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

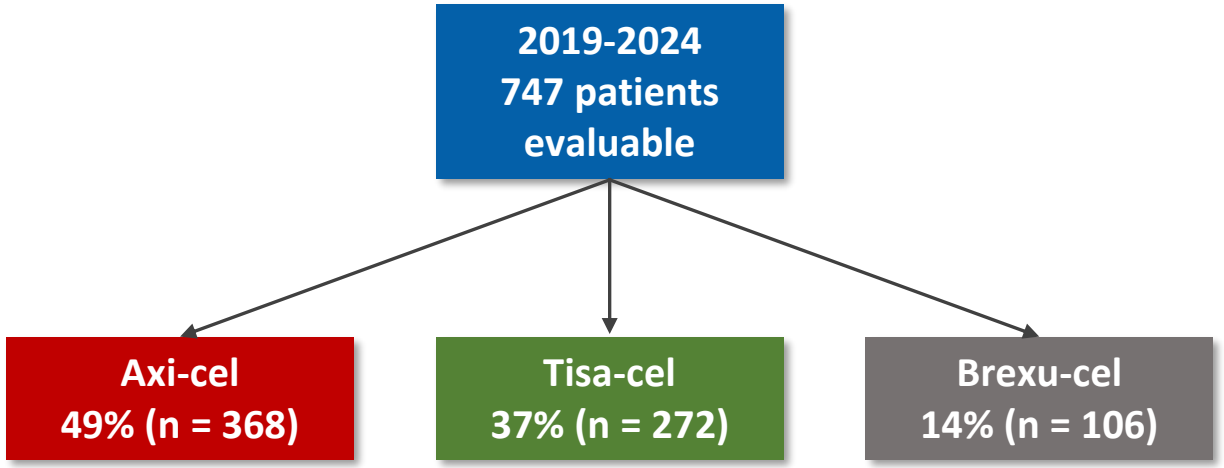
Prof. Paolo Corradini

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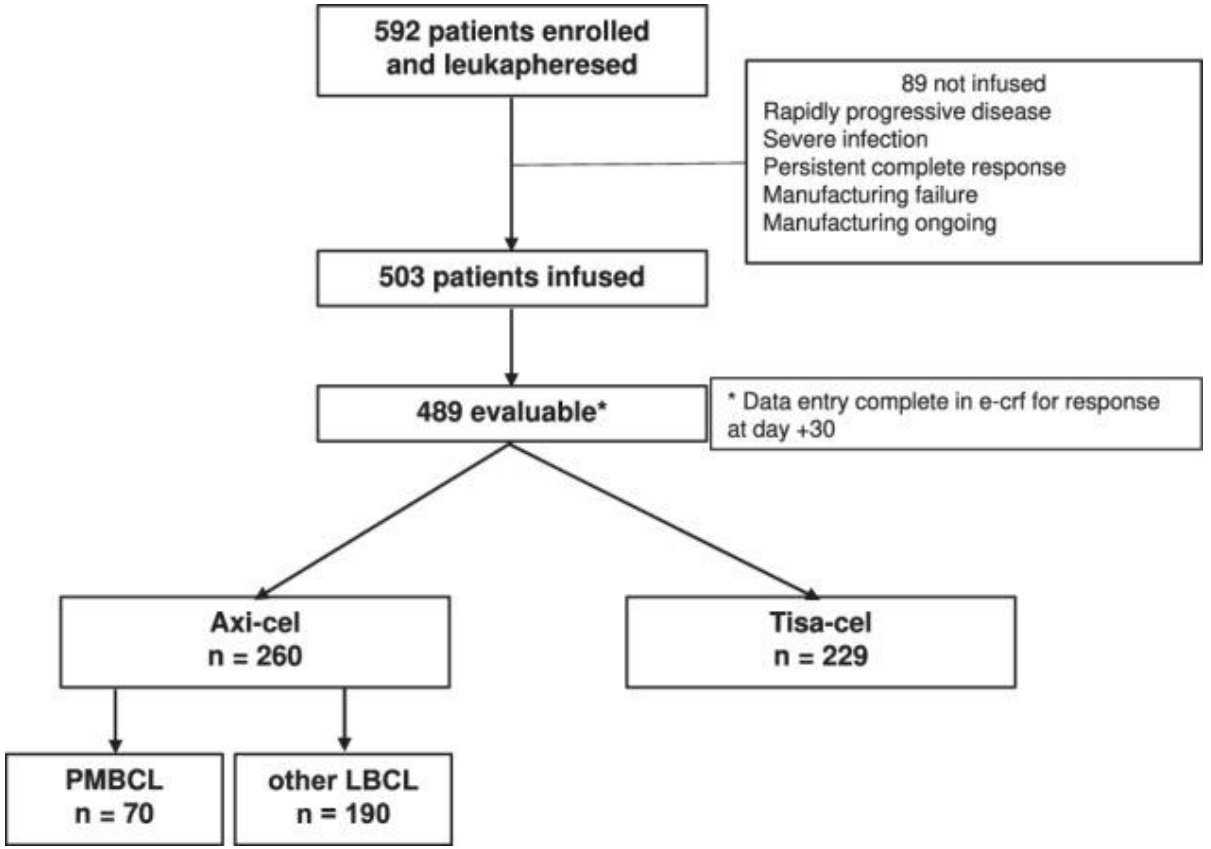
In Italy CAR-T for second relapse were reimboursed starting november 2019 (for first relapse nov 2023); 21 of 38 centers are enrolling.

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

Annalisa Chiappella[1✉], Beatrice Casadei[2], Patrizia Chiusolo[3], Alice Di Rocco[4], Silva Ljevar[5], Martina Magni[1], Piera Angelillo[6], Anna Maria Barbui[7], Ilaria Cutini[8], Anna Dodero[1], Francesca Bonifazi[2], Maria Chiara Tisi[9], Stefania Bramanti[10], Maurizio Musso[11], Mirko Farina[12], Massimo Martino[13], Mattia Novo[14], Giovanni Grillo[15], Francesca Patriarca[16], Giulia Zacchi[17], Mauro Krampera[18], Martina Pennisi[1], Eugenio Galli[3], Maurizio Martelli[4], Andrés J. M. Ferreri[6], Silvia Ferrari[7], Riccardo Saccardi[8,21], Anisa Bermema[1], Anna Guidetti[1,19], Rosalba Miceli[5], Pier Luigi Zinzani[2,20] and Paolo Corradini[1,19]



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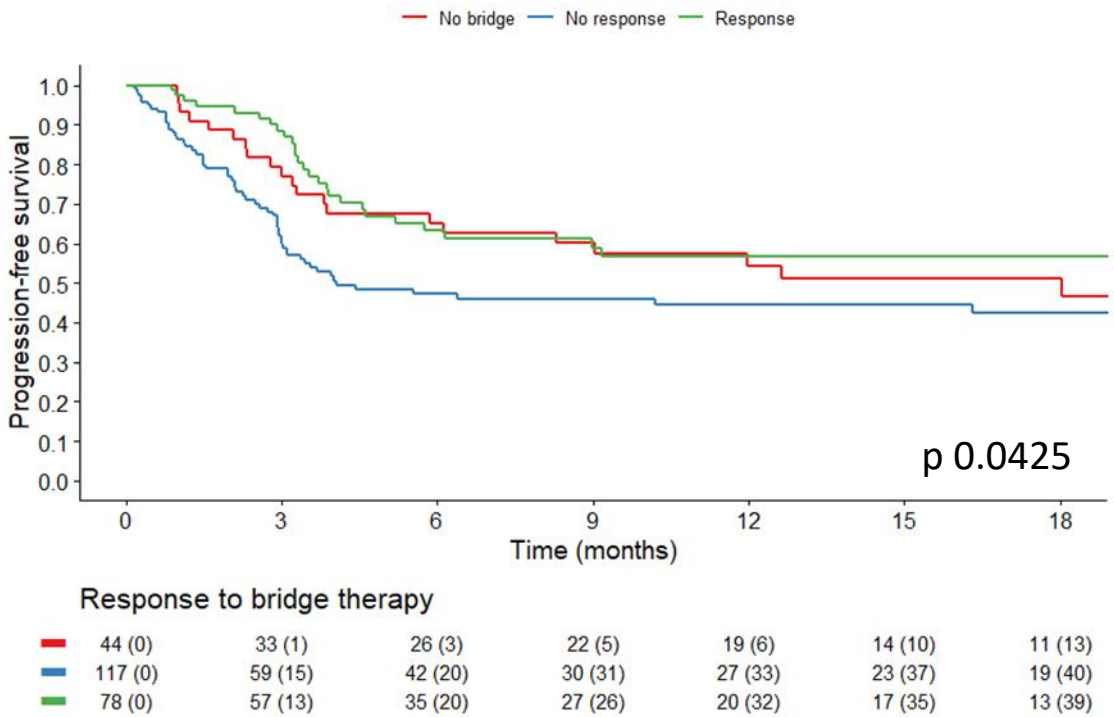
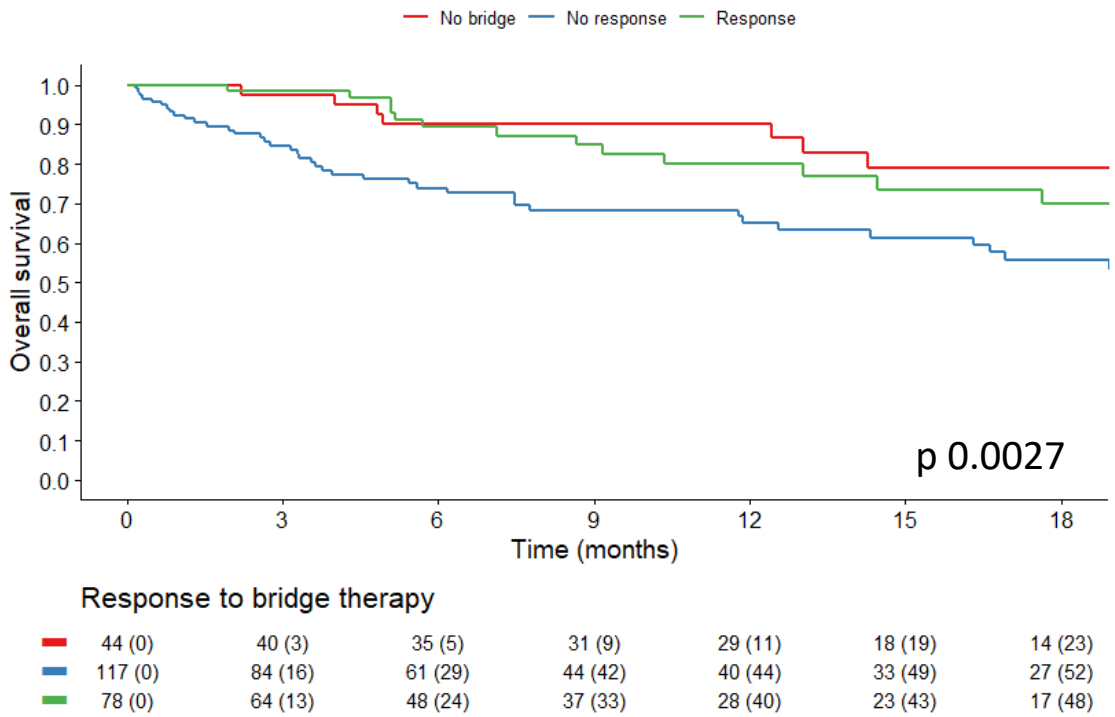
Leukemia 2024

Response to Bridging therapy

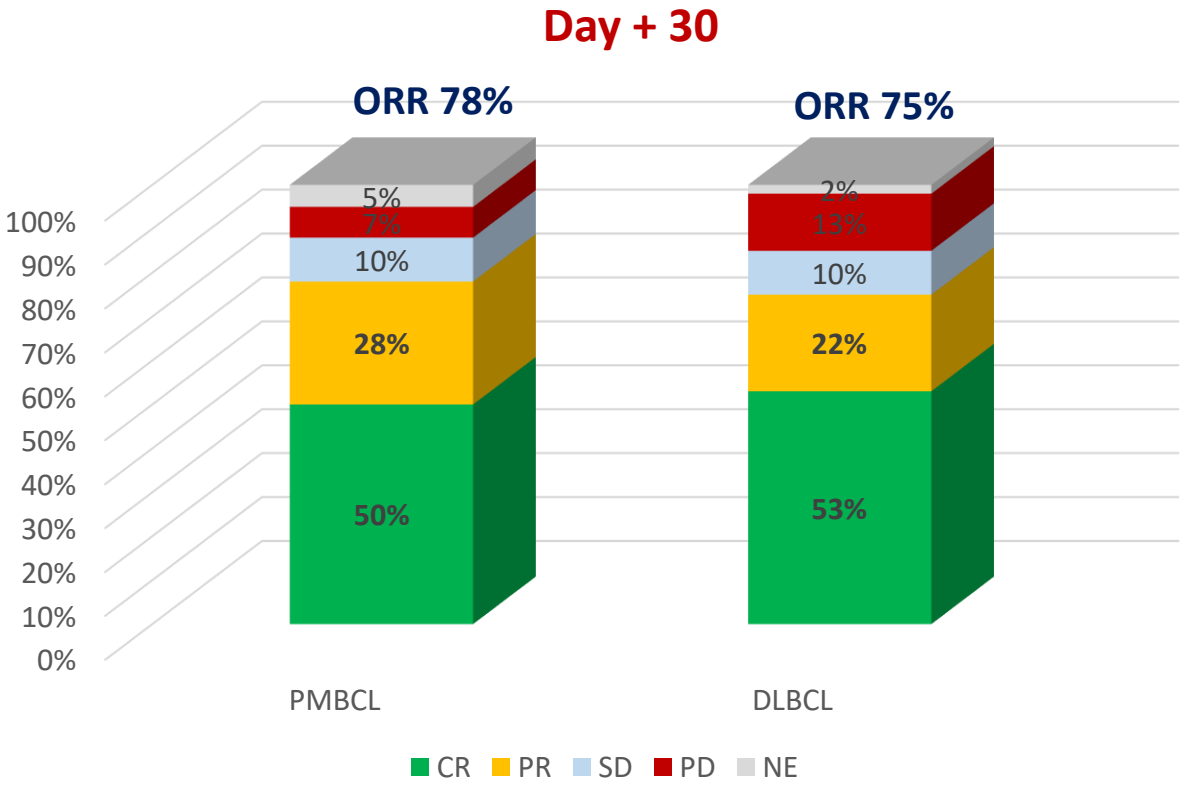
Response to bridging	PMBCL (n = 70)	DLBCL (n = 190)	p value
ORR/CR, n (%)	41%/17%	28%/6%	0.0102

Progression Free Survival (PFS) and Overall Survival (OS), by response to bridging therapy

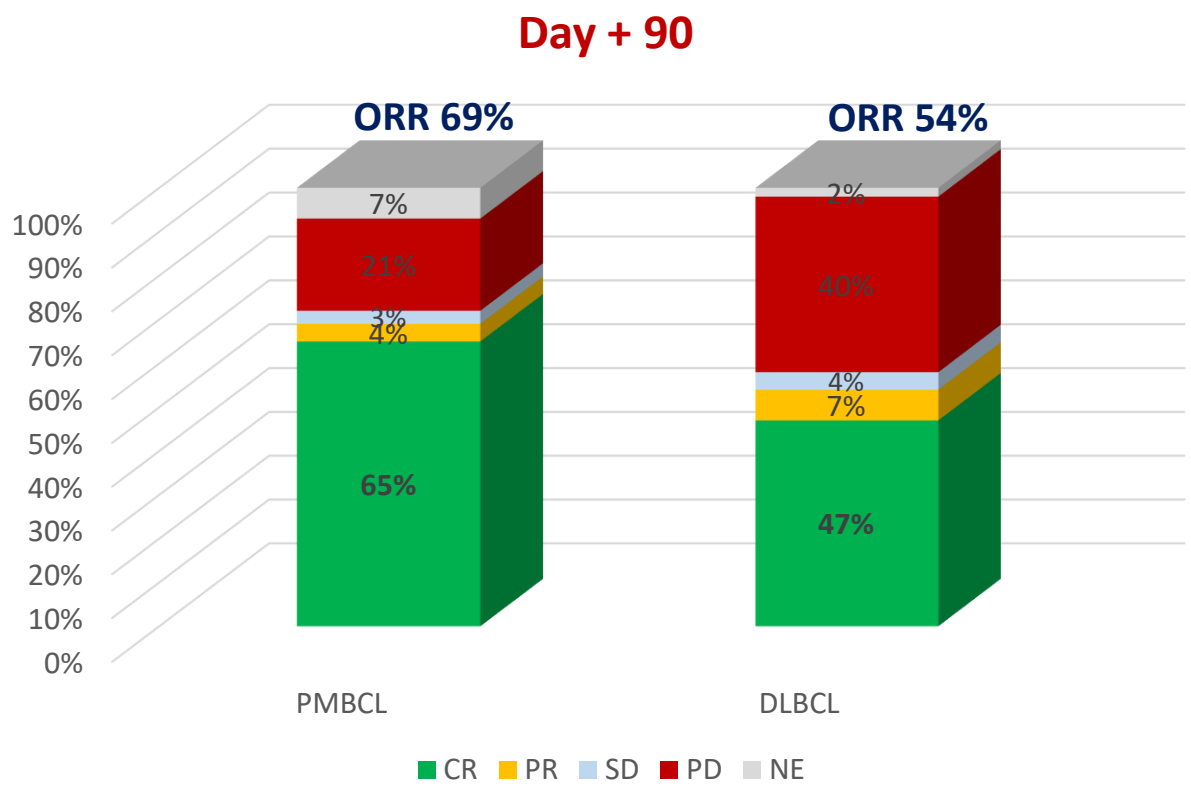




Response after CAR-T infusion, days +30 and +90



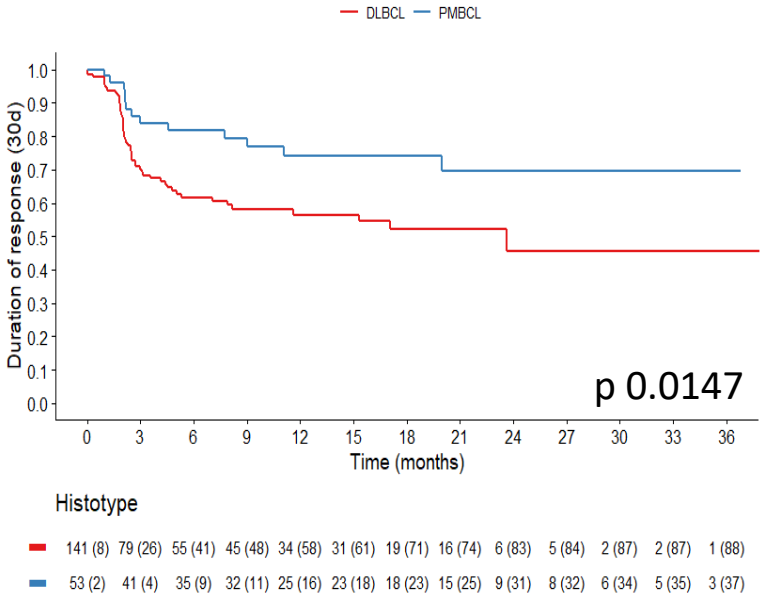
p 0.5457



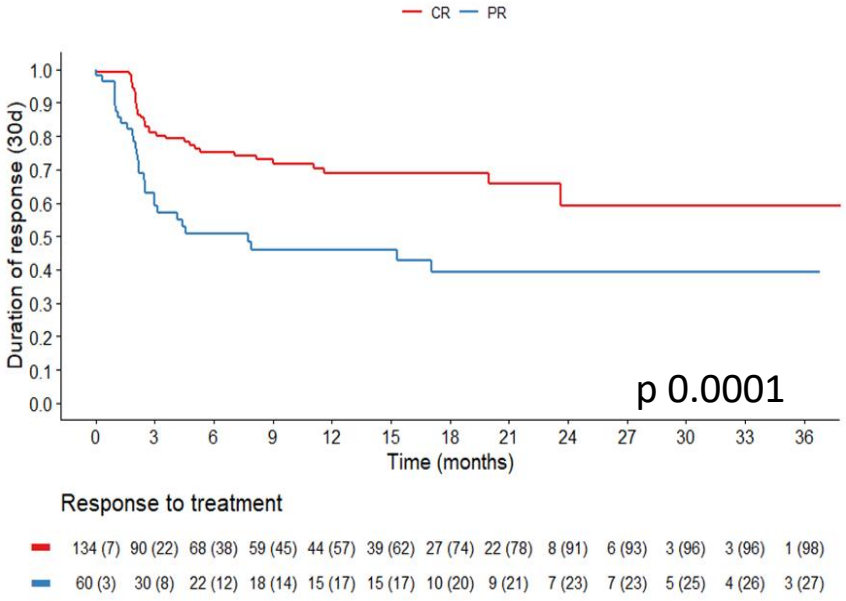
p 0.0336

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

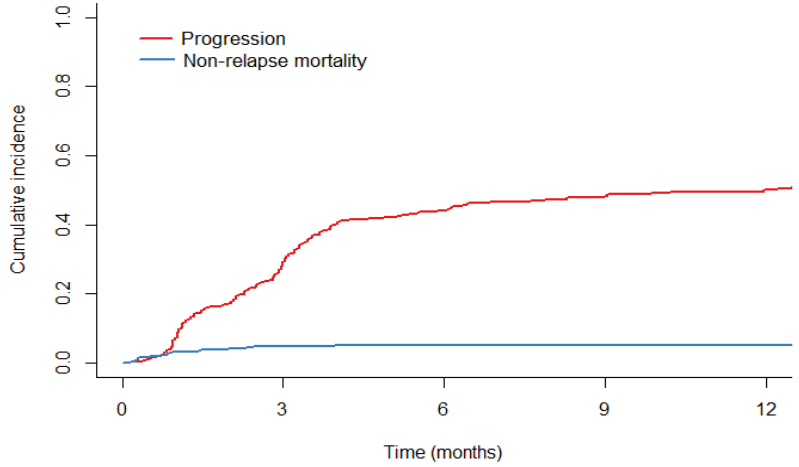
DoR: PMBCL vs DLBCL



DoR: CR vs PR (all)



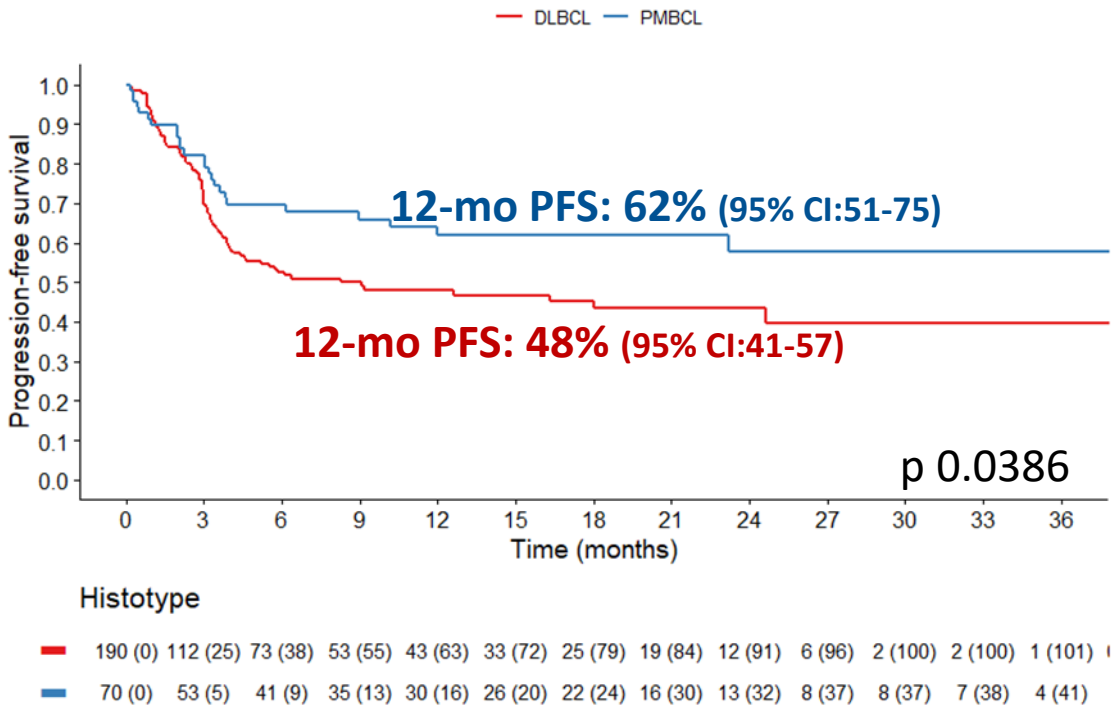
NRM at 12 months (all): 5.25% (95% CI: 3.52-7.83%)



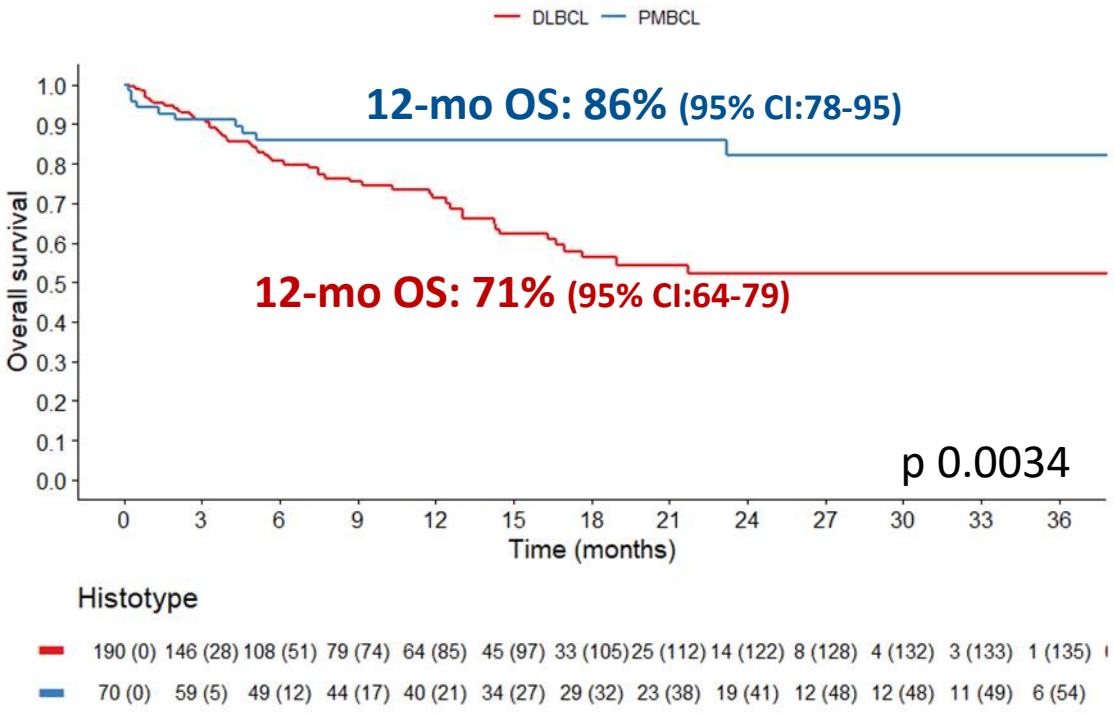
Progression-free and Overall Survival

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.

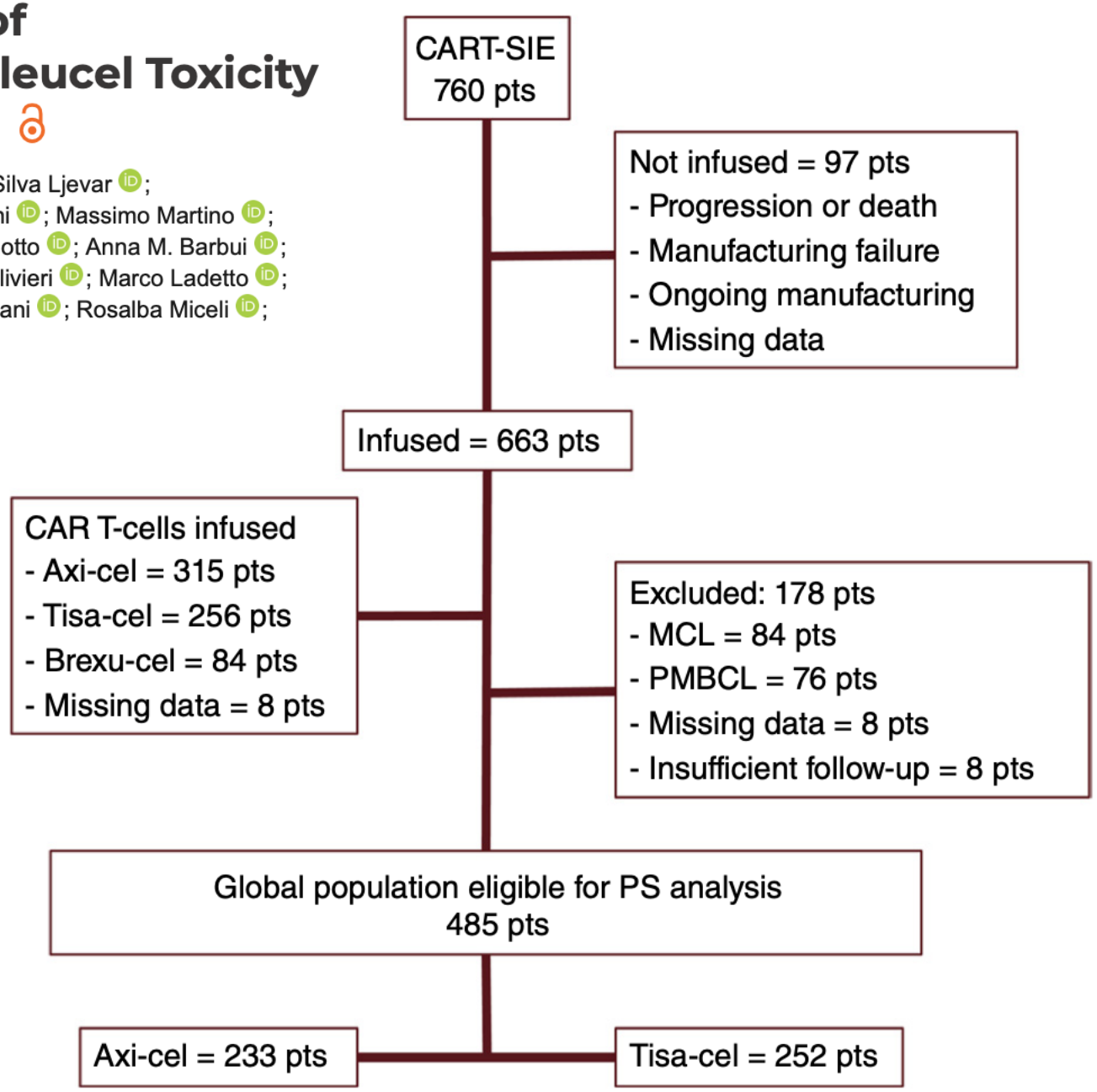
	PMBCL (N=70)	DLBCL (N=190)	p value
Anemia			**0.0236**
No	43%	27%	
Yes	57%	73%	
Grade 3-4	19%	23%	
Neutropenia			0.7242
No	17%	20%	
Yes	83%	80%	
Grade 3-4	74%	72%	
Thrombocytopenia			0.2532
No	44%	36%	
Yes	56%	64%	
Grade 3-4	23%	39%	
Febrile Neutropenia			0.0984
No	77%	66%	
Yes	23%	34%	
Grade 3-4	17%	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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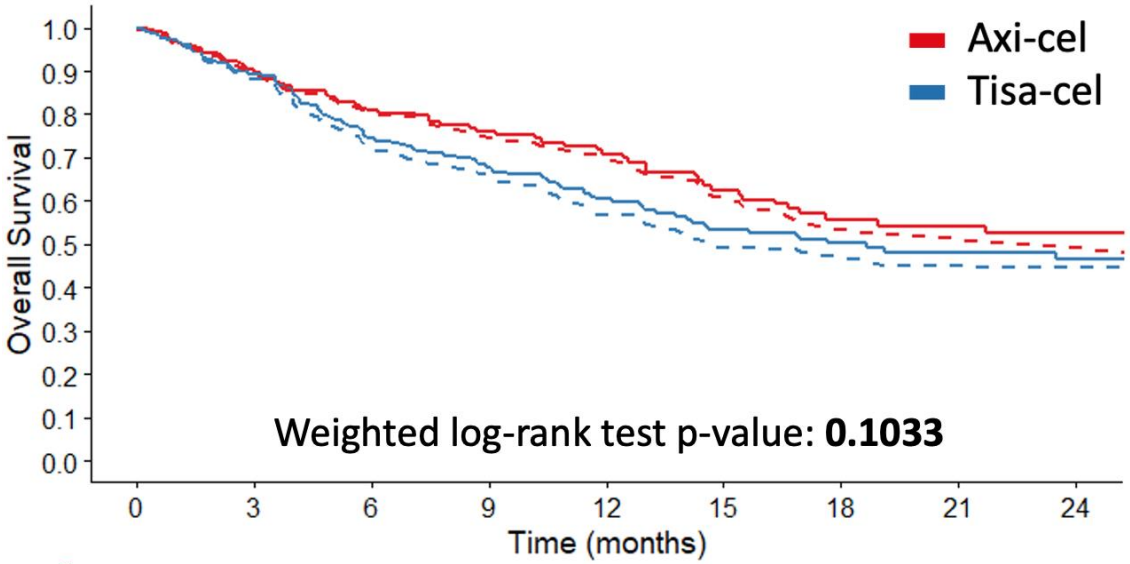
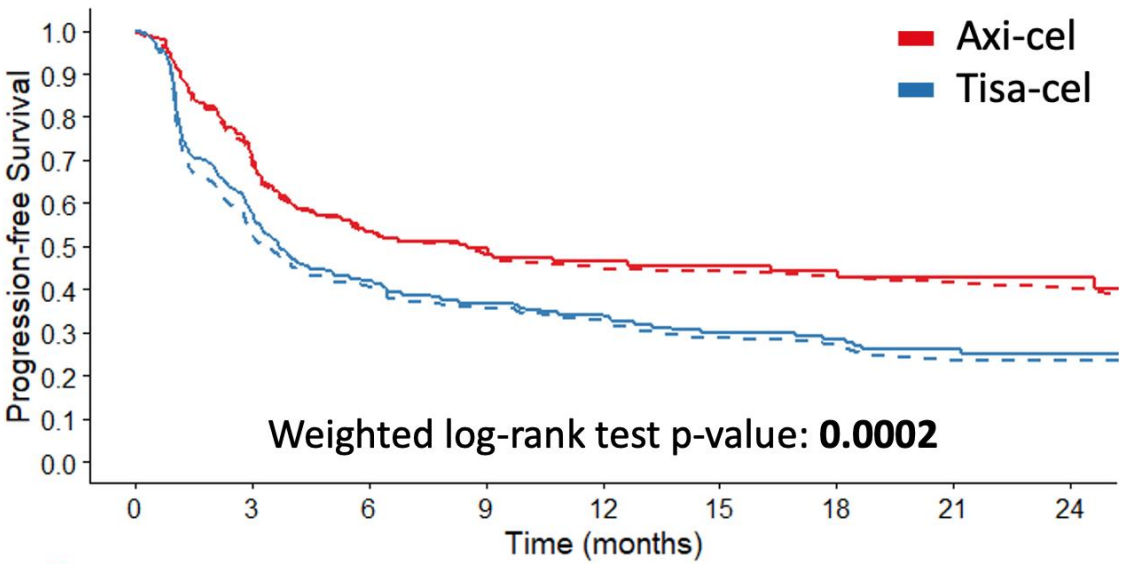
Overall Survival and Progression-Free Survival : Axi-cel vs Tisa-cel Propensity Score Analysis



A

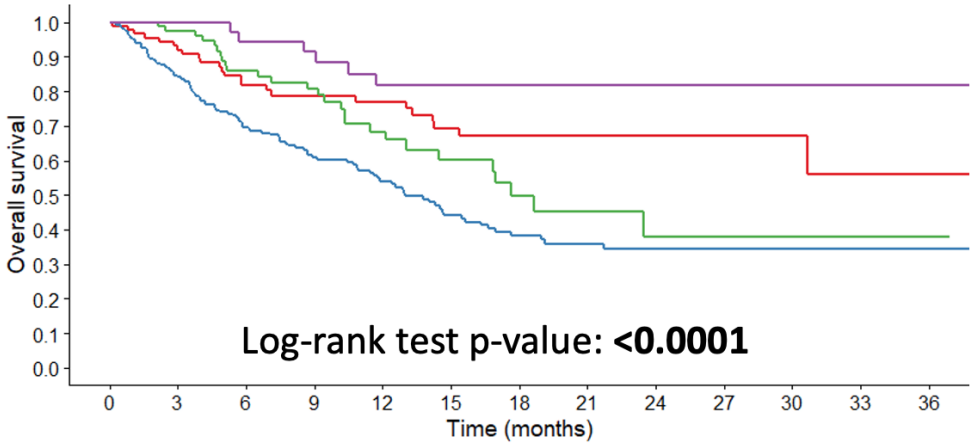
233 (0)	188 (22)	139 (55)	100 (87)	78 (103)	57 (116)	44 (123)	32 (134)	23 (142)
252 (0)	206 (20)	161 (32)	127 (53)	101 (66)	72 (85)	56 (97)	42 (109)	26 (124)



B

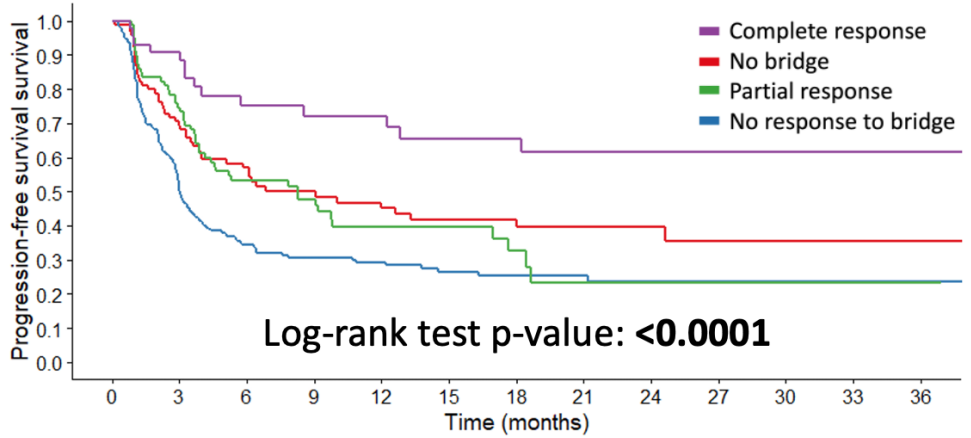
233 (0)	148 (18)	97 (37)	67 (61)	50 (74)	40 (83)	32 (90)	23 (98)	17 (104)
252 (0)	134 (14)	92 (21)	72 (30)	61 (36)	44 (46)	38 (50)	27 (58)	18 (66)

The role of bridging treatment



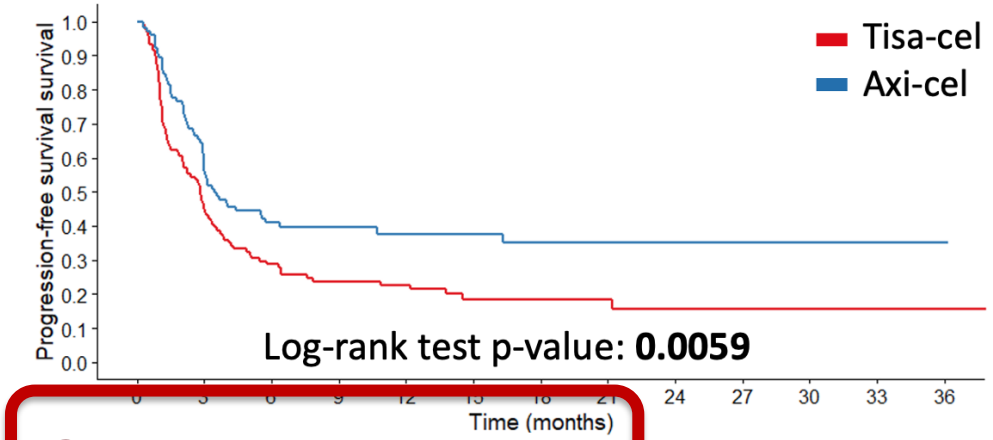
A Response to bridging therapy

	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)



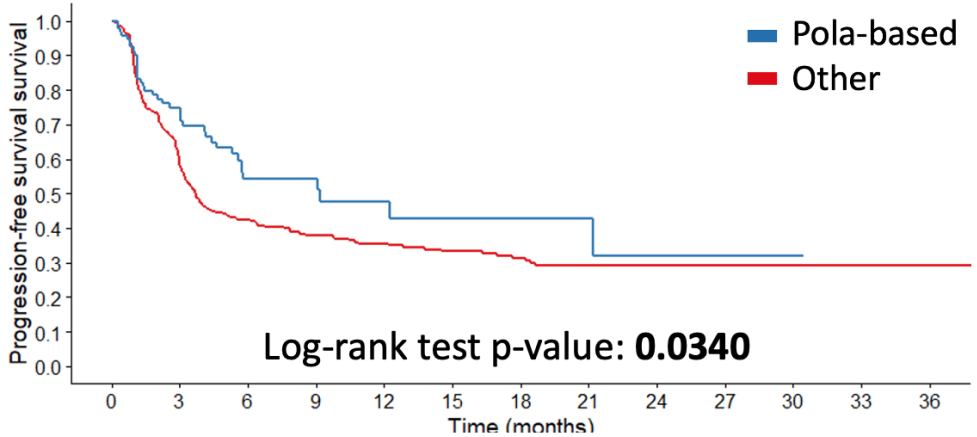
B Response to bridging therapy

	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

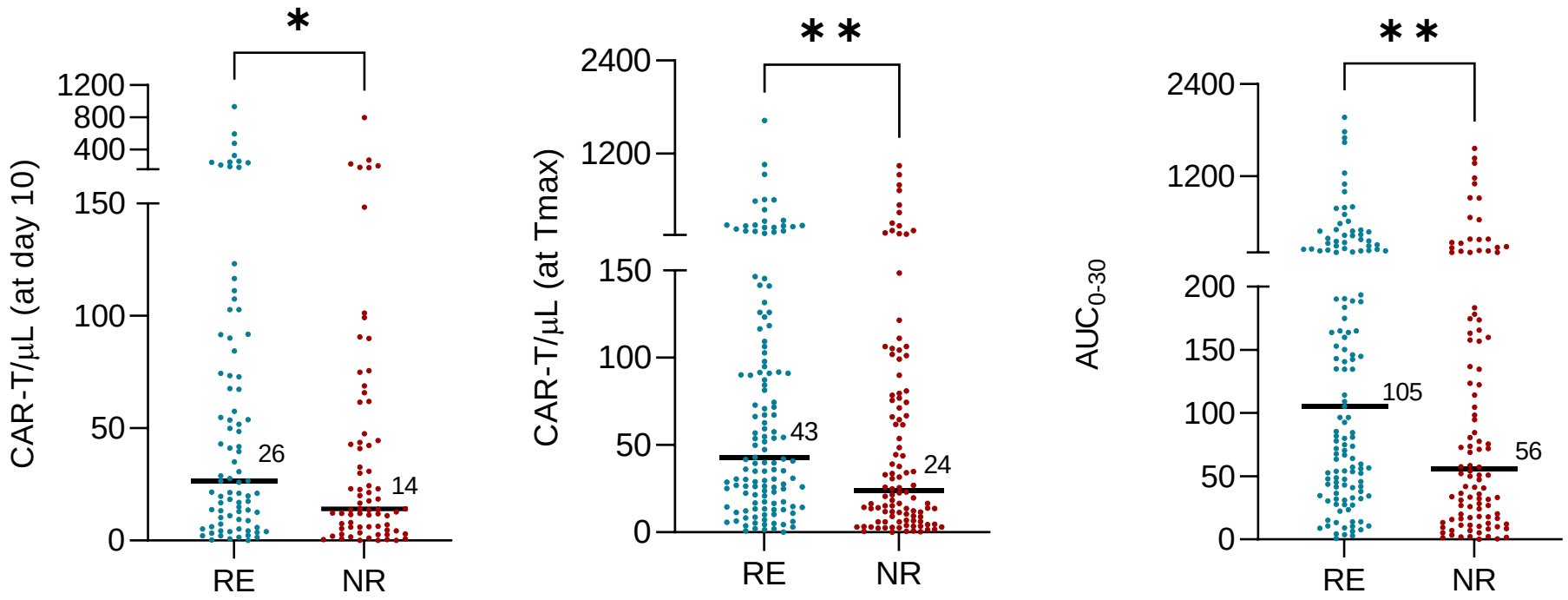
	119 (0)	51 (4)	32 (5)	22 (10)	19 (12)	11 (17)	10 (18)	7 (21)	4 (23)	3 (24)	2 (25)	2 (25)	1 (26)
	106 (0)	54 (8)	35 (13)	24 (23)	17 (29)	15 (31)	12 (33)	8 (37)	5 (40)	3 (42)	2 (43)	2 (43)	1 (44)



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)

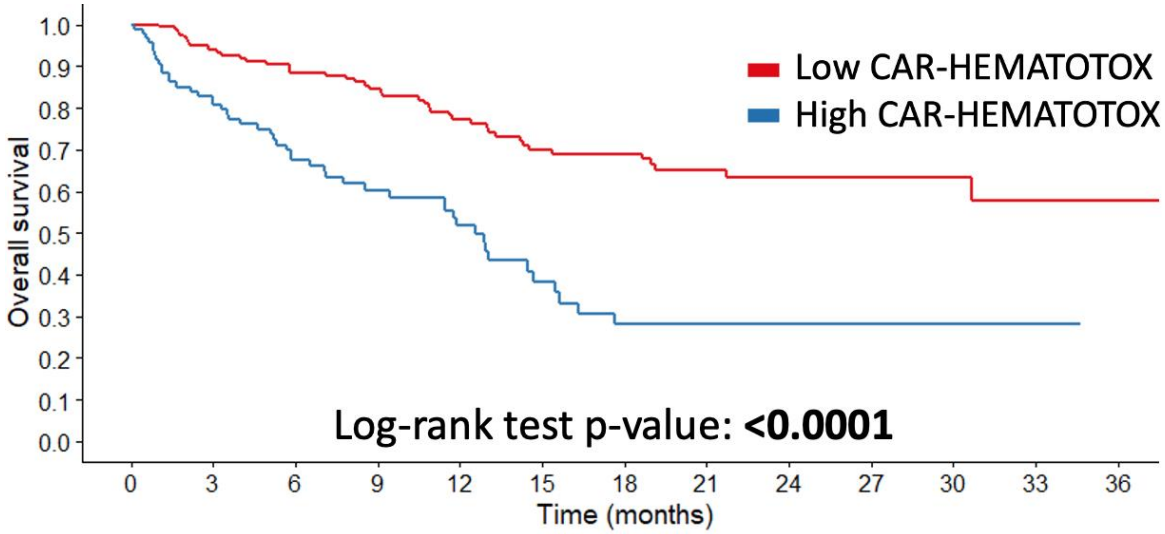
CAR T *in vivo* expansion in LBCL is associated with response at day 90 (262 pts)



Magni M et al, ASH2024 do not post

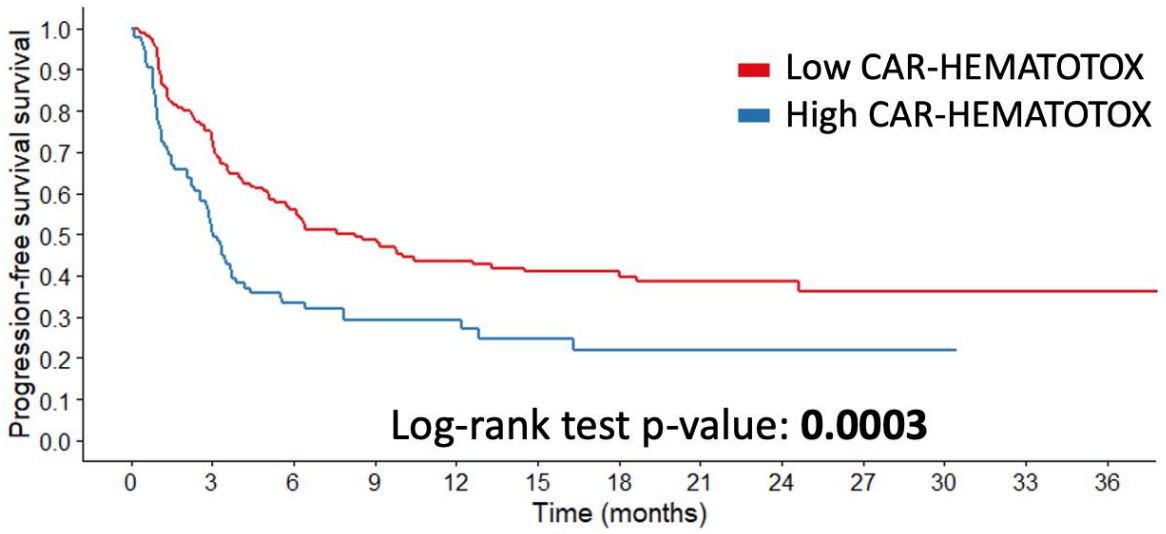
CAR – HEMATOTOX score in LBCL

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)	

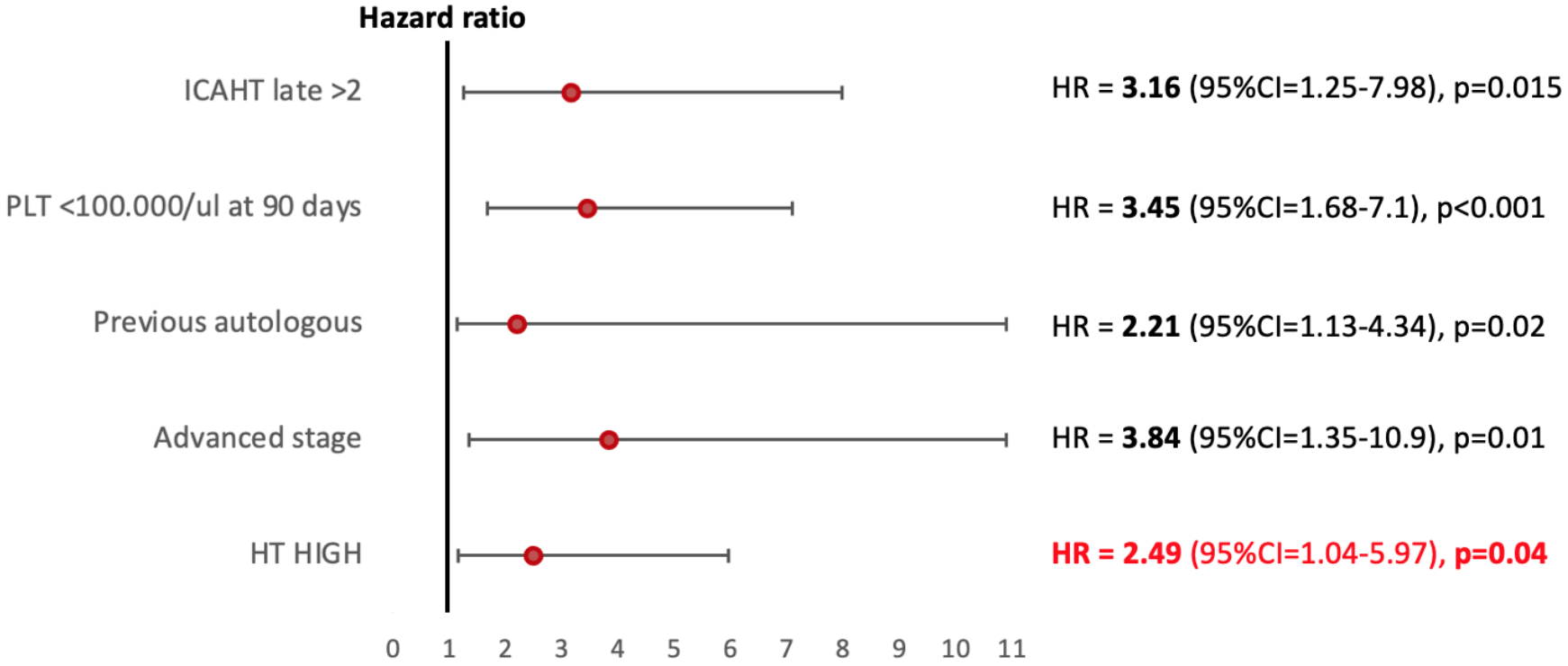
Stella F et al, submitted

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

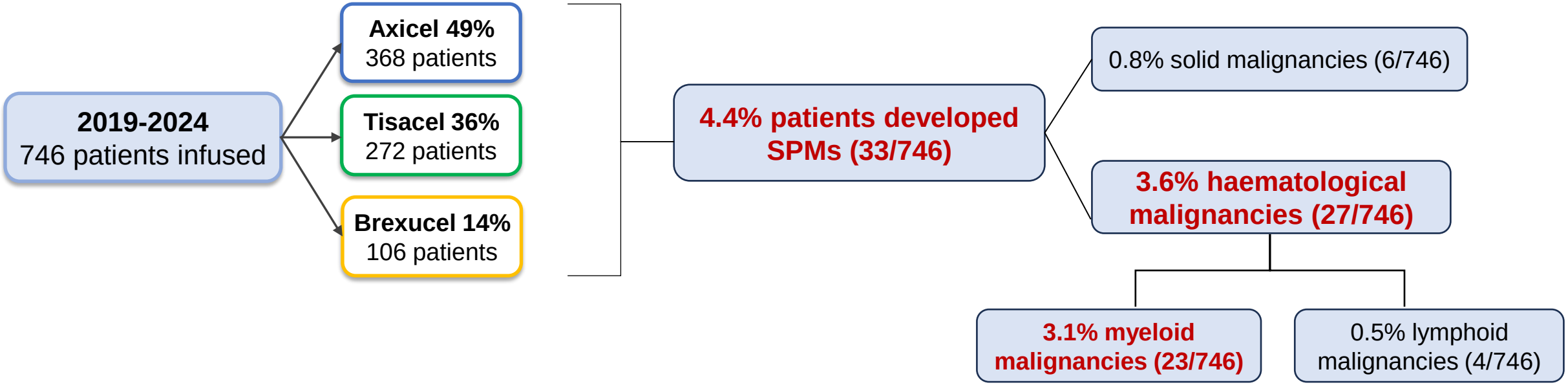
Haematological Malignancy – Clinical

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

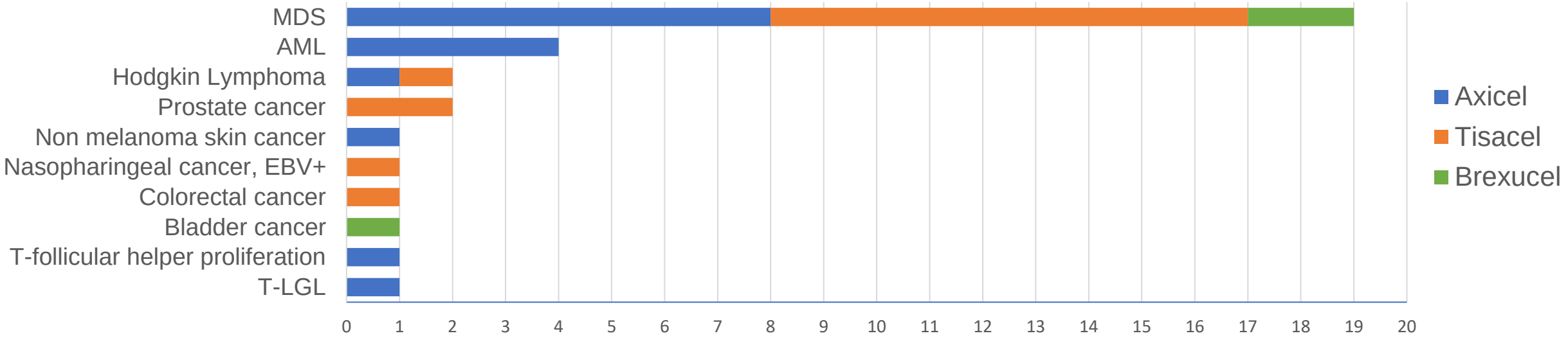
Angelica Barone[1] | Annalisa Chiappella[2] | Beatrice Casadei[3] | Stefania Bramanti[4] | Silva Ljevar[5] | Patrizia Chiusolo[6] | Alice Di Rocco[7] | Maria Chiara Tisi[8] | Anna Maria Barbui[9] | Mirko Farina[10] | Lucia Brunello[11] | Maria Chiara Di Chio[2] | Mattia Novo[12] | Maurizio Musso[13] | Jacopo Olivieri[14] | Gentiana Elena Trotta[15,2] | Anna Dodero[2] | Antonella Aiello[16] | Paolo Corradini[1,2]



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)

Journal of Clinical Oncology®
Original Reports | Hematologic Malignancy

2024 Aug 2:JCO2302786.
doi: 10.1200/JCO.23.02786. Online ahead of print.

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

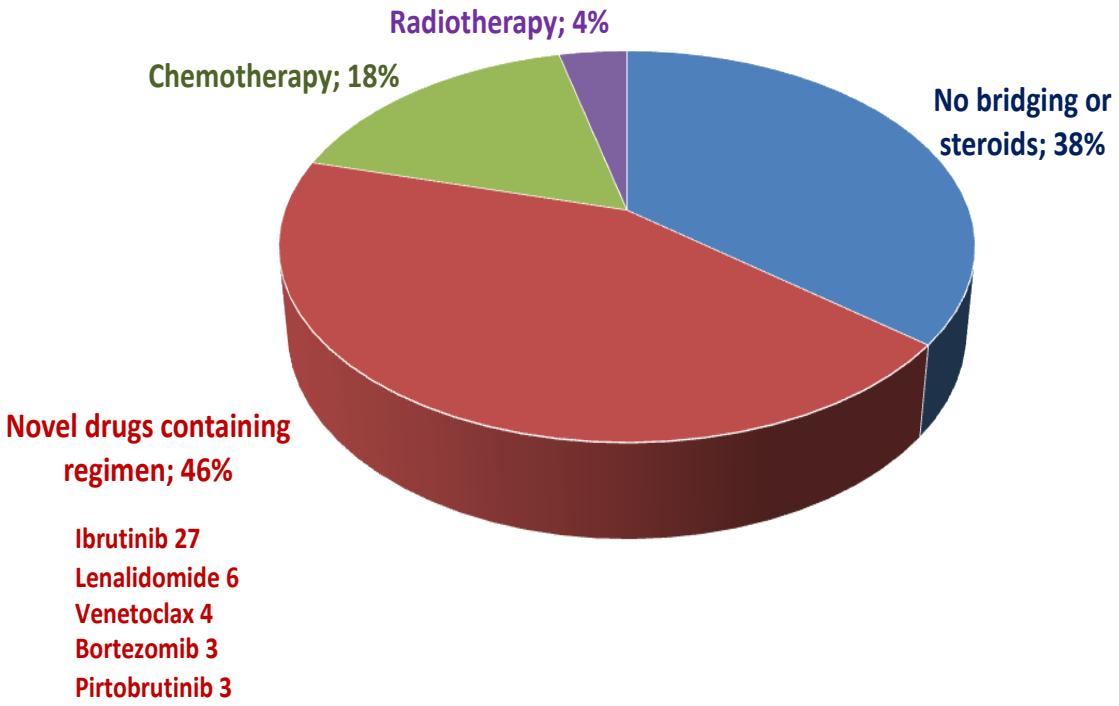
Among axi-cel–infused patients, PFS at 5 years was 29% and OS at 5 years was 40%. The 5-year lymphoma-specific survival was 53% with infrequent late relapses. However, **the 5-year NRM was 16.2%, with over half of NRM events occurring beyond 2 years**. Patients who were 60 years and older had a lower 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

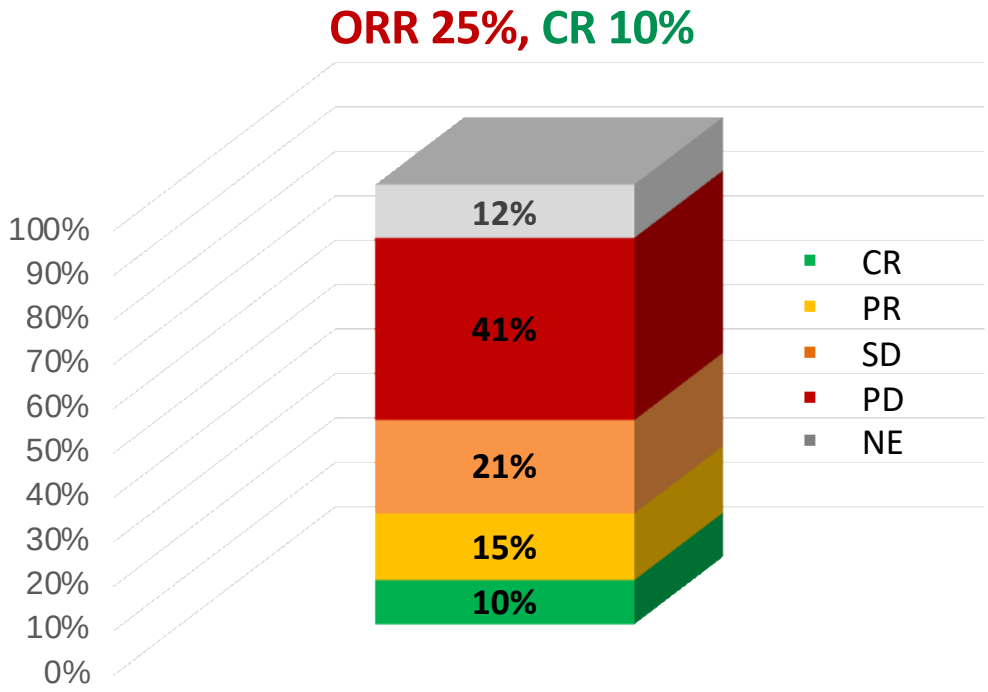
	% (N=106)		% (N)
Median age	63 (IQR 55; 69)	**N prior therapies (median)**	3 (range 2-5)
Histology - Classic MCL - Blastoid MCL - Pleomorphic MCL	 70% (74) 19% (20) 11% (12)	**Previous BTKi** - BTKi relapsed - BTKi primary refractory - Missing	100% 51% (54) 28% (29) 21% (23)
Stage III/IV	91% (96)	**Previous 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)

Stella F et al, unpublished data do not post

Bridging therapy



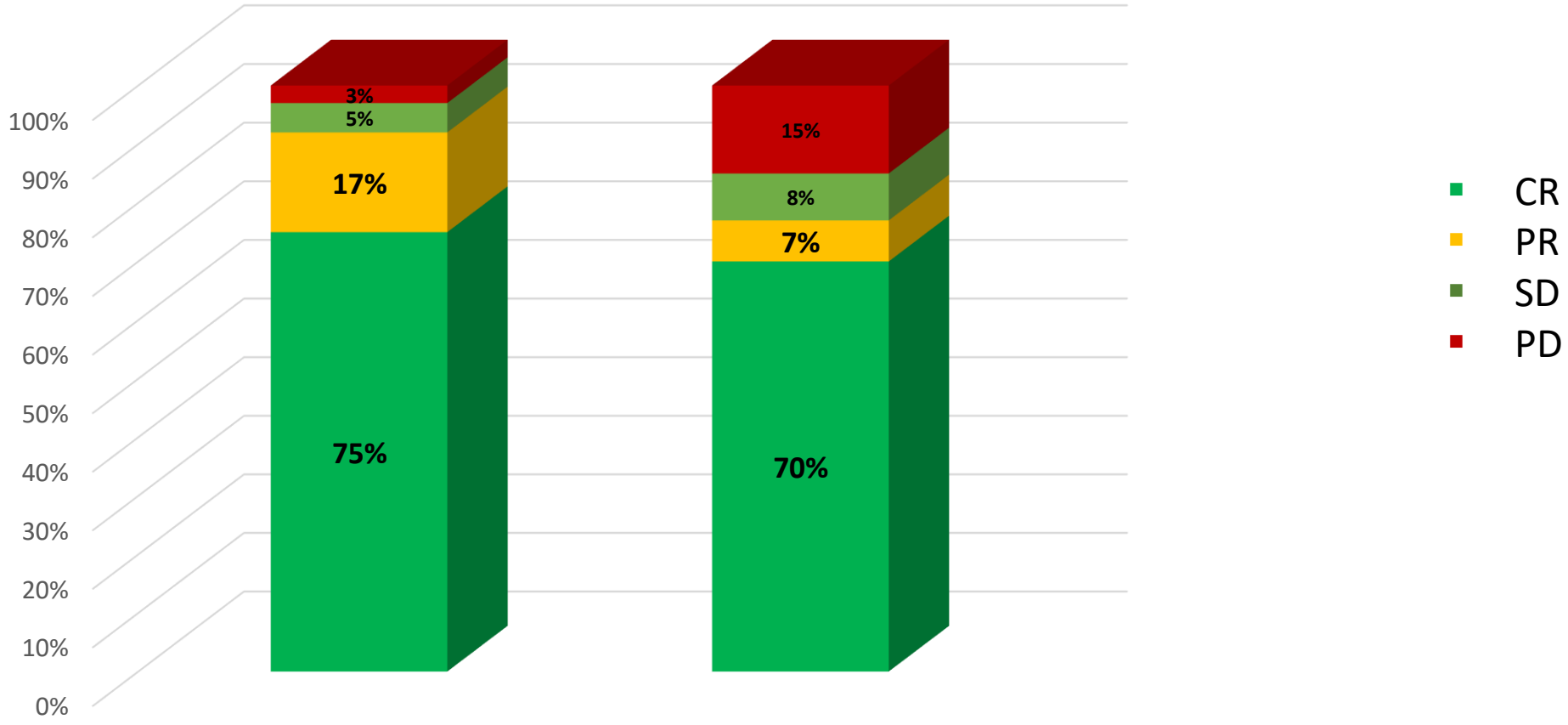
Response to bridging



Response after CAR-T infusion

Day + 30:
ORR 92%, CR 75%

Day + 90:
ORR 77%, CR 70%



Stella F et al, unpublished data do not post

Safety

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

Tocilizumab: 84%; Steroids: 54%

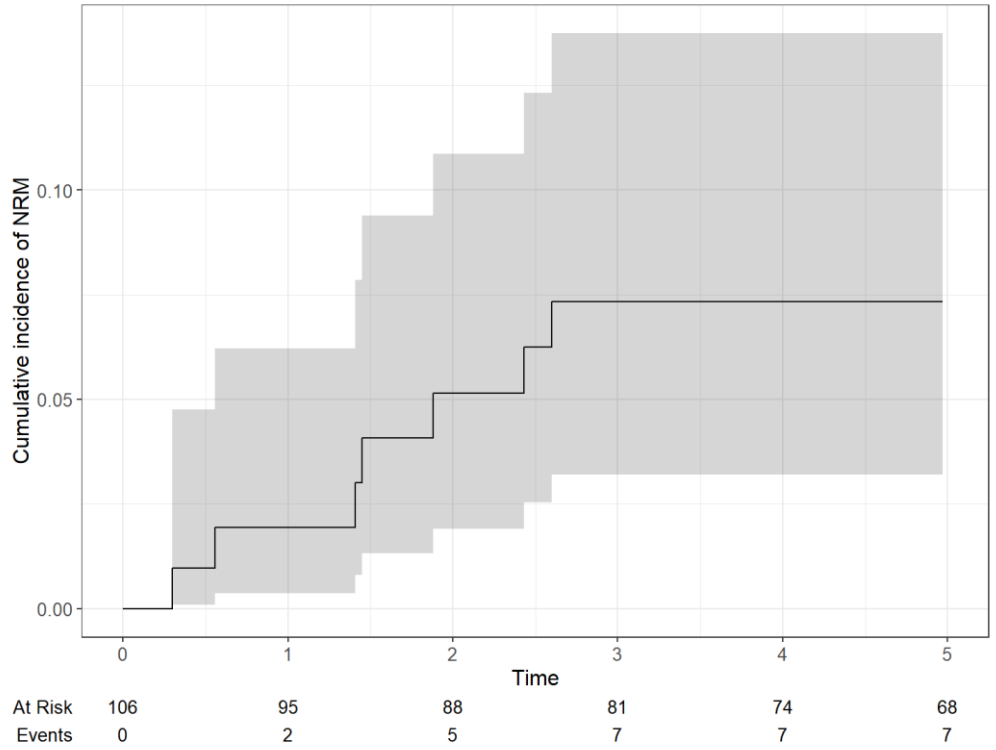
ICU admission: 18%

NRM: 7 patients

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

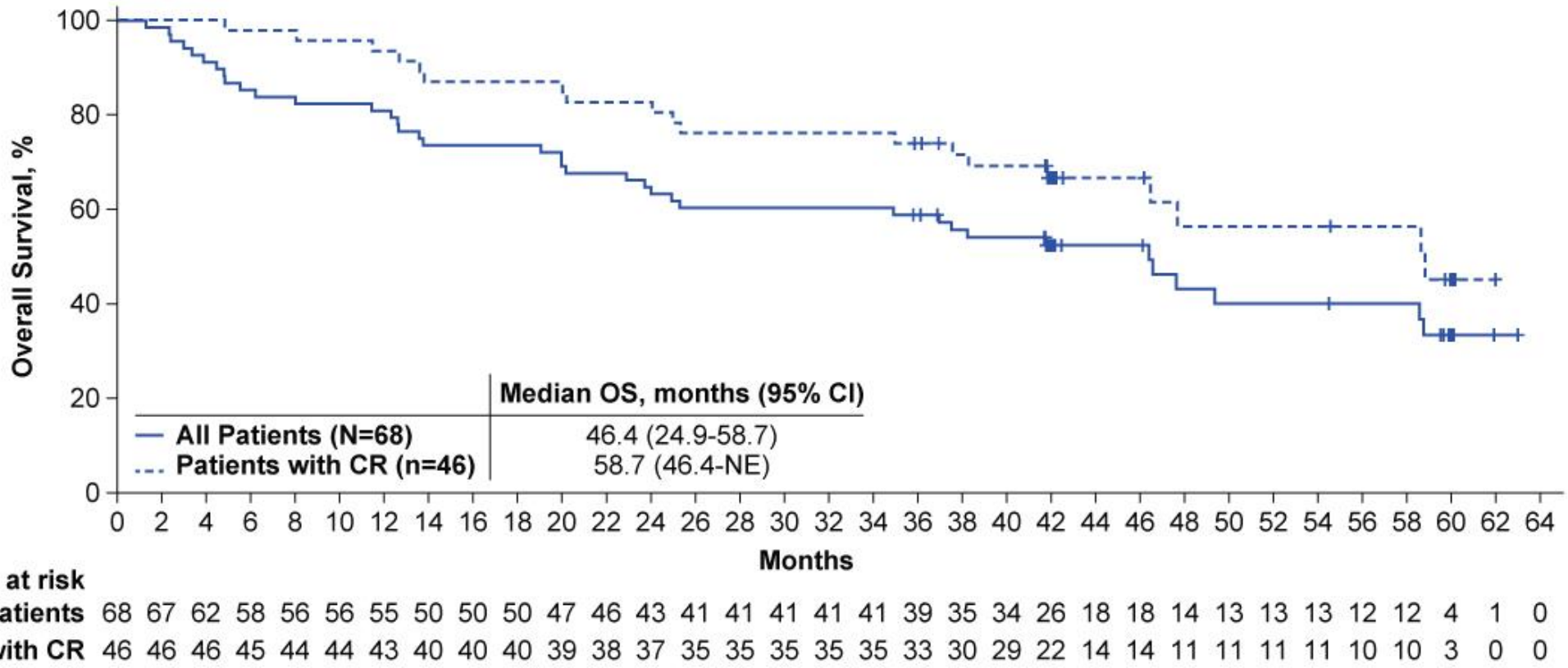
Non relapse mortality (NRM)

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



Stella F et al, unpublished data do not post

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



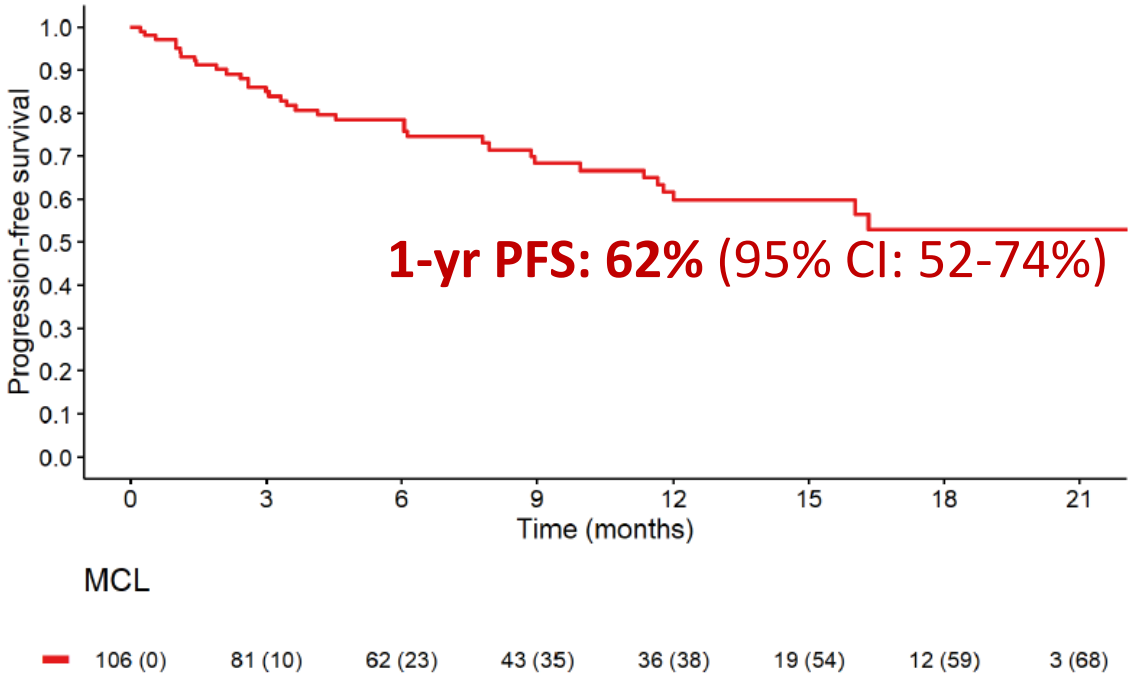
- As of July 23, 2022, median follow-up in ZUMA-2 was 47.5 months (N=68; range, 37.9-68.3)
- Median OS in ZUMA-2 was 58.7 months for patients with a CR (n=46)
- After almost 4 years of median follow-up, 30 patients (45%) were still alive, 27 of which had achieved a CR

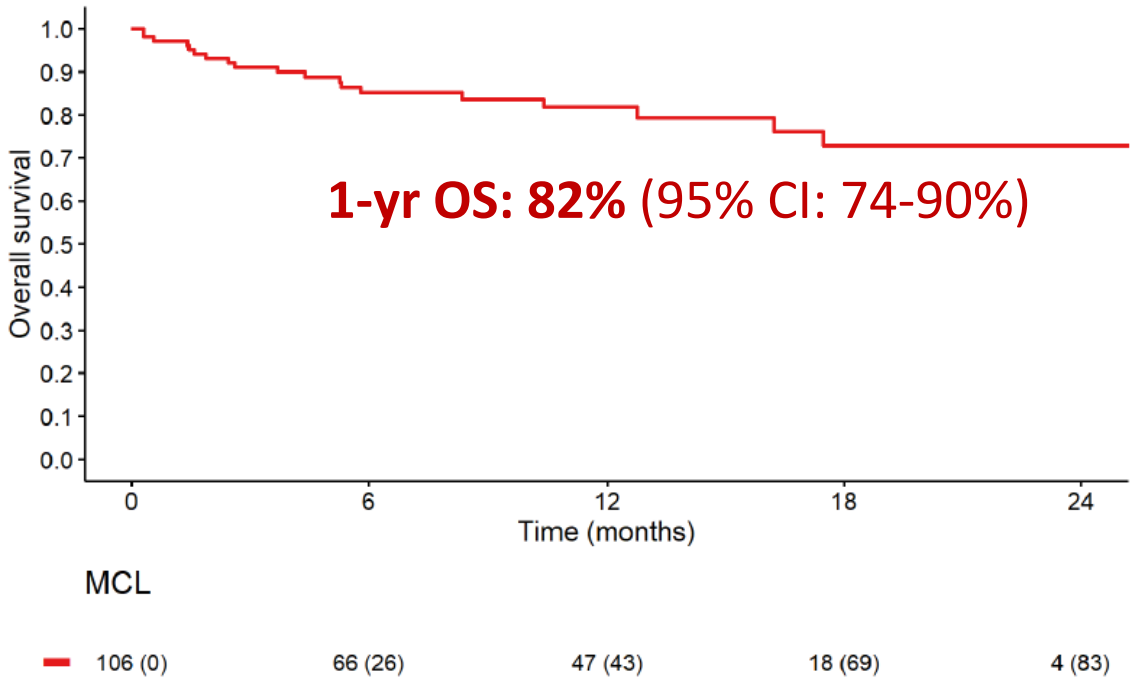
CR, complete response; mo, month; NE, not estimable; NR, no response; PR, partial response.

Goy et al, ASH 2023

Progression-free Survival and Overall Survival

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

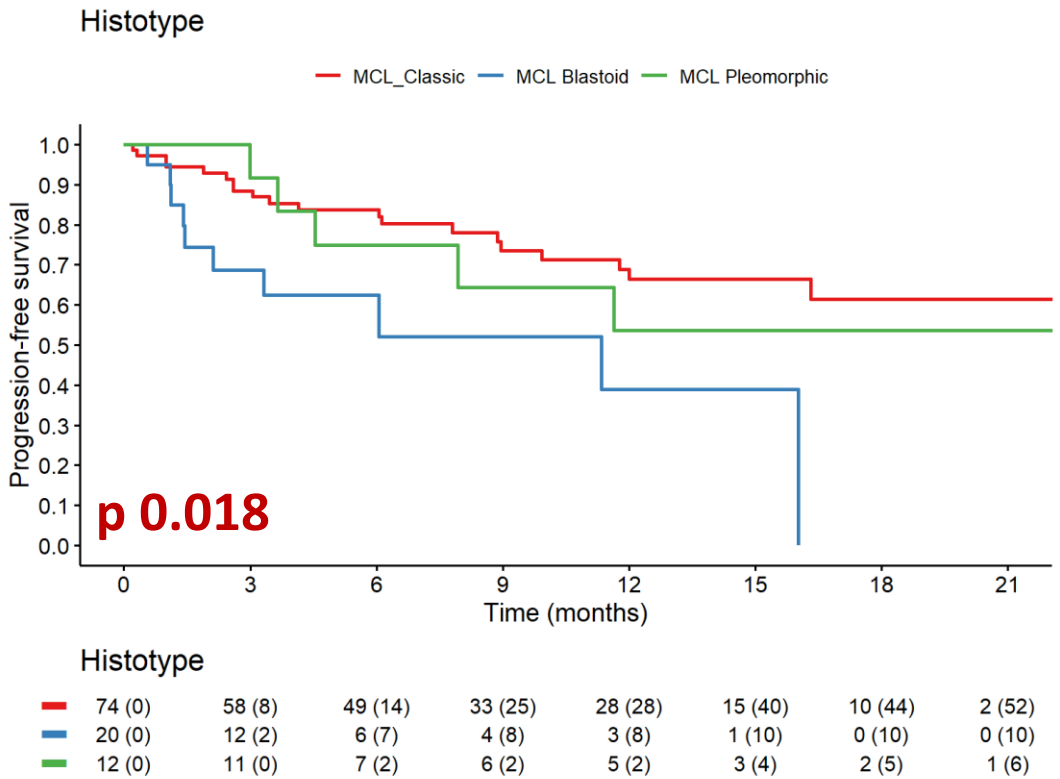


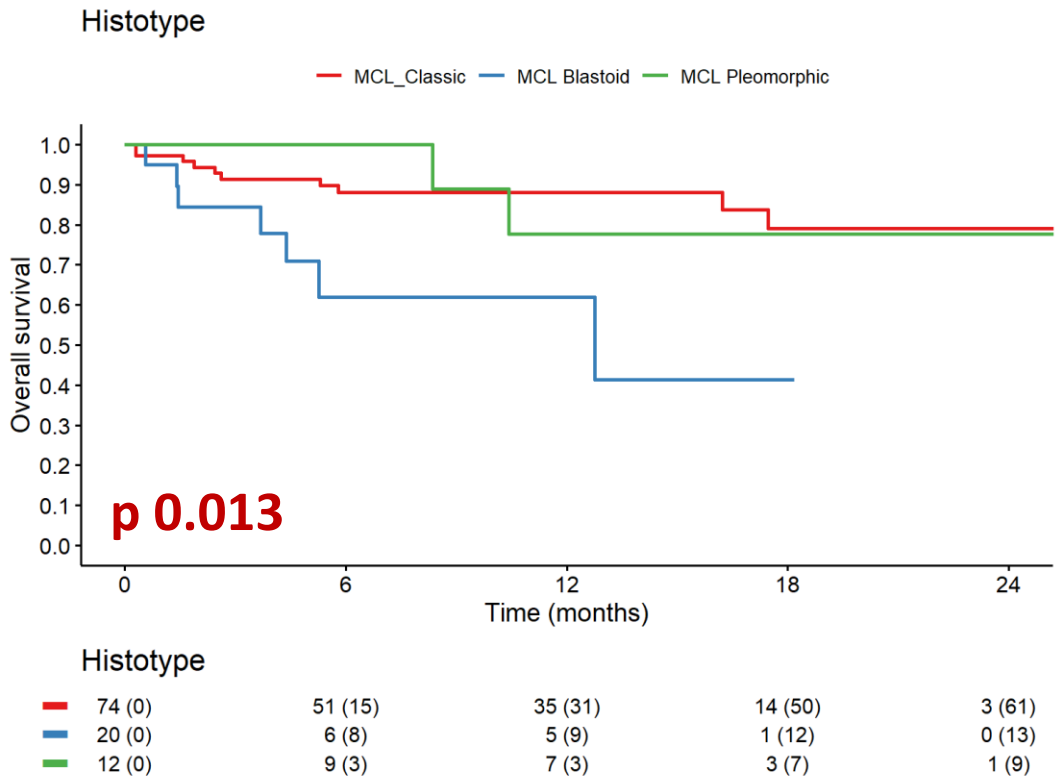


Stella F et al, unpublished data do not post

Progression-free Survival and Overall Survival, by histotype

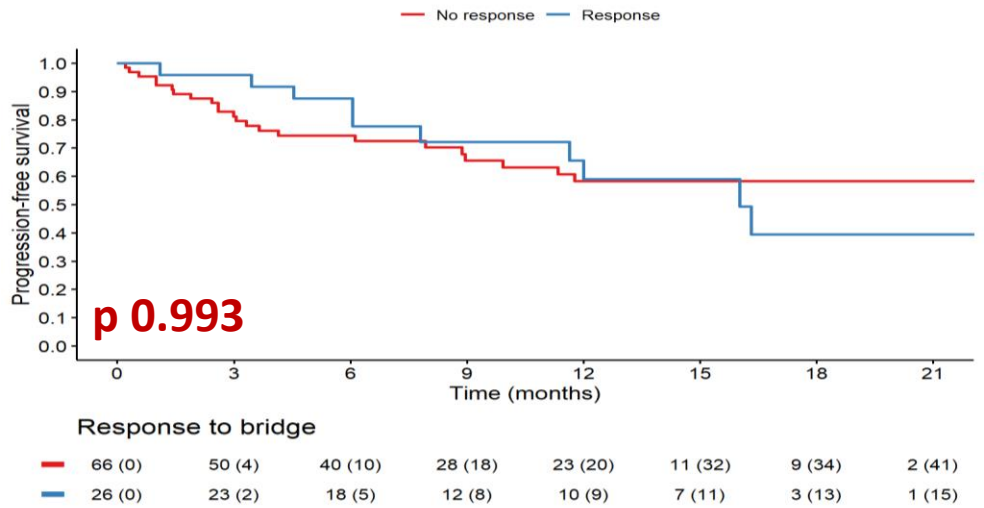
Median follow-up: 12.07 months (IQR: 5.95, 17.86)

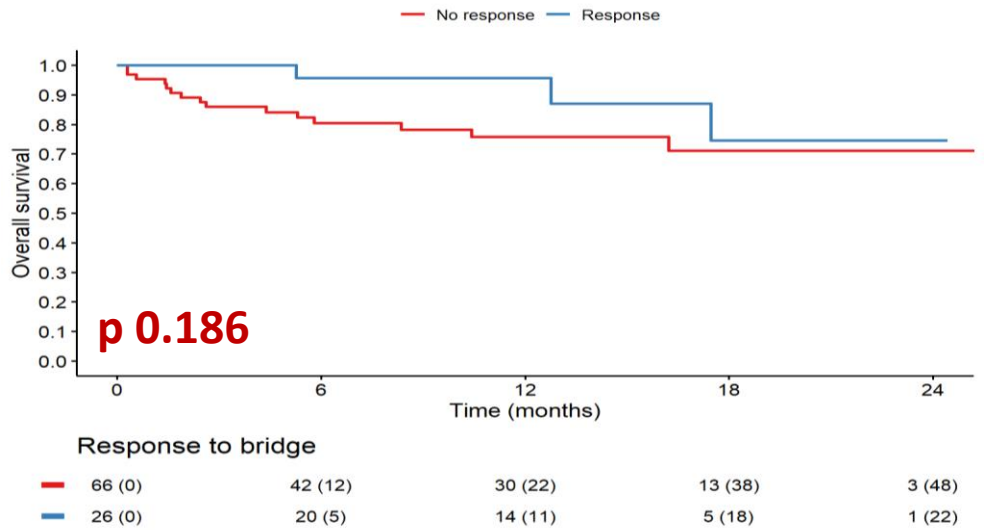




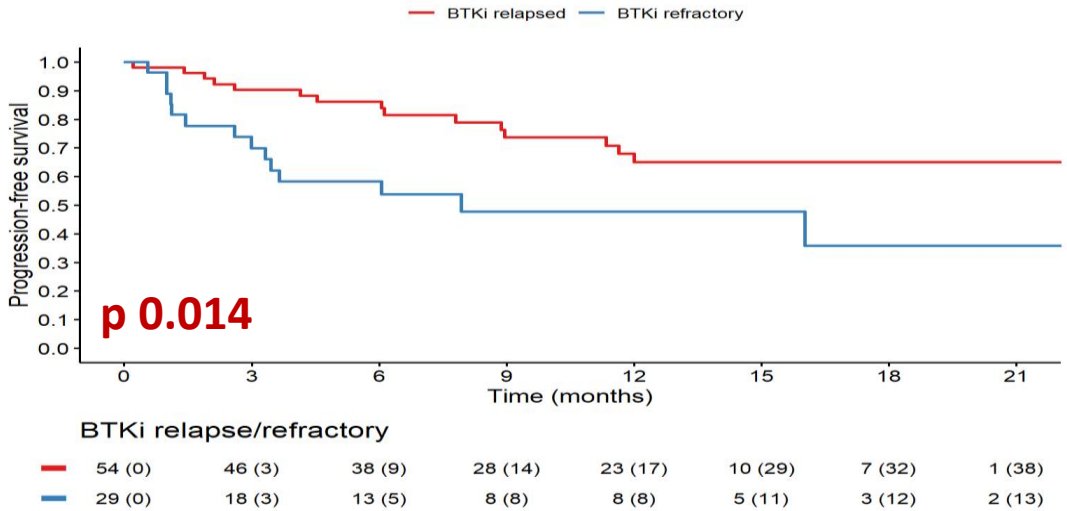
Stella F et al, unpublished data do not post

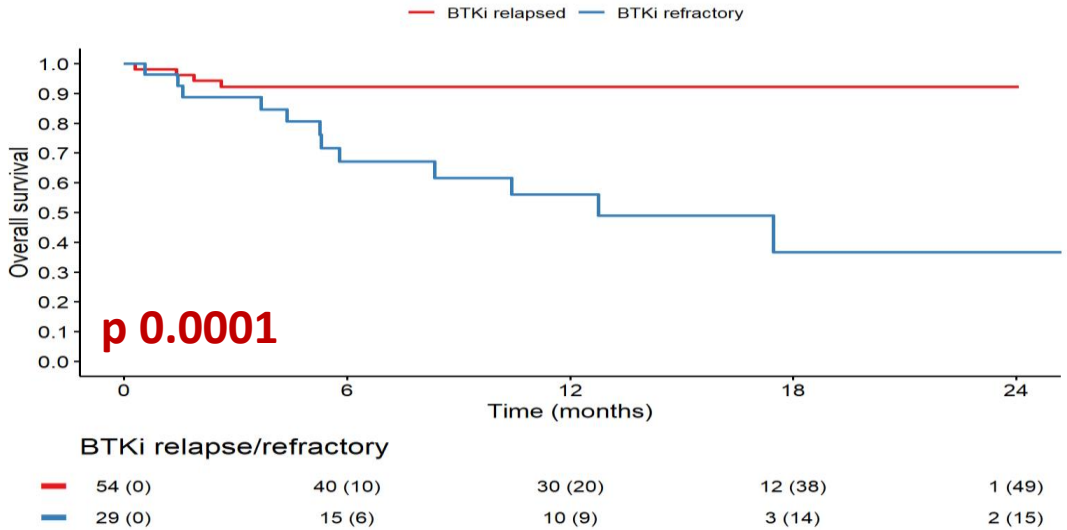
PFS and OS, by response to bridging





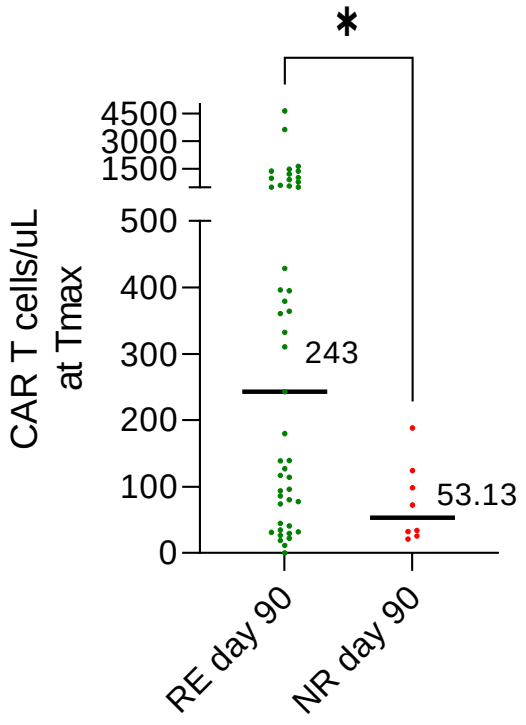
PFS and OS, by iBTK refractoriness

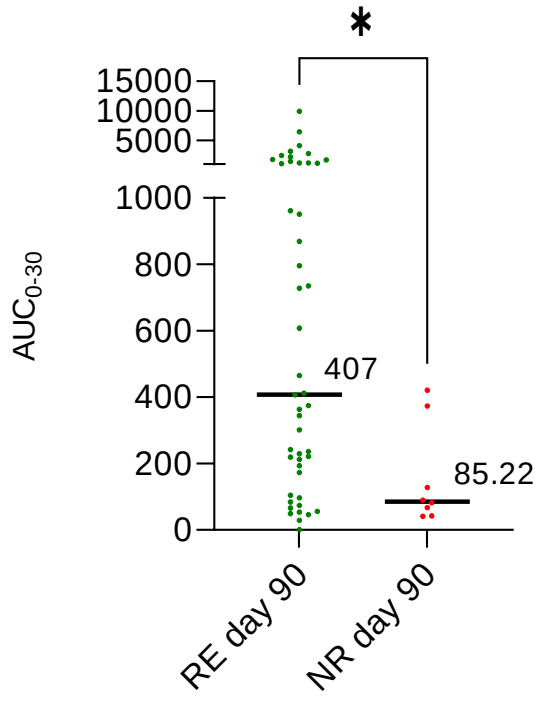


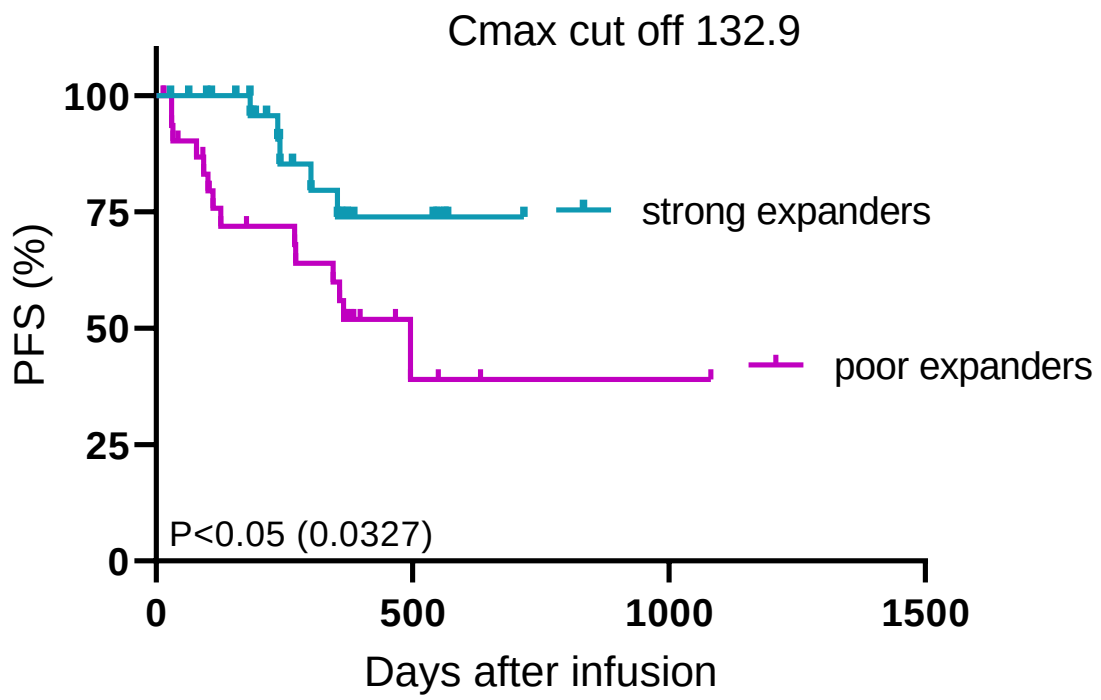


Stella F et al, unpublished data do not post

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





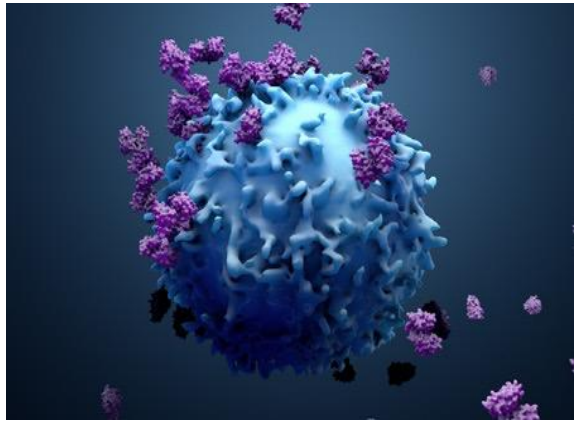


Stella F et al, unpublished data do not post

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

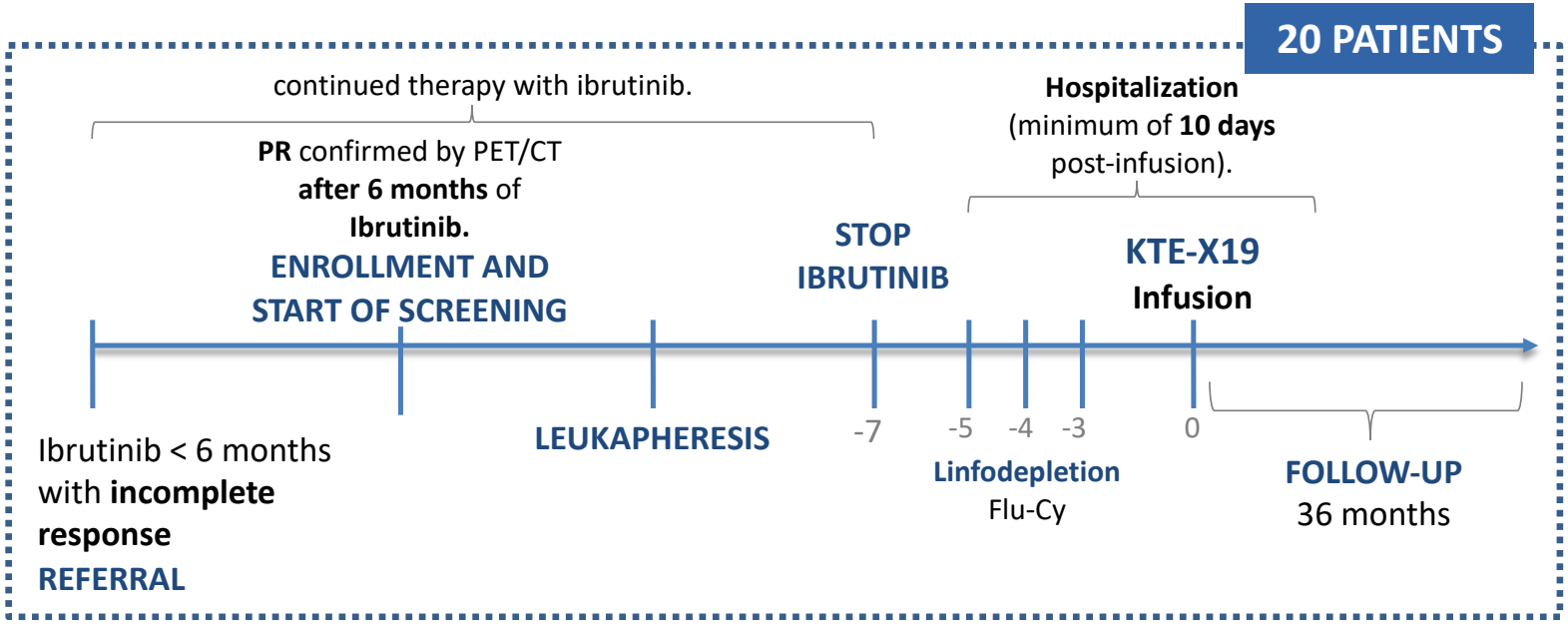
STUDIO DI FASE II PER VALUTARE L'EFFICACIA DELLA TERAPIA A CELLULE CAR-T CON KTE-X19 IN PAZIENTI CON LINFOMA MANTELLARE RECIDIVATO/REFRATTARIO CON OTTENUTA REMISSIONE PARZIALE IN CORSO DI TERAPIA DI SALVATAGGIO CON IBRUTINIB

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



Aknowledgments

Dept. of Hematology
Paolo Corradini
Annalisa Chiappella
Anna Dodero
Anna Guidetti
Martina Pennisi
Federico Stella
Angelica Barone

University of Bologna
Francesca Bonifazi

Pierluigi Zinzani

Lab and Pathology
Cristiana Carniti
Martina Magni
Nicole Caldarelli
Giada Zanirato
Sadhana Jonnalagadda
Federica Fuzio
Elena Irrigati
Daniele Lorenzini
Luca Agnelli

Research support and Statistics
Anisa Bermema
Elvira Pantano
Silva Lejvar
Rosalba Miceli

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

FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI

UNIVERSITÀ DEGLI STUDI DI MILANO

AIL ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Ministero della Salute

ALLEANZA CONTRO IL CANCRO

Exploring lymphoma related factors: Are lymphocyte count and fitness, monocyte count (leukoapheresis) important for expansion and outcome ?

REGULAR ARTICLE

blood advances

Monocytes in leukapheresis products affect the outcome of CD19–targeted CAR T-cell therapy in patients with lymphoma

Cristiana Carniti,[1,*] Nicole M. Caldarelli,[1,2,*] Luca Agnelli,[3,4] Tommaso Torelli,[3,4] Silva Ljevar,[5] Sadhana Jonnalagadda,[1] Giada Zanirato,[1] Eugenio Fardella,[1,2] Federico Stella,[1,2] Daniele Lorenzini,[3] Silvia Brich,[3] Flavio Arienti,[6] Anna Dodero,[1] Annalisa Chiappella,[1] Martina Magni,[1,†] and Paolo Corradini[1,2,†]

23 APRIL 2024 • VOLUME 8, NUMBER 8

1. A 4-gene signature in LK segregates pts with different progression free survival
2. The gene signature is the result of monocyte–T cell complexes present in leukapheresis products
3. High circulating AMC and the monocyte signature identifies an increased proportion of patients at high risk of progression