Making Cancer History®

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

The new algorithm for R/R DLBCL management

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Disclosure

Consulting:

Abbvie, ADC Therapeutics, AstraZeneca, BMS, Genentech, GenMab, Janssen, Kite/Gilead, Morphosys/Incyte, Novartis, Nurix, Regeneron, SeaGen

Research Funding:

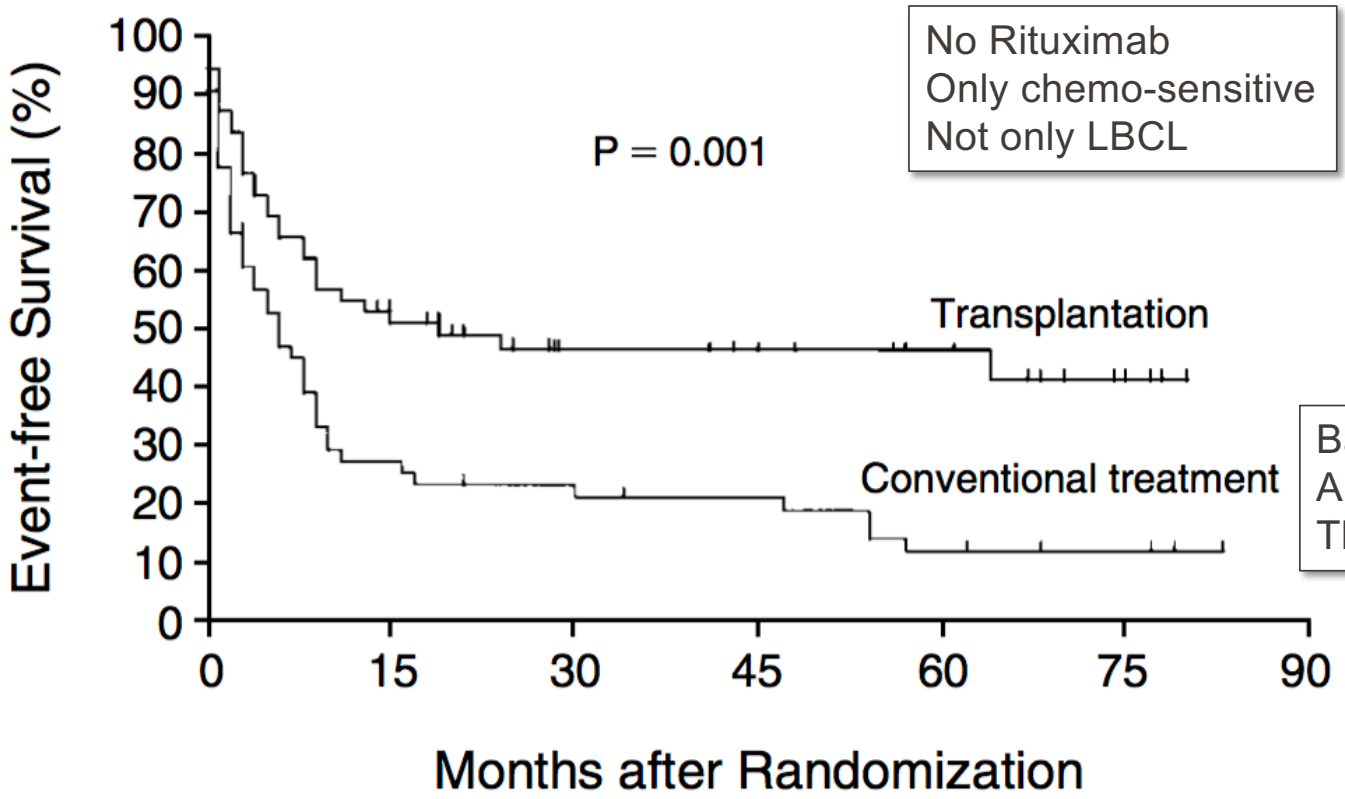
ADC Therapeutics, AstraZeneca, BMS, Genentech, Janssen, Kite/Gilead, Morphosys/Incyte, Novartis, Nurix, Regeneron

Paradigm shift?

What is a paradigm? A phrase diluted by overuse

Definition: A model or pattern

Auto Stem Cell Transplant in relapsed NHL Parma Trial



No Rituximab
Only chemo-sensitive
Not only LBCL

Based on these data, AutoSCT was THE 2L Therapy for nearly 30y

4 Philip NEJM 1995

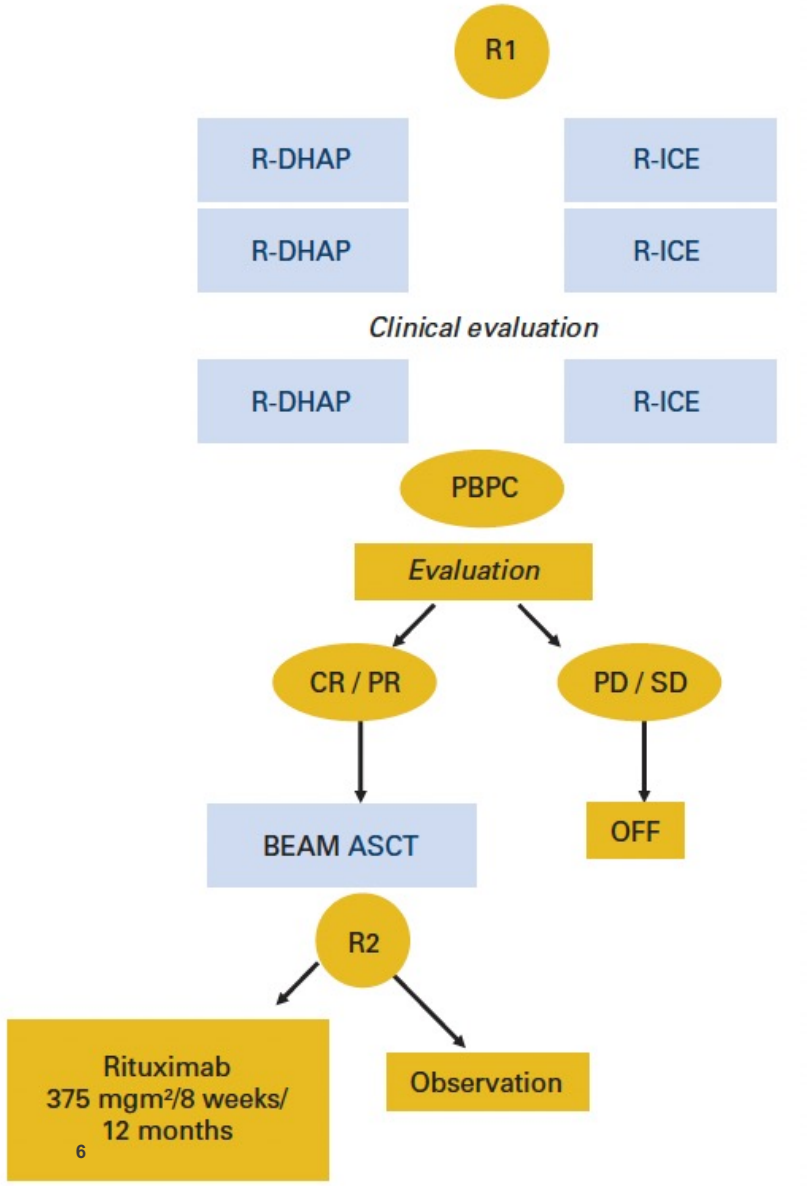
VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

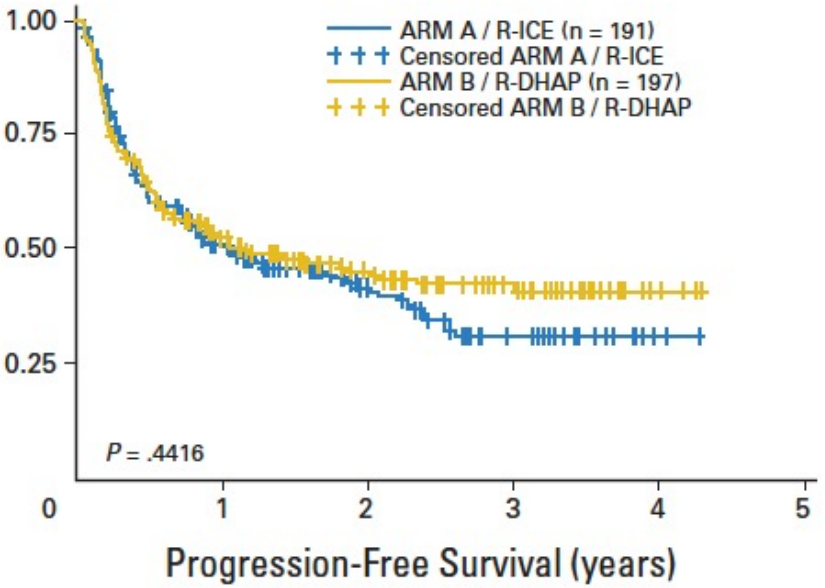
JOURNAL OF CLINICAL ONCOLOGY

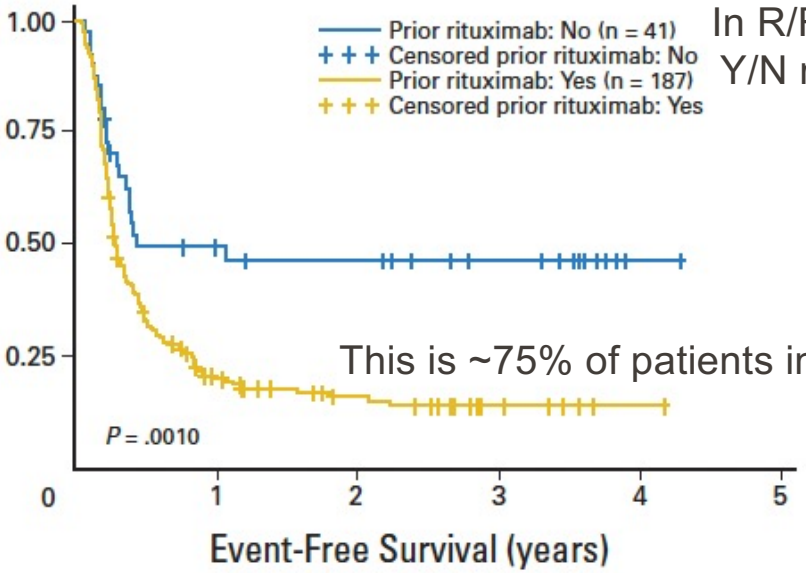
ORIGINAL REPORT

Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz







In R/R <12m from 1L, Y/N rituximab with 1L

This is ~75% of patients in 2L in 2024

VOLUME 35 · NUMBER 5 · FEBRUARY 10, 2017

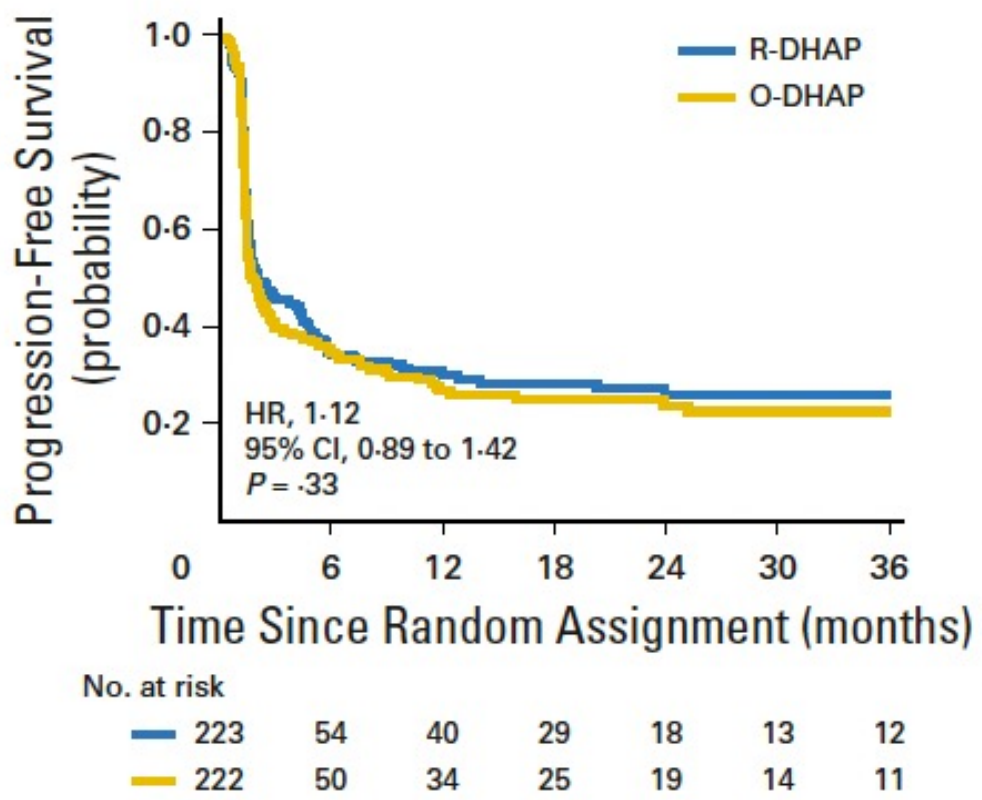
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study

Gustaaf W. van Imhoff, Andrew McMillan, Matthew J. Matasar, John Radford, Kirit M. Ardeshna, Kazimierz Kuliczkowski, WonSeog Kim, Xiaonan Hong, Jette Soenderskov Goerloev, Andrew Davies, María Dolores Caballero Barrigón, Michinori Ogura, Sirpa Leppä, Michael Fennessy, Qiming Liao, Bronno van der Holt, Steen Lisby, and Anton Hagenbeek

ORCHARRD


Progression-Free Survival (probability)
1·0
0·8
0·6
0·4
0·2
R-DHAP
O-DHAP
HR, 1·12
95% CI, 0·89 to 1·42
P = ·33
0
6
12
18
24
30
36
Time Since Random Assignment (months)
No. at risk
223 54 40 29 18 13 12
222 50 34 25 19 14 11

VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

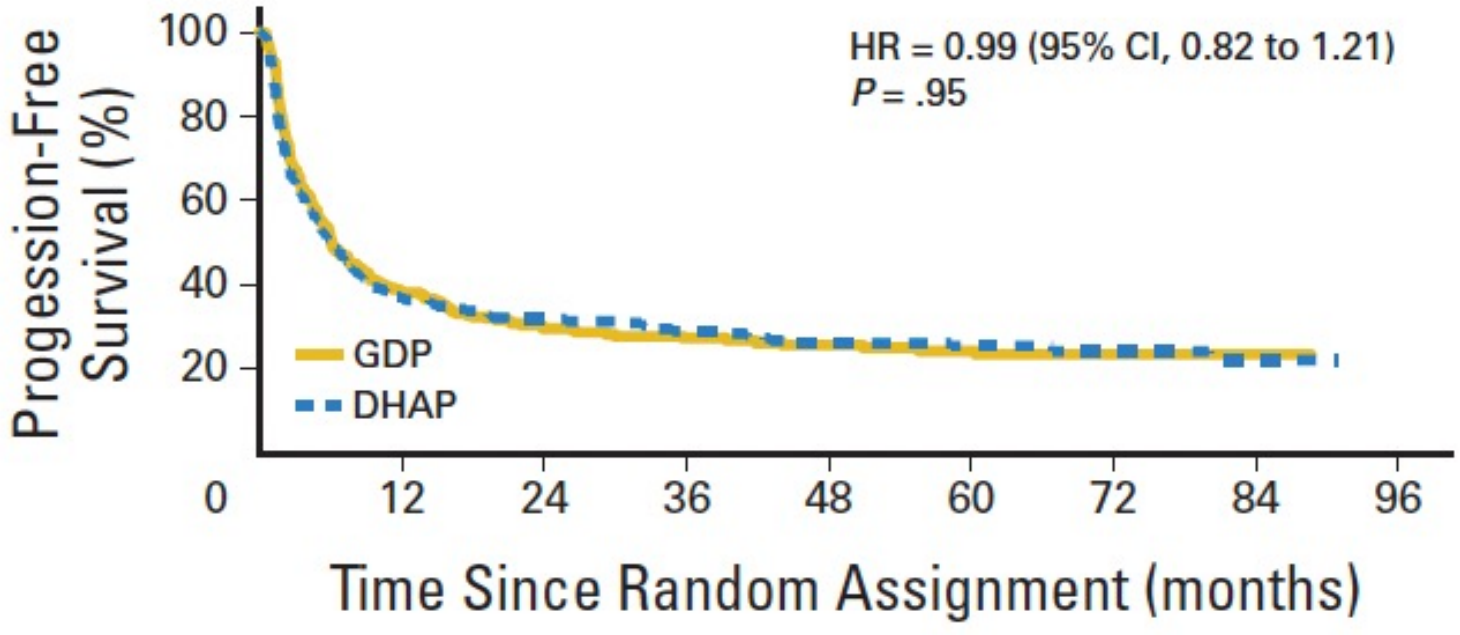
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12

Michael Crump, John Kuruvilla, Stephen Couban, David A. MacDonald, Vishal Kukreti, C. Tom Kouroukis, Morel Rubinger,† Rena Buckstein, Kevin R. Imrie, Massimo Federico, Nicola Di Renzo, Kang Howson-Jan, Tara Baetz, Leonard Kaizer, Michael Voralia, Harold J. Olney, A. Robert Turner, Jonathan Sussman, Annette E. Hay, Marina S. Djurfeldt, Ralph M. Meyer, Bingshu E. Chen, and Lois E. Shepherd

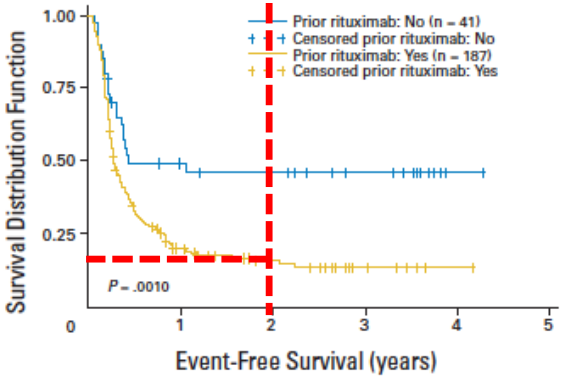
LY12



No. at risk									
GDP	310	104	71	57	45	30	17	8	0
DHAP	309	101	75	60	44	32	17	10	2

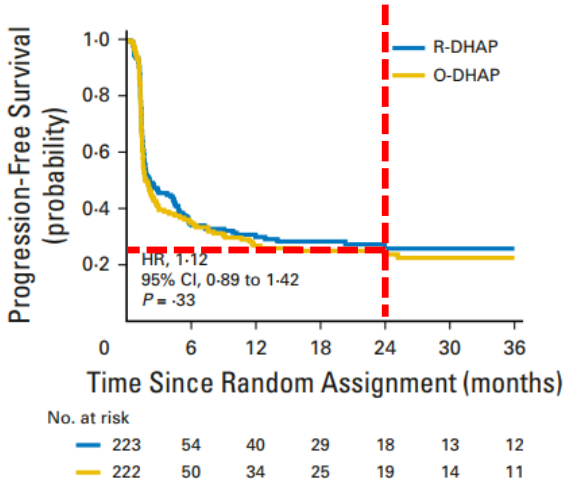
	CORAL		ORCHARRD		LY.12	
1 Refractory						
	NR (40% relapse <12m)		60%		30%	
ORR						
	RDHAP	64%	RDHAP	42%	RDHAP	45%
	RICE	63%	ODHAP	38%	RGDP	46%
CR Rate						
	RDHAP	40%	RDHAP	22%	RDHAP	15%
	RICE	36%	ODHAP	15%	RGDP	14%
Received ASCT						
	RDHAP	55%	RDHAP	37%	RDHAP	49%
	RICE	51%	ODHAP	33%	RGDP	53%

CORAL



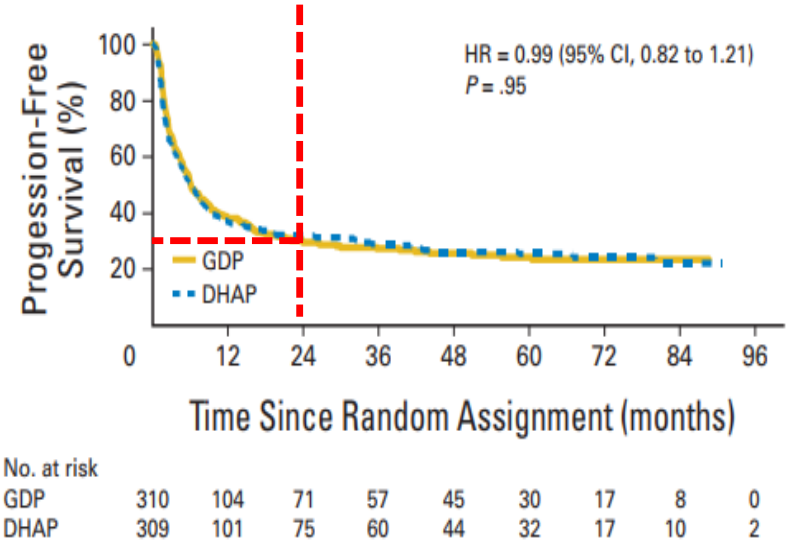
Gisselbrecht, et al. JCO 2010

ORCHARRD



van Imhoff, et al. JCO 2017

NCIC-CTG LY.12

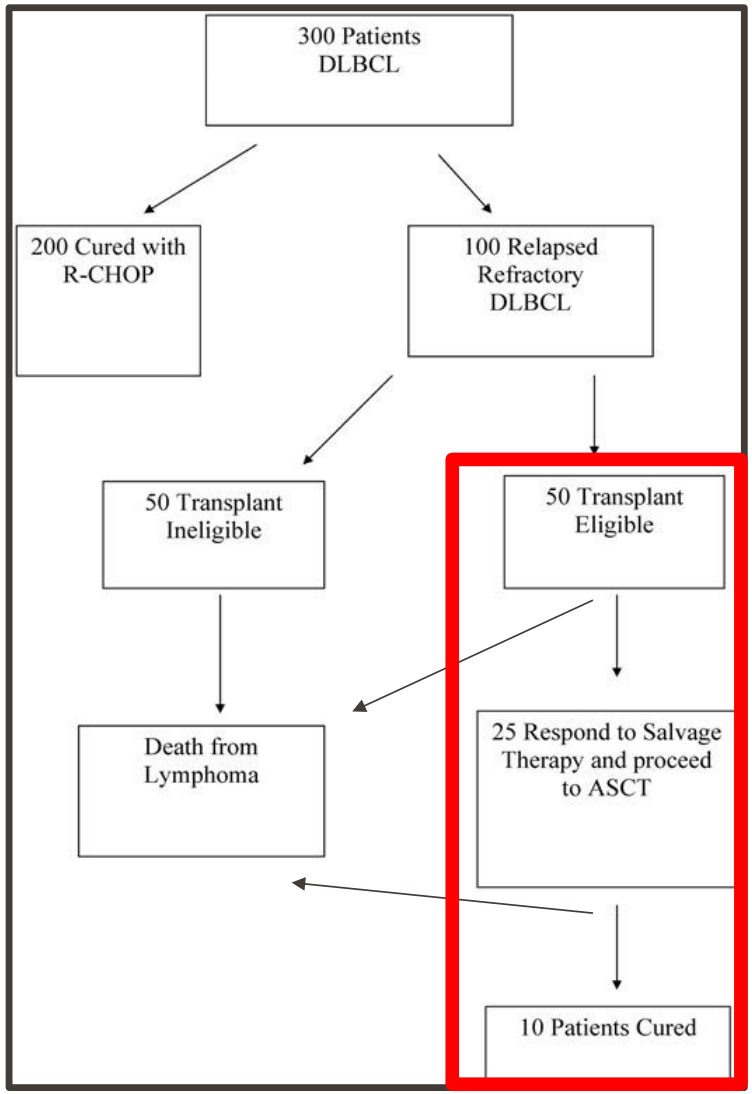


Crump, et al. JCO 2014

Of 10 patients,10 have significant toxicity

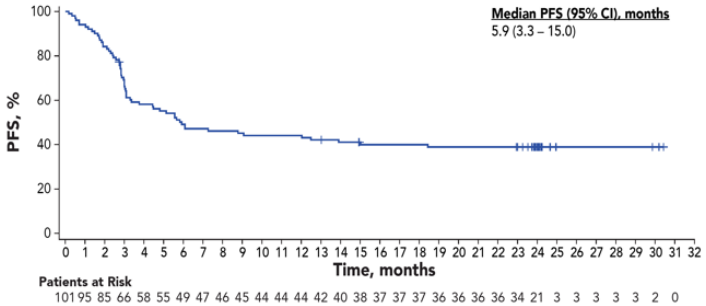
- 3 receive durable benefit with toxicity
- 7 receive toxicity without durable benefit

The algorithm

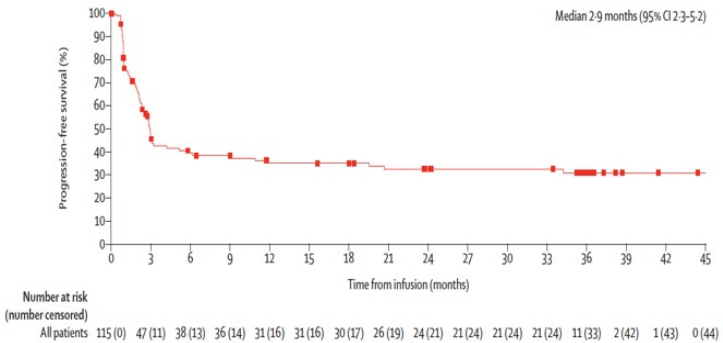


CAR T-cells in ≥3L for LBCL: PFS

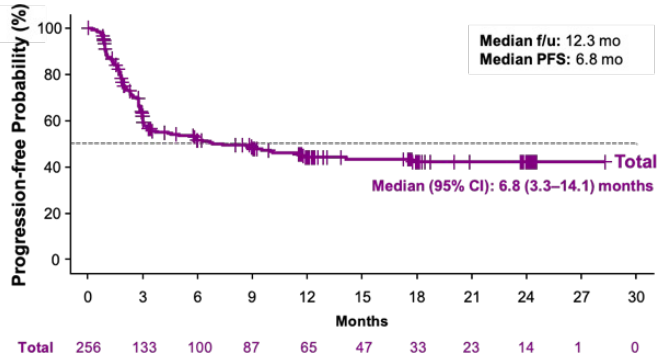
ZUMA-1
Axi-cel



JULIET
Tisa-cel



TRANSCEND
Liso-cel



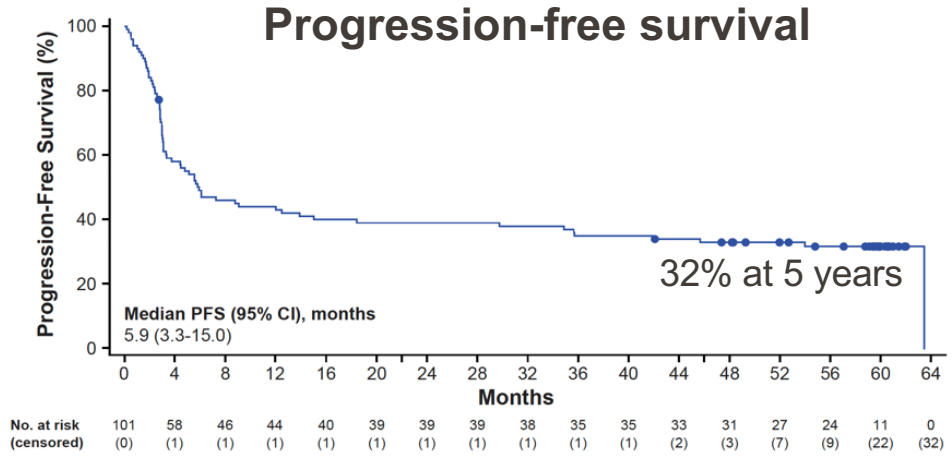
Approval

Axi-cel, tisa-cel, and liso-cel for adult patients with r/r LBCL after 2 or more lines of systemic therapy

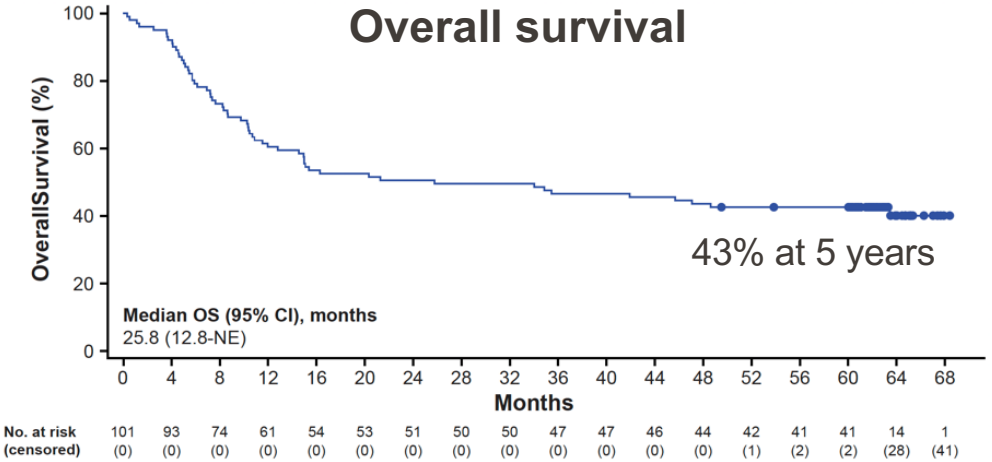
Neelapu SS et al. *N Engl J Med.* 2017;377:2531-2544. Locke FL et al. *Lancet Oncol.* 2019;20(1):31-42.
Schuster SJ et al. *N Engl J Med.* 2019;380:45-56. Schuster SJ et al. *Lancet Oncol.* 2021;22(10):1403-1415.
Abramson JS et al. *Lancet.* 2020;396(10254):839-852.

ZUMA-1 with 5 year follow up

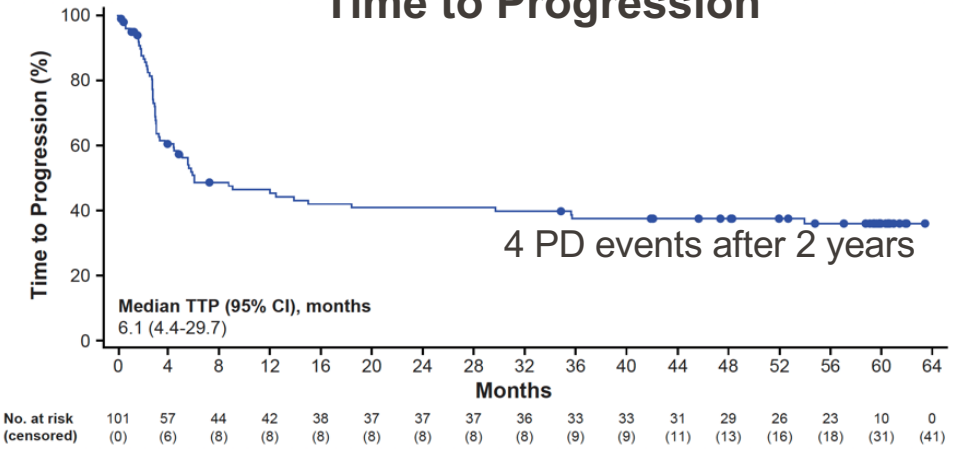
Progression-free survival



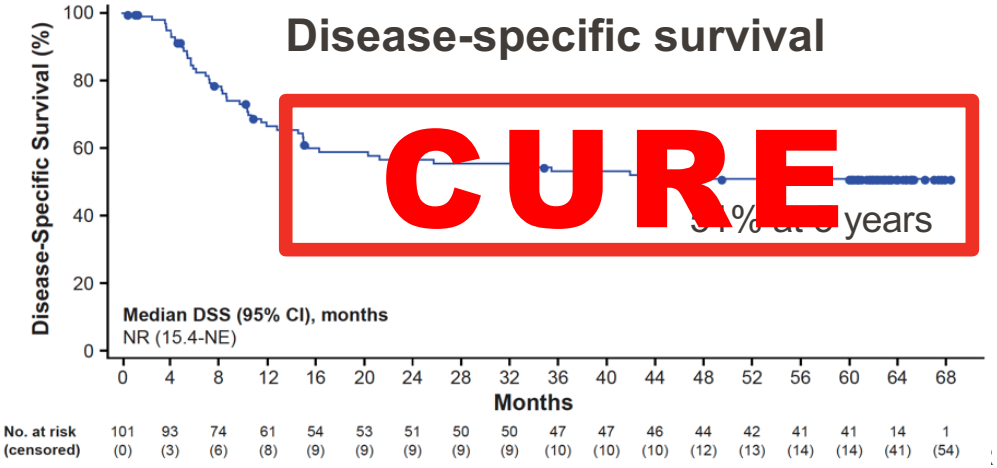
Overall survival



Time to Progression

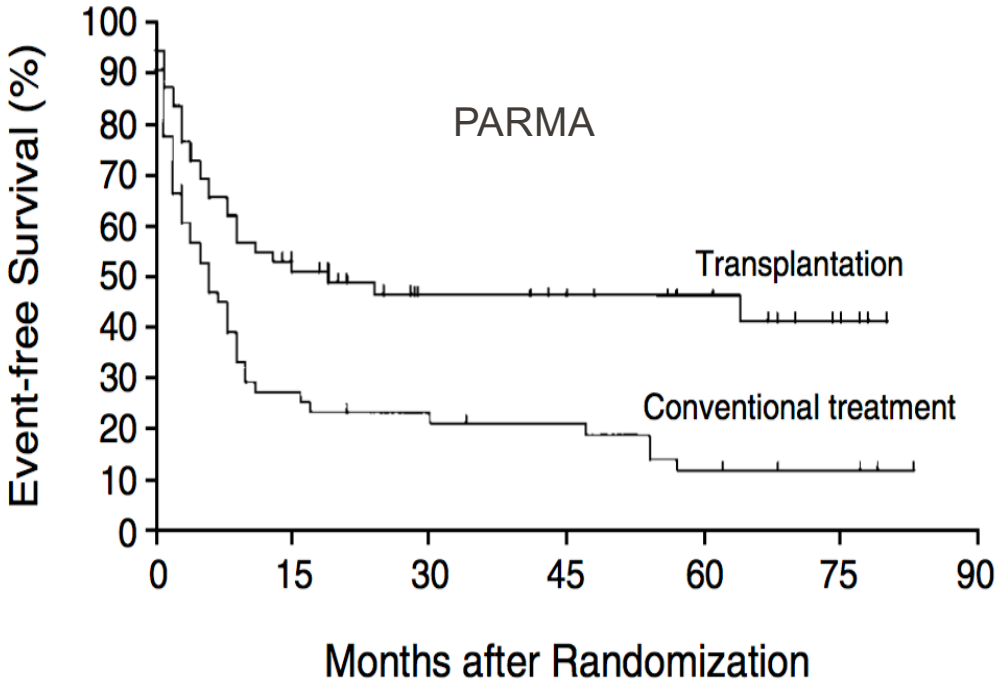


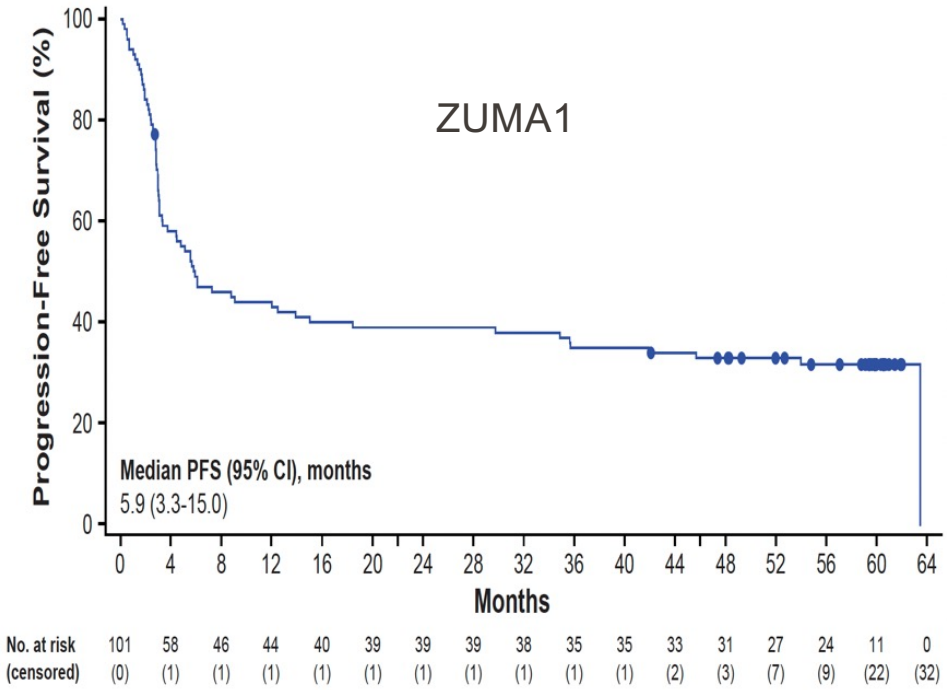
Disease-specific survival



1 Neelapu et al. *Blood,* 2023 May 11;141(19):2307-2315

Can we really claim CAR T-cell is curative?

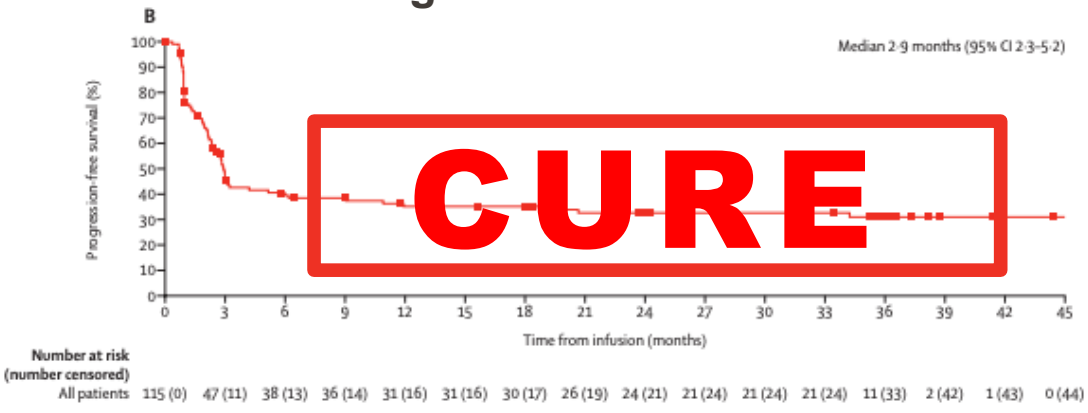




 Philip NEJM 1995, Neelapu et al. *Blood,* 2023 May 11;141(19):2307-2315

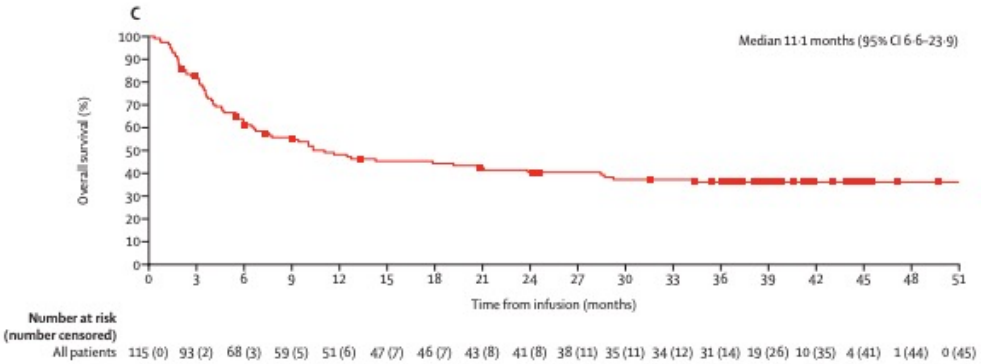
Juliet with 40 month follow up

Progression-free survival



CURE

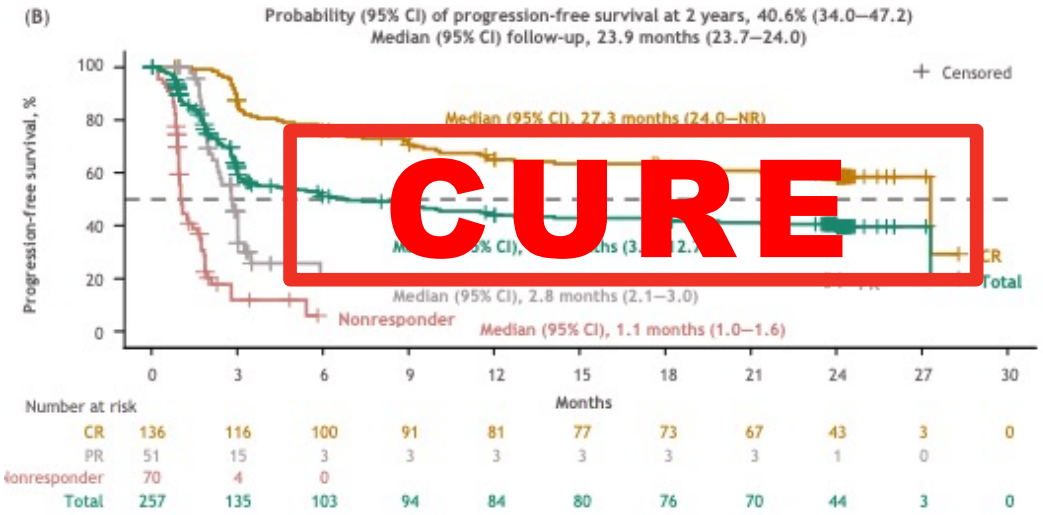
Overall survival



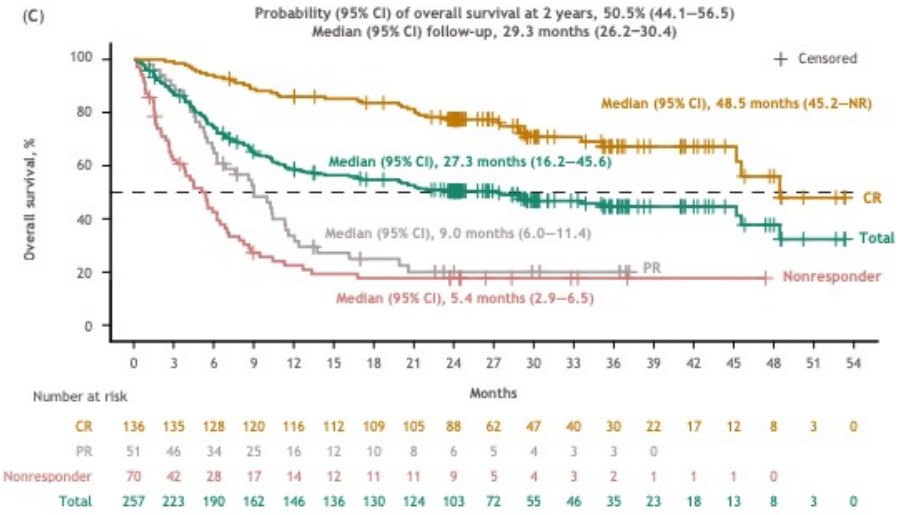
17 Schuster et al, Lancet Oncol, 2021 Oct; 22 (10) 1403-1415

Transcend with 24 month follow up

Progression-free survival



Overall survival

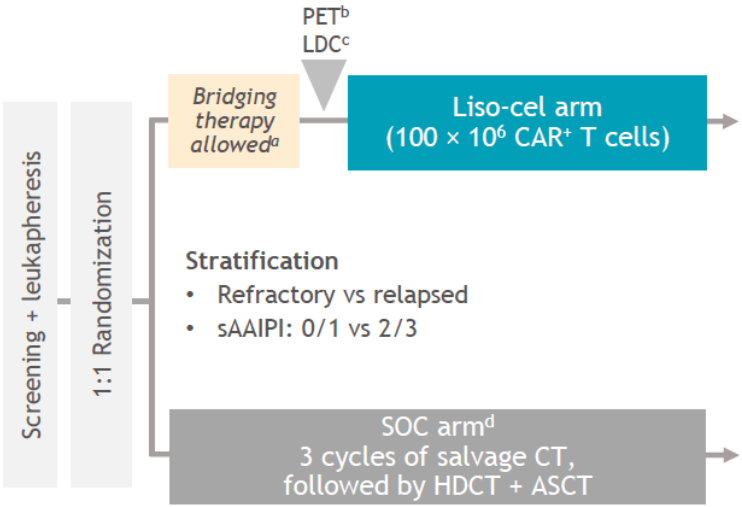


 Abramson et al, Blood 2023 Oct 27 online

If CAR T-cell is great in 3L, what about 2L?

TRANSFORM study design

Key eligibility
- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count



Response assessments
- Weeks 9 and 18
- Months 6, 9, 12, 18, 24, and 36

Primary endpoint
- EFS (per IRC)

Key secondary endpoints
- CR rate, PFS, OS

Other secondary endpoints
- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints
- Cellular kinetics
- B-cell aplasia

Crossover to liso-cel allowed
- Failure to respond by 9 weeks post-randomization
- PD at any time
- Start of new antineoplastic therapy after ASCT

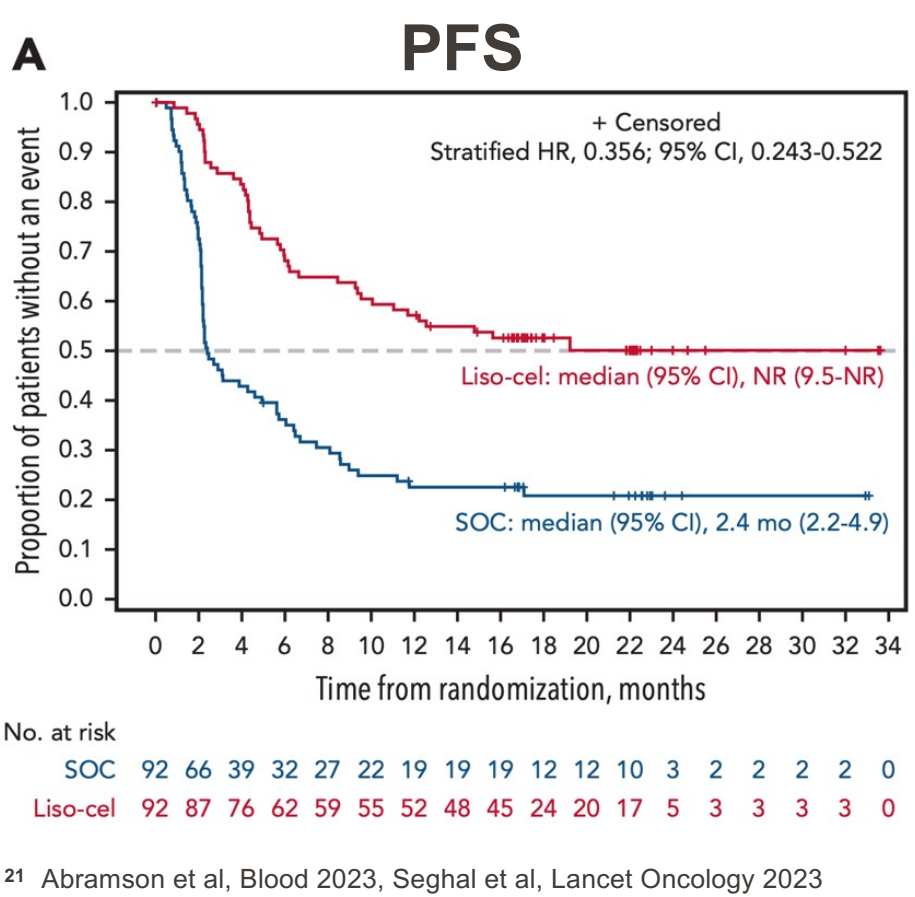
TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

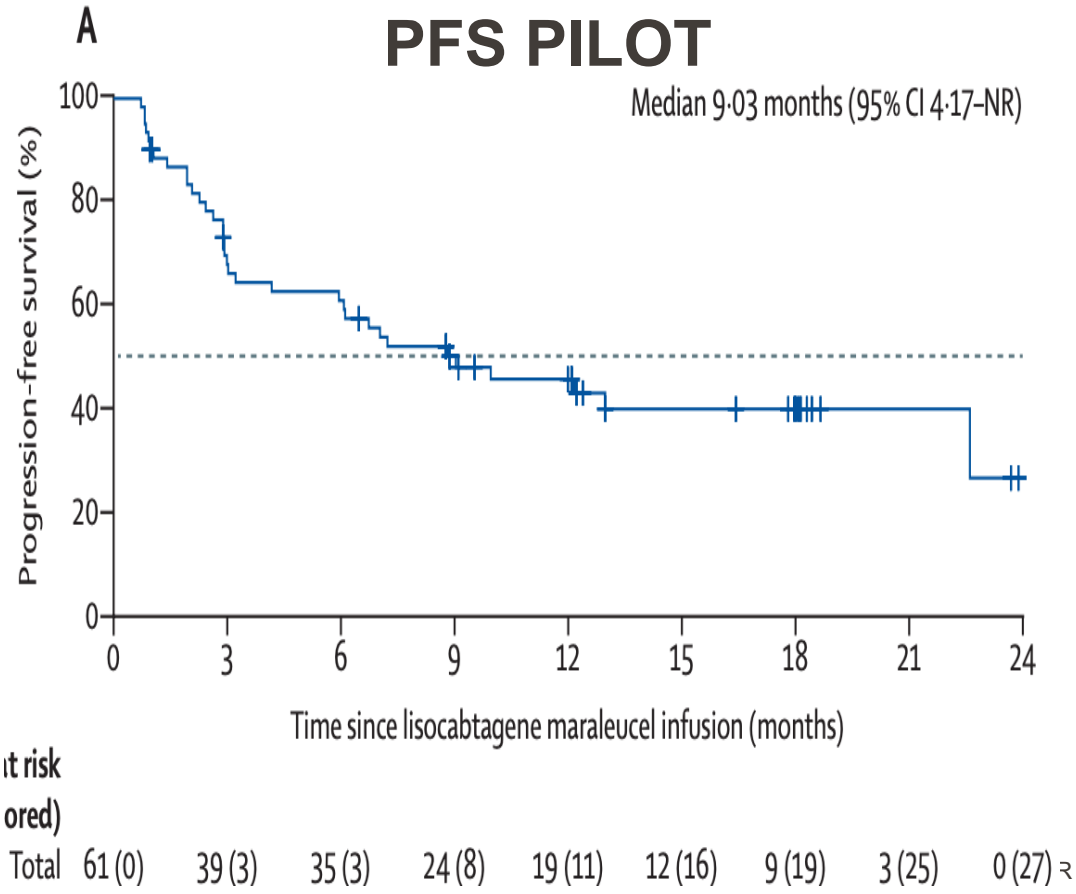
- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² for 3 days; [d]SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Kamdar M, et al. ASH 2021 [Abstract #91]

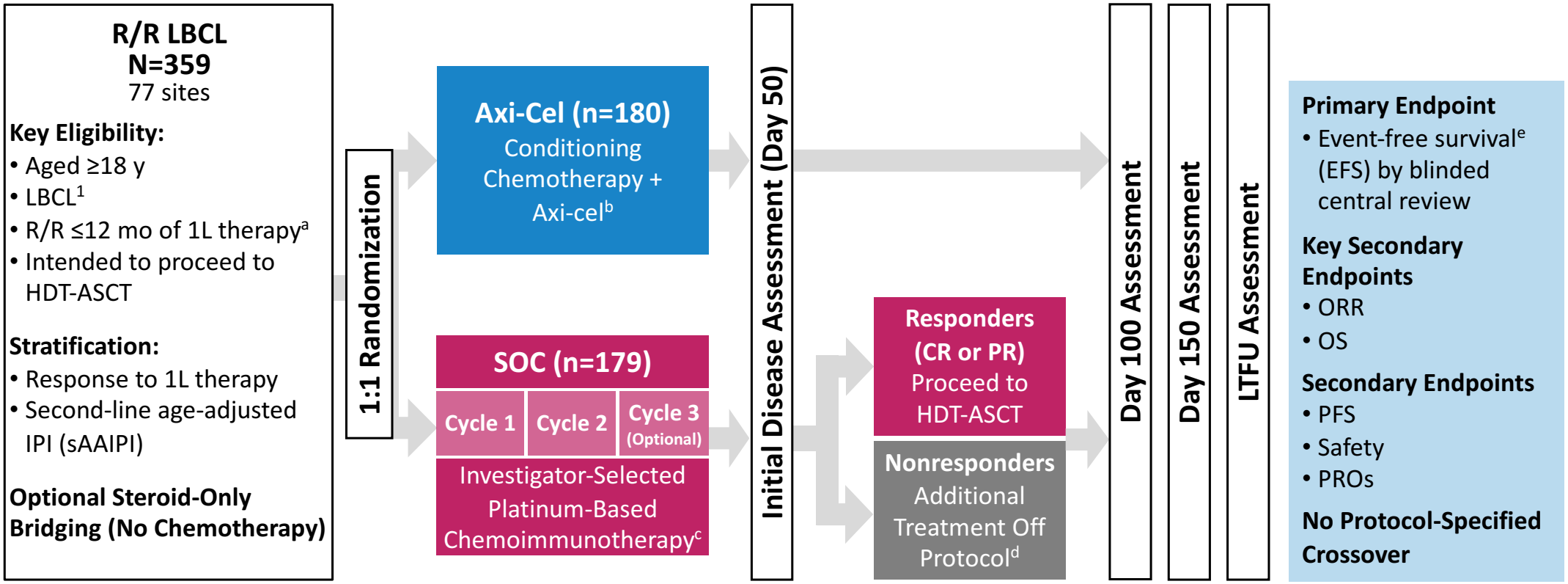
Transform: Liso-cel is superior to SOC





21 Abramson et al, Blood 2023, Seghal et al, Lancet Oncology 2023

ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL

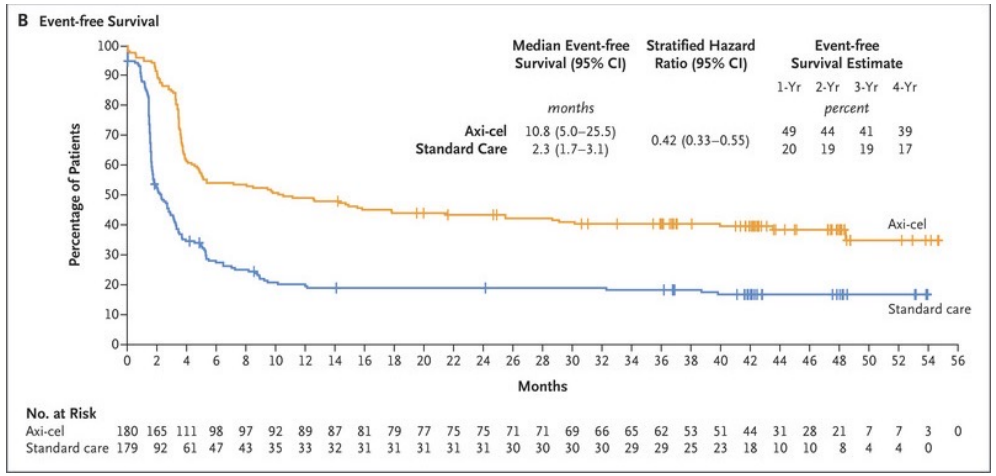


[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

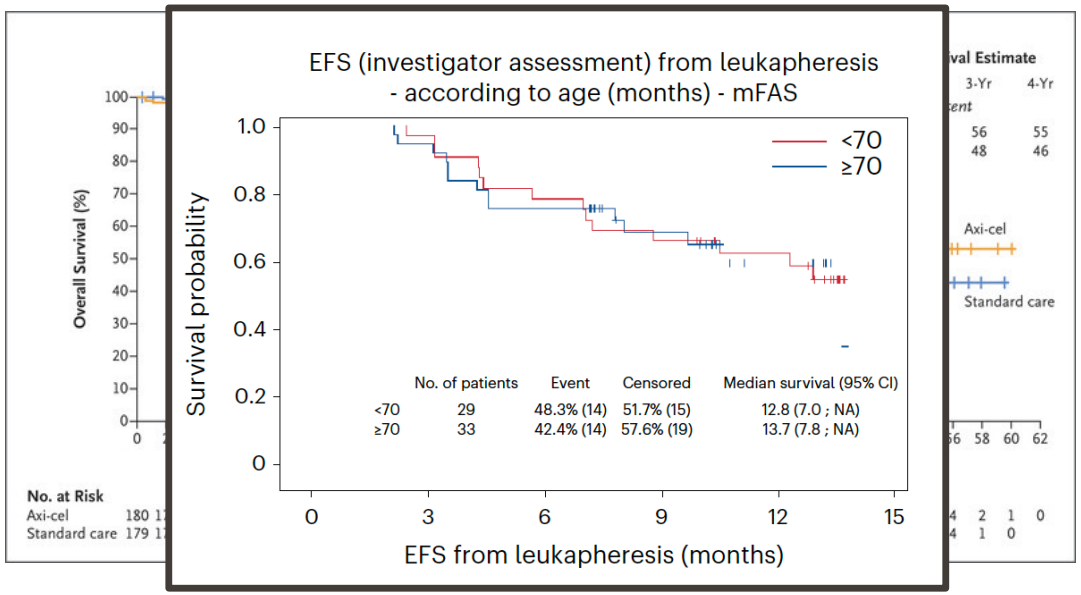
1. Swerdlow SH, et al. *Blood.* 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

ZUMA7: Axi-cel is superior to SOC

EFS



ALYCANTE



 Westin et al, NEJM 2023 Houot et al, Nat Med 2023

Comparing across studies

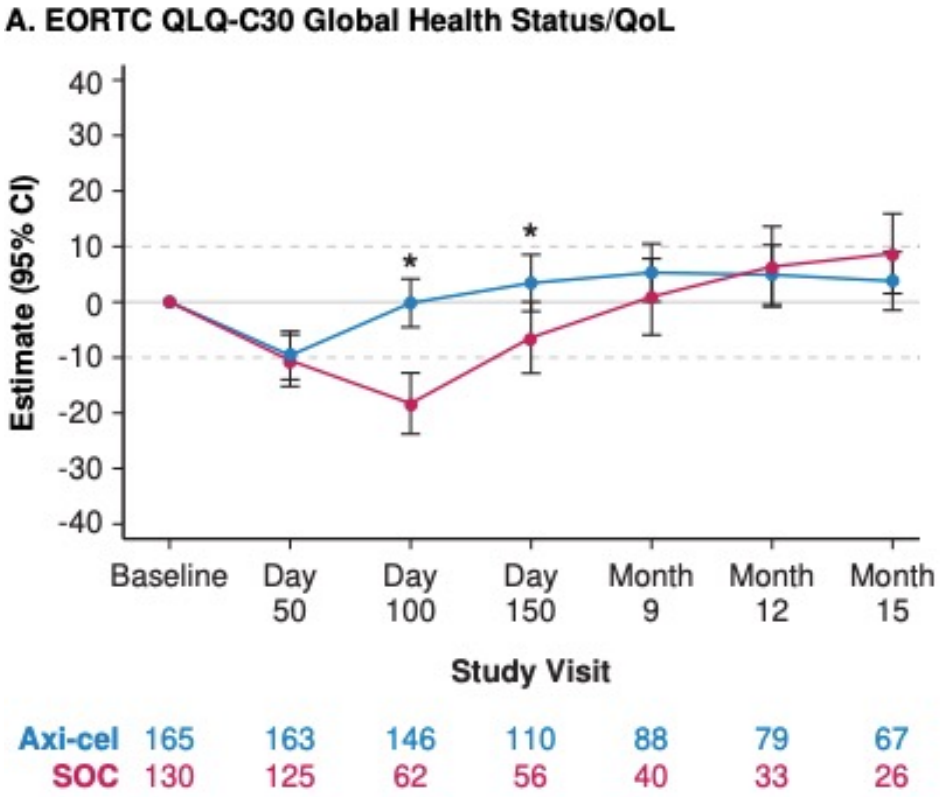
	ZUMA-7		Belinda		Transform	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
EFS, median in months	8.3	2	3	3	10.1	2.3
EFS, % (timepoint in months)	41 (24 mo)	16 (24 mo)	NR	NR	63 (6 mo)	33 (6 mo)
EFS HR (95% CI)	0.4 (0.31-0.51)		1.07 (0.82-1.4)		0.35 (0.23-0.53)	
PFS, median in months	14.7	3.7	NR	NR	14.8	5.7
PFS HR (95% CI)	0.49 (0.37-0.65)		NR		0.406 (0.21-0.66)	
OS, median in months	NE	25.7	16.9	15.3	NE	16.4
OS HR (95% CI)	0.708 (0.515-0.972)‡		NR		0.51 (0.26-1.004)	

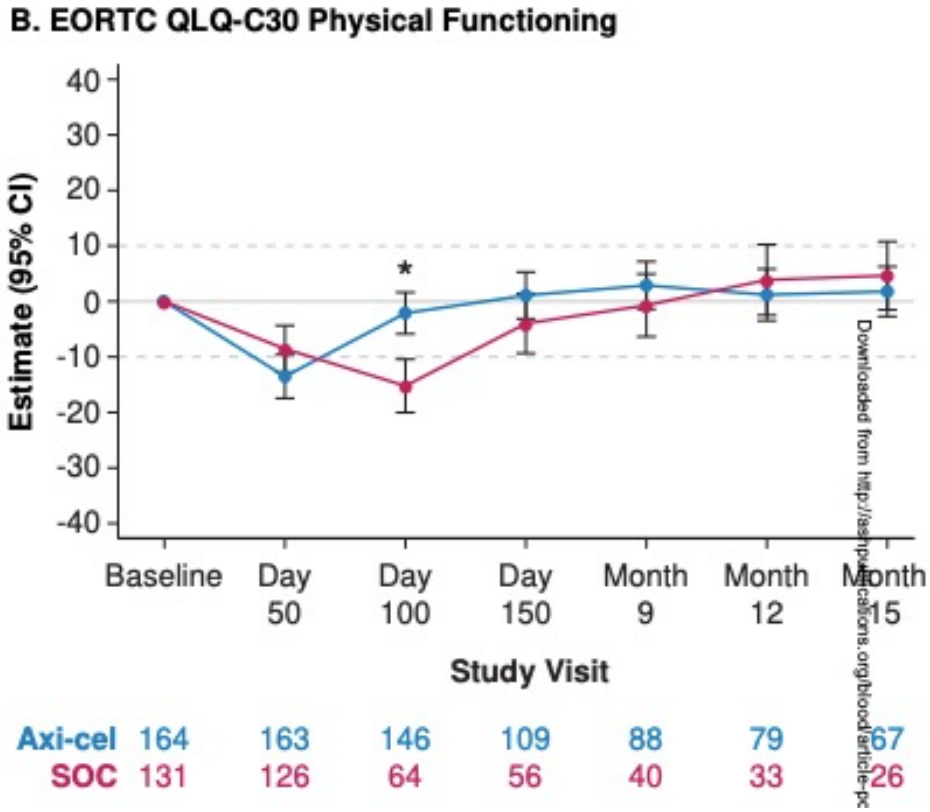
HR 0.73 p=0.03

HR 0.724 p=0.0987

 Westin & Sehn, Blood 2022

Quality of Life – ZUMA7

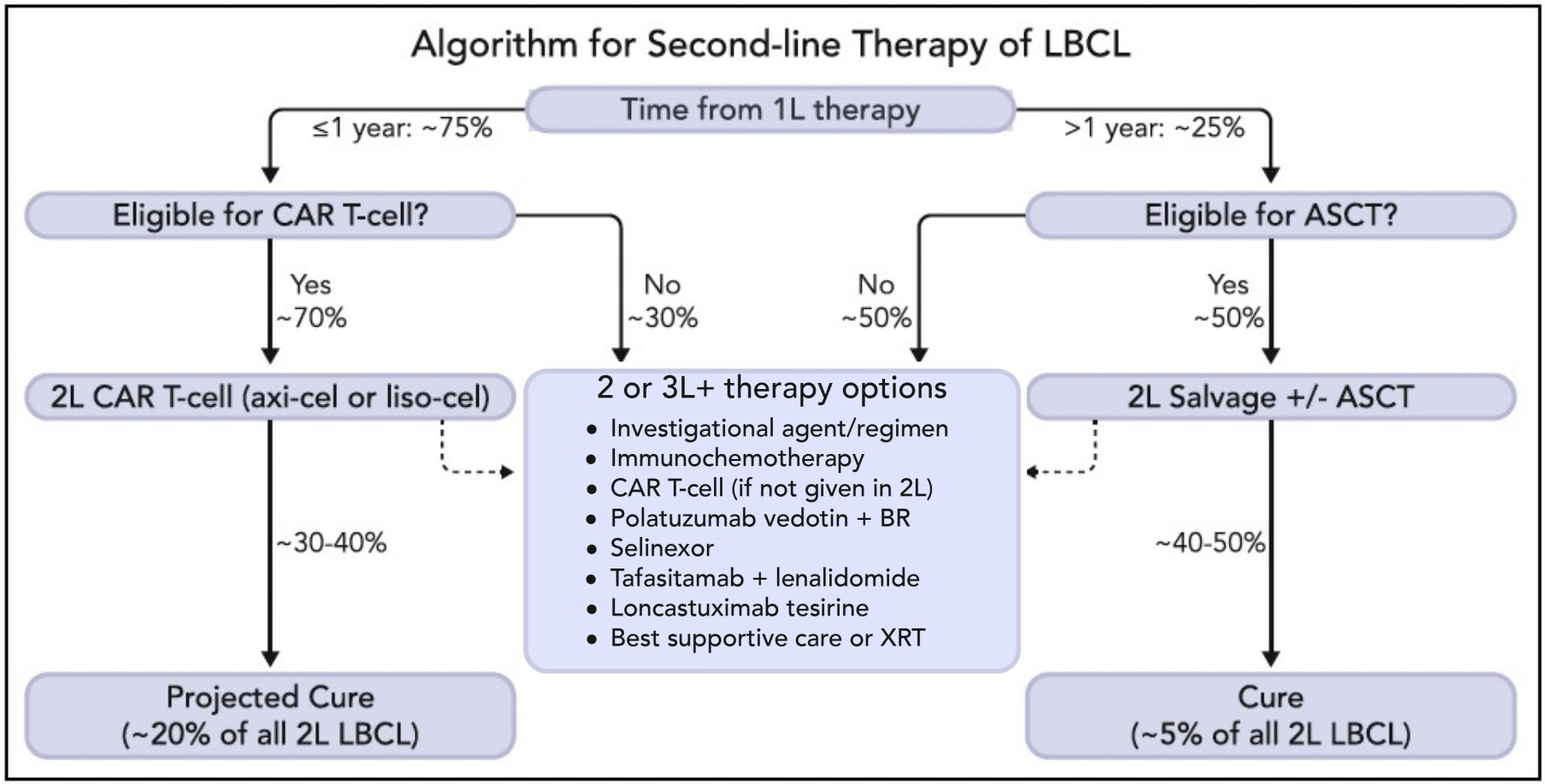




Elsawy Blood 2022

Similar findings with liso-cel, Abramson et al, Blood Advances 2022

New 2L algorithm



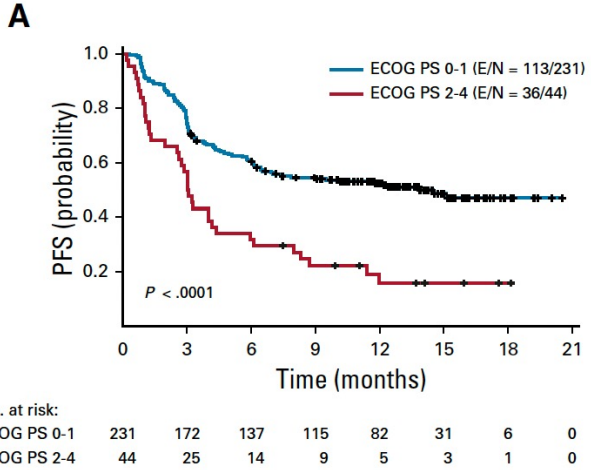
Westin & Sehn, Blood 2022

2L algorithm: <12m: When CAR T-cell not be the answer?

2L CAR T-cell (axi-cel or liso-cel)

2L Salvage +/- ASCT

- **Resources**
- **Frailty (PS, organ dysfunction)**
- **If chemo sensitive - ?**



s?

2 or 3L+ therapy options

- Investigational agent/regimen
- Immunochemotherapy
- CAR T-cell (if not given in 2L)
- Polatuzumab vedotin + BR
- Selinexor
- Tafasitamab + lenalidomide
- Loncastuximab tesirine
- Best supportive care or XRT

Elevated Bilirubin above 1.5 = HR 5.1 for inferior OS

 Nastoupil et al, JCO 2020

2L clinical trial: Glofitamab and Axi-cel

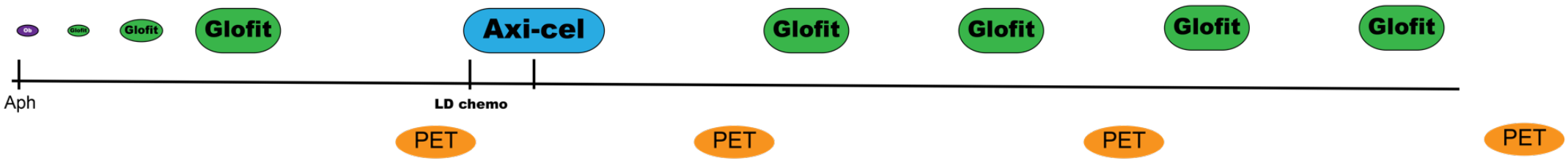
A Phase 2 Study of Axicabtagene Ciloleucel and Glofitamab as Second-Line Therapy for Relapsed or Refractory Patients With Large B Cell Lymphoma

ClinicalTrials.gov ID NCT06213311

Sponsor M.D. Anderson Cancer Center

Information provided by M.D. Anderson Cancer Center (Responsible Party)

Last Update Posted 2024-01-19



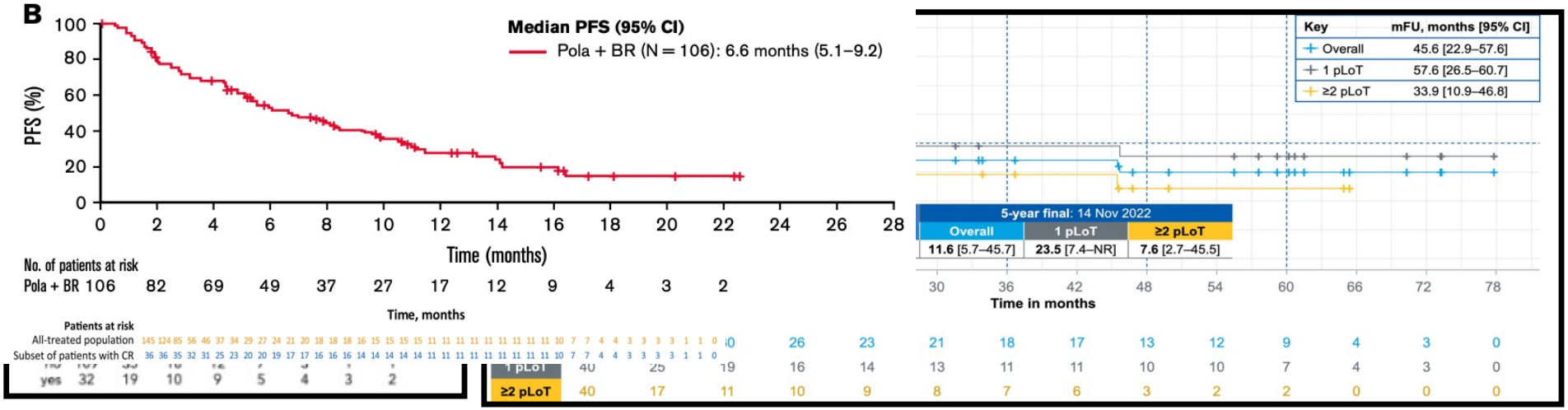
2L algorithm <12m: Not fit for CAR T-cell

2L CAR T-cell (axi-cel or liso-cel)

- Not fit for chemo/ASCT
- Bispecific antibodies?

2L Salvage +/- ASCT

- Tafa/Len
- LoncaT
- Pola/(B)/R



 Duell et al, Hematologica 2023, Qualls et al, Blood 2023, Caimi et al, Hematologica 2023

2L algorithm: >12m: When chemo->SCT may not be the answer?

2L CAR T-cell (axi-cel or liso-cel)

2 or 3L+ therapy options

- Investigational agent/regimen
- Immunochemotherapy
- CAR T-cell (if not given in 2L)
- Polatuzumab vedotin + BR
- Selinexor
- Tafasitamab + lenalidomide
- Loncastuximab tesirine
- Best supportive care or XRT

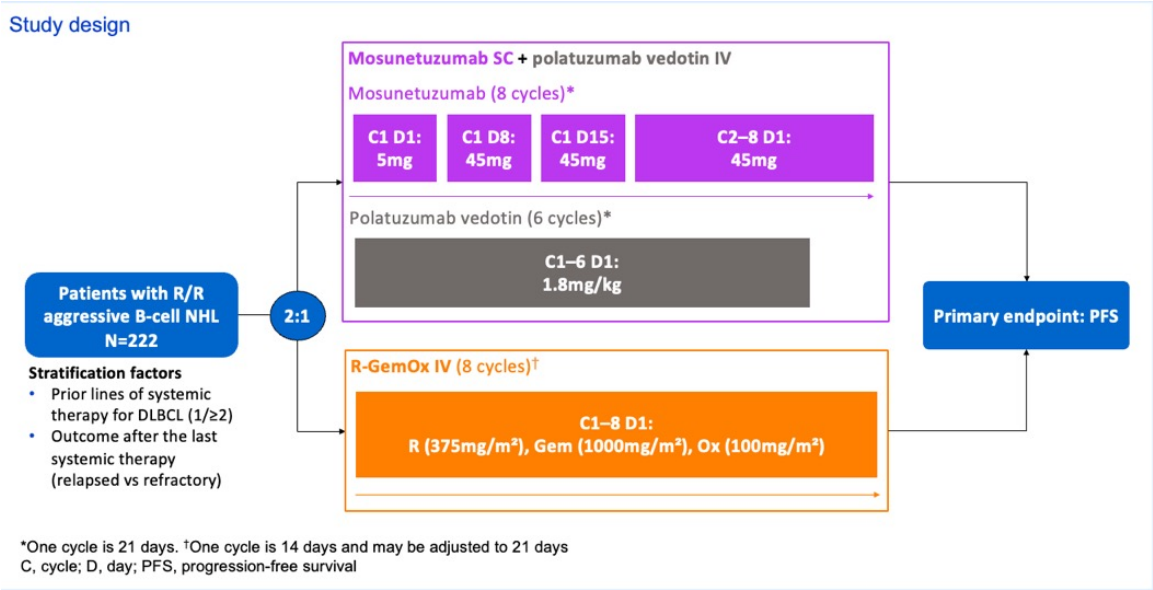
2L Salvage +/- ASCT

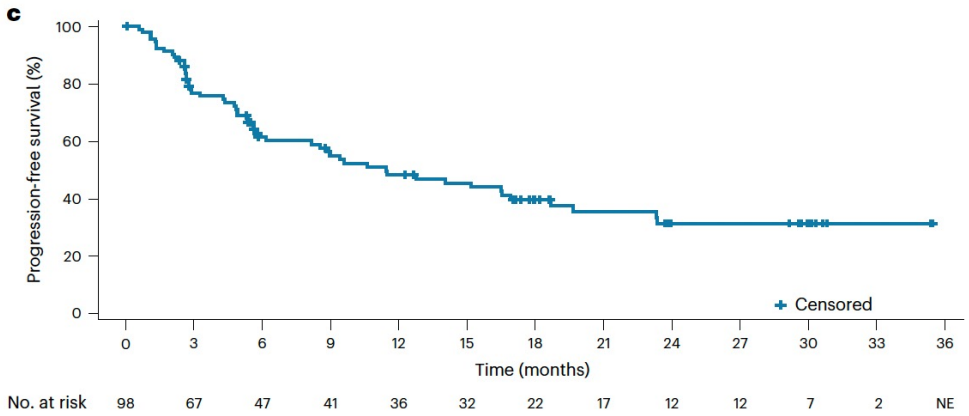
- **”Transplant ineligible”**
- **“+1 day”**
- **Bispecific antibodies?**
- **Tafa/Len, Pola/R, LoncaT**

- **Clinical trials**

2L+ clinical trial: SunMo

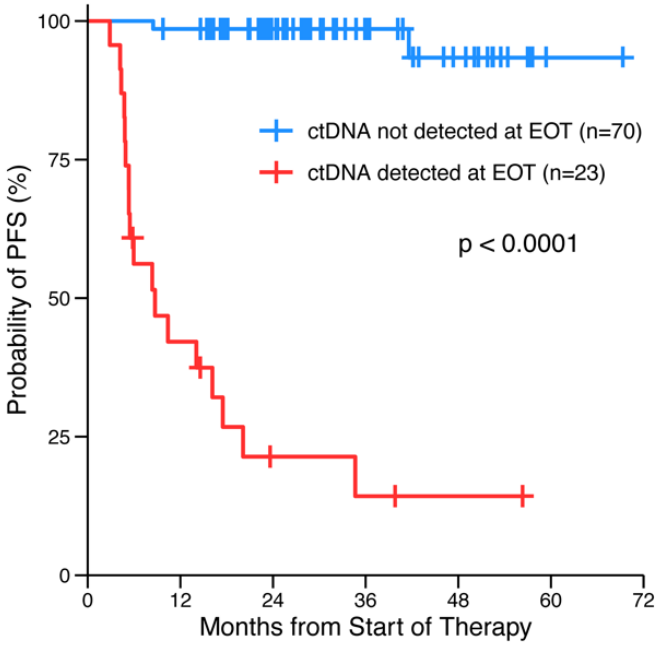
Mosun/Pola vs RGemox





 Westin et al, ASCO 2023, Budde et al, Nature Med 2023

2L algorithm: <12m: PET- with ctDNA+



DALLE-3

 Roschewski et al, ICML 2023

2L algorithm: <12m: PET- with ctDNA+

ALPHA3

Randomized phase 2 trial evaluating observation vs cemacabtagene ansegedleucel (ALLO501A)

Primary endpoint is EFS

2L algorithm: <12m: PET- with ctDNA+

Glofitamab as an “MRD Eraser”

Single arm phase 2 trial of 30 patients

Single center at MD Anderson

PI: Chihara (Westin)

What about 3L algorithm?

If no prior CAR T-cell:

- **Consider if available and feasible**

If prior CAR T-cell:

1. **Clinical trial**
2. **Bispecific antibody (how to choose which one?)**
3. **Tafa/Len or Pola/R or LoncaT**

Grazie mille!

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@Lymphoma_Doc

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Department of Lymphoma and Myeloma Fellowship Program

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Applications are due by Friday, Sept. 29

Contact us

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MD Anderson Cancer Center's Lymphoma-Myeloma Fellowship Program trains internists and oncologists in the evaluation and management of patients with **Hodgkin- and non-Hodgkin lymphoma**, **multiple myeloma**, and **plasma cell dyscrasias**. Through a combination of inpatient and outpatient **clinical responsibilities** and associated clinical teaching, fellows will learn to **evaluate, diagnose, treat, and monitor** disease of the lymphoid system and manage regimen-related toxicities, evaluate disease response and choose appropriate therapies for newly diagnosed and relapsed disease. Fellows will receive training in the use of **CAR T cell therapy** to improve treatment outcomes.

At the completion of one year of training, each fellow will be prepared to assume independent clinical responsibilities and investigations.

Our program includes:

- 2 months of inpatient service
- 2 clinic days per week
- 2 research days per week
- Weekly medical and scientific presentations and conferences
- Monthly didactic lectures from world-class faculty
- Active roles in lymphoma and myeloma research
- An assigned faculty mentor for each fellow
- 3-day course on Clinical Research Methodology; clinical trials, statistical design, biomarker trial design, utilizing of big data, and guidance on career development