CAR-T e Linfoma Diffuso a Grandi Cellule: update

Massimiliano Gambella

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma

Sattva S. Neelapu,[1,*] Caron A. Jacobson,[2] Armin Ghobadi,[3] David B. Miklos,[4] Lazaros J. Lekakis,[5] Olalekan O. Oluwole,[6] Yi Lin,[7] Ira Braunschweig,[8] Brian T. Hill,[9] John M. Timmerman,[10] Abhinav Deol,[11] Patrick M. Reagan,[12] Patrick Stiff,[13] Ian W. Flinn,[14] Umar Farooq,[15] Andre H. Goy,[16] Peter A. McSweeney,[17] Javier Munoz,[18] Tanya Siddiqi,[19] Julio C. Chavez,[20] Alex F. Herrera,[19] Nancy L. Bartlett,[21] Adrian A. Bot,[22] Rhine R. Shen,[22] Jinghui Dong,[22] Kanwarjit Singh,[22] Harry Miao,[22] Jenny J. Kim,[22] Yan Zheng,[22] and Frederick L. Locke[20,*]

CAR-T following at least 2 lines of systemic chemotherapy

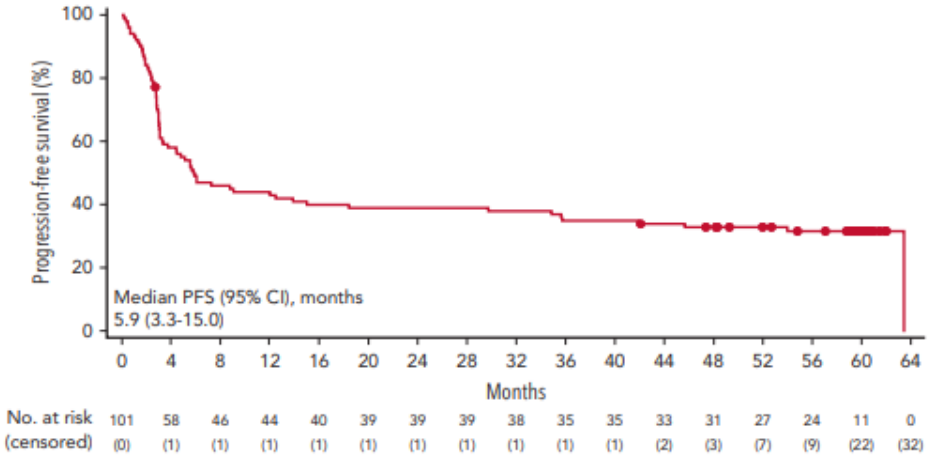
- N = 101 LBCL
- median FU 63.1 months

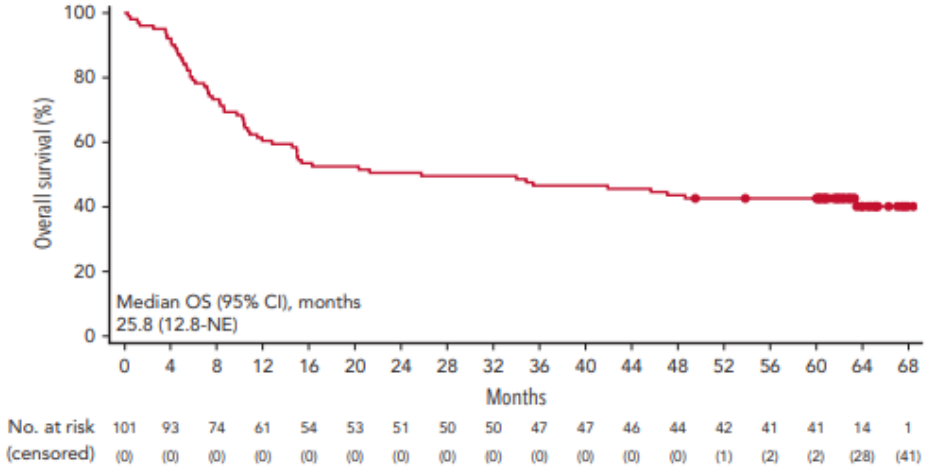
- 93% CRS, 11% Gr. 3-4
- 64% NE, 30% Gr. 3-4

- 84% ORR, 59% CR
- 5-year estimated PFS 31%

- **Prolonged, 5-year follow-up supports the curative potential of axi-cel in a substantial proportion of patients**

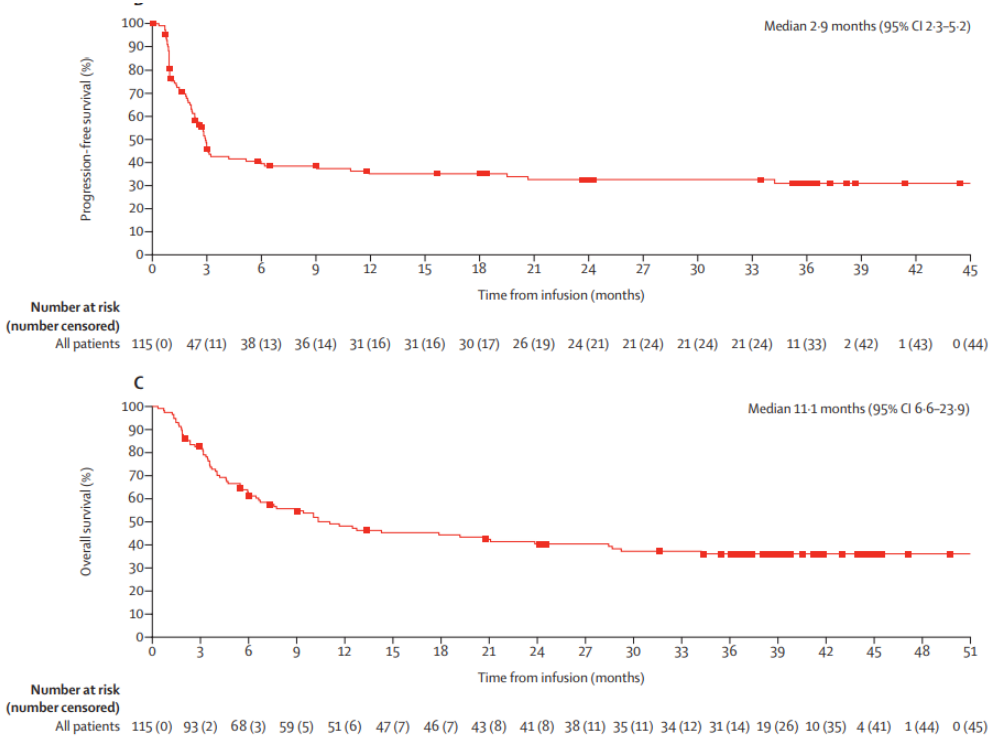
Neelapu et al. Blood 2023





JULIET Long Term Follow Up, Tisa-cel for R/R Agg BC Lymphoma

- N = 115; Median FU: 40.3 months
- CRS Gr 3-4 23%, NE Gr 3-4 11%
- ORR 53%, CRR 39%;



Schuster et al. Lancet Oncology 2021

TRANSCEND 2-year Follow Up, Liso-cel for R/R LBC lymphoma

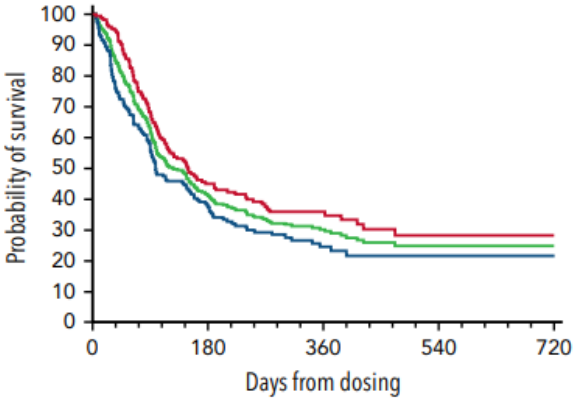
- N = 81
- Median FU: 29.3 months

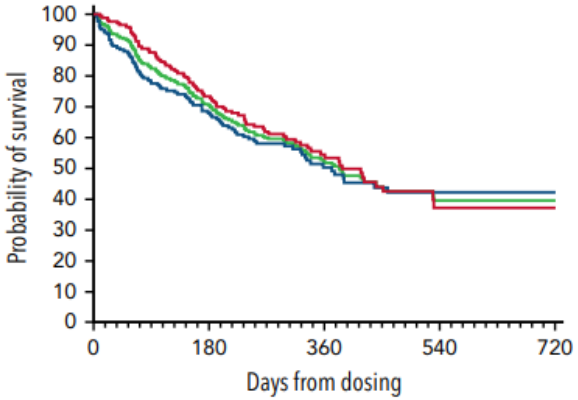
- CRS Gr 3-4 2% NE 10%

- ORR 73% CRR 53%;
- 2-year estimated PFS: 40.6%
- 2-year estimated OS: 50.5%

2022 Transplantation & Cellular Therapy Meetings; April 23-26, 2022. Abstract 65

Real-Life from German and French registry





GLA/DRST registry

356 infused pts

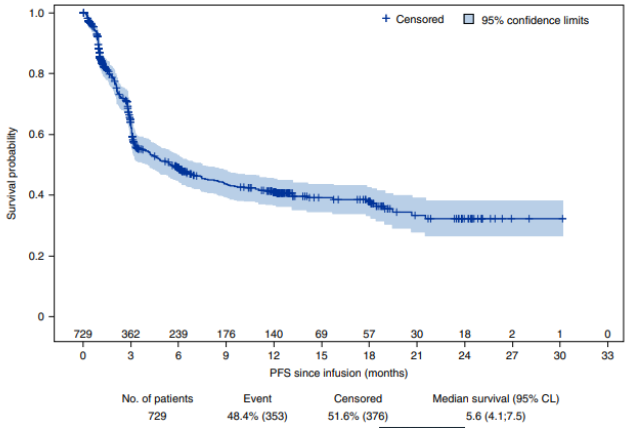
Median FU: 11.1 months

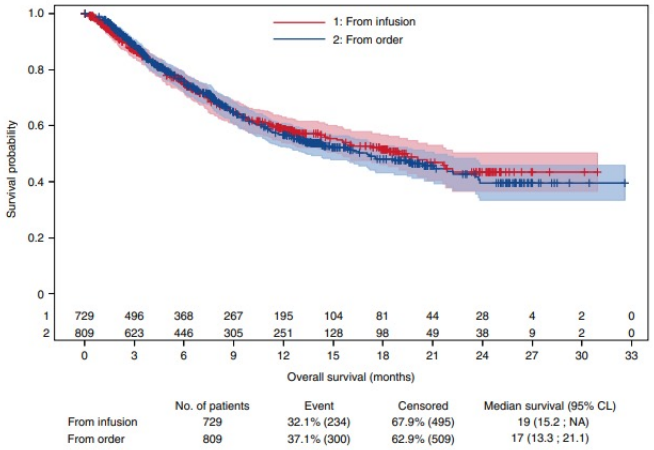
91% DLBCL

5% PMBCL

5% tNHL

Bethge et al. Blood 2022





DESCART registry

729 infused pts

Median FU: 13 months

75% DLBCL + HGL

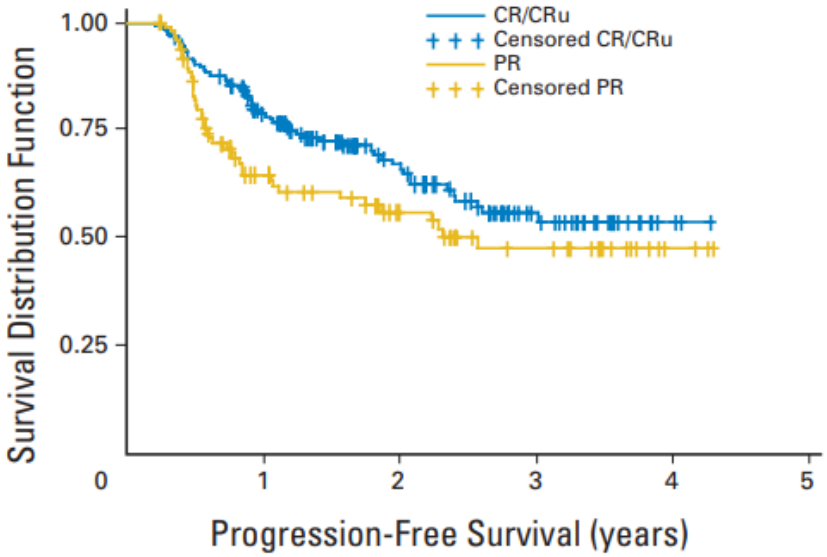
20% tNHL

4% PMBCL

Bachy et al. Nat Med 2022

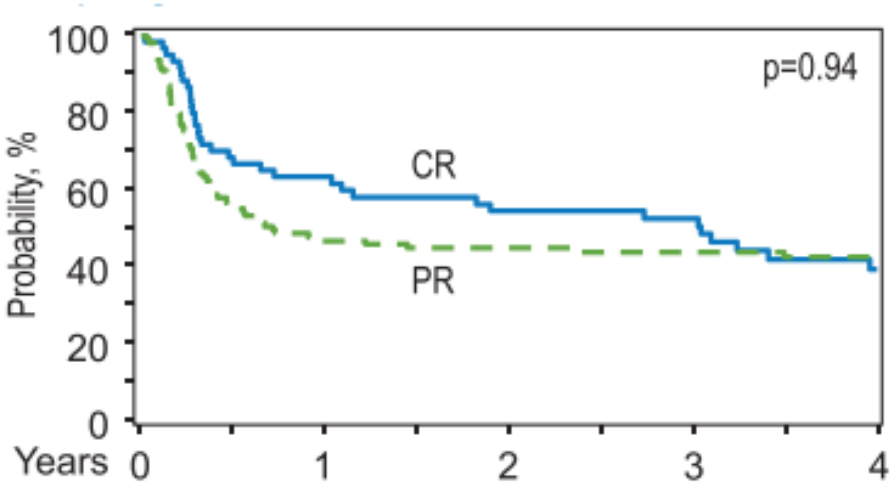
«The second-line treatment goal for relapsed LBCL is considered curative»

Perales et al. TCT 2023



CORAL trial
3-year PFS 53% in ASCT patients
2nd line salvage CT + HDCT and ASCT is curative

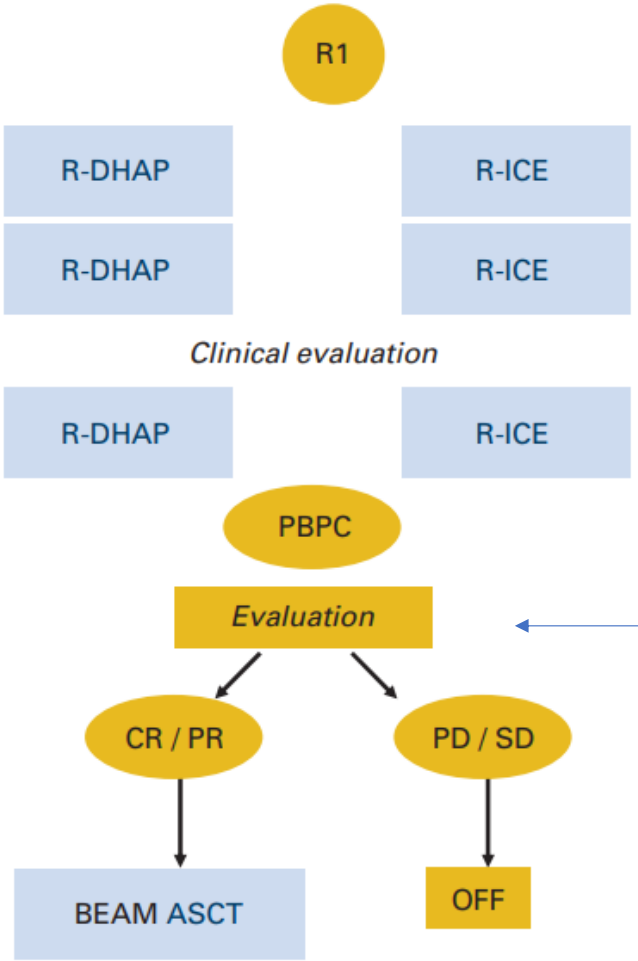
Gisselbrecht et al. JCO 2010



CIBMTR registry, PRIMARY REFRACTORY to 1st line
3-year PFS 52% (CR), 48% (PR) in ASCT patients
2nd line salvage CT + HDCT and ASCT is curative

Bal et al. TCT 2021

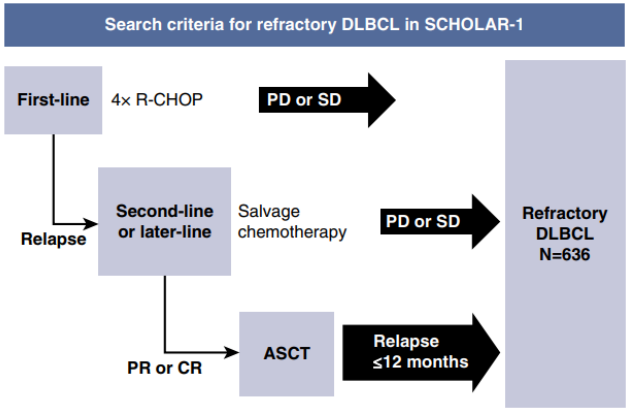
Overall, refractoriness matters: the problem to achieve a response

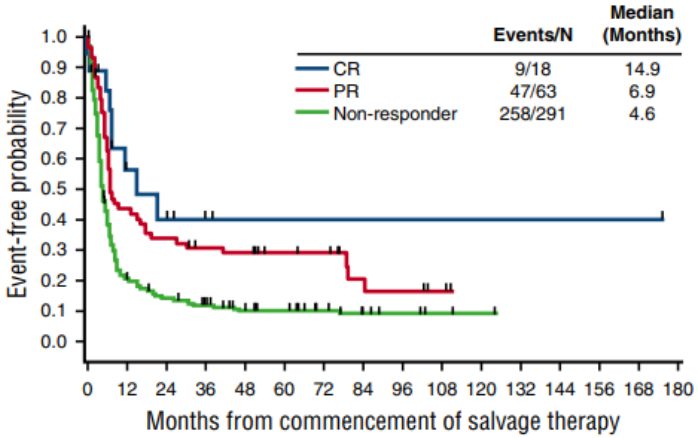


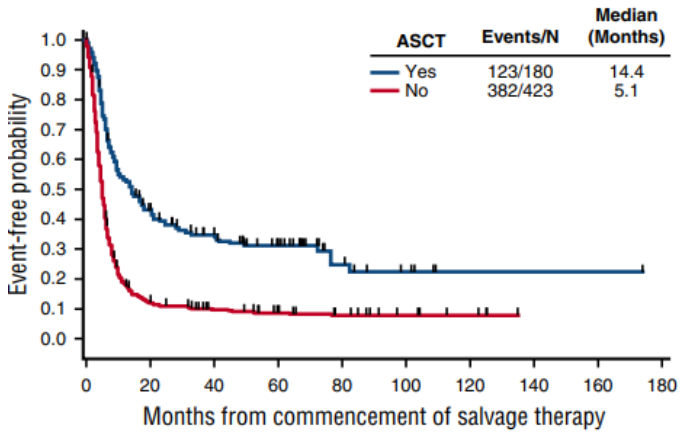
CORAL trial (396pts), ORR to R-DHAP/ICE
1st line Ref & Rel <12months: 46% ORR
Relapse >12months: 88% ORR

NCIC-CTG LY.12 trial (629pts), ORR to (R)-DHAP
1st line Ref: 18% ORR
Relapse <12months: 42% ORR
Relapse>12months: 76% ORR

SCHOLAR-1: pooled analysis of 636 patients affected by refractory DLBCL







	MDACC (n = 165)	IA/MC (n = 82)	LY.12 (CCTG) (n = 219)	CORAL (LYSARC) (n = 170)	Pooled* (N = 636)
Primary refractory					
RR	—	25	27	10	20 (11-34)
CR rate	—	10	1	2	3 (1-11)

Crump et al. Blood 2017

First line refractory and early relapse LBCL: salvage, platinum based CT + BEAM & ASCT is potentially CURATIVE in chemosensitive disease (CR/PR following salvage CT)

BUT

Only a small minority of patients (10-25% in Refractory) has a chemosensitive disease

Overall, REF + early Rel (<12m from diagnosis) have a dismall prognosis

Need for therapies that overcome chemosensitivity in high-risk LBCLs

Second-line CAR-T for REF and early Rel Aggressive BCLs

Parameter	ZUMA-7	BELINDA	TRANSFORM
Histology	LBCL	LBCL, PMBL, FL-3B	LBCL, PMBL, FL-3B
Inclusion	REF + rel <12m of frontline CT	REF + rel <12m of frontline CT	REF + rel <12m of frontline CT
Primary EP	EFS	EFS after week 12	EFS
Crossover	off-study	allowed	allowed
CAR-T	Axi-cel	Tisa-cel	Liso-cel
Bridging	steroids	allowed	allowed
Control arm salvage	second-line CIT	second-line CIT; third line allowed (not-EV)	second-line CIT; third line allowed (not-EV)

Second-line CAR-T, results

	ZUMA-7		BELINDA		TRANSFORM	
	CAR-T	SOC	CAR-T	SOC	CAR-T	SOC
Patients, n	180	179	162	160	92	92
Primary REF, %	74	73	66	67	73	73
Bridging,%	36	-	83	-	63	-
ORR,%	83	50	46	43	86	48
CR,%	65	32	28	28	66	39
Median EFS, months	8.2	2	3	3	10.1	2.3
Crossover, %	-	56	-	51	-	55

EFS from randomisation: impacted by the response rate to salvage CT (SOC arm)

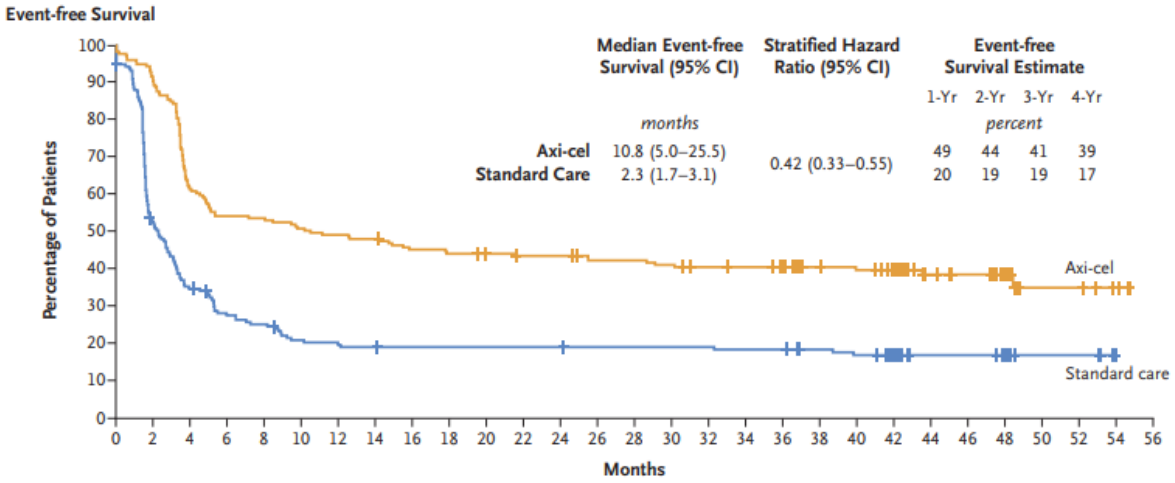
Open questions in advance of second-line CAR-T

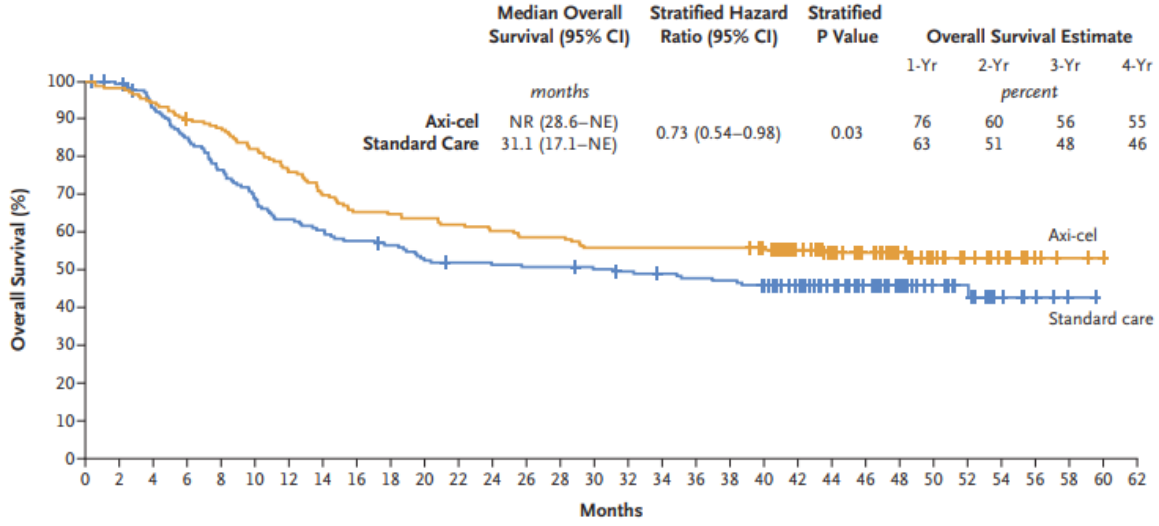
DATA from second line trials with CAR-T, who benefit most?

- High-Risk subgroups (Primary Ref, D-T HIT, HR REFINE criteria)
- CAREFUL: Relapse >6 months from upfront CT (not considered HR in CORAL)
- GRAY ZONE: referral of patients already responsive to salvage CT

EFS, a reasonable surrogate for cure?

- likely, according to the high-risk cohort
- but consider the impact of novel approaches (IIIrd line CAR-T, BiTEs, …)





EFS, a reasonable surrogate for cure?

SOC: **56% crossover** to CAR-T (off-study)

Median FU: 47.2 months

HR for OS, axi-cel vs SOC: 0.73 (p = .03)

Westin et al. NEJM 2023

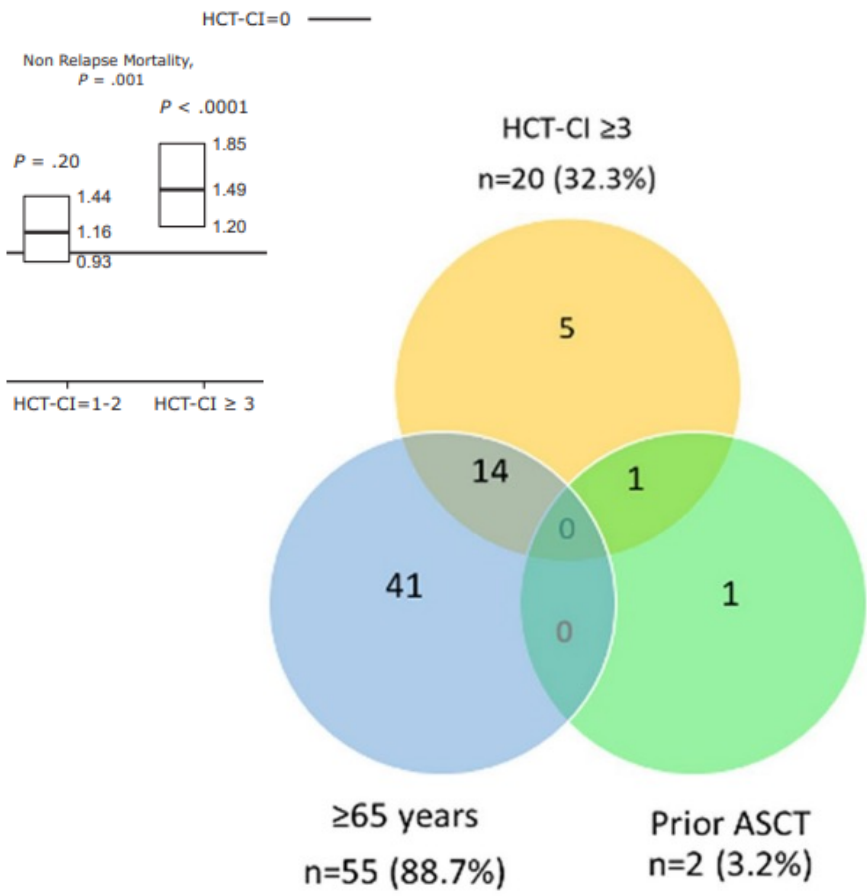
nature medicine

Article

https://doi.org/10.1038/s41591-023-02572-5

Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial

Infused Patients, N	62
ECOG 0-1, %	98.4
Primary REF, %	54.8
Median time from 1stL-end to Rel, months	5.9 (1.0-17.0)
HGBCL with MYC + BCL-2, %	9.7



Houot et al. Nat Med 2023; Sorror et al. BBMT 2015

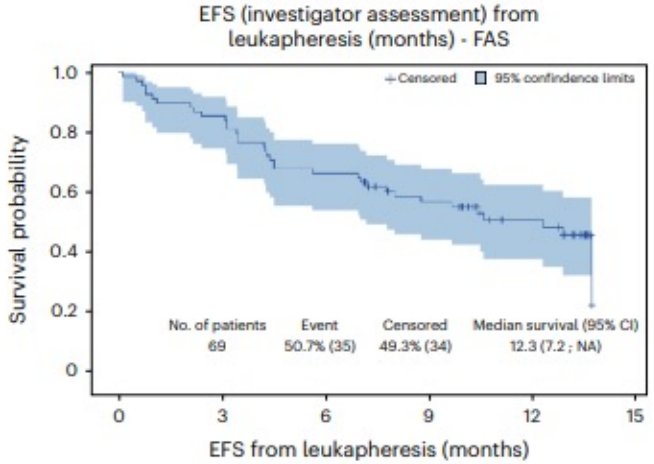
ALYCANTE trial

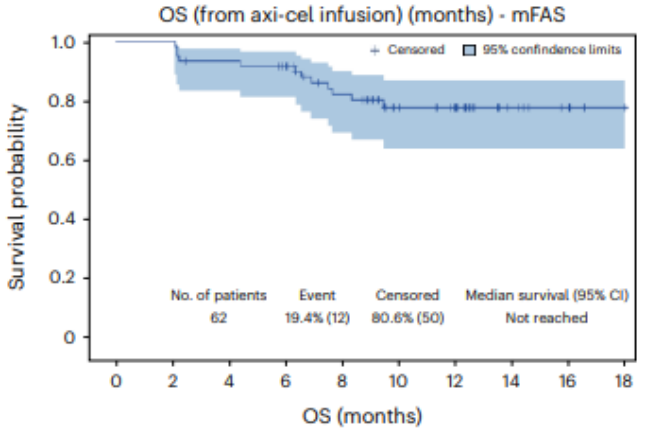
- median FU 12.0 months
- 83.9% received BT (GemOx)

- 93.5% CRS, 8.1% Gr. 3-4
- 51.6% NE, 14.5% Gr. 3-4
- 25.8% ICU transfer due to CAR-T tox

- 69.4% ORR, 66.1% CR
- 12-month estimated EFS 51.2%
- 12-month estimated OS 78.3%

- NRM: 9.7% (infectious complications, >2months)





Houot et al. Nat Med 2023

Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study

Infused Patients, N	**61**
Median age, yrs - 70-74yrs (%) - ≥75yrs (%)	74 (53-84) 20(33) 28(46)
ECOG 0-1, n (%) ECOG 2	45(74) 16(26)
- DLCO ≤60% - FE <50% - Creatinine clearance <60mL/min - ALT>2ULN	4(7) 1(2) 15(25) -
Primary REF, n (%)	33(54)
Median time from 1stL end to Liso, months	6.9 (3.5-16.4)
DH or TH, n (%)	20(33)

Transplant Not Intended (TNI) criteria, at least 1

- Age ≥70yrs
- ECOG 2
- DLCO ≤60%
- FE <50%
- Creatinine clearance <60mL/min
- ALT>2ULN

Adeguate organ function for CAR-T required
Secondary CNS lymphoma allowed

Primary EP: ORR

Sehgal et al. Lancet Onc 2022

PILOT trial

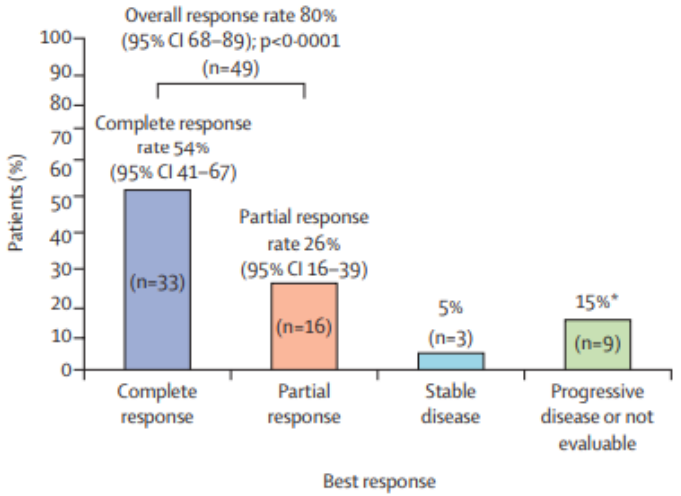
- median FU 13 months
- 52% received BT (IC)

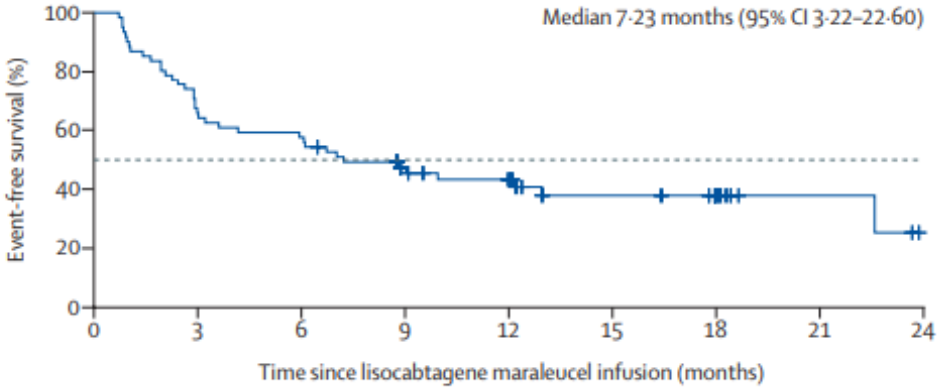
- 38% CRS, 2% Gr. 3-4
- 31% NE, 5% Gr. 3-4

- Toci, steroids, both for CRS: 26%
- Steroids for NT: 13%

- 80% ORR, 54% CR
- Median EFS 7.23months
- Median OS NR

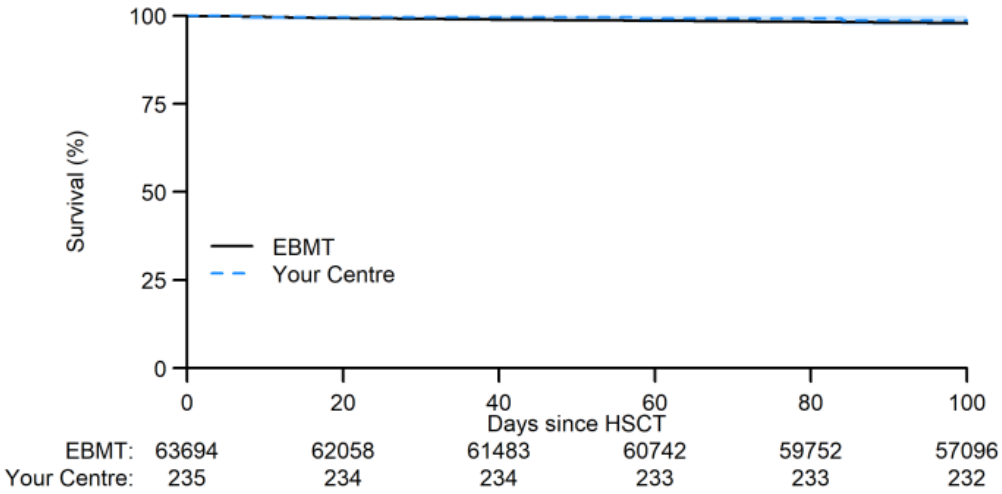
NRM: 3.3% (COVID, >1month)





Sehgal et al. Lancet Onc 2022

EBMT 2017-2021 autologous SCT benchmarking



	Day 100 Survival
EBMT	98% (98-98%)
Your Centre	99% (97-100%)

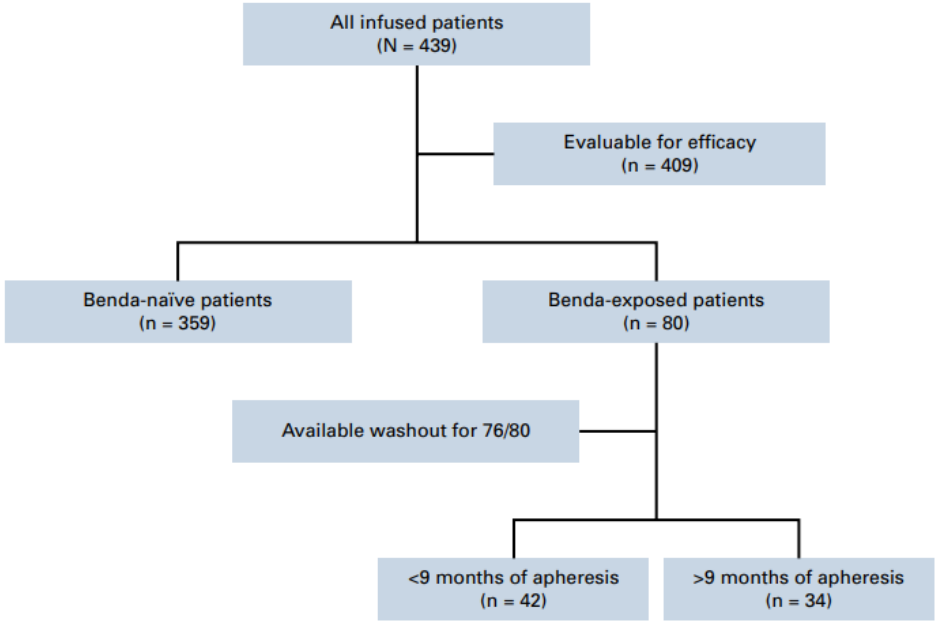
HSM, transplant unit
Median age (2019-2023),
ASCT for B-NHL: 59yrs (21-72)

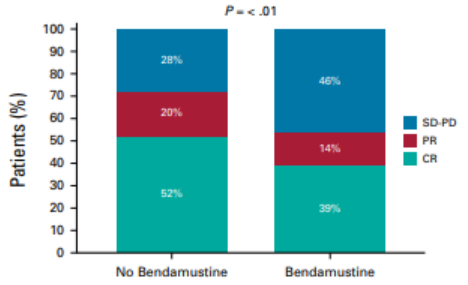
HCT-CI	Total	68791 (93.3)
	Low	43056 (62.6)
	Intermediate	15839 (23.0)
	High	9896 (14.4)

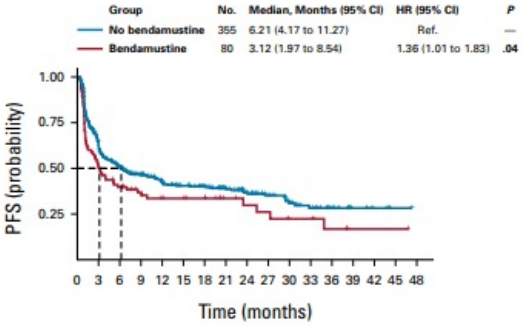
Bendamustine and CAR-T

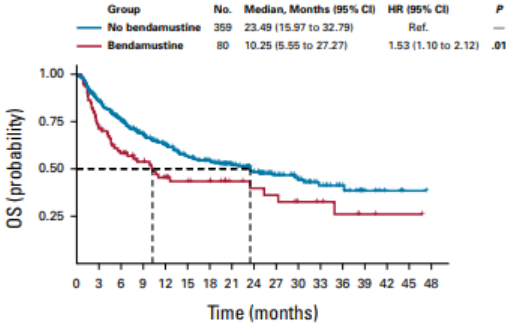
Recent Bendamustine Treatment Before Apheresis Has a Negative Impact on Outcomes in Patients With Large B-Cell Lymphoma Receiving Chimeric Antigen Receptor T-Cell Therapy

Retrospective study aimed to address the impact of Benda **before leukapheresis** on CAR-T outcomes for LBCL





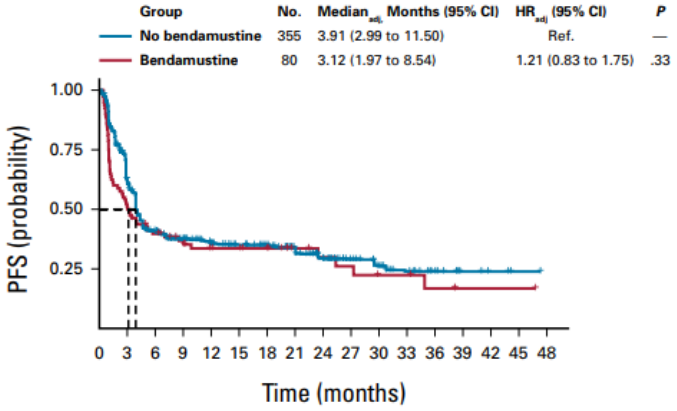


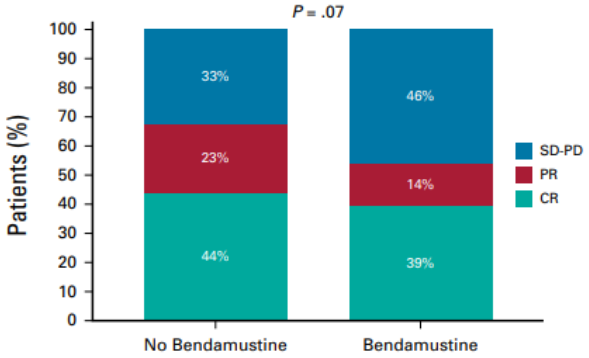


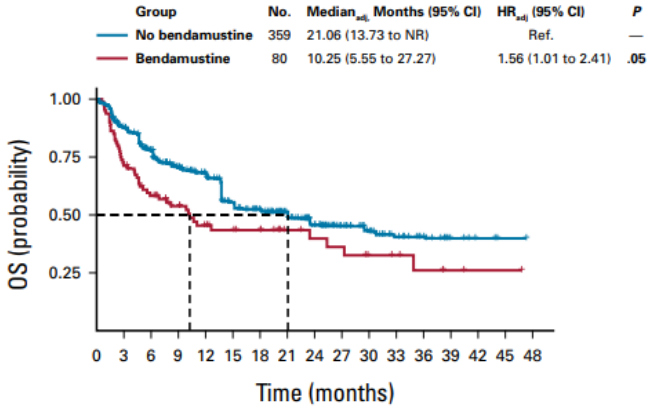
Iacoboni et al. JCO 2023

Adjustment for baseline risk-factors mitigates differences

Differences among cohorts	
Benda vs Benda-naïve	Equivalent for several baseline variables included median LDH, but more likely to be: - Older (median 66 vs 61)(<.01) - Frail (ECOG>1: 16% vs7%)(.02) - Transformed (45% vs 15%)(<.01) - Treated (>2 lines: 71 vs 28%)(<.01)



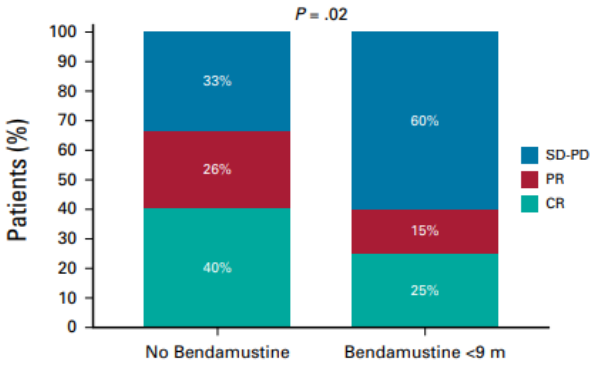


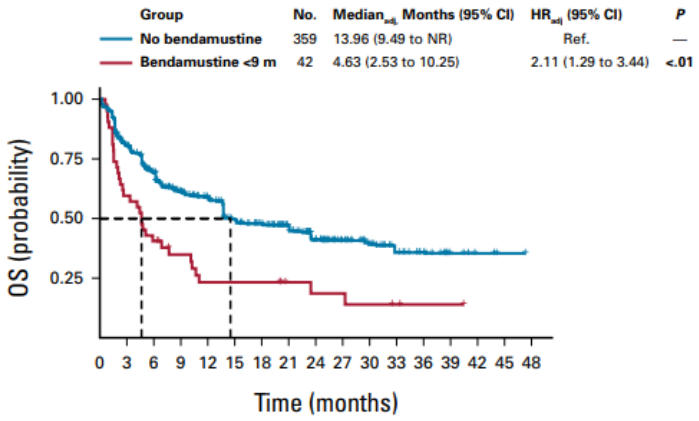


Following adjustment for baseline risk factors, **Benda vs B-naïve**

Iacoboni et al. JCO 2023

Recent bendmustine exposition is associated with a worse outcome, even following adjustment for baseline risk-factors





CONCLUSIONS

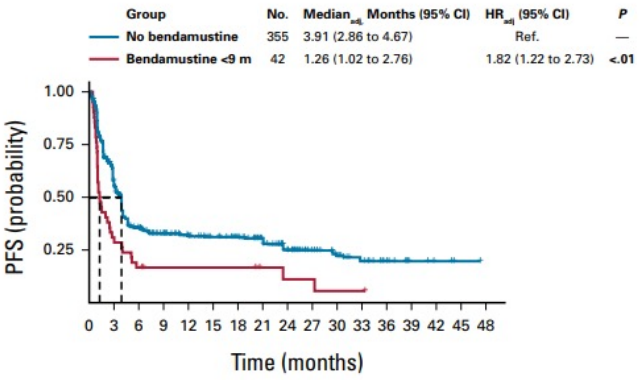
Recent bendamustine (before apheresis) is associated with a **worse outcome**

Bendamustine **should be avoided** immediately prior to CAR-T cell therapy

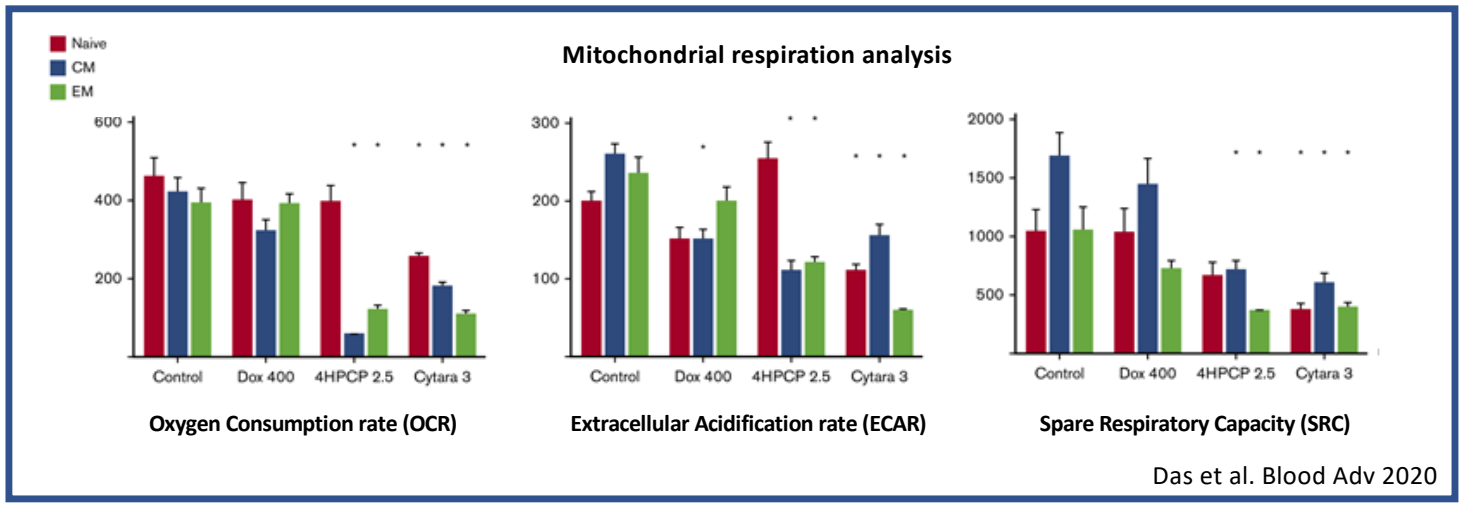
Investigations needed to understand mechanisms

-

Retrospective data with (only) 42 patients in the <9months cohort



Iacoboni et al. JCO 2023



Das et al. Blood Adv 2020

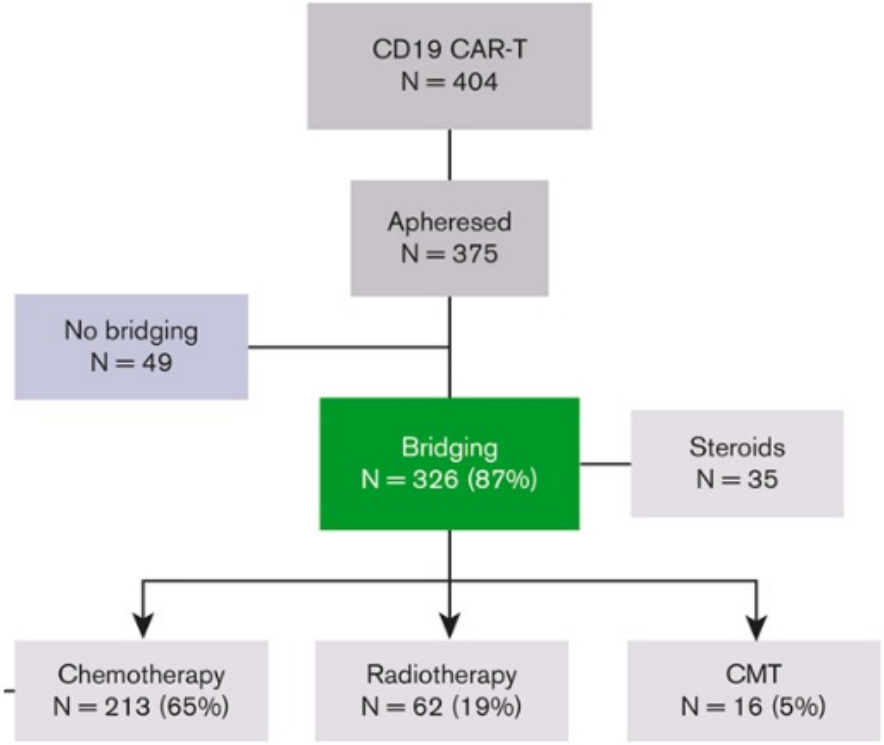
Bridging therapy

Bridging therapy refers to the administration of anticancer drugs including chemotherapy to maintain disease control during the period between lymphocyte collection and the final administration of the CAR T-cell product.

It is also hoped that treatment of rapidly proliferating disease will establish a balanced *in vivo* target-effector ratio to allow for effective CAR T-cell adoptive immunotherapy. In brief, the aim is not so much to achieve disease remission as to establish adequate disease control prior to the CAR T-cell infusion.

EBMT JACIE joined reccomendations for the management of CAR-T in the adult patient. Yakoub-Agha et al. Haematologica 2020.

Impact of bridging therapy on CD19 CAR-T outcomes



Baseline characteristics	
CT vs No bridging	More likely to have (p<.05) • Stage III/IV • EN-disease • ECOG 1 (vs 0)
RT vs No bridging	• less stage III/IV • lower LDH • less EN-disease
Performance Status (Fit for SCT, HCT-CI) superimposable among groups (no-BT, steroids, RT, CT) **2019-2020 vs 2018-2019 RPB become the CT regimen of choice (68% vs 6%)**	

Roddie et al. Blood Adv 2023

Bridging therapy can safely reduce disease burden

		Bridging therapy					CT bridging		
	No bridging	Steroids	RT	CT	CMT		Low dose	High dose§	RBP
Apheresed patients	**N = 49**	**N = 35**	**N = 62**	**N = 213**	**N = 16**	***P*-value‖**	**N = 51**	**N = 84**	**N = 77**
Response to bridging, N (%)									
CR/PR	-	-	40 (67.8)	64 (31.4)	5 (33.3)	<.001	8 (15.7)	23 (27.4)	33 (42.9)
SD/PD/death before infusion	-	-	19 (32.2)	140 (68.6)	10 (66.7)		35 (68.3)	60 (71.4)	43 (57.1)
Unknown	-	-	3	9	1		8	1	0
CR	-	-	4 (6.8)	19 (9.3)	0	<.001	1 (2.0)	7 (8.3)	11 (14.3)
Infused, N (%)									
Infused	40 (81.6)	29 (82.9)	54 (87.1)	166 (77.9)	11 (68.8)	.39	42 (82.4)	58 (69.1)	66 (85.7)
Not infused	9 (18.4)	6 (17.1)	8 (12.9)	47 (22.1)	5 (31.3)		9 (17.7)	26 (31.0)	11 (14.3)

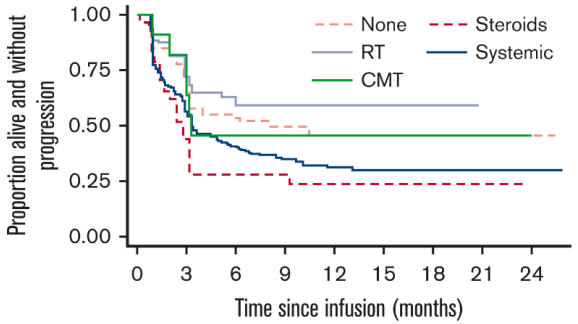
Despite application in more advanced pts, BT does not preclude infusion due to toxicities

RT-BT higher rate of CR/PR vs CT-BT (less stage III/IV and EN)

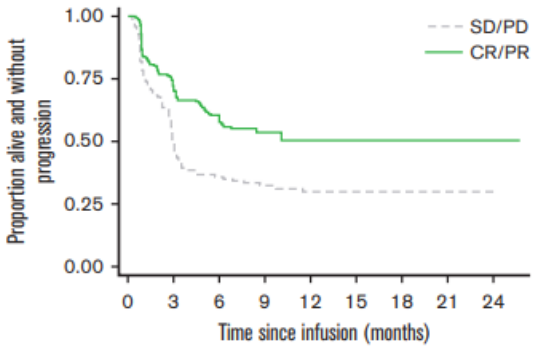
RPB associated with an higher rate of CR/PR vs other CT regimens

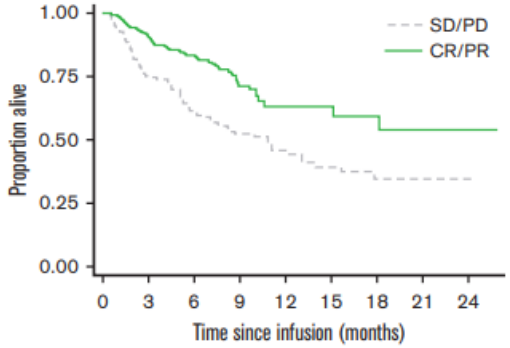
Roddie et al. Blood Adv 2023

Median PFS: **RT & None > CT**
(less extended disease at indication)



Median PFS & OS: **CR/PR > SD/PD**





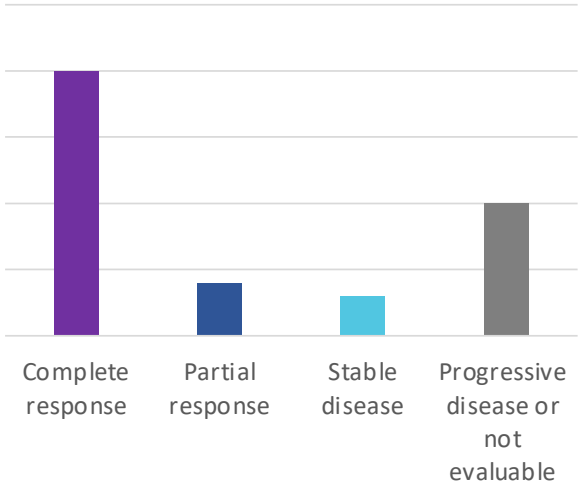
Factors affecting response to CAR-T	Events/N	HR (95% CI)	*P*-value
LDH at LD			
≤2ULN	74/141	1.00	.001
>2ULN	34/41	2.06 (1.34-3.16)	
Extra nodal sites			
<3	91.160	1.00	.001
≥3	17/22	2.51 (1.46-4.32)	
BT response			
SD/PD	68/100	1.00	.012
CR/PR	40/82	0.58 (0.38-0.89)	

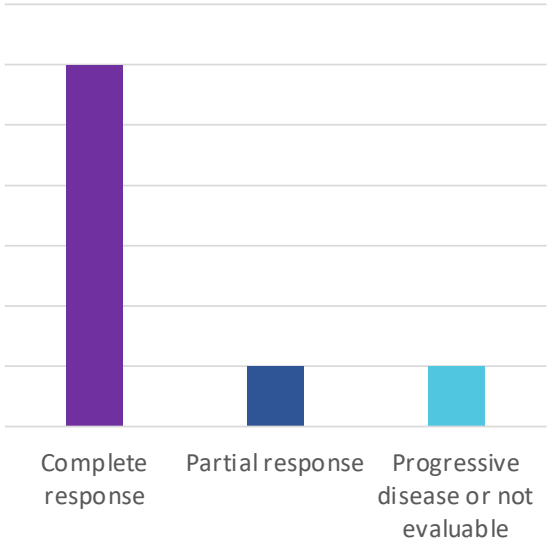
Factors affecting response to BT	Responder/N	OR (95% CI)	*P*-value
RBP bridging			
No	34/134	1.00	.010
Yes	35/83	2.21 (1.21-4.05)	
Response last line			
SD/PD	45/165	1.00	.023
CR/PR	24/52	2.16 (1.11-4.22)	
Bulky disease			
No	55/149	1.00	.045
Yes	14/68	0.49 (0.25-0.98)	

Roddie et al. Blood Adv 2023

Genova - CAR-T efficacy analysis, NHL

NHL Patients infused (N=45)	
Bridging therapy 45 (100%)	
Chemotherapy	22 (49%)
Radiotherapy	6 (13%)
Combined	17 (38%)
Status at CAR-T, following bridging	
CR/PR PR CR SD/PD	18 (40%) 15 (33%) 3 (7%) 27 (60%)
LDH <ULN >ULN	 17 (38%) 28 (62%)
Extranodal sites 0 1-2 ≥3	 21 (47%) 18 (40%) 6 (13%)

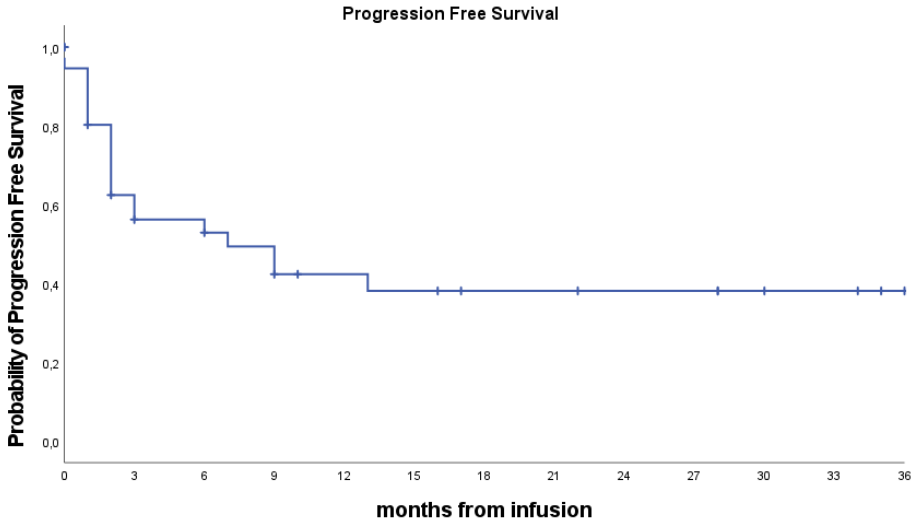


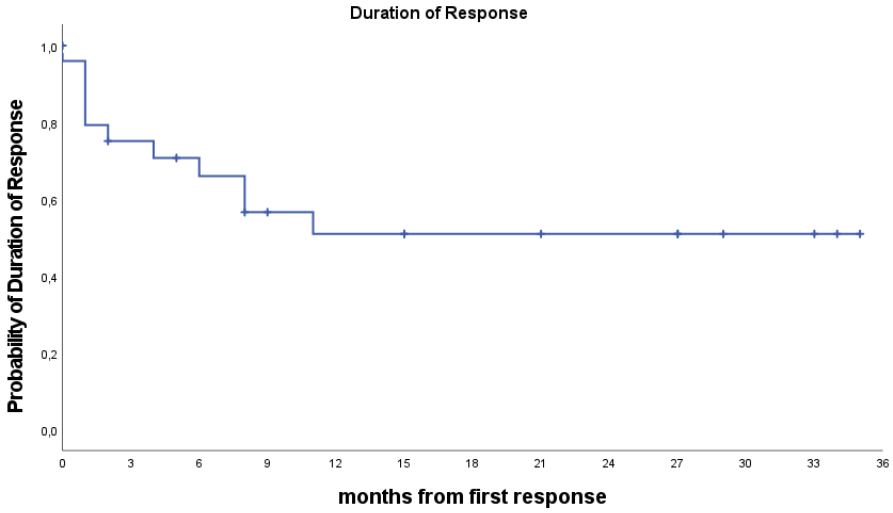


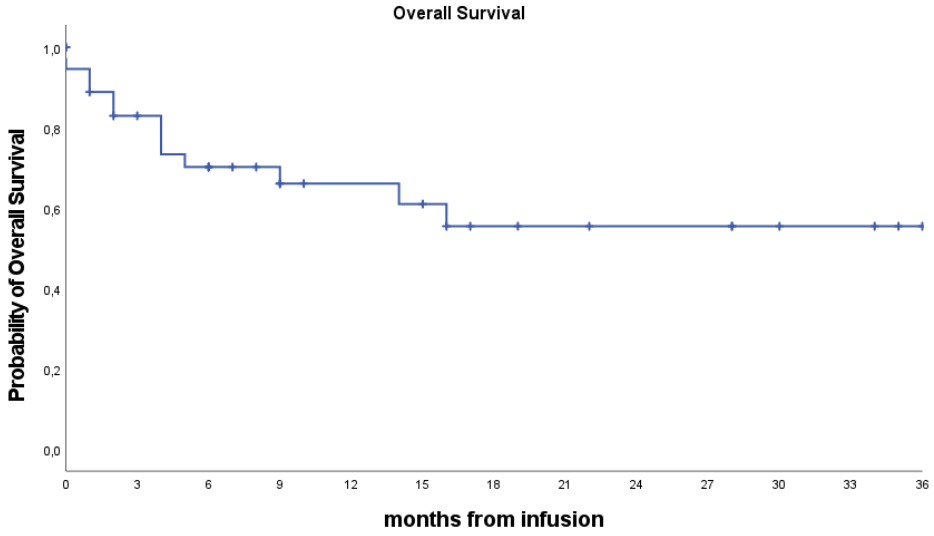
LBCLs (N=37)
CR 54% (N=20)
PR 11% (N=4)
ORR 65% (N=24)
SD 8% (N=3)
PD/not ev 27% (N=10)

Indolent-NHLs (N=8)
CR 75% (N=6)
PR 12.5%(N=1)
ORR 87,5% (N=7)
PD/not ev 12,5% (N=1)

Results, 2020-2023







Survival Analysis, LBCLs (N=37)
Median Follow Up (95%CI): 15 months (6.5-23.4)

PFS, median: 7 months
18-months est. PFS: 38% (21-55)
OS, median: NR
18-months est. OS: 55% (36-74)
DOR (N=25), median: NR
18-months est. DOR: 50.9% (29.9-71,9)

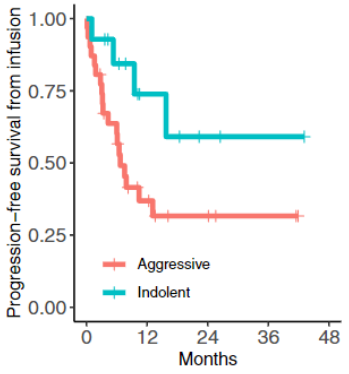
Genova - CAR-T efficacy analysis, Aggressive NHL

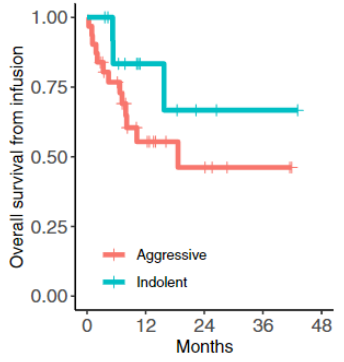
ORIGINAL PAPER
Haematological Malignancy - Clinical

The academic point-of-care anti-CD19 chimeric antigen receptor T-cell product varnimcabtagene autoleucel (ARI-0001 cells) shows efficacy and safety in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma

Characteristic	Patients ($n=51$)
Disease type, *n* (%)	
Diffuse large B-cell lymphoma	5 (10)
Primary mediastinal large B-cell lymphoma	2 (4)
High-grade lymphoma	1 (2)
Grey-zone lymphoma	2 (4)
Primary effusion lymphoma	1 (2)
Transformed follicular lymphoma	1 (2)
Primary central nervous system B-cell lymphoma	2 (4)
Richter transformation	10 (20)
Burkitt lymphoma	3 (6)
Follicular lymphoma	12 (23)
Mantle-cell lymphoma	9 (17)
Marginal zone lymphoma	2 (4)
Splenic diffuse red pulp small B-cell lymphoma	1 (2)

Outcome	CART19-BE-01 trial ($n=8$)	Compassionate use programme ($n=37$)
ORR at Day +100, % (95% CI)	75 (35–97)	73 (56–86)
CRR at Day +100, % (95% CI)	50 (16–84)	68 (50–82)
DOR at 3 years, % (95% CI)	50 (23–100)	57 (37–88)
PFS at 3 years, % (95% CI)	38 (15–92)	39 (23–65)
OS at 3 years, % (95% CI)	38 (15–92)	59 (41–85)





CRS: 84%, Gr.3-4: 4% NT 7%, Gr.3-4: 2% 3yrs-NRM: 7%

Martinez-Cibrian et al. BJ Haem 2023


Grazie.