Mass General Brigham
Mass General Cancer Center

Update on CAR T-cells as 2nd Line Therapy for Large B-cell Lymphomas

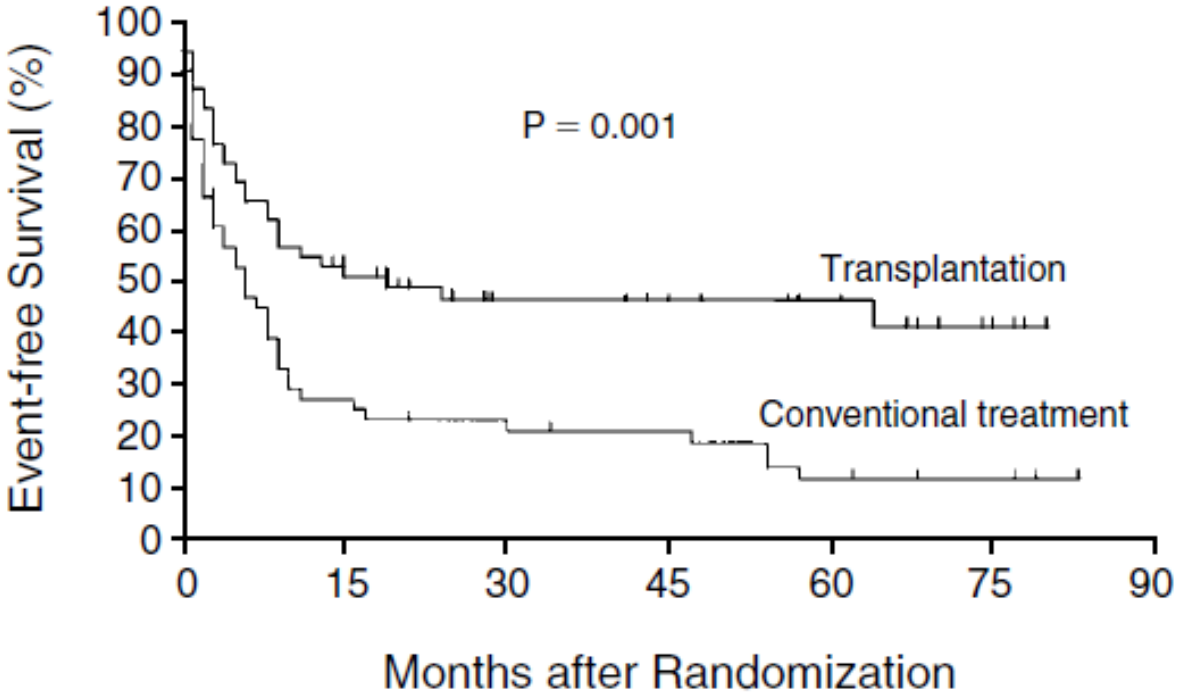
Jeremy S. Abramson, MD, MMSc

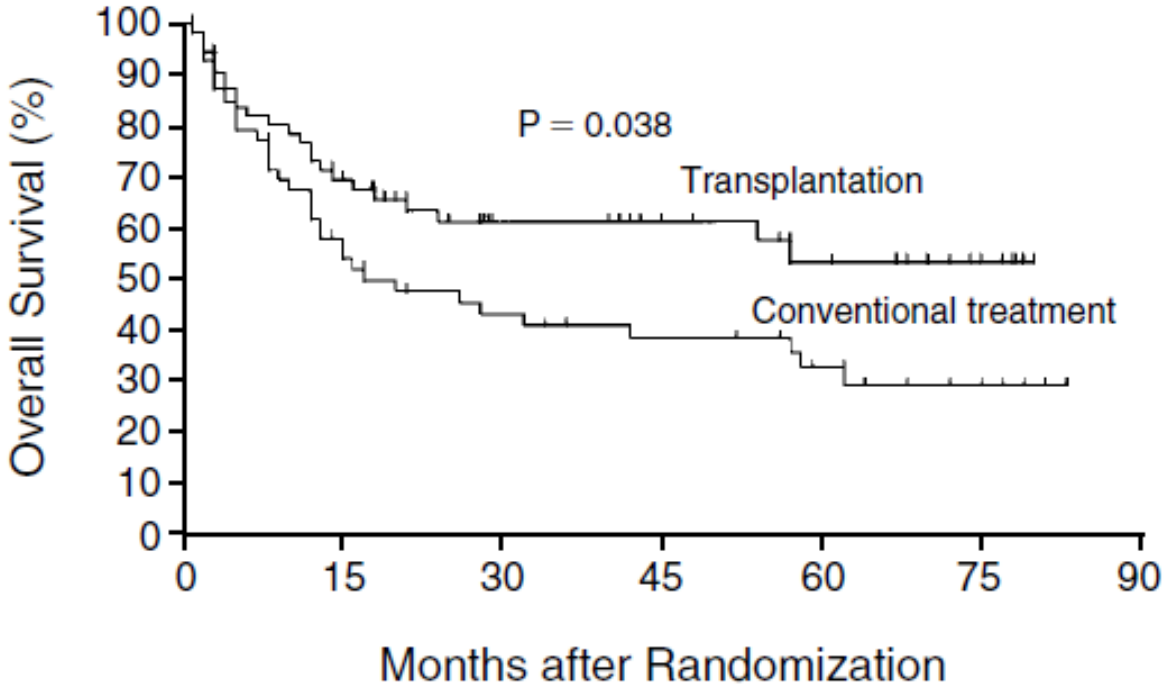
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures for Jeremy Abramson

Consulting for AbbVie, Astra-Zeneca, BeiGene, Bristol Myers Squibb, Caribou Biosciences, Cellectar, Genentech, Incyte, Interius, Janssen, Kite Pharma, Lilly, Regeneron, Takeda

The Good Old Days for ASCT in Relapsed/Refractory DLBCL

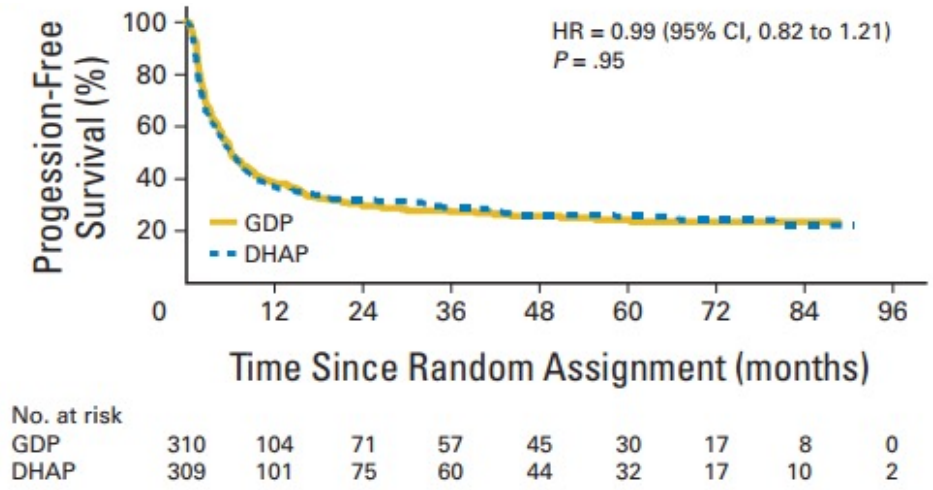




Philip, et al. NEJM. 1995

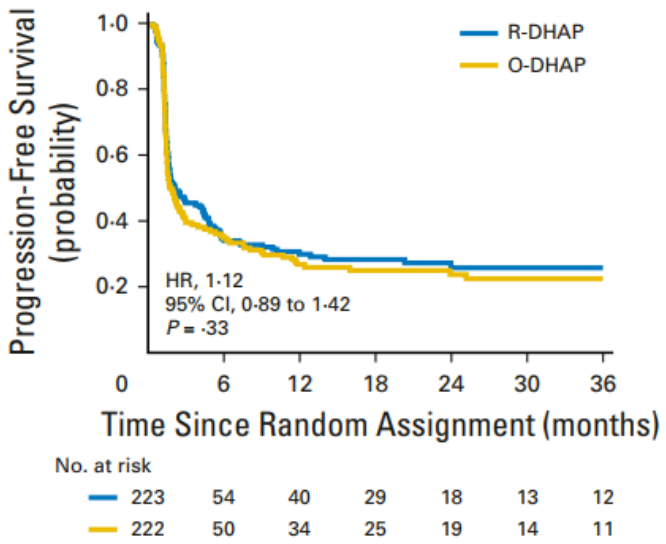
High dose chemotherapy and ASCT: A flawed SOC in the Modern Era

NCIC-CTG LY.12



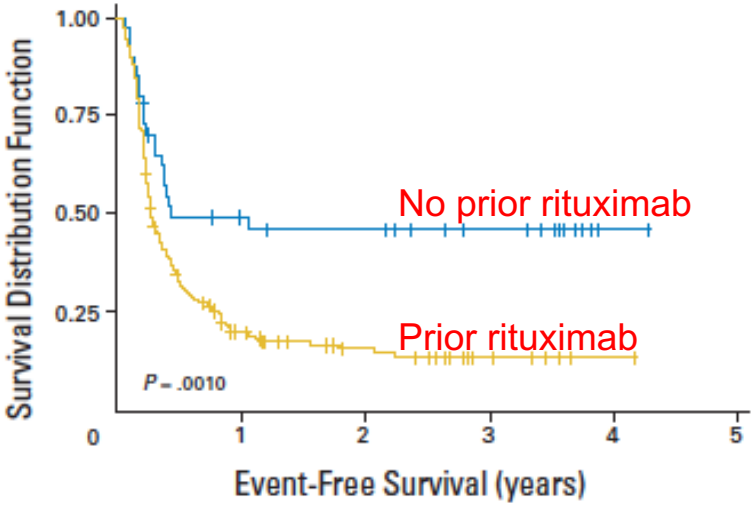
Crump, et al. JCO 2014

ORCHAARD



van Imhoff, et al. JCO 2017

CORAL (pts progressing ≤ 1 year)



Gisselbrecht, et al. JCO 2010

- About 3/4 of DLBCL relapses happen within one year, where outcomes with SOC is terrible!
- Plus, only half of relapsed DLBCL patients are candidates for HDT/ASCT due to age/comorbidities
- The SOC therefore fails in the vast majority of patients with relapsed DLBCL in the modern era

Three randomized trials of Chimeric Antigen Receptor (CAR) T-cell therapy versus SOC in transplant-eligible DLBCL with early relapse or primary refractory disease

Clinical trials of CD19 CAR T-cell therapies in 2L ≤ 12 months LBCL

ZUMA-7[1]
(N = 359)
Phase 3; axi-cel vs SOC

Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD[4];

POSITIVE!

TRANSFORM[2]
(N = 184)
Phase 3; liso-cel vs SOC

TRANSFORM Study: Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase 3 TRANSFORM Study

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami

POSITIVE!

BELINDA[3]
(N = 322)
Phase 3; tisa-cel vs SOC

Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

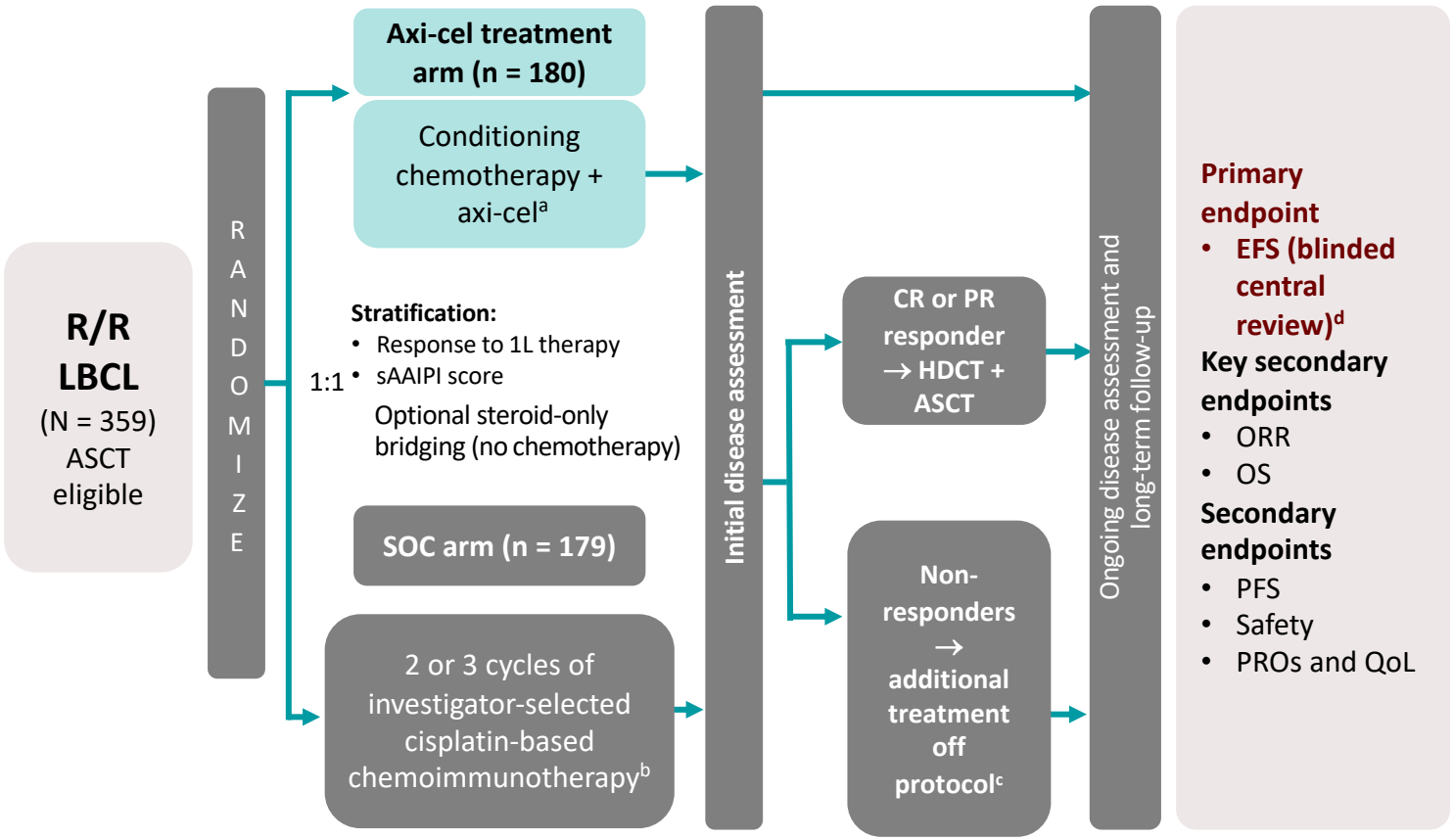
Michael R. Bishop,[1] Michael Dickinson[2], Duncan Purtill[3], Pere Barba[4], Armando Santoro[5], Nada Hamad[6], Koji Kato[7], Anna Sureda[8], Richard Greil[9],

NEGATIVE!

Inter-trial comparisons should not be made because of differences in study design, patient populations, treatment interventions, and duration of follow-up, among others. We cannot make direct comparisons or draw conclusions from one trial to another.

1. Locke FL, et al. N Engl J Med. 2022;386:640-54. 2. Kamdar M, et al. Oral presentation at ASH 2021; abstract 91. 3. Bishop MR, et al. N Engl J Med. 2022;386:629-39.

ZUMA-7: axi-cel versus SOC in 2L LBCL



Characteristics	Axi-cel (n = 180)	SOC (n = 179)
Median age (range), years	58 (21–80)	60 (26–81)
Disease stage III-IV, n (%)	139 (77)	146 (82)
Primary refractory, n (%)	**133 (74)**	**131 (73)**
Relapse ≤ 12 months of 1L therapy, n (%)	**47 (26)**	**48 (27)**
HGBCL (incl. DHL/THL), n (%)	**31 (17)**	**25 (14)**
ECOG PS of 1	85 (47)	79 (44)
Elevated LDH level	101 (56)	94 (53)

Axi-cel has been approved by FDA for adult patients with LBCL that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy

Data cutoff: March 18, 2021.

[a] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with Cy (500 mg/m^2/day) and Flu (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). [b] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [c] 56% of patients received subsequent cellular immunotherapy. [d] EFS was defined as time from randomization to the earliest date of PD per Lugano Classification. [e] Disease type according to central laboratory.

1L, first line; PRO, patient-reported outcome; QoL, quality of life; R-ESHAP, rituximab, etoposide, methylprednisolone, high-dose cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; sAAIPI, second-line age-adjusted International Prognostic Index; THL, triple-hit lymphoma.

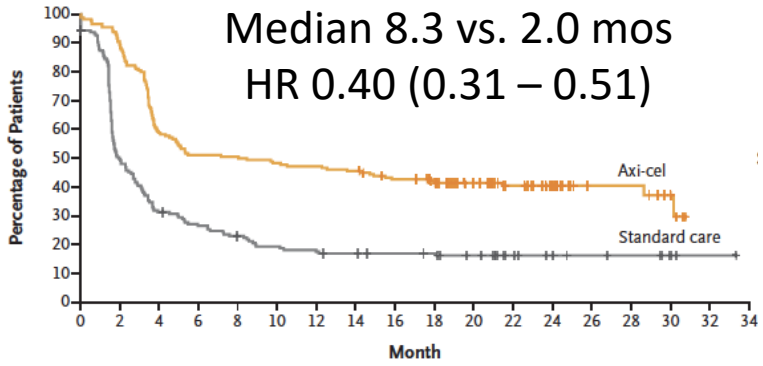
Locke FL, et al. N Engl J Med. 2022;386:640-54. Locke FL, et al. Oral presentation at ASH 2021; abstract 2. NCT03391466. Available from: https://clinicaltrials.gov/ct2/show/NCT03391466.

Axi-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas

ORR: 83% vs. 50%
CRR: 65% vs. 32%

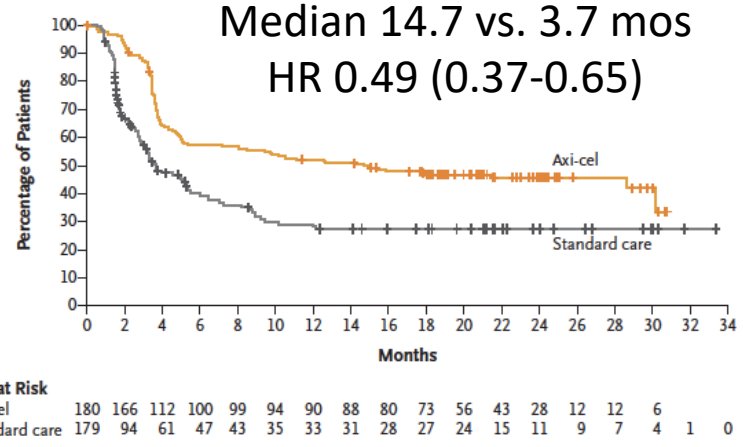
EFS

Median 8.3 vs. 2.0 mos
HR 0.40 (0.31 – 0.51)



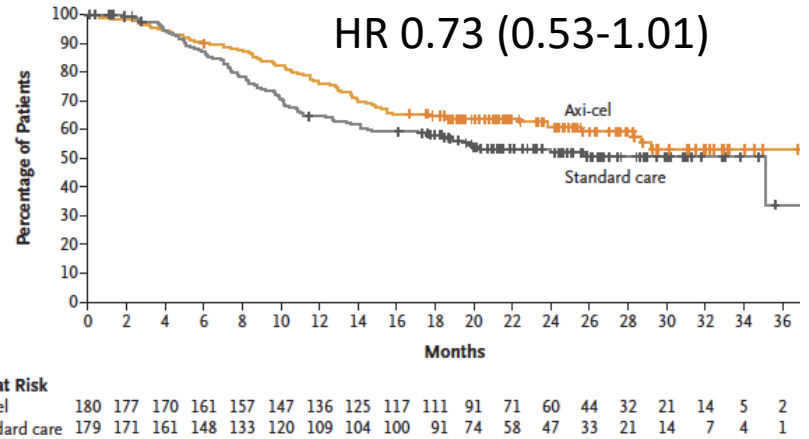
PFS

Median 14.7 vs. 3.7 mos
HR 0.49 (0.37-0.65)



OS

Median NR vs. 35.1 mos
HR 0.73 (0.53-1.01)



Median Follow-up: 24.9 mo

Toxicity	Grade	%
CRS	Any grade Grade 3	92 6
Neurotox	Any grade Grade 3	60 21

Axi-cel associated with improved QOL by PRO

Locke, et al. NEJM 2021

ZUMA-7 SOC Patients Who Received 3rd Line CAR T-cells

- 127 of 129 (71%) of SOC patients required 3rd line therapy

- 68 received 3rd line CAR T-cells
  - ORR 57%, CRR 34%
  - Median PFS 6.3 mos
  - Median OS 16.3 mos

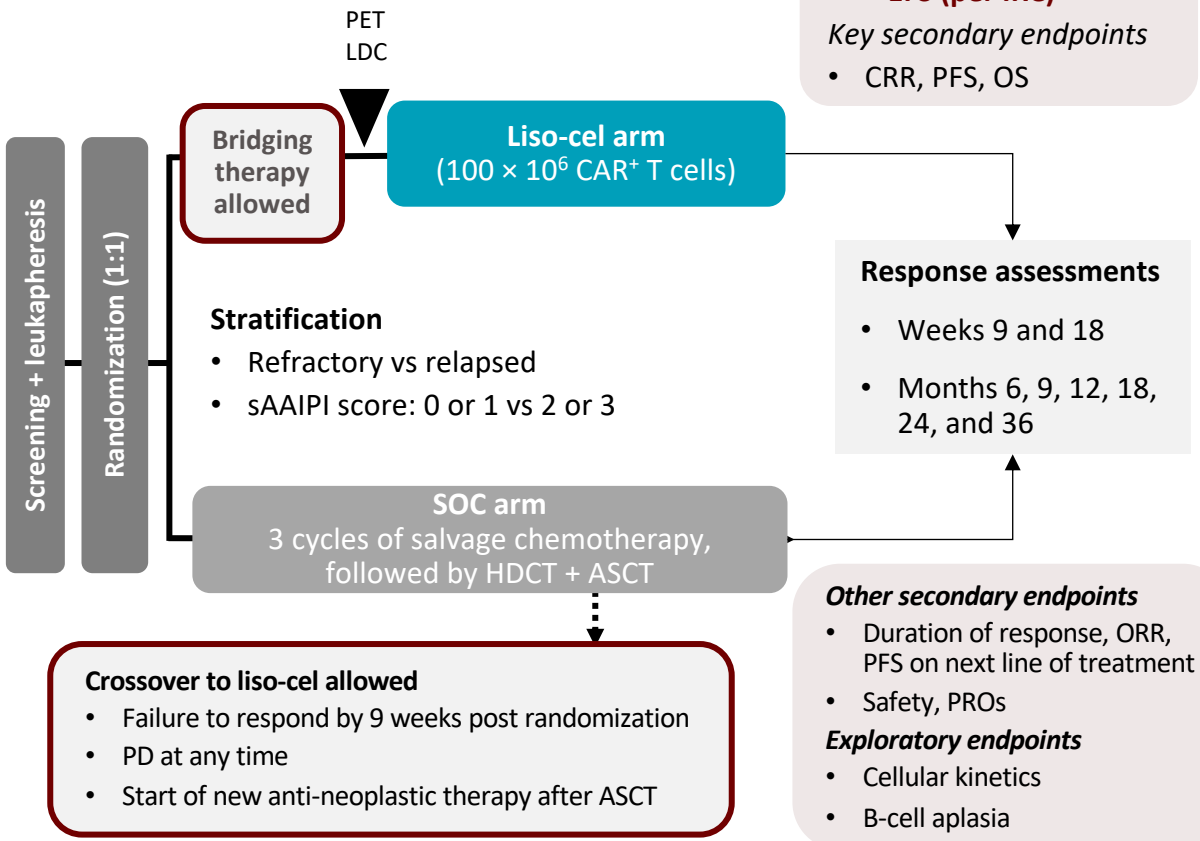
Efficacy of CAR T-cells appears greater in patients randomized to receive them as 2nd line therapy

Ghobadi, et al. Proc. ASH 2022

TRANSFORM: liso-cel versus SOC in 2L LBCL

Key eligibility

- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from iNHL), HGBCL (DHL/THL) with DLBCL histology, grade 3B FL, PMBCL, THRBCL
- R/R ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS score ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum ALC



Characteristic	Liso-cel (n = 92)	SOC (n = 92)
Median age (range), years	60 (53.5–67.5)	58 (42–65)
LBCL subtypes, n (%)		
DLBCL NOS	53 (58)	49 (53)
HGBCL (DHL/THL), n (%)	**22 (24)**	**21 (23)**
PMBCL	8 (9)	10 (11)
DLBCL transformed from iNHL	7 (8)	8 (9)
Primary refractory, n (%)	**67 (73)**	**68 (74)**
Relapsed, n (%)	**25 (27)**	**24 (26)**
sAAIPI score, n (%)		
0 or 1	56 (61)	55 (60)
2 or 3	36 (39)	37 (40)
ECOG PS score of 1, n (%)	44 (48)	35 (38)

Abramson, et al. Blood 2023

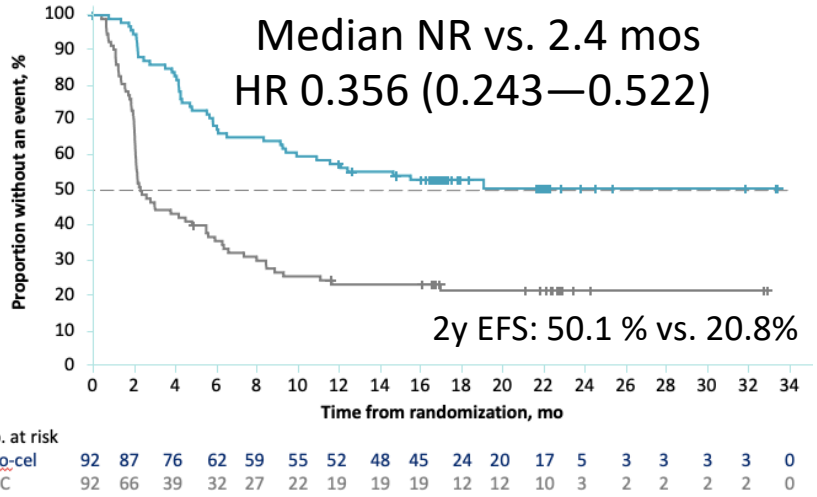
Liso-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas

ORR: 87% vs. 49%
CRR: 74% vs. 43%

66% of SOC pts crossed over

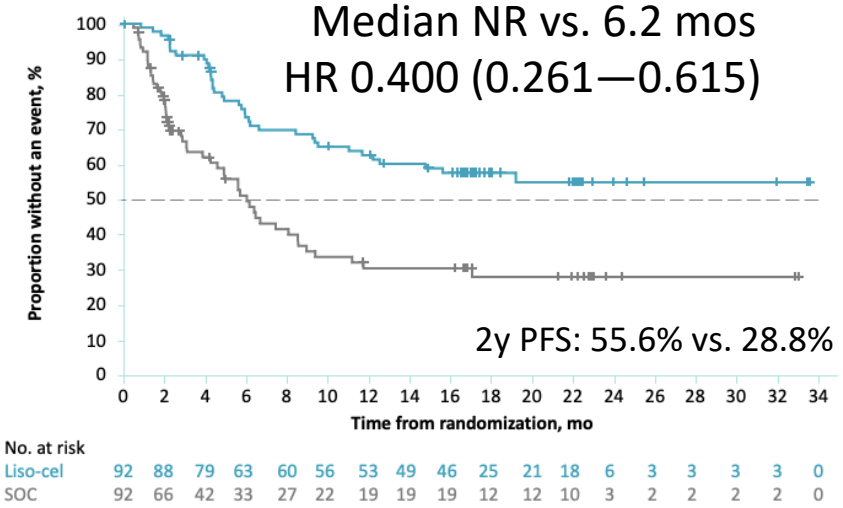
EFS

Median NR vs. 2.4 mos
HR 0.356 (0.243—0.522)



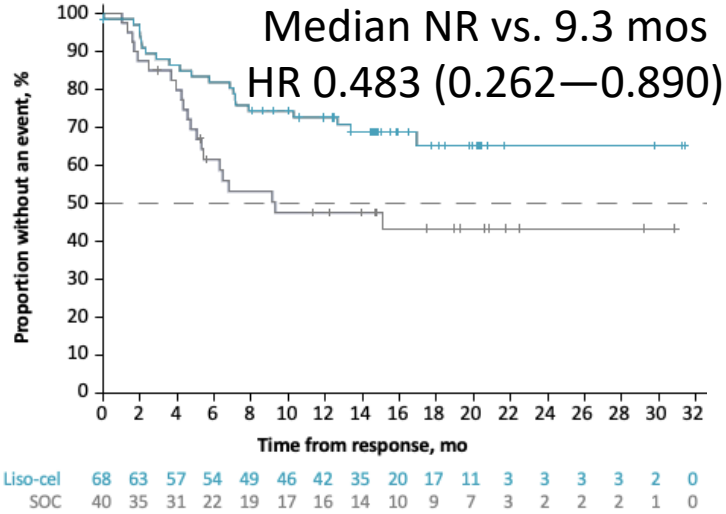
PFS

Median NR vs. 6.2 mos
HR 0.400 (0.261—0.615)



DoCR

Median NR vs. 9.3 mos
HR 0.483 (0.262—0.890)



Median Follow-up: 17.5 mo

Toxicity	Grade	%
CRS	Any grade Grade 3	49 1
Neurotox	Any grade Grade 3	11 4

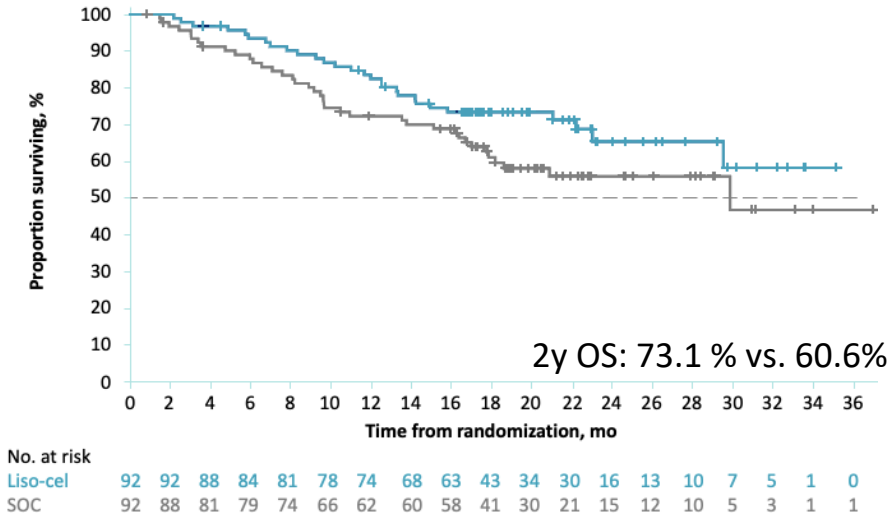
Liso-cel associated with improved QOL by PRO

Abramson, et al. Blood 2023

Liso-cel vs. SOC as 2nd line therapy: Overall Survival and Crossover

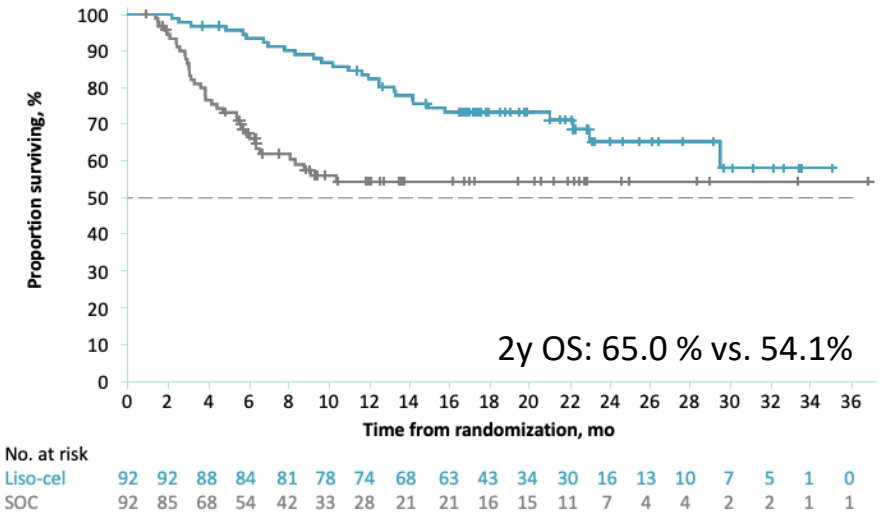
OS

Median NR vs. 29.9 mos
HR 0.724 (0.443—1.183)



OS adjusted for crossover

Median NR vs. NR
HR 0.415 (0.251—0.686)



Crossover subgroup

N=61 (66% of SOC)

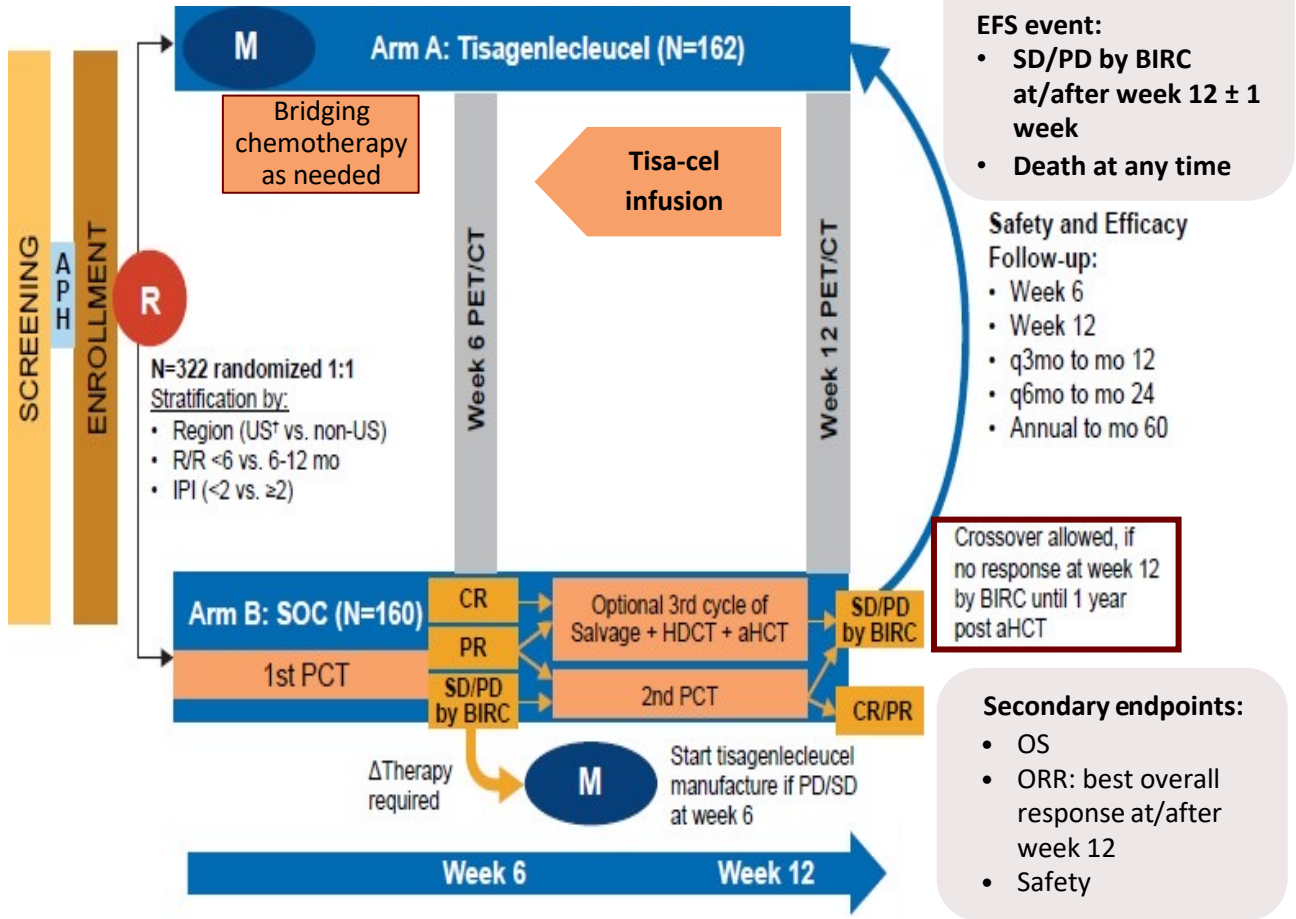
	Crossover subgroup (n = 57 treated)
Median f/u	12.0 m (1.4—28.1)
ORR / CRR	61% / 53%
Median EFS	5.9 m (3.1—15.1)
Median PFS	5.9 m (3.2—26.5)
Median OS	15.8 m (11.8—NR)

Median Follow-up: 17.5 mo

Abramson, et al. Blood 2023

BELINDA: tisa-cel versus SOC in 2L LBCL

Key eligibility criteria:
- Age ≥ 18 years
- Histologically confirmed aNHL R/R within 12 months of 1L treatment
- aHCT eligible
- ECOG PS score of 0 or 1



Primary endpoint:
- **EFS**

EFS event:
- **SD/PD by BIRC at/after week 12 ± 1 week**
- **Death at any time**

Safety and Efficacy Follow-up:
- Week 6
- Week 12
- q3mo to mo 12
- q6mo to mo 24
- Annual to mo 60

Crossover allowed, if no response at week 12 by BIRC until 1 year post aHCT

Secondary endpoints:
- OS
- ORR: best overall response at/after week 12
- Safety

Characteristic	Tisa-cel (n = 162)	SOC (n = 160)
Median age (range), years	59.5 (19–79)	58 (19–77)
Disease stage III or IV, n (%)	107 (66)	98 (61.2)
Refractory to 1L therapy, n (%)	**107 (66)**	**107 (66.9)**
Relapse ≤ 12 months of 1L therapy, n (%)	**55 (33.9)**	**53 (33.1)**
HGBCL (incl. DHL/THL), n (%)	**32 (19.8)**	**19 (11.9)**
ECOG PS score of 1, n (%)	70 (43.2)	65 (40.6)
IPI score ≥ 2	106 (65.4)	92 (57.5)

Bishop, et al. NEJM 2022

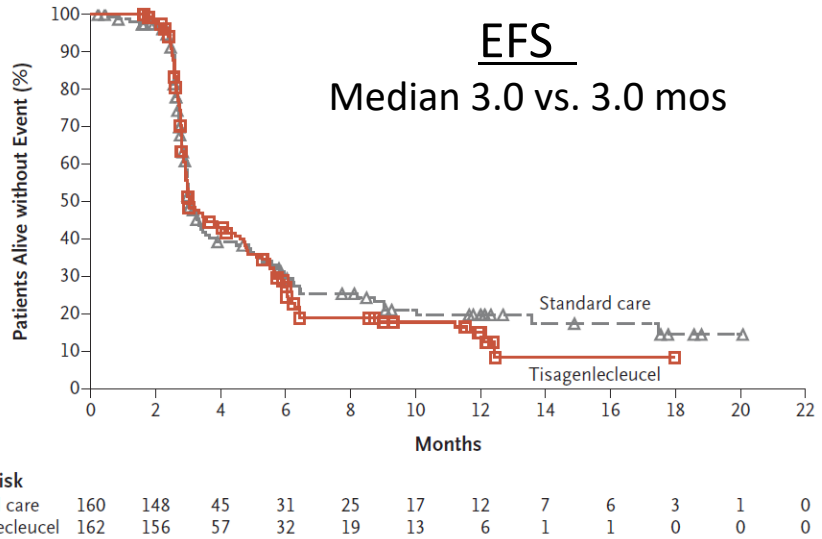
Tisa-cel vs. SOC as 2nd line therapy in primary refractory or early relapsed large B-cell lymphomas

ORR: 46% vs. 43%
CRR: 28% vs. 28%

51% of SOC crossed over

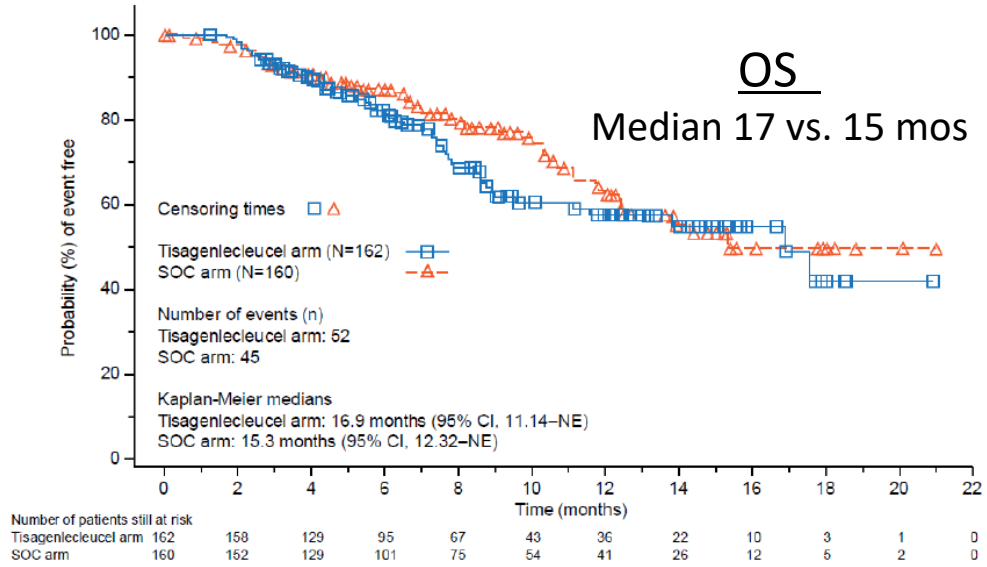
EFS

Median 3.0 vs. 3.0 mos



OS

Median 17 vs. 15 mos



Median Follow-up: 10 mo

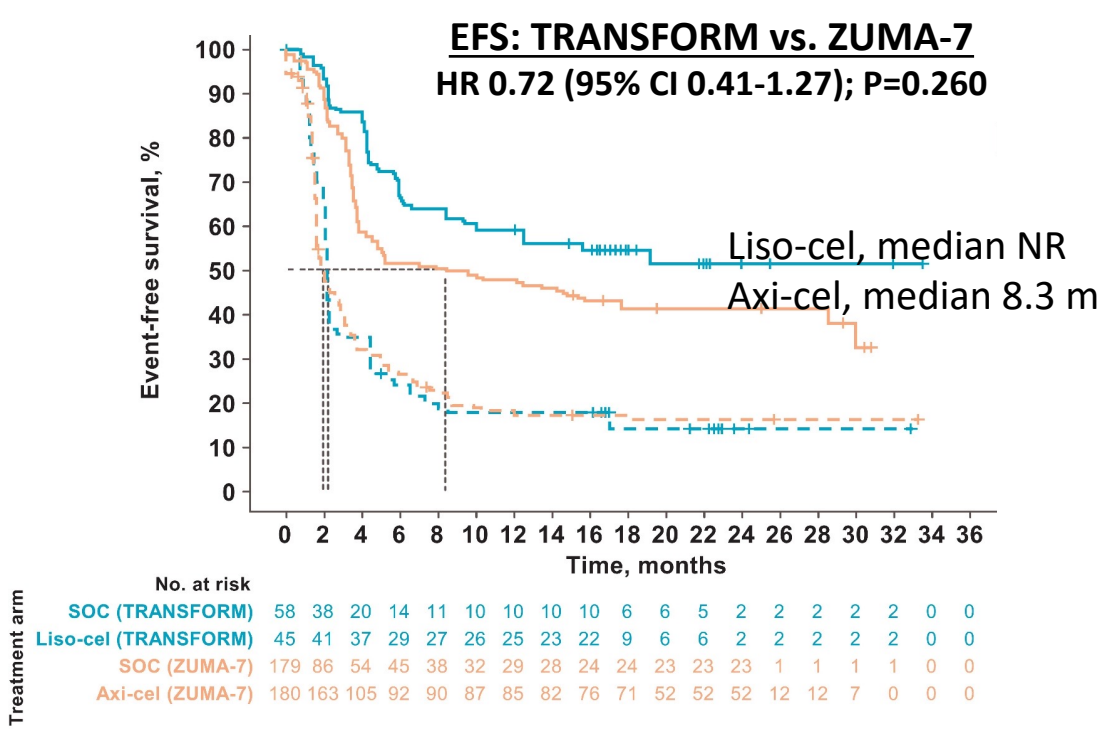
Toxicity	Grade	%
CRS	Any grade Grade 3	61 5
Neurotox	Any grade Grade 3	10 2

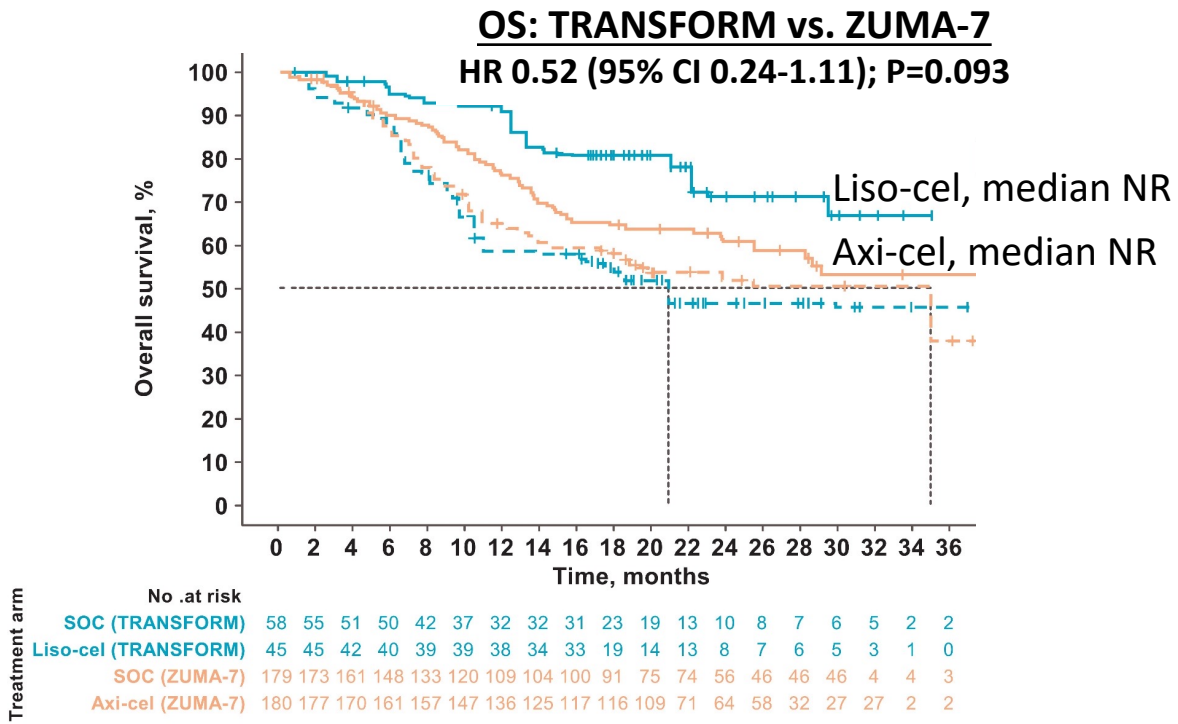
Bishop, et al. NEJM 2021

A tale of two 4-1BB co-stimulated CAR T-cell trials

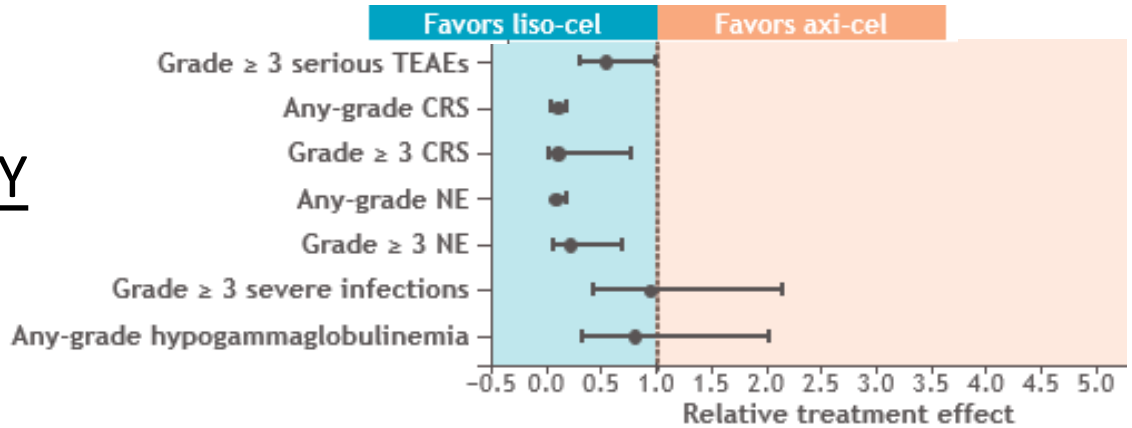
	TRANSFORM	BELINDA
CAR T-cell	Lisocabtagene Maraleucel	Tisagenlecleucel
Construct	FMC63-**CD28tm**-41BB-CD3z	FMC63-**CD8αtm**-4-1BB-CD3z
Cell dose	100 x 10^6 (equal CD4:CD8)	0.6 - 6.0 x 10^8 (uncontrolled CD4:CD8)
Lymphodepleting chemo	Flu 30 / Cy 300 x 3d	Flu 25 / Cy 250 x 3d, or Benda 90 x 2d
Bridging tx on CAR arm	63% (one cycle only)	83% (>1 cycles in 48%)
Salvage chemo on SOC arm	3 cycles of PCT	2-3 cycles of PCT. Non-responders had to get a 2nd PCT regimen (54%)
% infused in CAR arm	98% Median 34 d	96% Median 52 d
% transplanted in SOC	46%	32%
EFS definition	SD or PD by week 9, start of new tx, or death	SD or PD by week 12, or death
Peak CAR expansion	**33,349 copies/µg**	**3,255 copies/µg**
	Kamdar, et al. Lancet 2022.	Bishop, et al. NEJM 2022.

Matched Adjusted Indirect Comparison of TRANSFORM vs. ZUMA-7





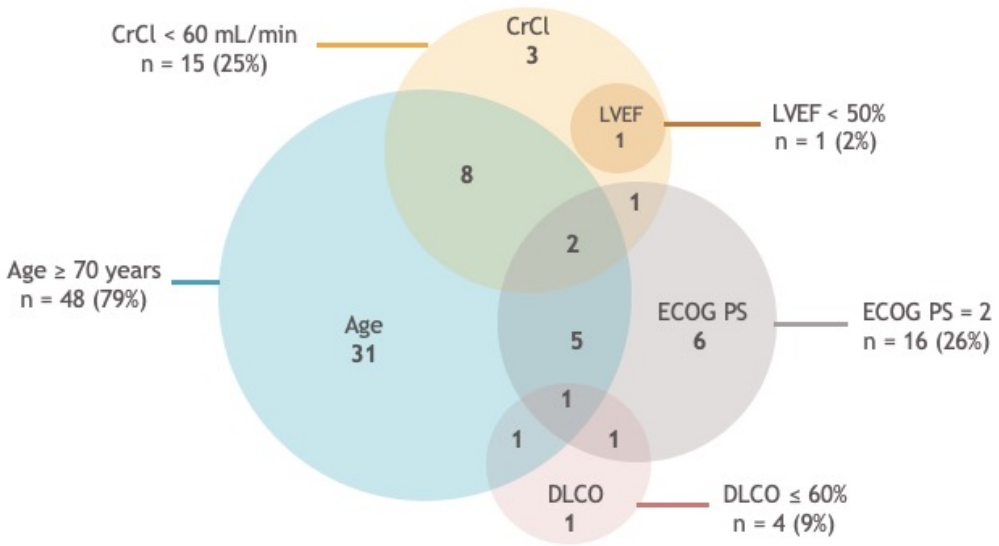
SAFETY



Abramson, et al. Proc. ASH 2022

What about non-transplant eligible patients?

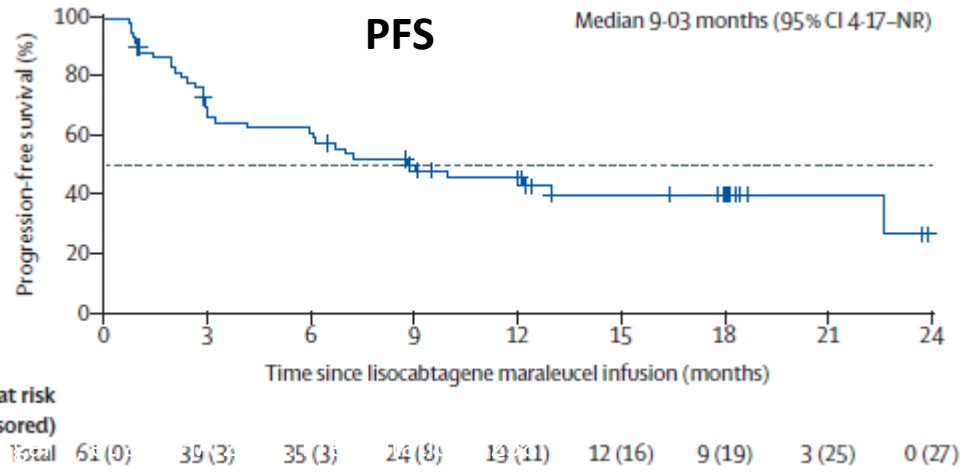
Pilot study: Liso-cel for 2nd line non-transplant eligible LBCL



Baseline Characteristics	N=61
Median age (range)	74 (53-84)
Histology	
DLBCL NOS	54%
Transformed FL	15%
Double hit lymphoma	33%
Primary refractory disease	54%

20 (33%) met ≥ 2 of the 6 protocol-specified TNI criteria

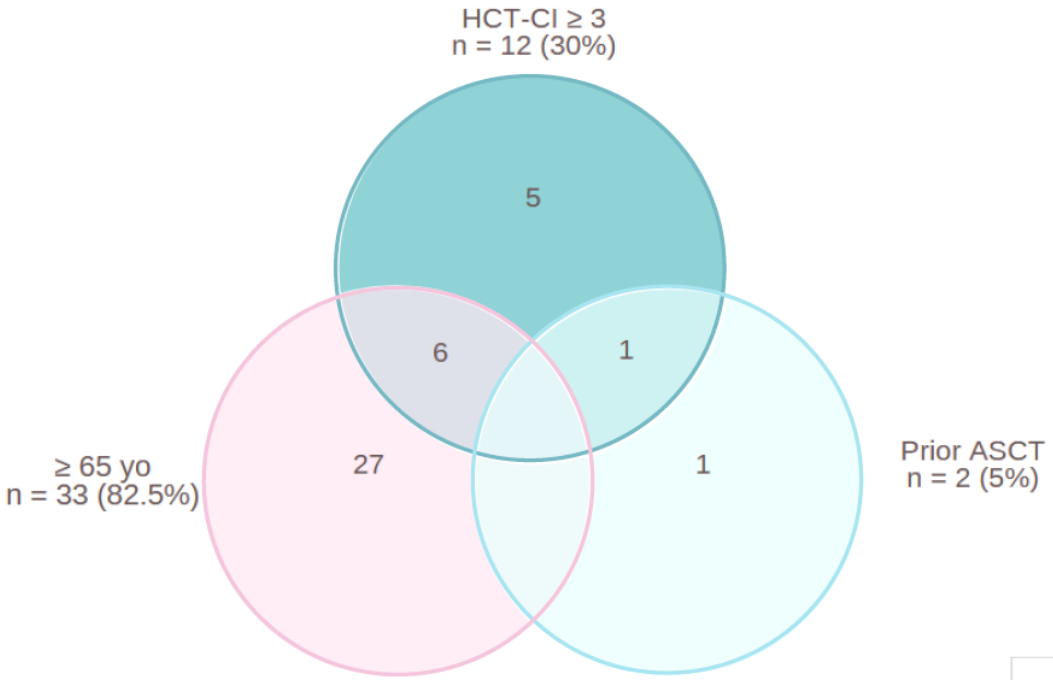
Endpoint	
ORR	80%
CRR	54%
mDOR	12 mo (22 in CR pts)



Toxicity	
CRS	38%
Grade 1-2	36%
Grade 3	2%
NT	31%
Grade 1-2	26%
Grade 3	5%
TRM	3.3%

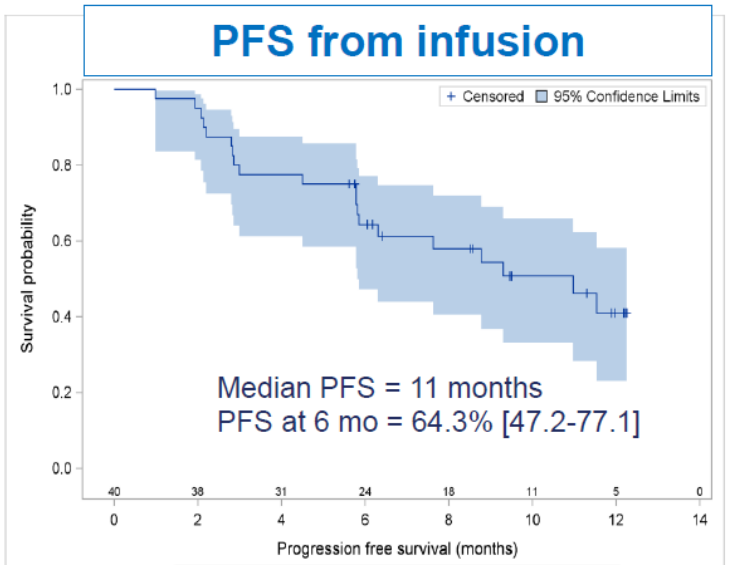
Seghal, et al. Lancet Onc 2022

ALYCANTE: 2nd line Axi-cel for non-transplant eligible LBCL



Baseline Characteristics	N=40
Median age (range)	68 (49-81)
Histology	
DLBCL NOS	82.5%
Transformed iNHL	2.5%
Double hit lymphoma	10%
Primary refractory disease	52.5%

Endpoint	
ORR at 3 mo	75%
CRR at 3 mo	70%
mDOR	12 mo (22 in CR pts)



Toxicity	
CRS	90%
Grade 1-2	80%
Grade 3	10%
ICANS	55%
Grade 1-2	35%
Grade 3	20%
TRM	**12.5%**

Houot, et al. Proc. ASH 2022

Conclusions

- Axi-cel and Liso-cel are now preferred 2nd line therapies for any patients with relapsed or refractory LBCL within 12 months of initial treatment
- Toxicity profile favors liso-cel
- Presently, Axi-cel provides the most rapid turnaround time and most reliable manufacturing, which is an important real-world consideration
- Liso-cel is also an option as 2nd line therapy with curative intent for any non-transplant eligible patients regardless of duration of initial remission
- Elephant in the room is improving access to CAR T-cell therapy, as the majority of patients with relapsed/refractory LBCL will now benefit from this approach

Thank you for your attention!

jabramson@mgh.harvard.edu