CAR-T: rimpiazzeranno le terapie standard di prima e seconda linea nei LNH aggressivi a grandi cellule B ?

Marco Ruggeri
Vicenza

Disclosures of Marco Ruggeri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

If Standard Therapy Not Feasible or If Anthracycline Contraindicated: dose reduction or drug substitution with curative intent

Limited-Stage
- 3 Cycles of R-CHOP+XRT
- 4 Cycles of R-CHOP (bulk <7.5 cm, age-adjusted IPI=0)
- PET-guided 4–6 cycles R-CHOP with or without XRT

Advanced-Stage
- 6 Cycles R-CHOP considered standard of care
- New regimens to be considered in clinical trials
- High CNS risk: role of systemic prophylaxis unclear

5–10% Limited-Stage Relapse

20–25% Advanced-Stage Relapse

Relapsed or Refractory Disease
Repeat biopsy recommended and staging as outlined above

~50% ASCT Eligible

Platinum-Based Salvage Therapy

~50% Response

ASCT

~50% Response

~25–35% of ASCT-Eligible Patients Are Cured

~50% Relapse

~50% Refractory

No ASCT

After ASCT

~50% Not Candidates for ASCT

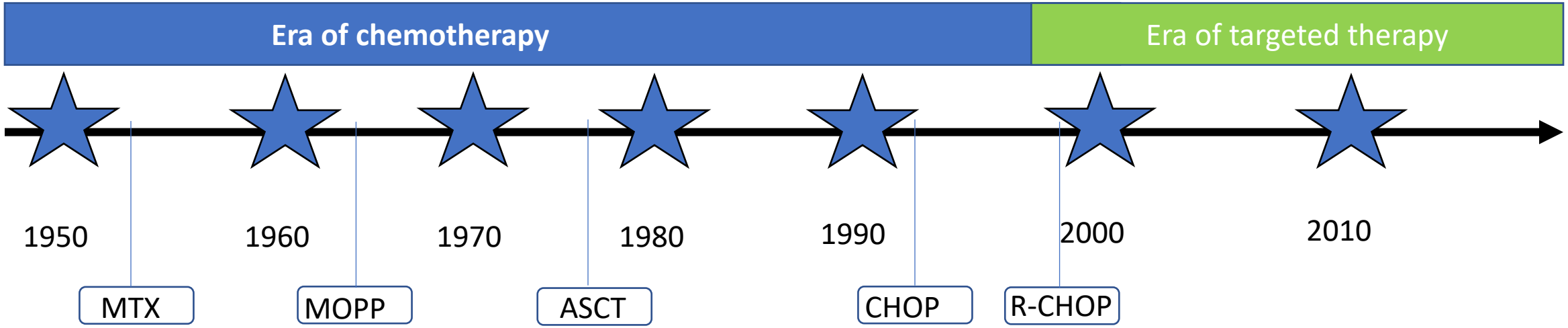
Second-Line Therapy

Third-Line Therapy or More

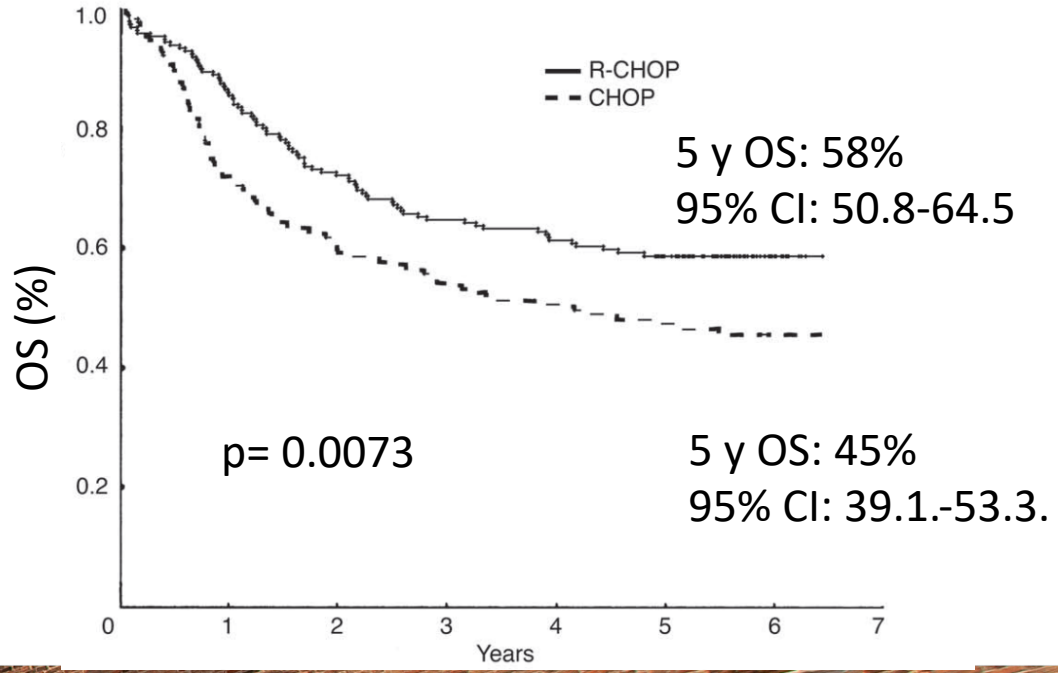
Available Options for ASCT-Ineligible Patients
- Immunochemotherapy
- CAR T-cell therapy
- Polatuzumab vedotin+BR
- Selinexor
- Tafasitamab–lenalidomide
- Investigational agent or regimen
- Allogeneic stem-cell transplantation
- Best supportive care (including XRT)

~50% Response
~50% Relapse
~25–35% of ASCT-Eligible Patients Are Cured
No ASCT
After ASCT
Third-Line Therapy or More
or regimen
• Allogeneic stem-cell transplantation
• Best supportive care (including XRT)

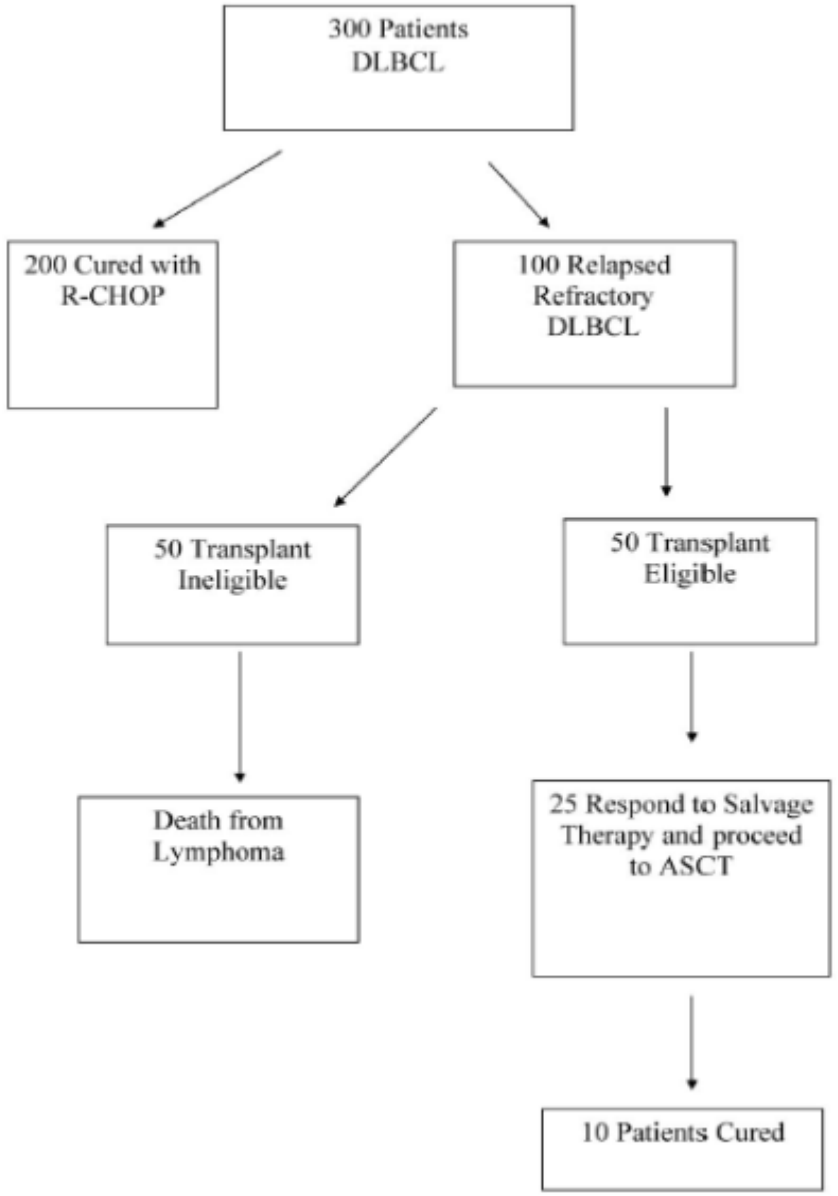
DLBCL treatment approaches have advanced over time



Targeted therapies (R-CHOP) have led to significant improvement in the outcome of DLBCL patients



Feugier P et al; J Clin Oncol 2005



1/3 DLBCL patients will relapse after 1 line therapy

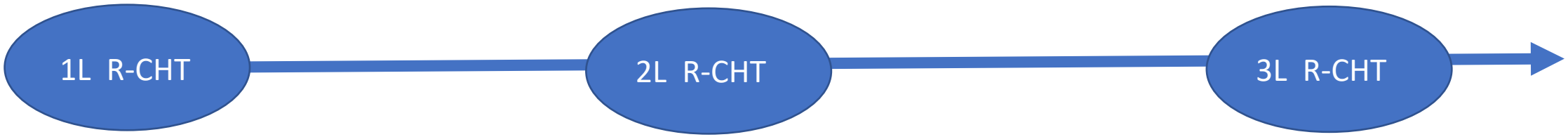
90% of R/R DLBCL patient are ineligible for, or fail, further treatments

This cohort of patients do not have standard of care options (Parma and Coral trials)

Friedberg JW; Hematology, 2011

There are subsets of patients with R/R DLBCL who do not achiede the 2 – years survival milestone

Patients who relapse after or are refractory to last salvage chemotherapy



Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL study)

~40% are refractory

Median OS: 4.4 months

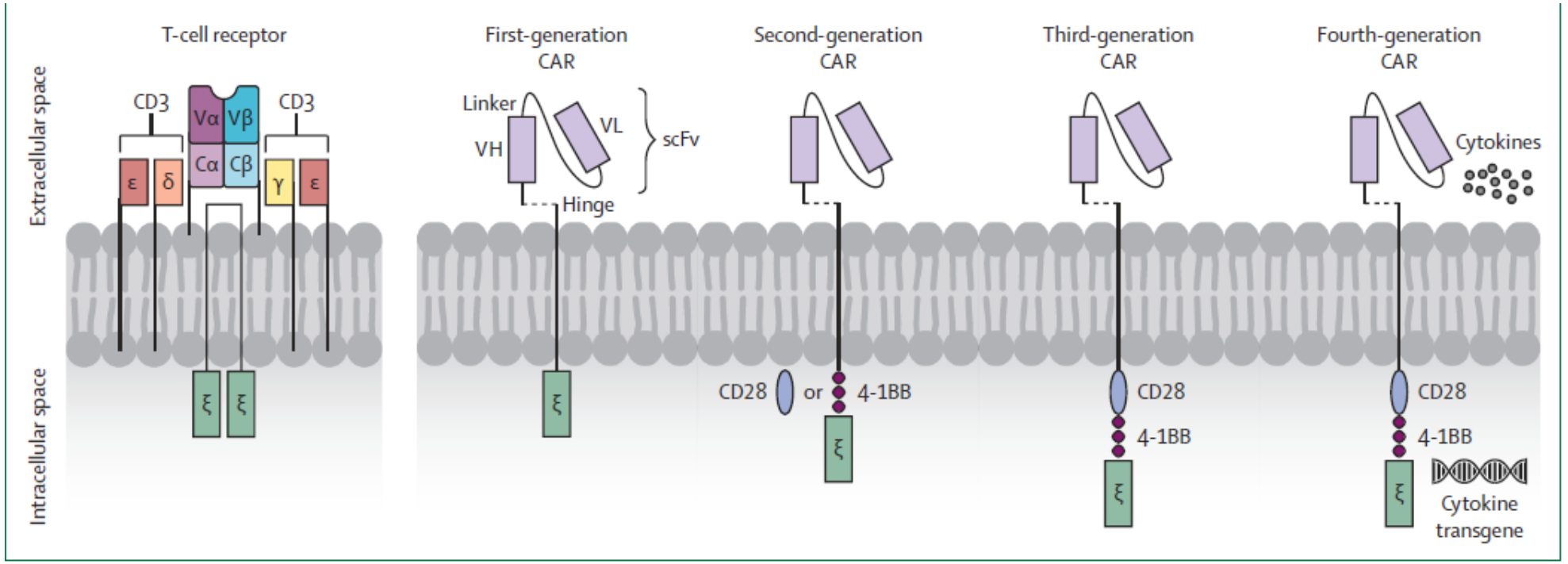
~60% are refractory

Median OS: 3.7 months

Giesselbrecht C et al; J Clin Oncol 2010

Monoclonal antibodies					
Tafasitamab	CD19	2a	26	6	Jurczak et al.[70]
Tafasitamab plus lenalidomide	CD19	2	60	43	Salles et al.[71]
Antibody–drug conjugates					
Loncastuximab tesirine	CD19	1	42	23	Hamadani et al.[72]
Brentuximab vedotin	CD30	2	44	17	Jacobsen et al.[73]
Polatuzumab vedotin	CD79b	1	52‡	13‡	Palanca-Wessels et al.[7
Polatuzumab vedotin plus BR vs. BR	CD79b	2, randomized	45 vs. 17.5	40 vs. 17.5	Sehn et al.[75]
Bispecific antibodies					
Blinatumomab	CD19–CD3	2	43	19	Viardot et al[76]
Mosunetuzumab	CD20–CD3	1/1b	35§	19§	Schuster et al.[77]
Glofitamab	CD20–CD3	1/1b	41	29	Hutchings et al.[78]
Odronextamab	CD20–CD3	1	42¶	35¶	Bannerji et al.[79]
Epcoritamab	CD20–CD3	1/2	76‖	32‖	Hutchings et al.[80]
NF-κB and BCR modifiers					
Ibrutinib	BTK	1/2	37 ABC, 5 GCB	16 ABC, 0 GCB	Wilson et al.[81]
Lenalidomide vs. investigator's choice	Multiple, NF-κB	2, randomized	28 vs. 12	10 vs. 2	Czuczman et al.[82]
Agents with other targets					
Venetoclax	BCL2	1	18	12	Davids et al.[83]
Selinexor	XPO1	2b	28	12	Kalakonda et al.[84]
Checkpoint inhibitors					
Nivolumab	PD-1	2	≤10	≤3	Ansell et al.[85]
Magrolimab	CD47	1b	40	33	Advani et al.[86]
Epigenetic modifiers					
Tazemetostat	EZH2	2	17 EZH2 mt, 17 EZH2 wt	3 EZH2 mt, 9 EZH2 wt	Ribrag et al.[87]

Sehn HL; Salles G. NEJM, 2021

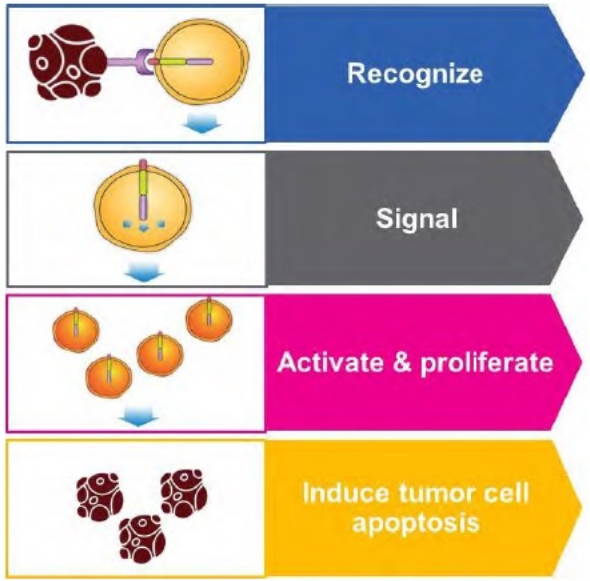


CAR T cells: continuation in a revolution of immunotherapy

Anurag K Singh, Joseph P McGuirk

Lancet Oncol 2020; 21: e168–78

How CAR-T cells work



CAR T cells recognize their target

This binding causes signaling through the two CAR intracellular domains

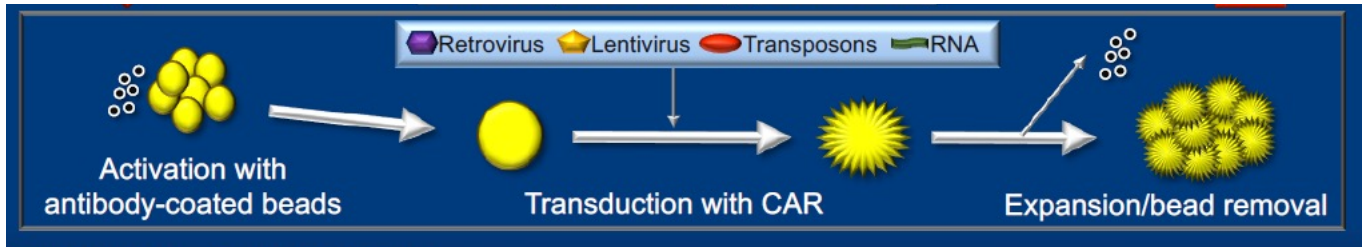
Activated CAR T cells are now capable of rapid proliferation

Activated CAR T cells can induce apoptosis of target-expressing cells

Kite illustration developed from references.

Approved for Use on 11 Nov 2019

1. Dotti G, *et al. Immunol Rev* 2014; 257:107–126.
2. Sadelain M, *et al. Cancer Discov* 2013; 3:388–398.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

N Engl J Med 2017;377:2531-44.

The NEW ENGLAND JOURNAL of MEDICINE

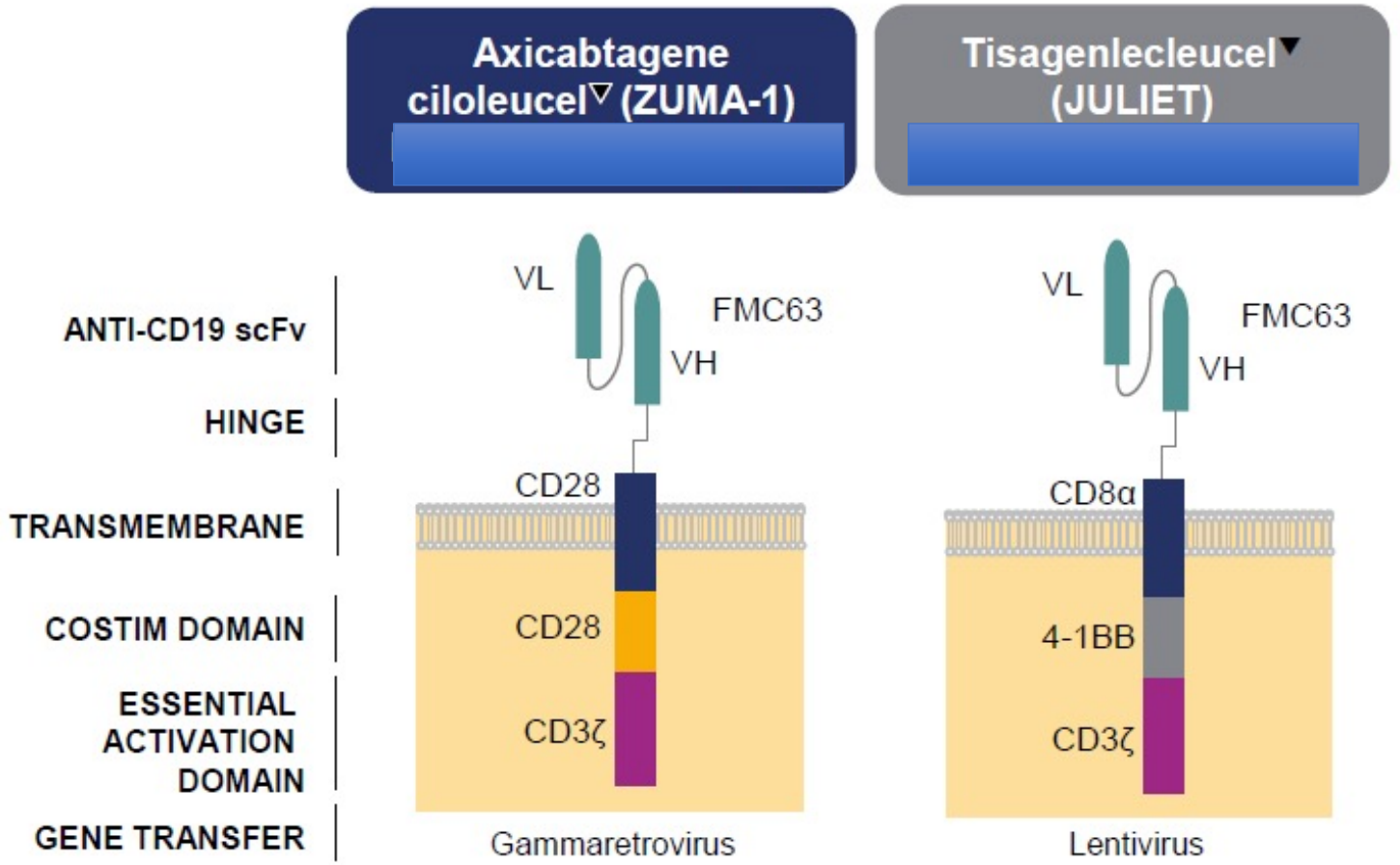
ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

N Engl J Med 2019;380:45-56.

FDA, EMA and AIFA CAR-T cells registered drugs



IO_103 CRITERI DI INCLUSIONE PER TERAPIA CON CAR-T

INDICAZIONI SPECIFICHE / CRITERI DI INCLUSIONE

Prodotto	Indicazioni approvate	
	Patologie	**età**
Tisa	• linfoma diffuso a grandi cellule B (DLBCL)* in recidiva o refrattario dopo due o più linee di terapia sistemica.	pazienti adulti (età ≥ 18 anni e ≤ 70 anni)
	• leucemia linfoblastica acuta (LLA) a cellule B refrattaria, in recidiva post-trapianto** o in seconda o ulteriore recidiva	pazienti pediatrici ed adulti fino ai 25 anni di età compiuti (il farmaco non è stato testato in bambini di età inferiore ai 3 anni)
Axi	• linfoma diffuso a grandi cellule B (DLBCL)*** • linfoma primitivo del mediastino a grandi cellule B (PMBCL), refrattario o recidivato dopo due o più linee di terapia sistemi	pazienti adulti (età ≥ 18 anni e ≤ 70 anni)

* sono esclusi: linfoma a grandi cellu
linfoma primitivo cuta
linfoma a grandi cellu
linfoma diffuso a gra
linfoma aggressivo e
linfoma di Burkitt

** sono esclusi i pazienti con recidiva dc
entro 4 mesi dal trapianto.

***sono esclusi: linfoma primitivo del SNC
Sindrome di Richter

STIMULUS REPORT

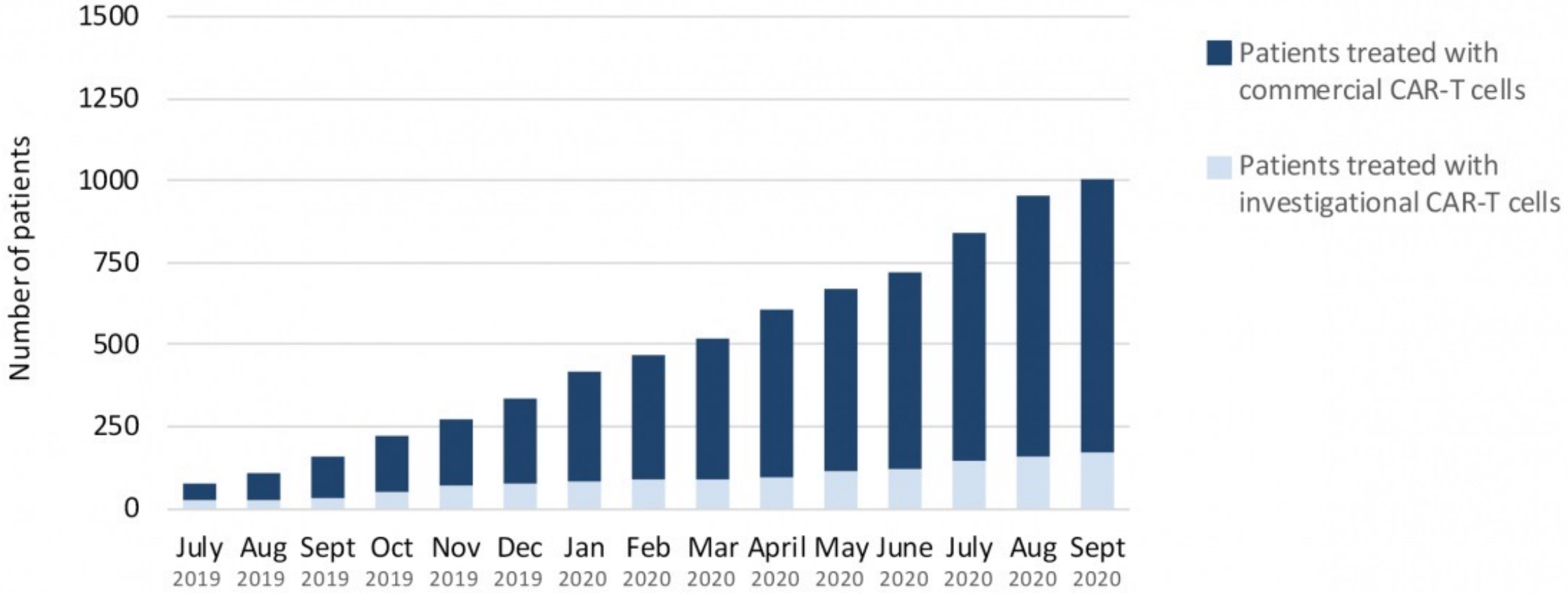
blood advances

CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma

Tanya Siddiqi,[1] Xiuli Wang,[1] M. Suzette Blanchard,[2] Jamie R. Wagner,[3] Leslie L. Popplewell,[1] L. Elizabeth Budde,[1] Tracey L. Stiller,[2] Mary C. Clark,[4] Laura Lim,[1] Vibhuti Vyas,[1] Christine E. Brown,[1] and Stephen J. Forman[1]

[1]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Medical Center, Duarte, CA; [2]Department of Computational and Quantitative Medicine/Beckman Research Institute, City of Hope Medical Center, Duarte, CA; [3]Department of Hematology T-Cell Therapeutics Research Laboratories, City of Hope Medical Center, Duarte, CA; and [4]Department of Clinical and Translational Project Development, City of Hope Medical Center, Duarte, CA

Number of CAR-T cell treated patients registered in the EBMT Registry

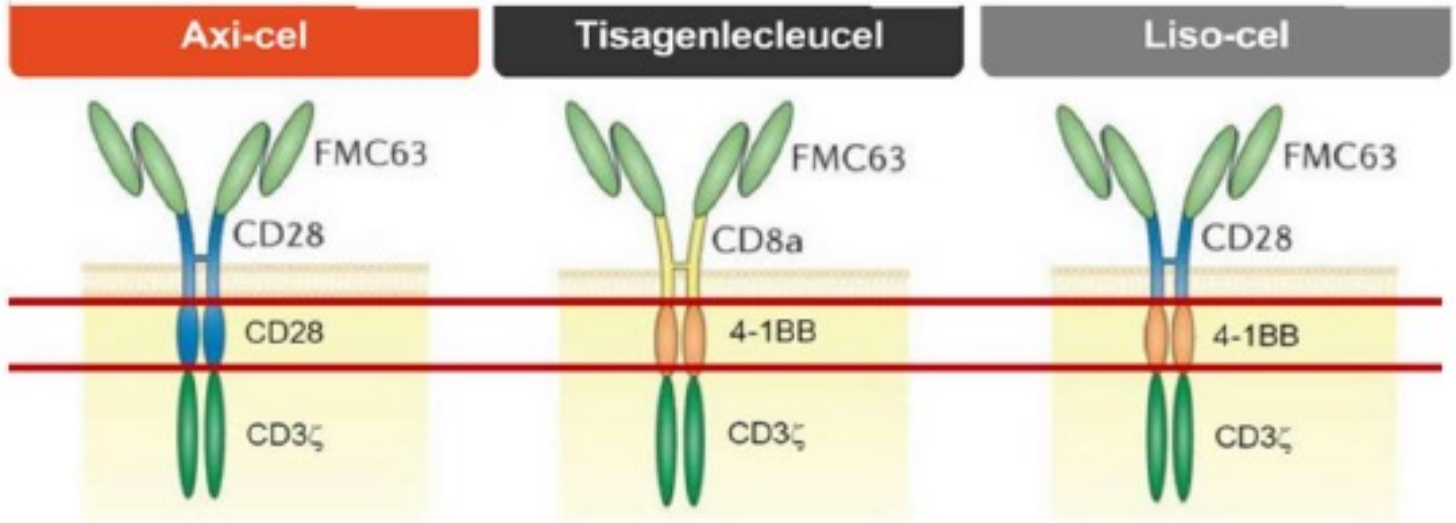


Source: EBMT Registry, September 2020

Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study

Jeremy S Abramson, M Lia Palomba, Leo I Gordon, Matthew A Lunning, Michael Wang, Jon Arnason, Amitkumar Mehta, Enkhtsetseg Purev, David G Maloney, Charalambos Andreadis, Alison Sehgal, Scott R Solomon, Nilanjan Ghosh, Tina M Albertson, Jacob Garcia, Ana Kostic, Mary Mallaney, Ken Ogasawara, Kathryn Newhall, Yeonhee Kim, Daniel Li, Tanya Siddiqi

Lancet 2020



Apheresis product	warm	frozen	warm
Production	Expansion/stimulation with macrophages	Selection with CD28	Selection/isolation with CD4/CD8
End product	0.4-2x10^8 vital cells in 68 ml	0.6-6x10^8 vital cells in 1-3 bags	5x10^7 CD8 in few ml 5x10^7 CD4 in few ml
Approval	DLBCL, HGBCL PMBL, TFL	DLBCL, HGBCL TFL, B-ALL <25y	no (studied in DLBCL, HBGCL, PMBL, TFL, FL3B)

Multicenter CD19 CAR-T cells trials in aggressive B-cell NHL

Study	ZUMA1	JULIET	TRANSCEND
Reference	Neelapu et al. NEJM 2017	Schuster et al. NEJM 2019	Abramson et al. Lancet 2020
CAR – T design	CD19/CD3ζ/**CD28**	CD19/CD3ζ/**4-1BB**	CD19/CD3ζ/**4-1BB**
CAR-T dose	$2x10^6$/Kg (Max $2x10^8$)	Up to 0,6 - $6x10^8$	0,5 – $1x10^8$ (CD4:CD8 = 1:1)
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL / Gr 3B
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	23%	49%	40%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	99%
Treated / Apheresed	108/119 (91%)	111/147 (76%)	114/134 (85%)

Efficacy in multicenter CD19 CAR-T trials in B-cell NHL

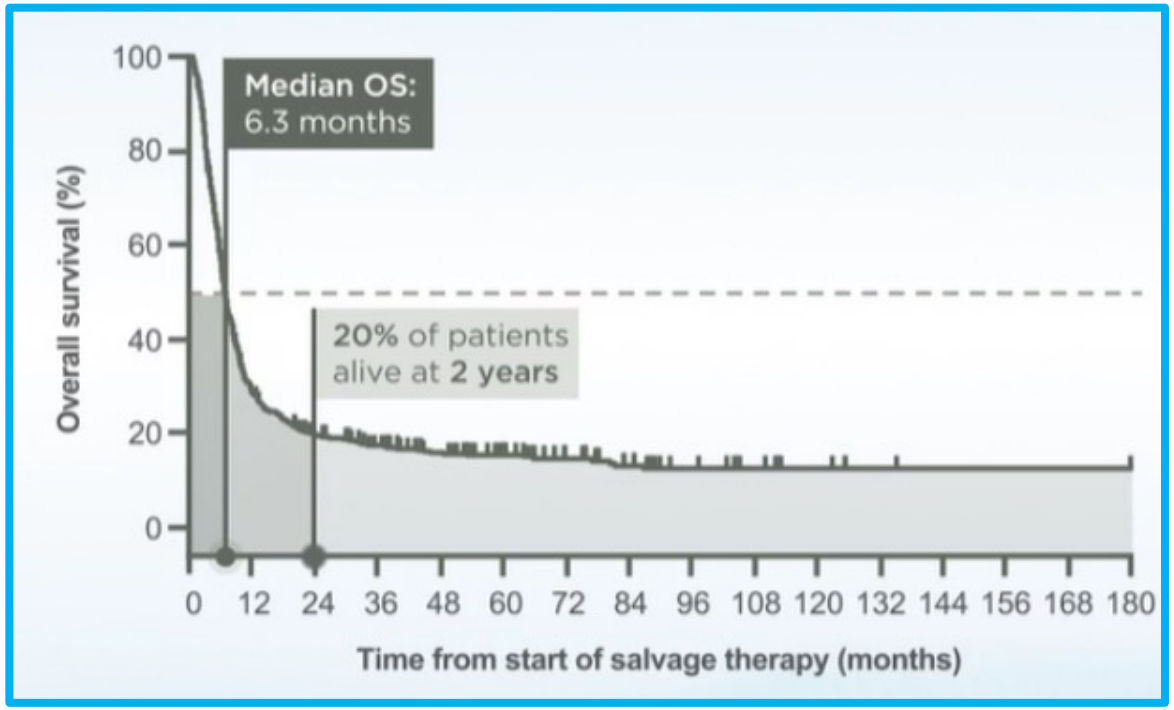
Best Response					Durability				
Study	Product	N	Best ORR	Best CR rate	F/U mo	N	Durable ORR	Durable CR rate	Ref
ZUMA 1	CD19/CD3ζ/**CD28**	108	82%	58%	12	108	42%	40%	Neelapu et al. NEJM 2017
JULIET	CD19/CD3ζ/**4-1BB**	93	52%	40%	12	93	34%	29%	Schuster et al. NEJM 2019
TRANSCEND	CD19/CD3ζ/**4-1BB**	73	80%	59%	6	73	47%	41%	Abramson et al. Lancet 2020

Safety in multicenter CD19 CAR –T trials in adult NHL

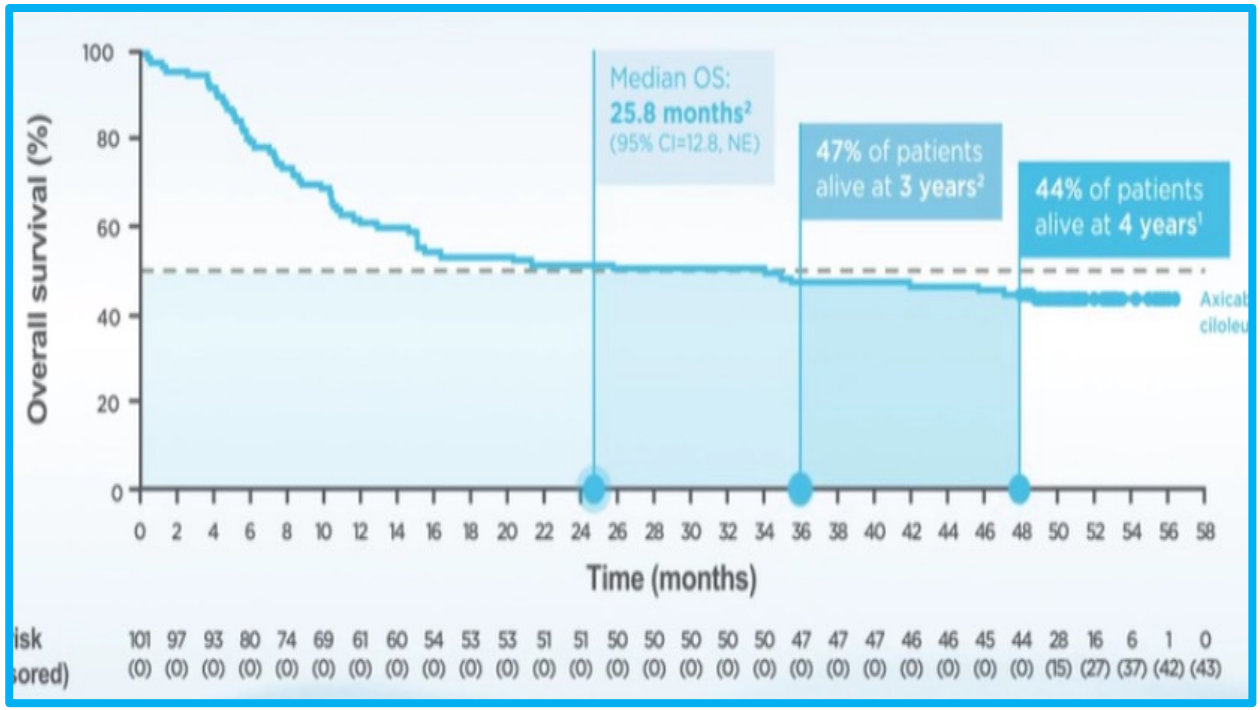
Study	Product	N	CRS All Grades	CRS Grade≥3	NT All Grades	NT Grade≥3	Toci usage	Steroid Usage	Ref
ZUMA 1	CD19/CD3ζ/ **CD28**	108	93%	13%	65%	31%	45%	29%	Neelapu et al. NEJM 2017
JULIET	CD19/CD3ζ/ **4-1BB**	111	58%	22%	21%	12%	15%	11%	Schuster et al. NEJM 2019
TRANSCEND	CD19/CD3ζ/ **4-1BB**	102	37%	1%	23%	13%	17%	21%	Abramson et al. Lancet 2020

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria or neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs - 1 cardiac arrest, 1 HLH, 1 pulmonary embolism

" Since most patients did not experience cytokine release syndrome or neurological events, in addition to the low incidence of grade 3 or worse cytokine release syndrome and neurological events, and the late median onset, additional clinical studies are investigating which patients can receive liso-cel and be safely monitored in the outpatient setting "



Crump et al, SCHOLAR 1, Blood 2017



Locke et al, Lancet Oncol 2018

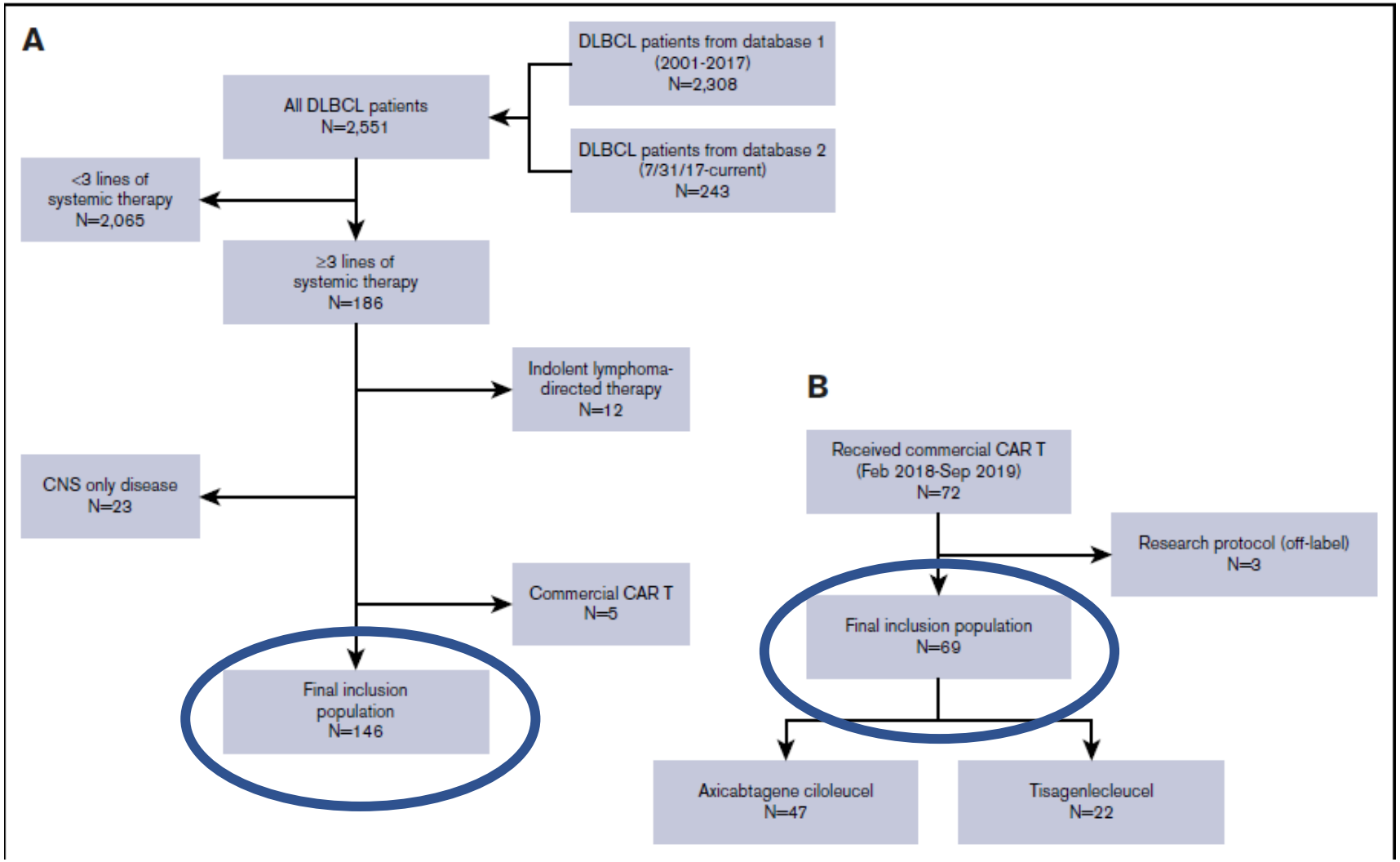
REGULAR ARTICLE

blood advances

Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies

David Sermer,[1] Connie Batlevi,[1,2] M. Lia Palomba,[1,2] Gunjan Shah,[2,3] Richard J. Lin,[2,3] Miguel-Angel Perales,[2,3] Michael Scordo,[2,3] Parastoo Dahi,[2,3] Martina Pennisi,[3] Aishat Afuye,[3] Mari Lynne Silverberg,[3] Caleb Ho,[4] Jessica Flynn,[5] Sean Devlin,[5] Philip Caron,[1,2] Audrey Hamilton,[1,2] Paul Hamlin,[1,2] Steven Horwitz,[1,2] Erel Joffe,[1,2] Anita Kumar,[1,2] Matthew Matasar,[1,2] Ariela Noy,[1,2] Colette Owens,[1,2] Alison Moskowitz,[1,2] David Straus,[1,2] Gottfried von Keudell,[1,2] Ildefonso Rodriguez-Rivera,[1,2] Lorenzo Falchi,[1,2] Andrew Zelenetz,[1,2] Joachim Yahalom,[6] Anas Younes,[1,2] and Craig Sauter[2,3]

[1]Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Department of Medicine, Weill Cornell Medical College, New York, NY; and [3]Adult Bone Marrow Transplant Service, Department of Medicine, [4]Department of Pathology, [5]Department of Epidemiology and Biostatistics, and [6]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY



Single centre, retrospective study of adult patients (≥ 18 years), diagnosed with R/R DBCL and treated with CAR-T or alternate therapies

Characteristics	Alternate	CAR T	P
Total, n	146	69	
Age			
Median (range), y	66 (27-91)	63 (19-85)	.5
>60 y, n (%)	90 (62)	43 (62)	>.9
ECOG			.4
0-1, n (%)	130 (92)	60 (87)	
≥2, n (%)	12 (8.5)	9 (13)	
Unknown, n	4	0	
Bulk >10 cm, n (%)	23 (16)	12 (17)	>.9
Unknown, n	3	0	
Number of EN sites, n (%)			.5
0-1	97 (66)	42 (61)	
>1	49 (34)	27 (39)	
Elevated LDH, n (%)	86 (66)	31 (45)	**.007**
Unknown, n	15	0	
Stage			>.9
Limited, n (%)	24 (16)	11 (16)	
Advanced, n (%)	122 (84)	58 (84)	
BM involvement, n (%)	5 (3.6)	10 (21)	**<.001**
Unknown, n	9	22	
Refractory disease			**<.001**
No, n (%)	31 (21)	46 (67)	
Yes, n (%)	114 (79)	23 (33)	
Missing, n	1	0	
Prior AHCT, n (%)	20 (14)	14 (20)	.2
Prior allogeneic-HCT, n (%)	3 (2)	4 (6)	.2

Outcomes	Alternate	CAR T	P
Total, n	146	69	
CR rate, %	22	52	<.001
ORR, %	32	72	<.001
6-mo OS, % (95% CI)	55 (47-64)	71 (61-82)	
12-mo OS, % (95% CI)	39 (31-48)	64 (54-77)	
Median OS, mo	6.5	19.3	.006
6-mo PFS, % (95% CI)	29 (23-38)	49 (39-63)	
12-mo PFS, % (95% CI)	25 (19-33)	44 (33-58)	
Median PFS, mo	2.3	5.2	.01

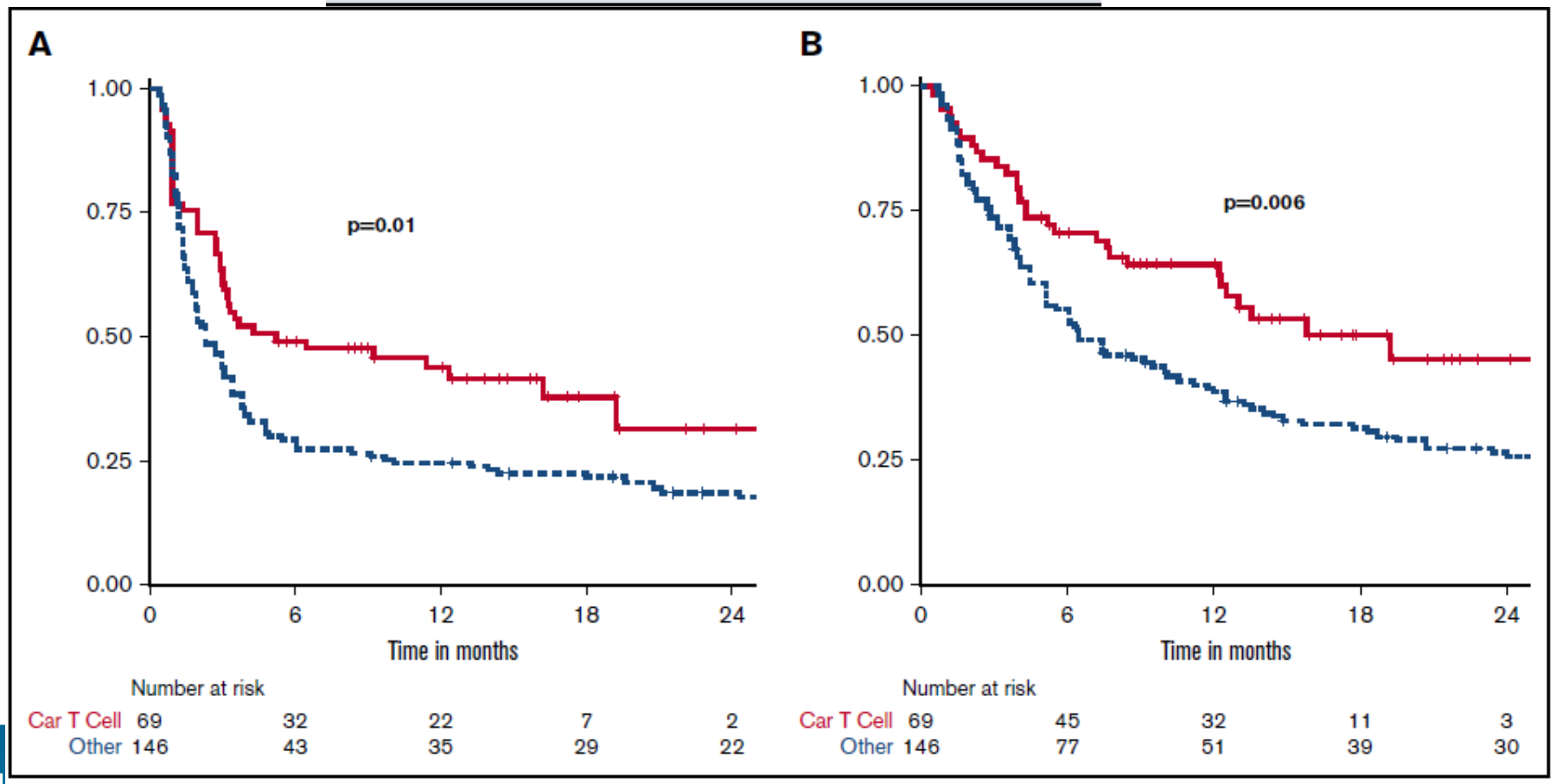


Figure 2. Kaplan-Meier curves of all 215 patients comparing outcomes by treatment cohort. (A) PFS. (B) OS.

CAR-T cell therapy in R/R in DLBCL patients: novel targets and combination trials

In RR disease						
Novel targets and constructs						
NCT03277729	CD20	1/2		Safety		Recruiting
NCT04088890	CD22	1		Rate of successful manufacture, safety		Recruiting
NCT03870945[71]	CD19/CD20	1/2		Safety	ORR 75% in 12 patients, CR 42%.	Phase 2 recruiting
NCT04215016	CD19/CD20	1		Safety		Recruiting
NCT04007029	CD19/CD20			Safety		Recruiting
NCT03233854	CD19/CD22	1		Safety		Recruiting
Combinations with CPIs and targeted agents						
ZUMA-6 / NCT02926833[72]	CD19	1/2	Followed by atezolizumab	Phase 1: safety Phase 1 and 2: CR	No DLT seen in 3 patients treated	Recruiting completed
ALEXANDER (NCT03287817)[73]	CD19/CD22	1/2	Followed by pembrolizumab	Phase 1: safety Phase 2: ORR	No DLT seen in phase 1. ORR 69%; CRR 52%.	Recruiting completed
NCT02706405	CD19	1	Followed by durvalumab	Safety and pharmacokinetics		Recruiting
NCT04257578	CD19	1/2	BTK inhibitor acalabrutinib prior	Safety		Recruiting
ZUMA-19 (NCT04314843)[74]	CD19	1/2	Prior Lenzilumab, a humanized anti-GM-CSF MoAb	Incidence of Grade ≥ 2 NEs within 28 days of axi-cel administration		Recruiting

Adaniya SS et al, AJH, 2021

CAR-T cell trials in the treatment of DLBCL: Shifting to earlier lines

In first relapse						
Title/NCT	**Target**	**Phase**	**Additional agents**	**Primary endpoint**	**Preliminary data**	**Status**
ZUMA-7 / NCT03391466*	CD19	3		EFS		Recruiting completed
BELINDA / NCT03570892*	CD19	3		EFS		Recruiting
TRANSFORM NCT03575351*	CD19	3		EFS		Recruiting
*Comparator arm: Platinum-based immunochemotherapy followed by high dose chemotherapy and autoSCT in responding patients						

Adaniya SS et al, AJH, 2021

Up-front therapy

Title / NCT	Trial population	Patients	Intervention	Primary outcome
ZUMA-12/ NCT03761056[42]	HGBL, with MYC and BCL2 and/or BCL6 translocations, or LBCL with IPI score ≥ 3 and positive iPET	37	Conditioning Chemotherapy Flu/Cy + Axi-Cel Infusion	CR Preliminary data: ORR 85%, (74% CR; 11% PR)
NCT02481310[46]	Aggressive MYC-aberrant NHL (MYC-overexpression by IHC (> 40%), MYC-amplification (>4 copies) by FISH, and/or MYC-rearrangement by FISH)	38	Ixazomib + DA-EPOCH-R x6 followed by ixazomib maintenance	Safety and 12 month-PFS After induction, ORR 89%, CR 61%. Estimated 24-months PFS and OS were 66.9 and 78.7%, respectively.
ACCEPT/ NCT03571308[48]	Untreated CD20+ DLBCL	39	R-CHOP and acalabrutinib	Safety and ORR. No DLT events. Of 24 patients, ORR 95%, CR 82%, 12-month PFS and OS 100%.
NCT03147885[49]	Untreated stage III/IV DLBCL	44	Selinexor + R-CHOP followed by Selinexor maintenance for 1 year	PFS In 10 pts at Median follow up of 476 days, ORR 100%: CR 90%, PR 10%
NCT03995147[50]	Previously untreated DLBCL, transformed lymphoma and grade 3 B follicular lymphoma	30	Pembrolizumab +R-CHOPx6	PFS. At median follow-up of 32 months, 3-year estimated PFS is 83% and OS is 86% irrespective of COO by OHC
POLARIX/NCT03274492[51]	Untreated CD20-positive DLBCL, IPI 2–5	1000	Polatuzumab with R-CHP vs R-CHOP	Investigator-assessed PFS
NCT04231877[44]	Untreated aggressive B-cell large-B cell lymphoma (non-Hodgkin lymphoma) with adverse features per investigator assessment	18	Polatuzumab plus DA-EPCH-R	Safety
NCT03677141[44]	Previously untreated DLBCL, IPI 2–5	160	Monetuzumab plus CHOP or CHP-Polatuzumab Vedotin vs R-CHP-Polatuzumab	Safety and CR rate
First-MIND / NCT04134936[52]	Previously untreated DLBCL, IPI 2–5	60	Tafasitamab +R-CHOPx6 or R2-CHOPx6	Safety

Adaniya SS et al, AJH, 2021

Outlook for CAR-T Cell Therapy

Shifting CAR-T Cell Therapy to Earlier Lines

- Adult patients with B-cell NHL
- Phase III study comparing tisagenlecleucel with standard of care (platinum-based immunochemotherapy followed in responding patients with high-dose chemotherapy and autoSCT)

- Adult patients with r/r DLBCL
- Phase III study comparing axicabtagene ciloleucel to standard of care (platinum-based chemotherapy followed by high-dose therapy and autoSCT in responders)

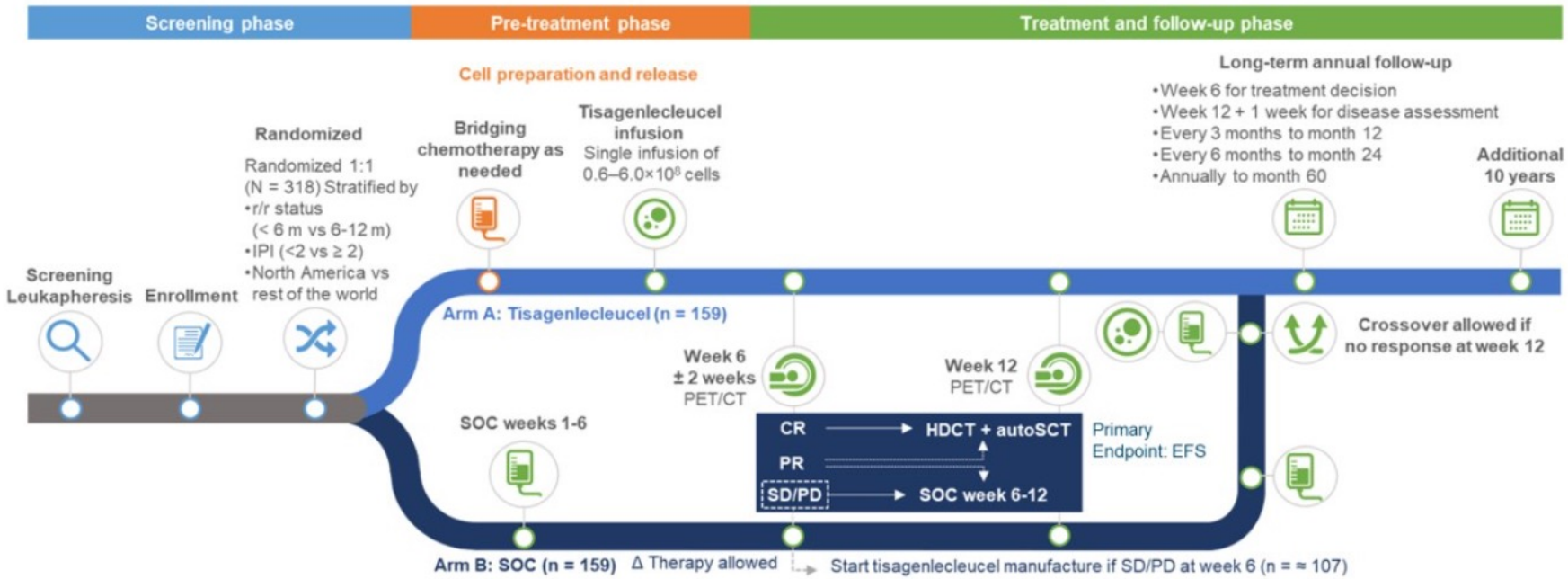
- Adult patients with B-cell NHL
- Phase III study comparing lisocabtagene maraleucel to standard of care (R-DHAP, R-ICE, or R-GDP followed by high-dose chemotherapy and HSCT)

autoSCT, autologous stem cell transplant; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; HSCT, hematopoietic stem cell transplant; NHL, non-Hodgkin lymphoma; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; R-GDP, rituximab, gemcitabine, cisplatin, and dexamethasone; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; r/r, relapsed or refractory.

NB!!! R/R DLBCL after ≤ 12 months after 1 L therapy

BELINDA: Phase III Study Comparing Tisagenlecleucel With Standard of Care

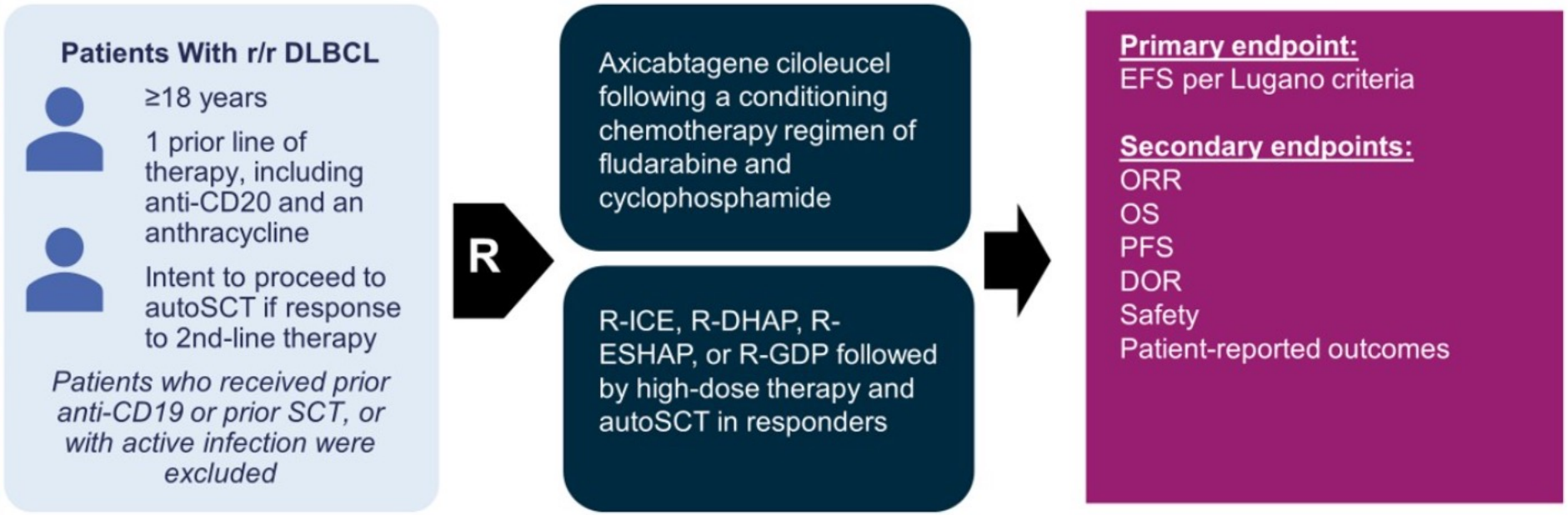
- Randomized, open-label study to evaluate the efficacy, safety, and tolerability of tisagenlecleucel compared to standard of care in adult patients with r/r B-cell NHL (NCT03570892)



autoSCT, autologous stem cell transplant; CR, complete response; CT, computed tomography; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index (1993); NHL, non-Hodgkin lymphoma; PD, progressive disease; PET, positron emission tomography; PR, partial response; r/r, relapsed or refractory; SD, stable disease; SOC, standard of care.

ZUMA-7: Phase III Study Comparing Axicabtagene Ciloleucel With Standard of Care

- Randomized, open-label study to evaluate the efficacy of axicabtagene ciloleucel compared to standard of care in adult patients with r/r DLBCL (NCT03391466)



autoSCT, autologous SCT; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomization; r/r, relapsed or refractory; R-DHAP, rituximab, cisplatin, cytarabine, and dexamethasone; R-ESHAP, rituximab, etoposide, cytarabine, cisplatinum, and methylprednisolone; R-GDP, rituximab, gemcitabine, cisplatin, and dexamethasone; R-ICE, rituximab, ifosfamide, etoposide, and carboplatin; SCT, stem cell transplant.

Locke FL et al; ASH 2021

ZUMA 7: results after a median follow-up of 24.9 months

	Axi-cell (single infusion of 2 x 10^6 CART/kg after CTX + Fluda conditioning)*	SOC (2-3 platinum-based CHT). Patients with CR/PR proceeded to ASCT	
N patients	180 enrolled; 170 infused	179 enrolled; 64 (36%) reached ASCT	
EFS§ months ,median (95% C.I.)	8.3 (4.5-15.8)	2 (1.6-2.8)	HR: 0.398 (P< 0.0001)
ORR °	83%	50%	OR: 5.31 (95% C.I. 3.1-8.9) P< 0.0001
CR °	65%	32%	
OS (months)	Not reached	35.1 #	HR: 0.730 (P = 0.027)
AE (N; %) ≥ G3	155 (91)	140 (83)	
Tx related death	1	2	
CRS ≥ G3 (N; %)	11 (6)	NA	

*: Bridging therapy limited to CTS

§: time to earlest date to disease progression; death from any causes; new lymphoma

° : Lugano classification

100 (56%) patients received CAR-T cell therapy as subsequent treatment

Locke FL et al; ASH 2021

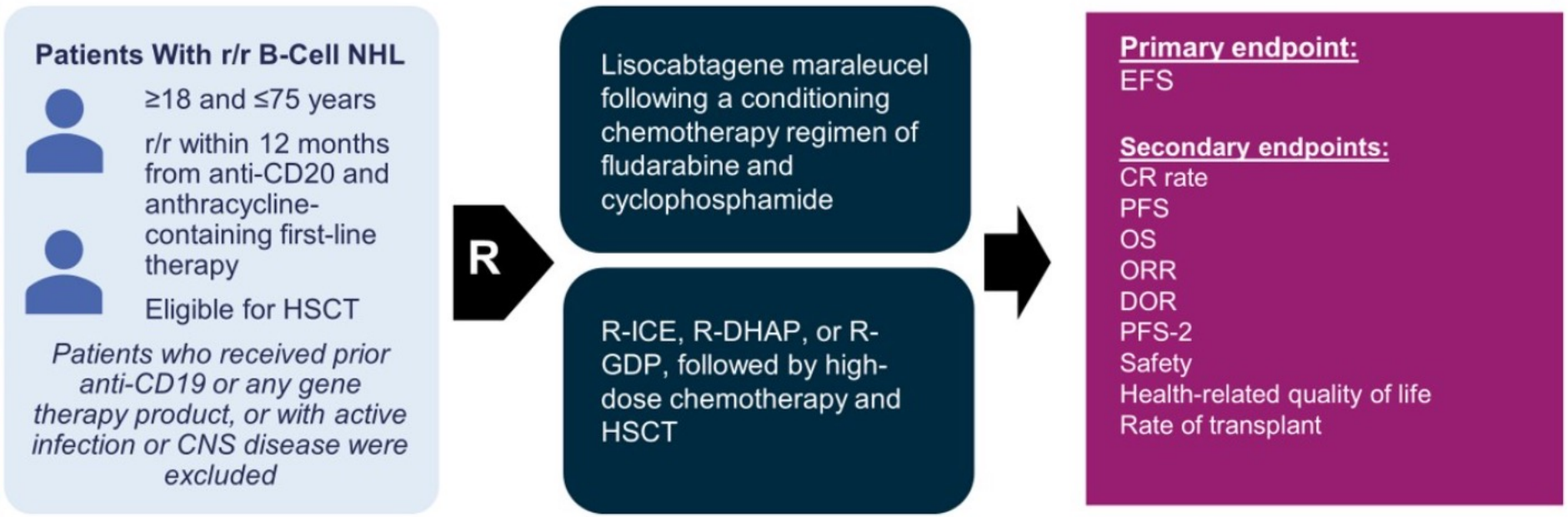
ZUMA 7: conclusions

- In this Phase 3 study in 2L therapy in R/R DLBCL, Axi - cel showed a > 4 –fold greater median EFS, 2.5-fold greater EFS at 2 y, double the CR rate over SOC
- Safety of Axi - cel was manageable
- Axi - cel may replace CHT + ASCT as SOC for 2L in R/R DLBCL

Locke FL et al; ASH 2021

TRANSFORM: Phase III Study Comparing Lisocabtagene Maraleucel With Standard of Care

- Randomized, open-label study to evaluate the efficacy and safety of lisocabtagene maraleucel compared to standard of care in adult patients with aggressive r/r B-cell NHL (NCT03575351)



CD, cluster of differentiation; CNS, central nervous system; CR, complete response; DOR, duration of response; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS-2, progression-free survival on next line of treatment; R, randomization; r/r, relapsed or refractory; R-DHAP, rituximab, cisplatin, cytarabine, and dexamethasone; R-GDP, rituximab, gemcitabine, cisplatin, and dexamethasone; R-ICE, rituximab, ifosfamide, etoposide, and carboplatin.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03575351. Accessed January 21, 2021.

Kamdar M et al; ASH 2021

TRANSFORM: results after a median follow-up of 6.2 months

	Liso-cell (single infusion of 100 x 10^6 CART/kg after CTX + Fluda conditioning)*	SOC (3 platinum-based CHT). Patients with CR/PR proceeded to ASCT	
N patients	92 enrolled; 90 infused	92 enrolled; 43 (46.7%) reached ASCT)	
Age median (range), y	60 (20-74)	58 (26-75)	
EFS§ months ,median (95% C.I.)	10.1 (6-1-NR)	2.2 (2.2-4.3)	HR: 0.349 (P< 0.0001)
ORR n (%) (95% C.I.)	79 (86) (77.0-92.3)	44 (48) (37.3-58.5)	P< 0.0001
CR °	61 (66) (55.7-75.8)	36 (39) (29.1-49.9)	P<0.0001
OS median (95% C.I.)months	NR (15.8-NR)	16.4 (11.0-NR) #	HR: 0.509 (P = 0.0257)
AE (N; %) ≥ G3	85 (92)	79 (87)	
CRS ≥ G3 (N; %)	1 (1)	NA	

*: Bridging therapy with CHT was allowed

§: death from any causes; PD; failure to achieve CR or PR by 9 weeks after randomization; start of new antineoplastic therapy

° : Lugano classification

50 (54%) patients received CAR-T cell therapy as subsequent treatment

Kamdar M et al; ASH 2021

TRANSFORM: conclusions

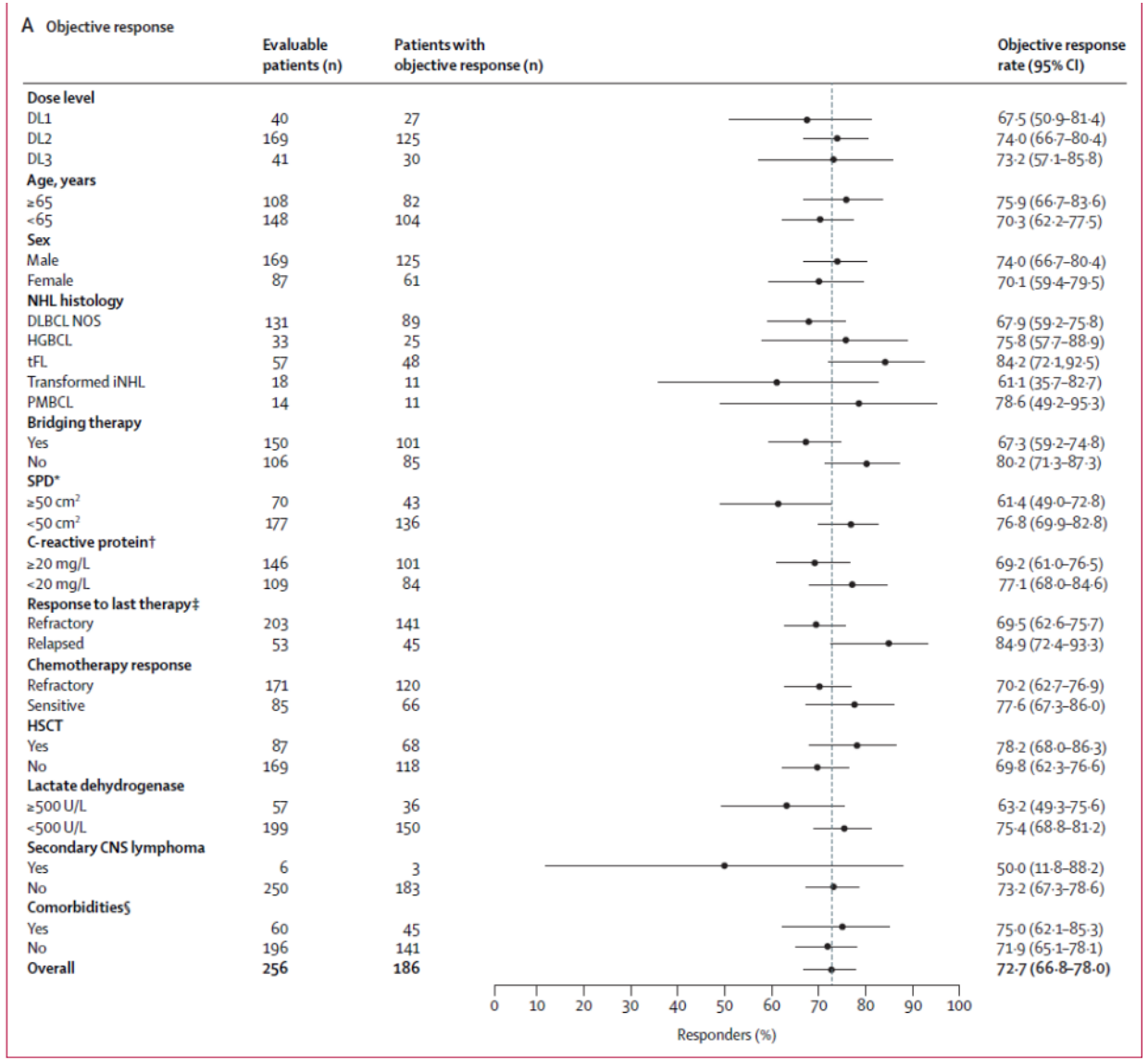
- In this Phase 3 study in 2L therapy in R/R DLBCL, Liso - cel showed a statistically significant and clinically meaningful improvement in EFS and CR rate compared with 2L SOC
- Safety of Liso - cel was manageable
- Liso - cel may replace CHT + ASCT as SOC for 2L in R/R DLBCL

Kamdar M et al; ASH 2021

Management of DLBCL at first relapse: transplantation – inelegible patients

- Patients treated with palliative intent regimen: R-GemOX; R-Bendamustine; Lenalidomide; Ibrutinib….
- Could CAR-T cell therapy represent an appealing option for patients considered ASCT inelegible, providing the first curative approach ?

Lisocabtagene maraleucel for patients with relapsed or	
Chemotherapy refractory**	181 (67%)
Received previous HSCT	94 (35%)
Autologous HSCT	90 (33%)
Allogeneic HSCT	9 (3%)
Never achieved complete response with previous therapy††	119 (44%)
Received bridging therapy	159 (59%)
Secondary CNS lymphoma	7 (3%)
Creatinine clearance >30 to <60 mL/min§	51 (19%)
Baseline C-reactive protein, mg/L	27·6 (7·9–81·6)
Left-ventricular ejection fraction ≥40% and <50%¶	13 (5%)



Objective responses were achieved across all subgroups, including in patients with

- high-risk feature
- those aged 65 years or older
- patients with chemotherapy-refractory disease
- patients with comorbidities

Outlook for CAR-T Cell Therapy
High-Risk Patient Populations

- Phase II study evaluating tisagenlecleucel in pediatric and young adult patients with high-risk B-cell ALL who are MRD-positive at EOC therapy

- Phase II study evaluating tisagenlecleucel in pediatric and young adult patients with r/r B-cell NHL

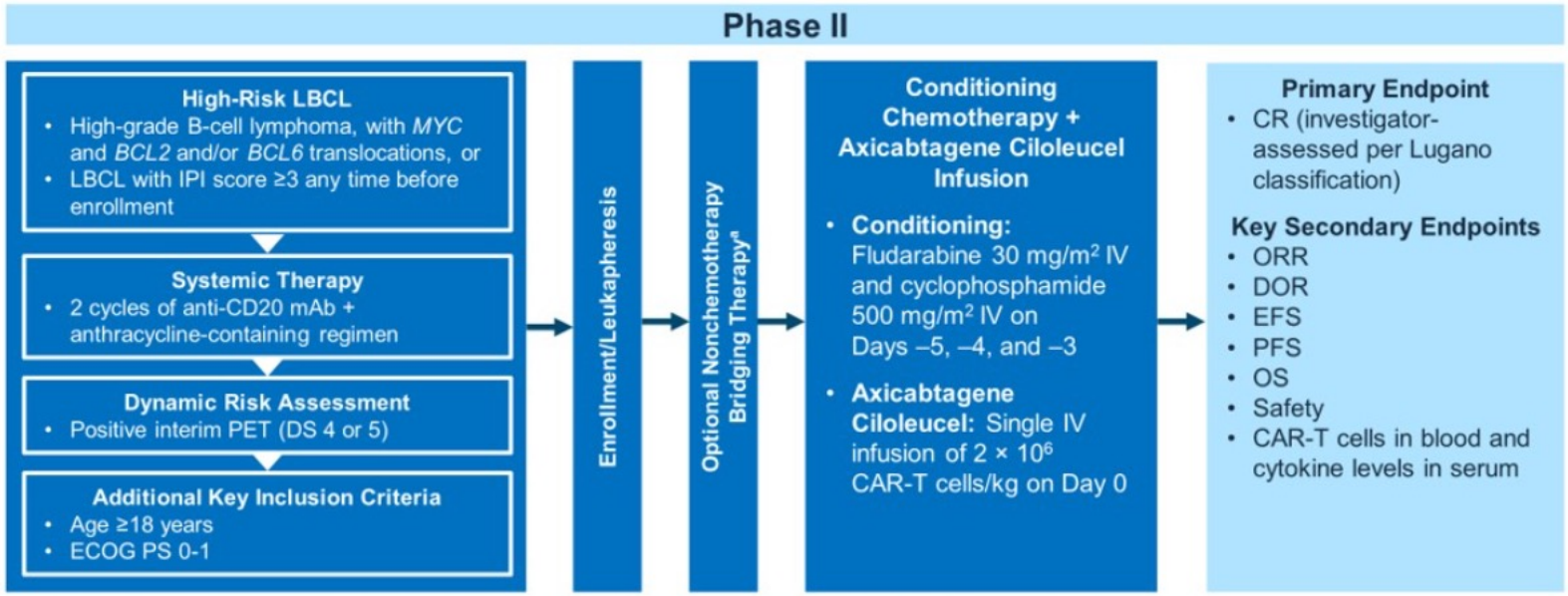
- Phase II study evaluating axicabtagene ciloleucel in adult patients with high-risk LBCL with suboptimal response to first-line therapy

- Phase II study evaluating lisocabtagene maraleucel in adult patients with aggressive B-cell NHL, including patients with primary central nervous system involvement

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; EOC, end of consolidation; LBCL, large B-cell lymphoma; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; r/r, relapsed or refractory.

ZUMA-12: Phase II Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients With High-Risk LBCL

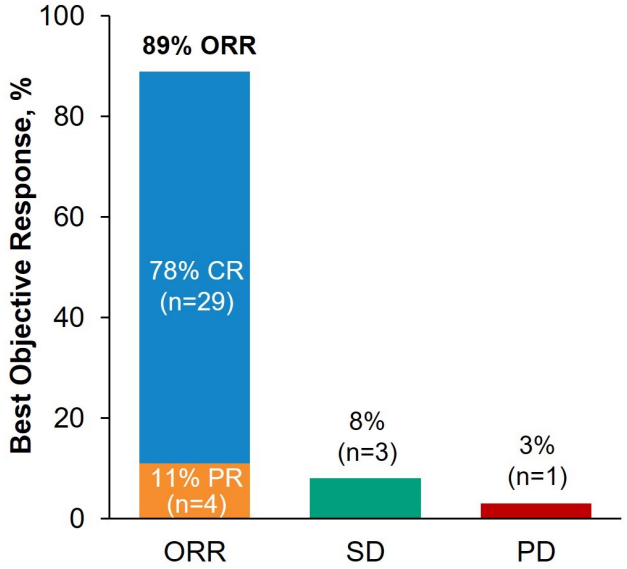
- Single-arm, open-label study to evaluate the efficacy and safety of axicabtagene ciloleucel as first-line therapy in adult patients with high-risk LBCL (NCT03761056)



[a]Administered after leukapheresis and completed prior to initiating conditioning chemotherapy; PET-CT was required after bridging.
CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; DOR, duration of response; DS, Deauville score; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival.

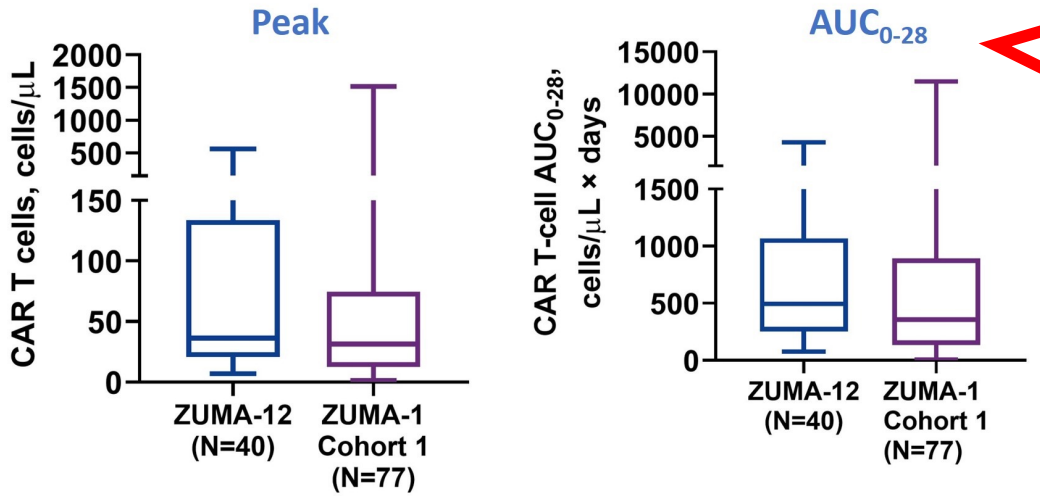
Neelapu SS et al; ASH 2021

Responses with axi-cel in high-risk LBCL.



	Response Evaluable (N=37)
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

CAR T-cell expansion by peak and AUC in ZUMA-12 and ZUMA-1.[a]



Frequency of CCR7-positive phenotype greater in Zuma-12 vs Zuma-1, suggesting better T cell fitness

Neelapu SS et al; ASH 2021

[a] ZUMA-1 Phase 2 Cohort 1 includes all treated patients who received any dose of axi-cel and have ≥24 months of follow-up.
Axi-cel, axicabtagene ciloleucel; AUC, area under the curve; CAR, chimeric antigen receptor; CR, complete response; LBCL, large B-cell lymphoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Zuma 12: results (2)

Median follow-up 15 months

Age median (range), years	61 (23-86)
OS at 12 months	91%
DOR, EFS, PFS (median)	NR
AE grade ≥ 3 %	85
CRS grade ≥ 3 n (%) *	3 (8)
ICAN AE grade ≥ 3 n (%) §	9 (23)

* median time to onset: 4 days (1-10); median duration: 6 days; tocilizumab in 63%; CTS in 35%; all events resolved by 14 days post-infusion

§ median time to onset: 9 days (2-24); median duration: 7 days; tocilizumab in 3%; CTS in 33%; all events but one resolved by 21 days post-infusion

Neelapu SS et al; ASH 2021

ZUMA 12 : conclusions

- In this Phase 2, single arm study in patients with high-risk DLBCL, axi - cel showed a high rate and complete response, as part of first-line therapy
- Safety of axi - cel was manageable
- Prognostic value of interim PET still controversial: RCT will be needed!

Neelapu SS et al; ASH 2021

CAR-T therapy up-front and after 1st relapse in DLBCL patients

- Ongoing trials are showing exciting opportunities
- Further trials are warranted, to confirm preliminary, positive data of OS, ORR, DOR, EFS and PFS
- An earlier use on the disease of CAR-T may be more effective and safer since their efficacy relies on the fitness of the endogenous T cell repertoire, not compromised by extensive prior therapy
- Need of a more standardized molecular profiling, that may inform patient selection and clinical trial design (concomitant target drug; consolidation treatment; maintenance program)