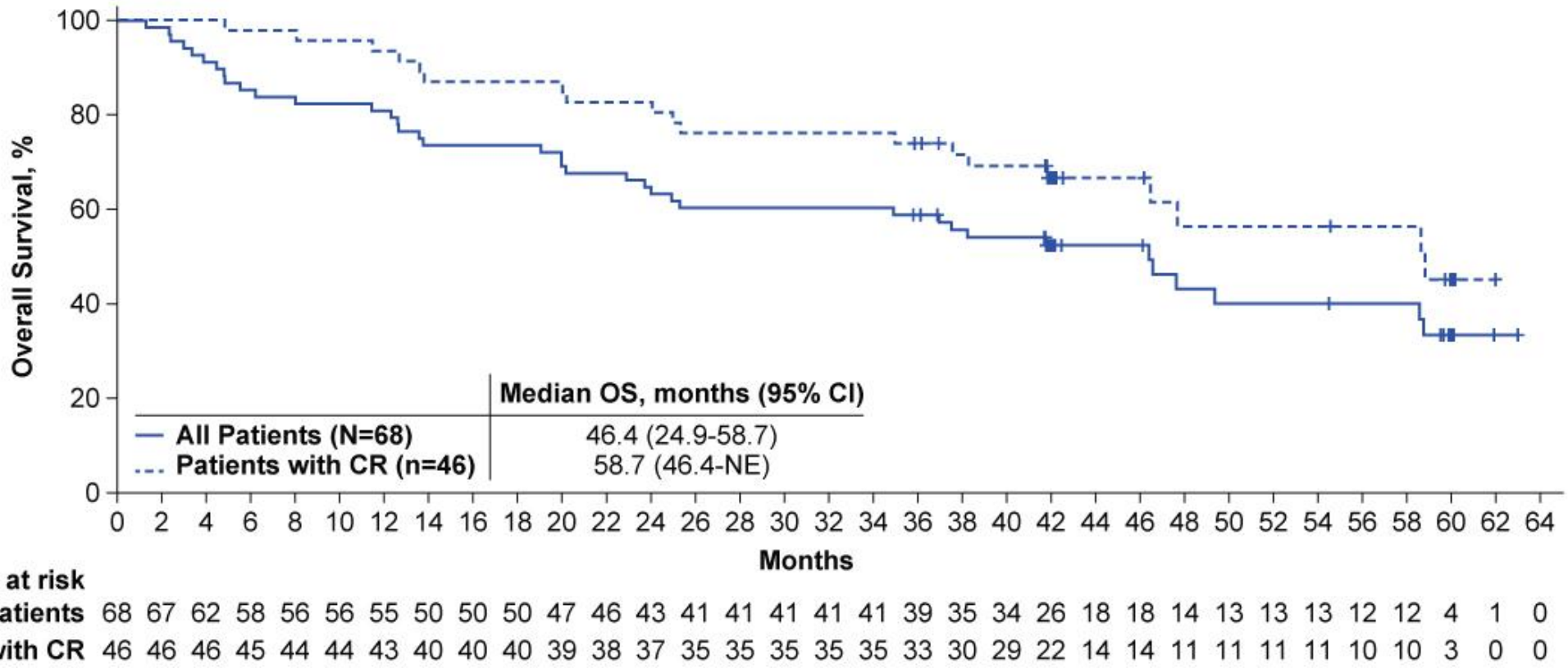
Overall Survival in ZUMA-2 (MCL) at 4 years (N=68)



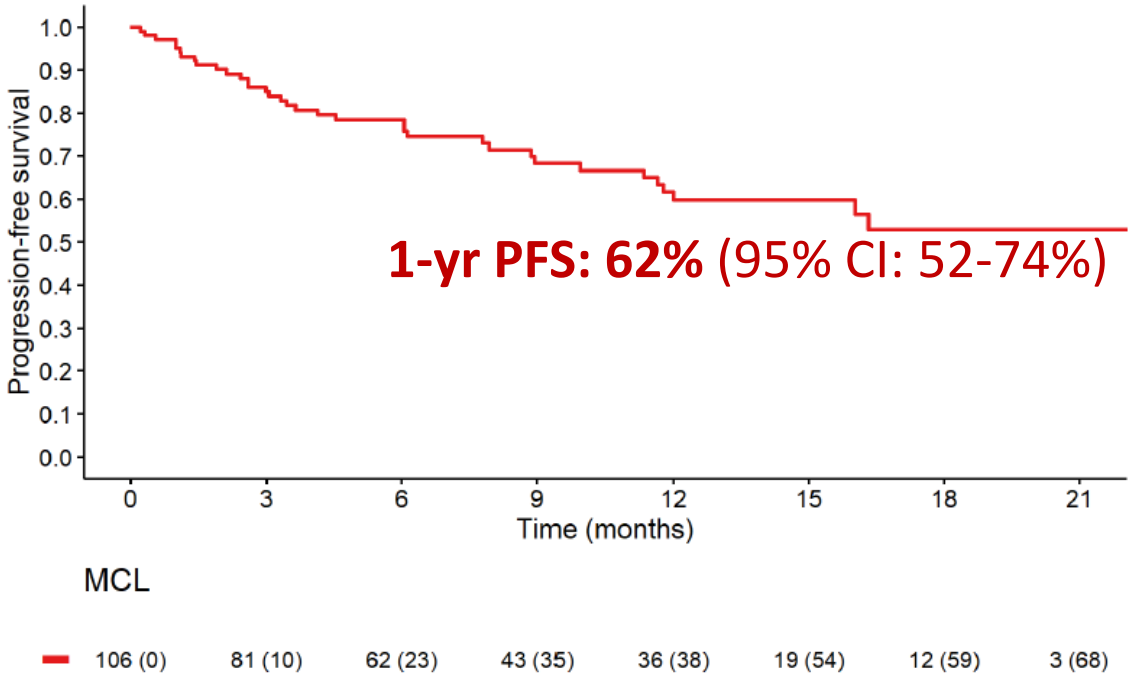
- As of July 23, 2022, median follow-up in ZUMA-2 was 47.5 months (N=68; range, 37.9-68.3)
- Median OS in ZUMA-2 was 58.7 months for patients with a CR (n=46)
- After almost 4 years of median follow-up, 30 patients (45%) were still alive, 27 of which had achieved a CR

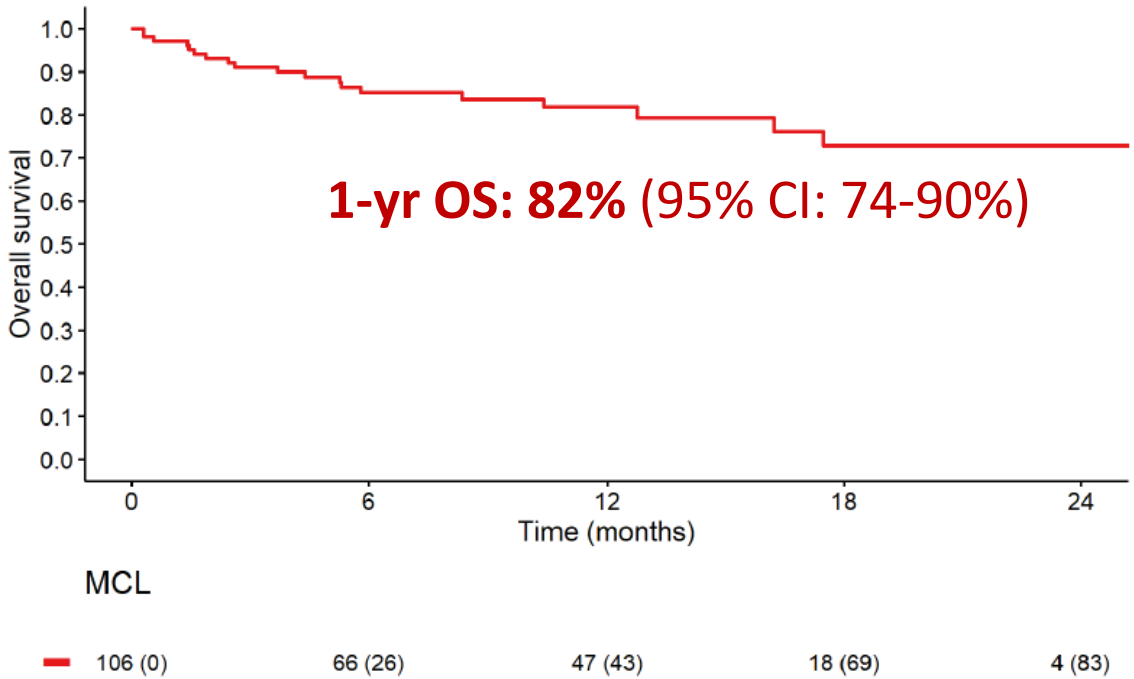
CR, complete response; mo, month; NE, not estimable; NR, no response; PR, partial response.

Goy et al, ASH 2023

Progression-free Survival and Overall Survival

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





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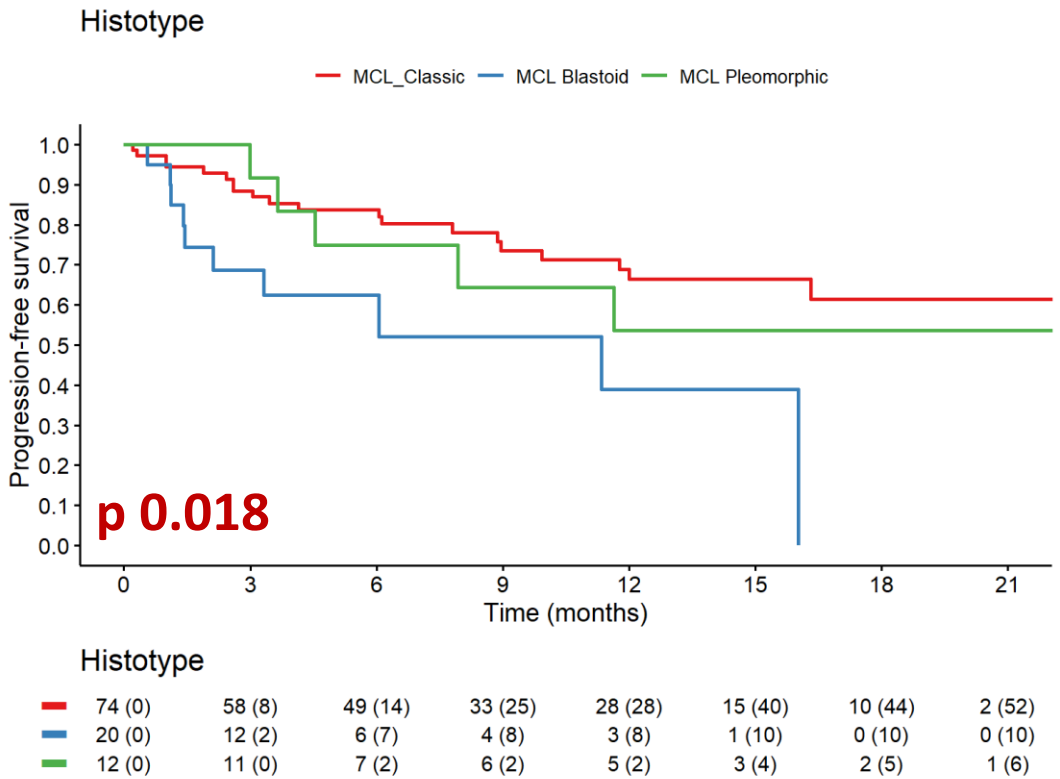
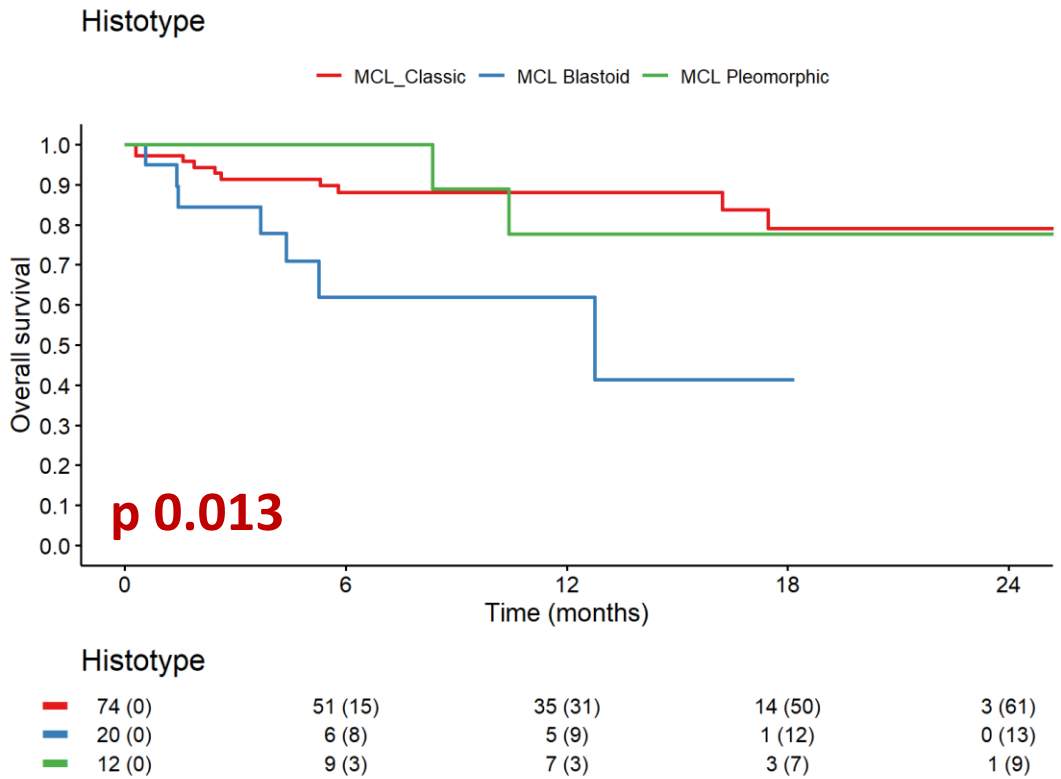
Progression-free Survival and Overall Survival, by histotype

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





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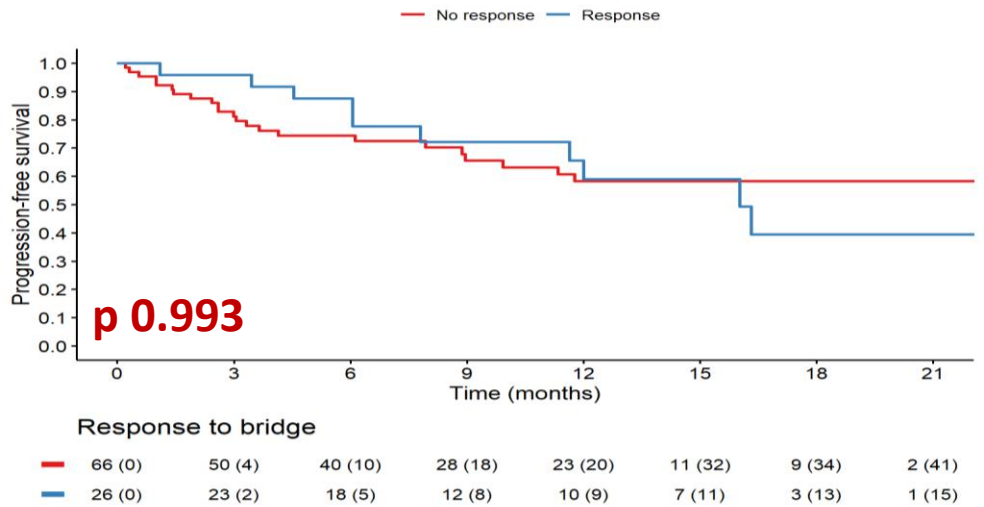
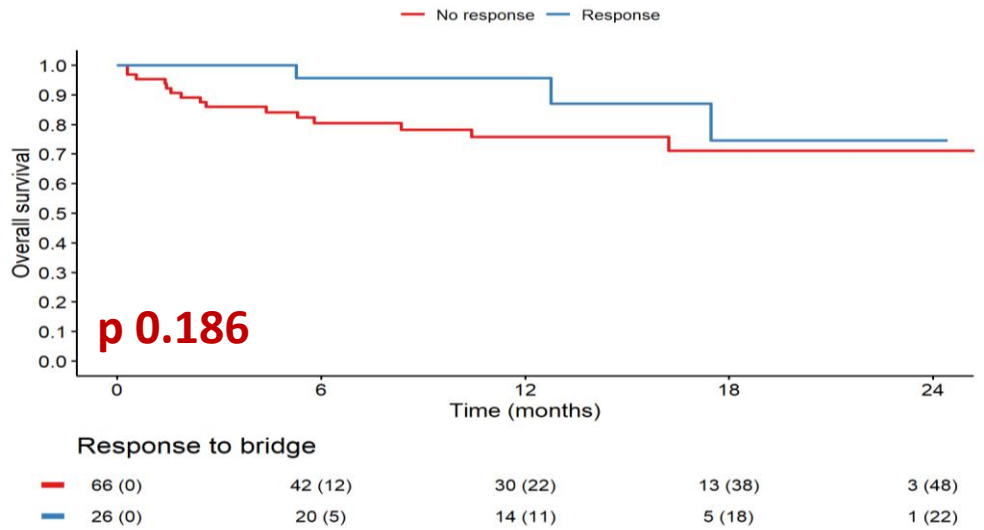
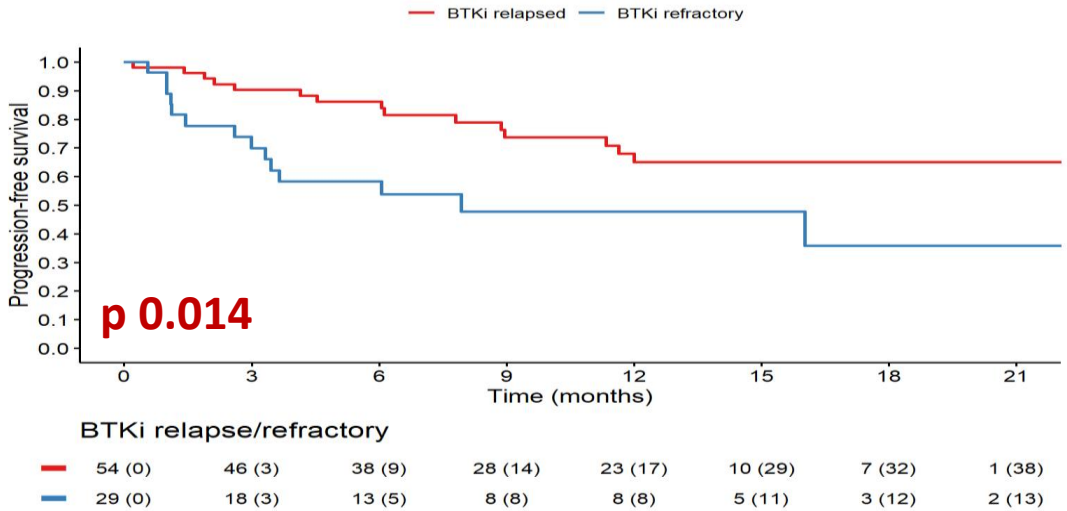
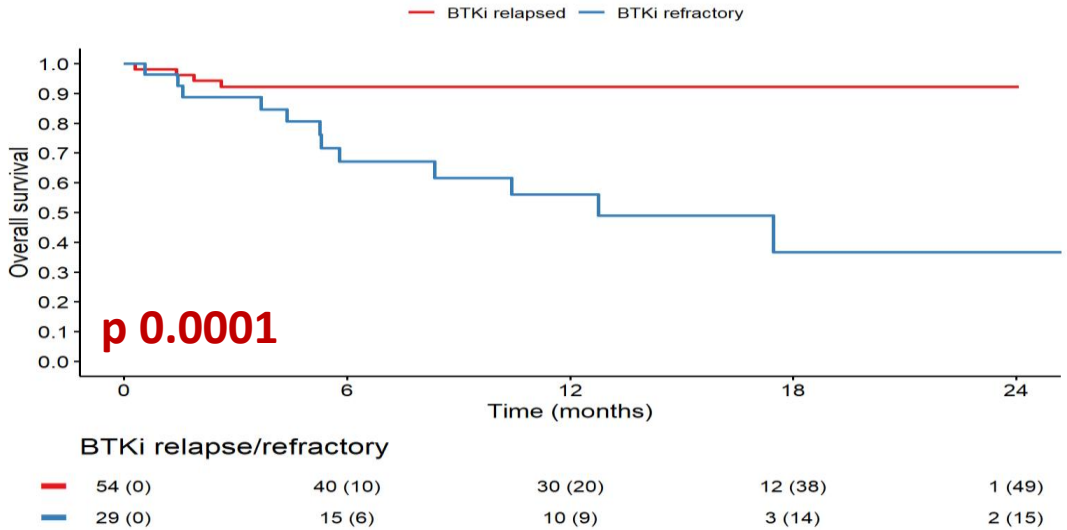
PFS and OS, by response to bridging





PFS and OS, by iBTK refractoriness





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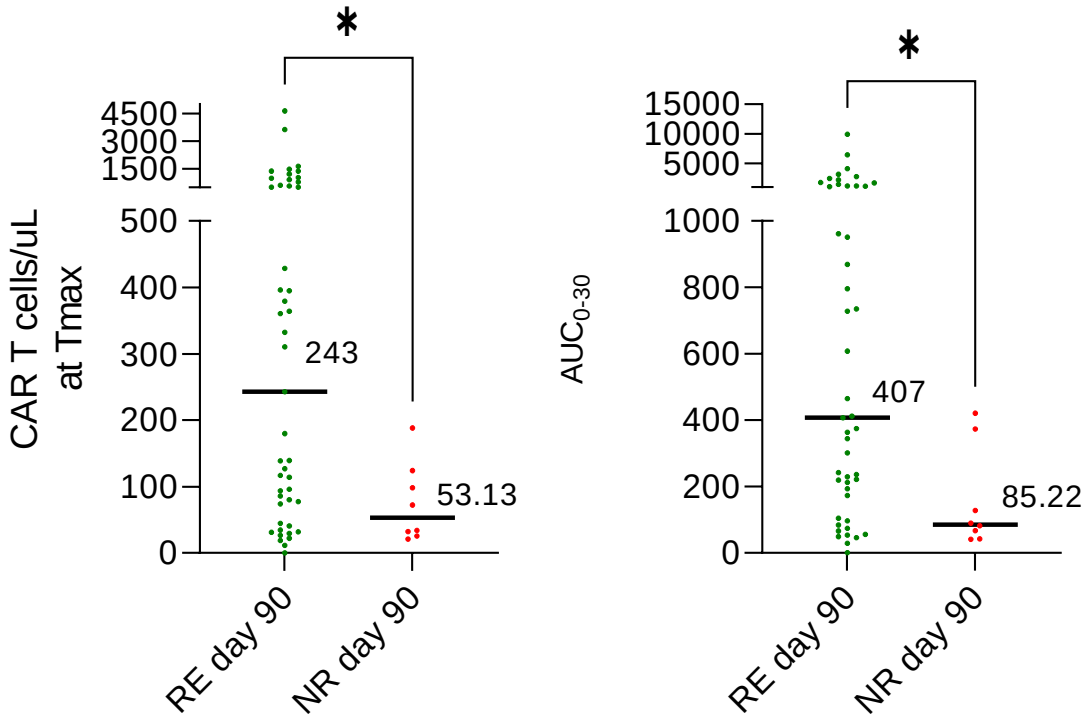
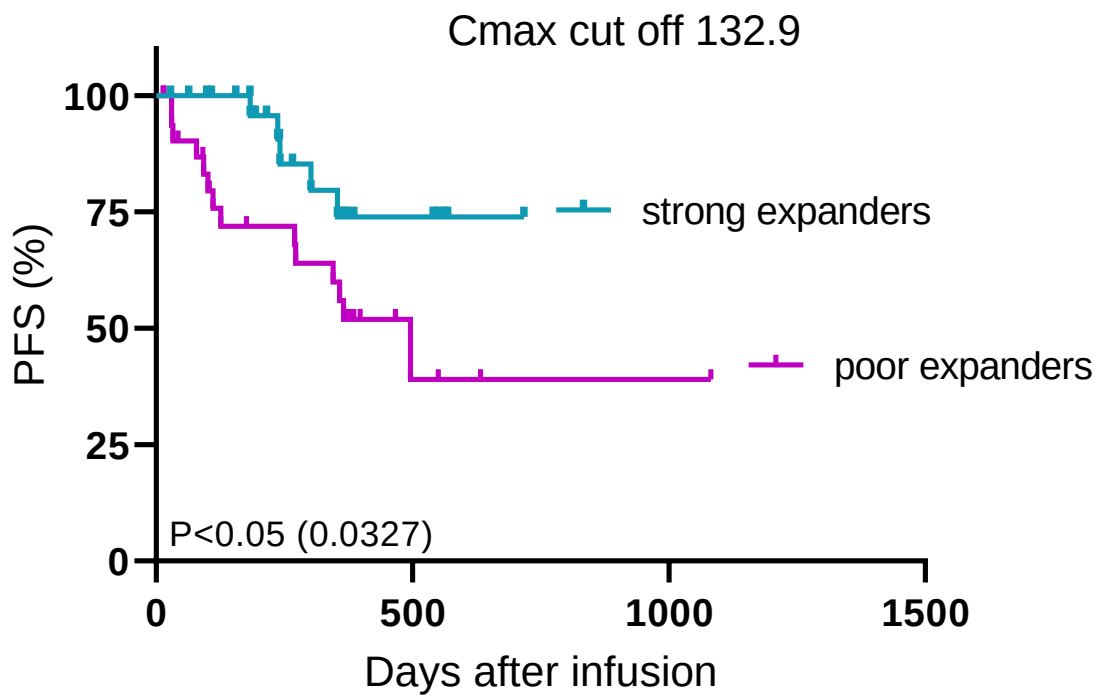
Brexu-cel in vivo expansion is associated with response at day 90 and PFS





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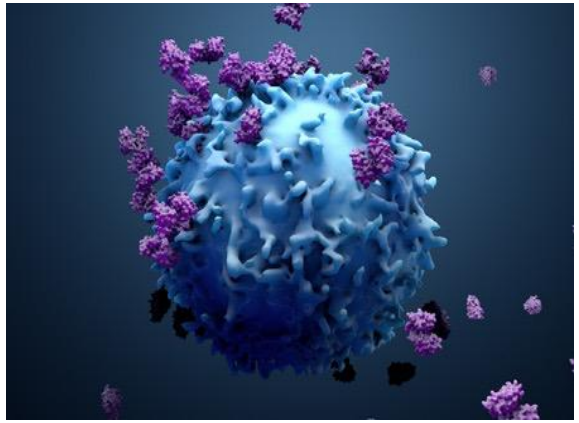
Conclusions

- In the ZUMA-2 trial and in real-life experiences, brexu-cel demonstrated high rates of durable responses in R/R MCL with prior iBTK failure, but without a clear plateau in the survival curves.
- In the CAR-T SIE study, brexu-cel provided a high response rate at day 30 (ORR 92%, CR 75%) and day 90 (ORR 77%, CR 70%), with a 1-year PFS of 62% (95% CI: 52-74%). NRM at one year is not negligible.
- In vivo CAR-T expansion correlates with response at day +90 and PFS, representing a potentially important “early” prognostic biomarker.
- Refractoriness to iBTK represents a challenge, and new strategies are needed.

Phase II study PRIMACART. PI: Prof. Paolo Corradini



PRIMACART

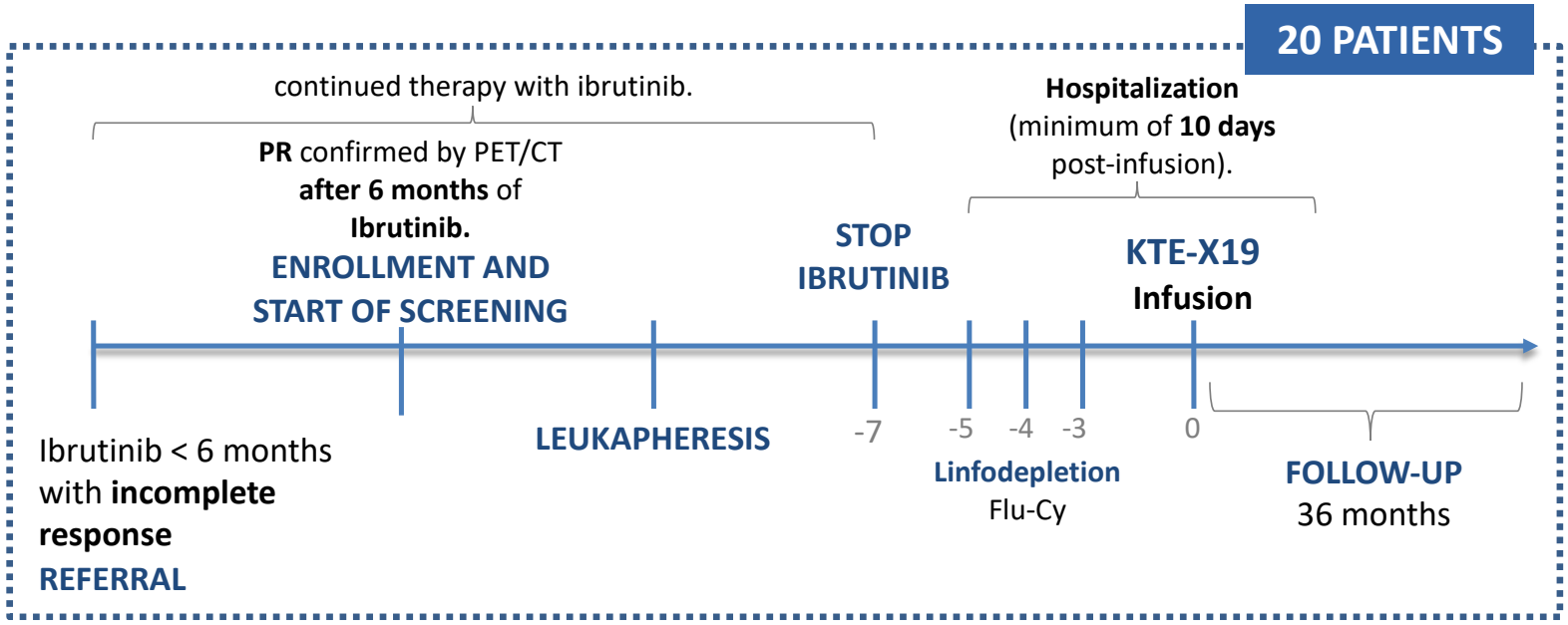
STUDIO DI FASE II PER VALUTARE L'EFFICACIA DELLA TERAPIA A CELLULE CAR-T CON KTE-X19 IN PAZIENTI CON LINFOMA MANTELLARE RECIDIVATO/REFRATTARIO CON OTTENUTA REMISSIONE PARZIALE IN CORSO DI TERAPIA DI SALVATAGGIO CON IBRUTINIB

Primary Objective: CR at 90 days after infusion of KTE-X19.

Secondary Objectives: CR at 6 months; PFS/OS at 1, 2, and 3 yrs; DOR, NRM; AEs; biological study.

2 centers:

- Fondazione IRCCS Istituto Nazionale dei Tumori, Milano
- Istituto di Ematologia L.A. Seragnoli, Bologna



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All the Italian qualified centers for CAR-T treatment, the referral centers, patients, families and nurses.

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