Novità nella terapia cellulare nel mondo dei pazienti R/R DLBCL

Dati dagli studi registrativi delle terapia cellulari

Napoli 25/9/2023

NOME COMMERCIALE	INN*	INDICAZIONE	SOMMINISTRAZIONE E VETTORE	AZIENDA	APPROVAZIONE EUROPEA	AIC* IN EUROPA	AIC* IN ITALIA
Kymriah®	tisagenlecleucel	**leucemia linfoblastica acuta a cellule B** e **linfoma diffuso a grandi cellule B**	**ex vivo** lentivirus	Novartis Europharm Limited	**agosto 2018** farmaco orfano	✓	✓ Classe H* **agosto 2019**
		linfoma follicolare recidivante o refrattario			**maggio 2022**	✓	✓
Yescarta®	axicabtagene ciloleucel	**linfoma diffuso a grandi cellule B** e **linfoma primitivo del mediastino a grandi cellule B refrattari o recidivanti**	**ex vivo** retrovirus	Kite Pharma EU	**agosto 2018** farmaco orfano	✓	✓ Classe H* **novembre 2019**
		linfoma follicolare recidivante o refrattario			**giugno 2022**	✓	✗
		linfoma diffuso a grandi cellule B e **linfoma a cellule B di alto grado** con ricaduta entro 12 mesi o refrattari			**ottobre 2022**	✓	✗
Tecartus™	brexucabtagene autoleucel	**linfoma a cellule mantellari** recidivante o refrattario	**ex vivo** retrovirus	Kite Pharma EU	**dicembre 2020** farmaco orfano	✓	✓ Classe H* **marzo 2022**
		leucemia linfoblastica acuta da precursori delle cellule B recidivante o refrattaria			**settembre 2022**	✓	✗
Breyanzi®	lisocabtagene maraleucel	**DLBCL, linfoma primitivo del mediastino a grandi cellule B e linfoma follicolare**	**ex vivo** lentivirus	Bristol-Myers Squibb / Celgene	**aprile 2022**	✓	✗
		linfoma a grandi cellule B refrattario o recidivante			**luglio 2023**	✓	✗

Dati OTA, settembre 2023

CAR-T cells in R/R DLBCL as 3rd line

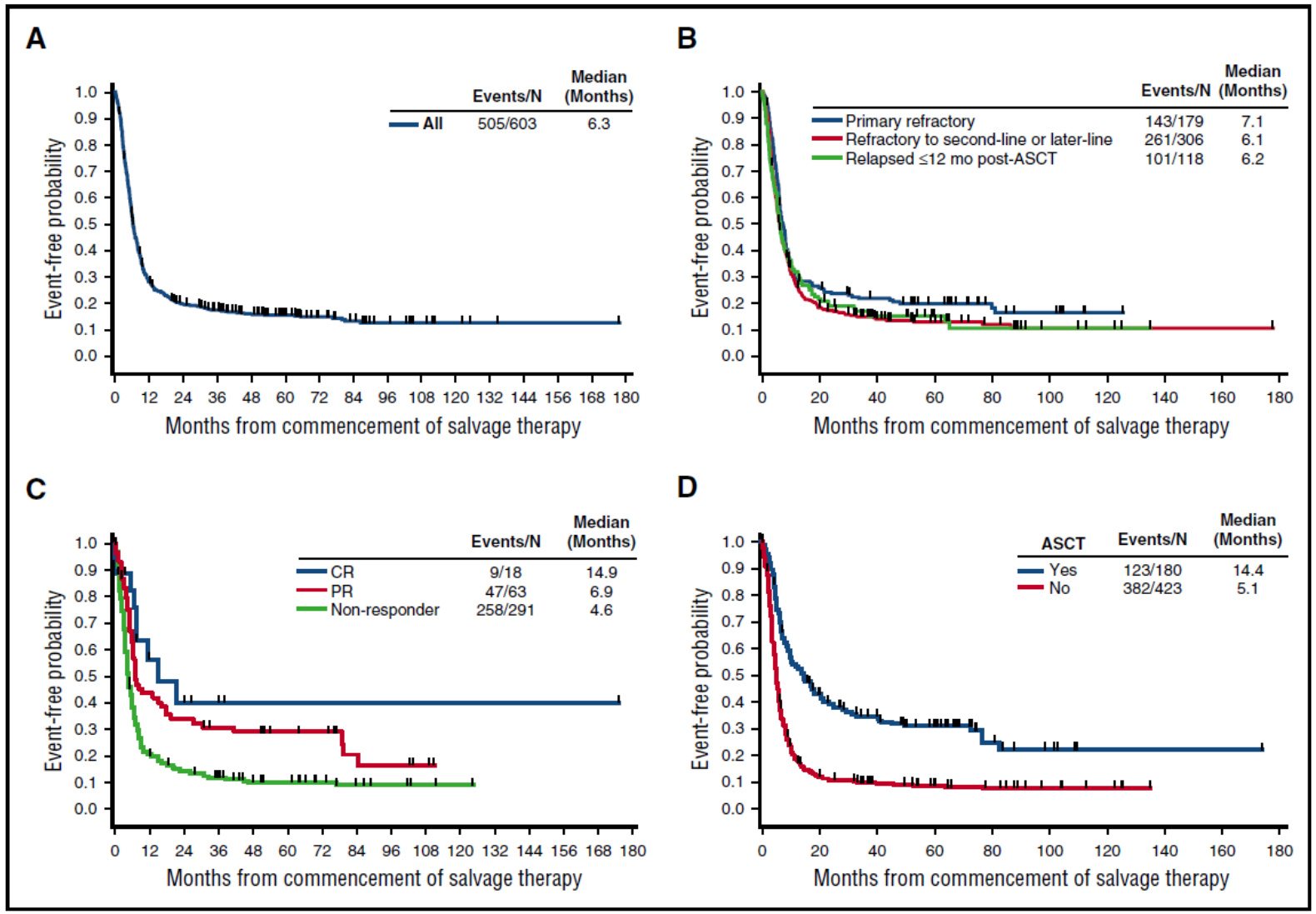
Background: unmet clinical need

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR			3-Year Event-Free Survival		3-Year Overall Survival	
		No. of Patients	%	*P*	%	*P*	%	*P*
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saaIPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

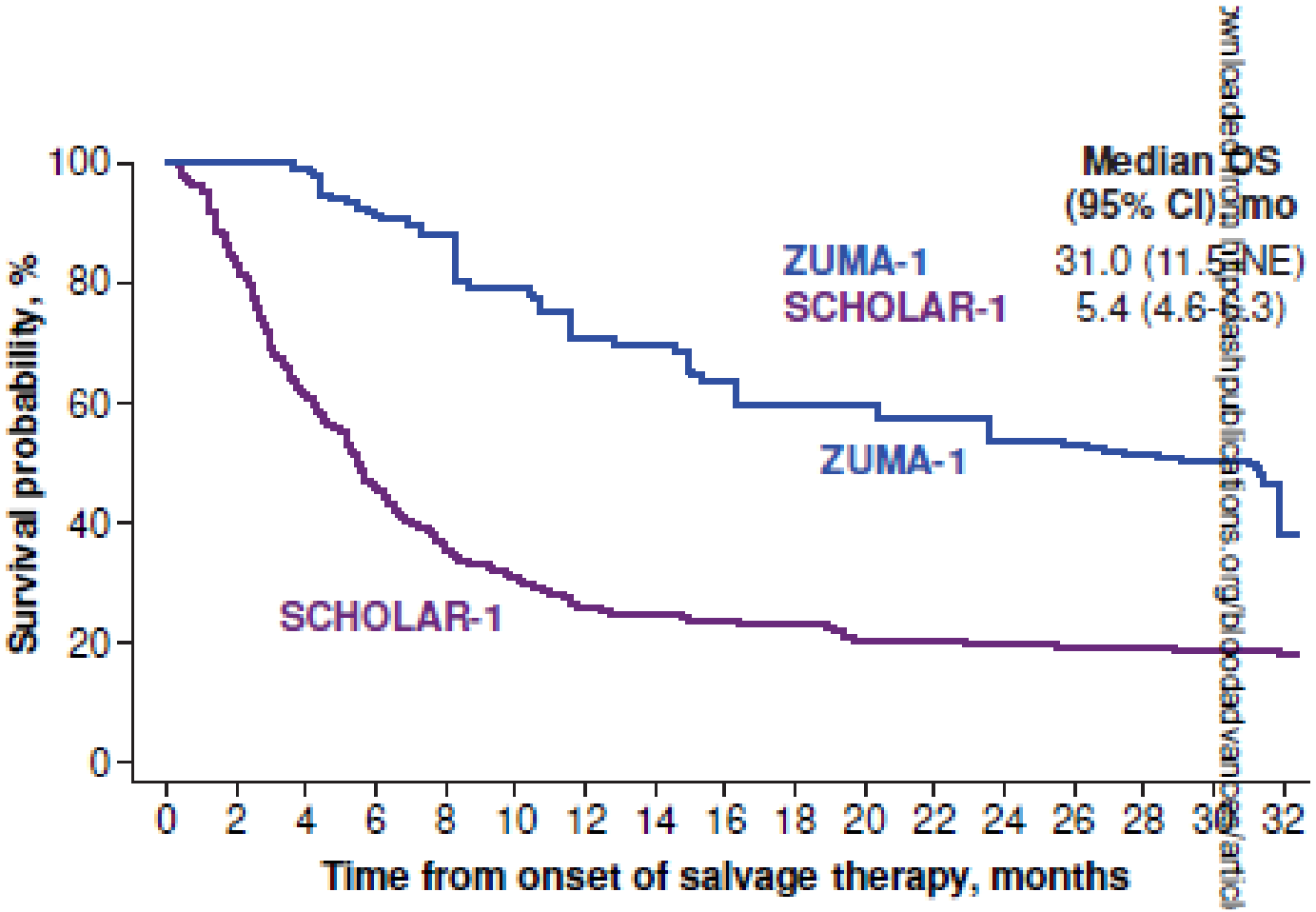
Gisselbrecht, JCO 2010

Background: unmet clinical need



Crump, Blood 2017

ZUMA vs Scholar1



Neelapu, Blood Adv 2021

Results from clinical trials in advanced patients

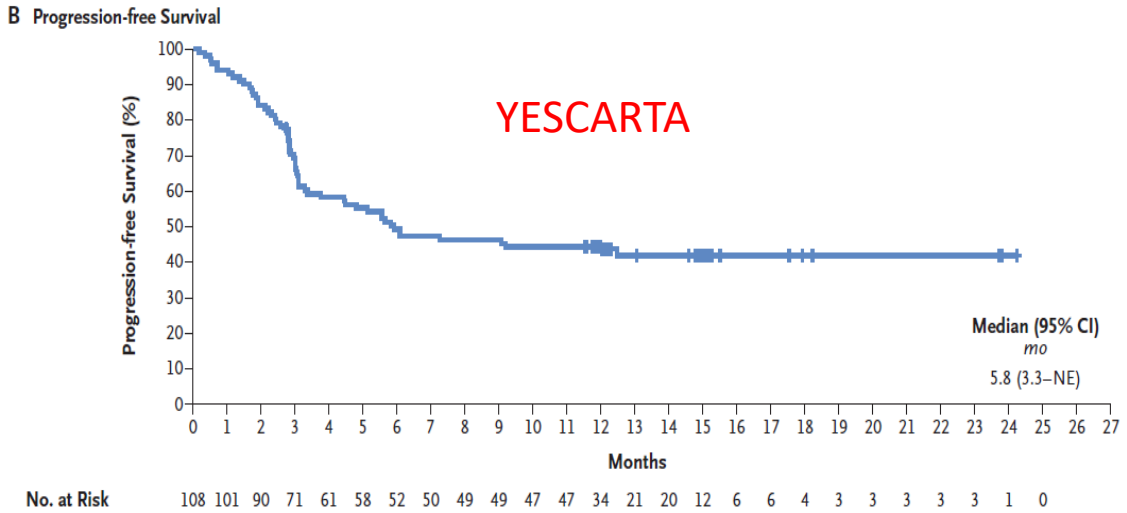
	ZUMA-1[4] (N = 101)	JULIET[2,10,11] (N = 115)	TRANSCEND[6] (N = 256)
Median DOR, (95% CI)	NR (10.9-NE)	NR (10.0-NE)	NR (8.6-NR)
DOR at month 12, % (95% CI)	–	65 (49–78)	54.7 (46.7–62.0)
DOR at month 24, % (95% CI)	–	–	52.1 (43.6–49.8)
Median OS, months (95% CI)	NR (12.8-NE)[a]	11.1 (6.6–23.9)	21.1 (13.3-NR)
OS at month 12, % (95% CI)	59 (49–68)[5]	48.2 (38.6–57.1)	57.9 (51.3–63.8)
OS at month 24, % (95% CI)	50.5 (40.2–59.7)	40.0 (30.7–49.1)	44.9 (36.5–52.9)
Median PFS, months (95% CI)	5.9 (3.3–15.0)[a]	NR	6.8 (3.3–14.1)
PFS at month 12, % (95% CI)	44 (34–53)[5]	–[b]	44.1 (37.3–50.7)
PFS at month 24, % (95% CI)	–[c]	–	42.1 (35.0–48.9)
Follow-up, months	27.1	32.6	12.0–17.5[d]

Westin, AJH 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

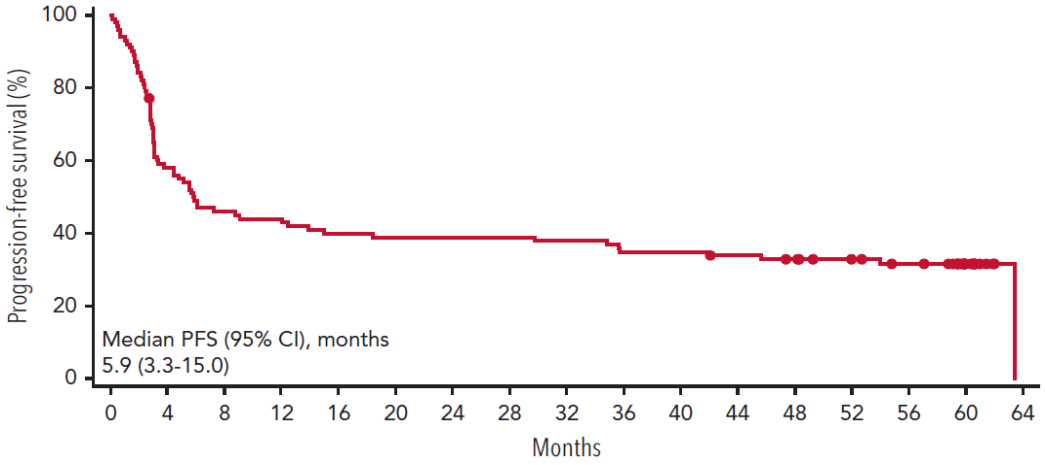


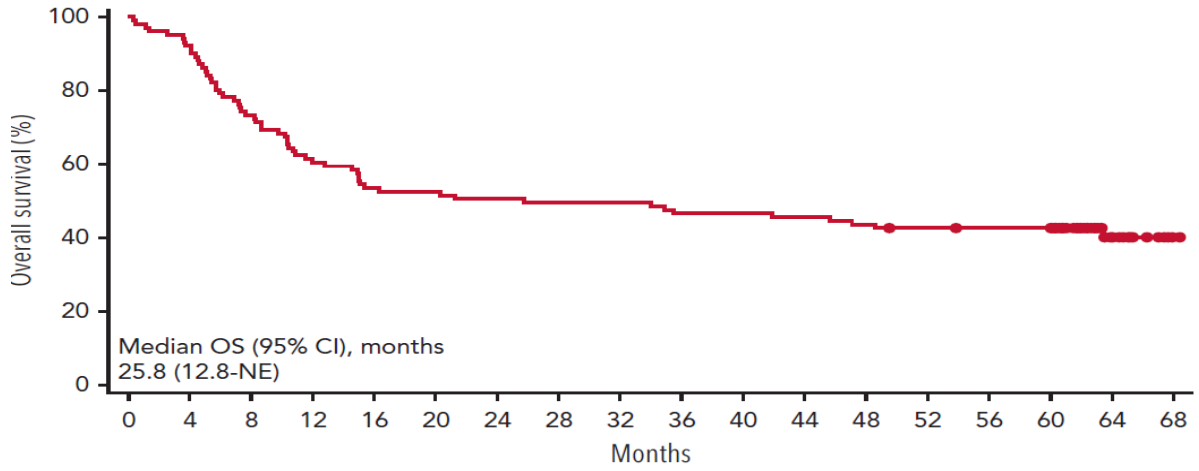
111 patients with DLBCL
median follow-up of 15.4 months
ORR 82%; CR 54%
Median PFS: 5.8 months

Neelapu, NEJM 2017

Update ZUMA1

Median FUP 63 months





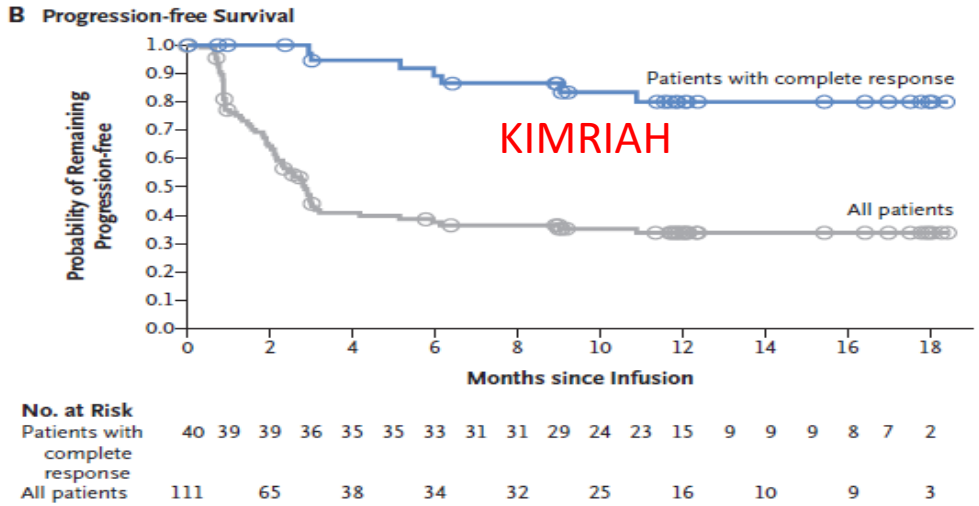
n (%)	N = 101						
	Total	Year 1	Year 2	Year 3	Year 4	Year 5	Year >5
Patients who died	59 (58)	40 (40)	10 (10)	4 (4)	3 (3)	1 (1)	1 (1)
Primary cause of death							
Progressive disease*	45 (45)	32 (32)	9 (9)	3 (3)	0	1 (1)	0
AE†	4 (4)	3 (3)	1 (1)	0	0	0	0
Secondary malignancy	1 (1)	0	0	0	0	0	1 (1)
Other‡	9 (9)	5 (5)	0	1 (1)	3 (3)	0	0

Neelapu, Blood 2023

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

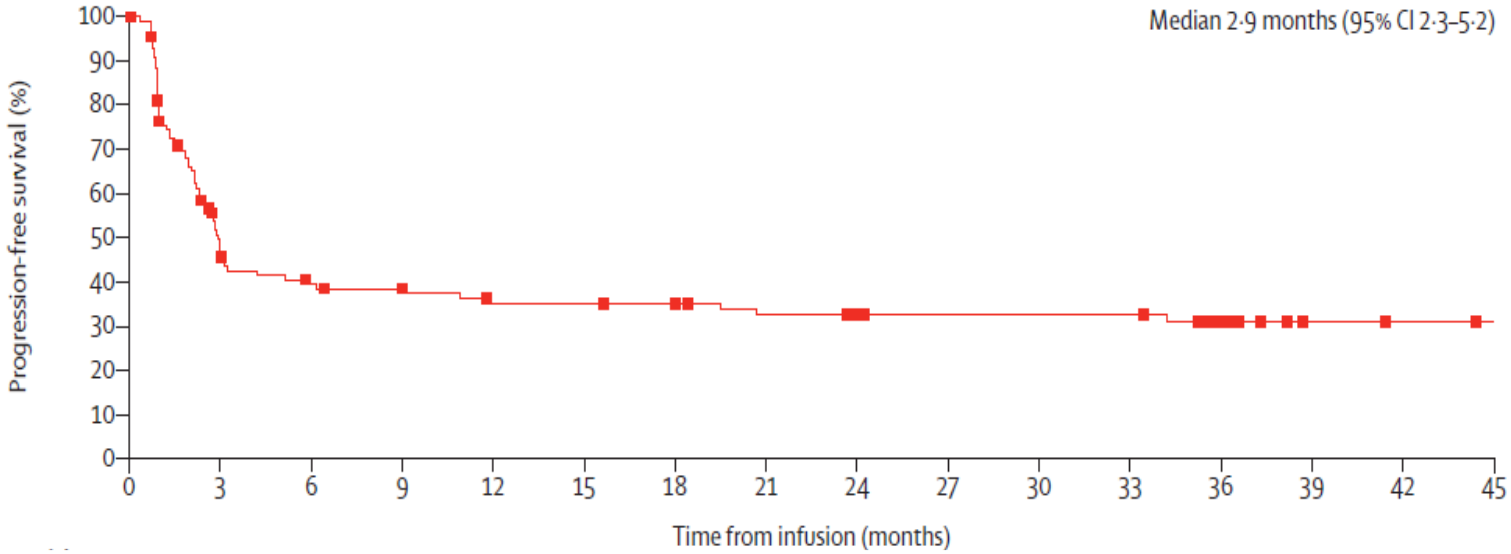


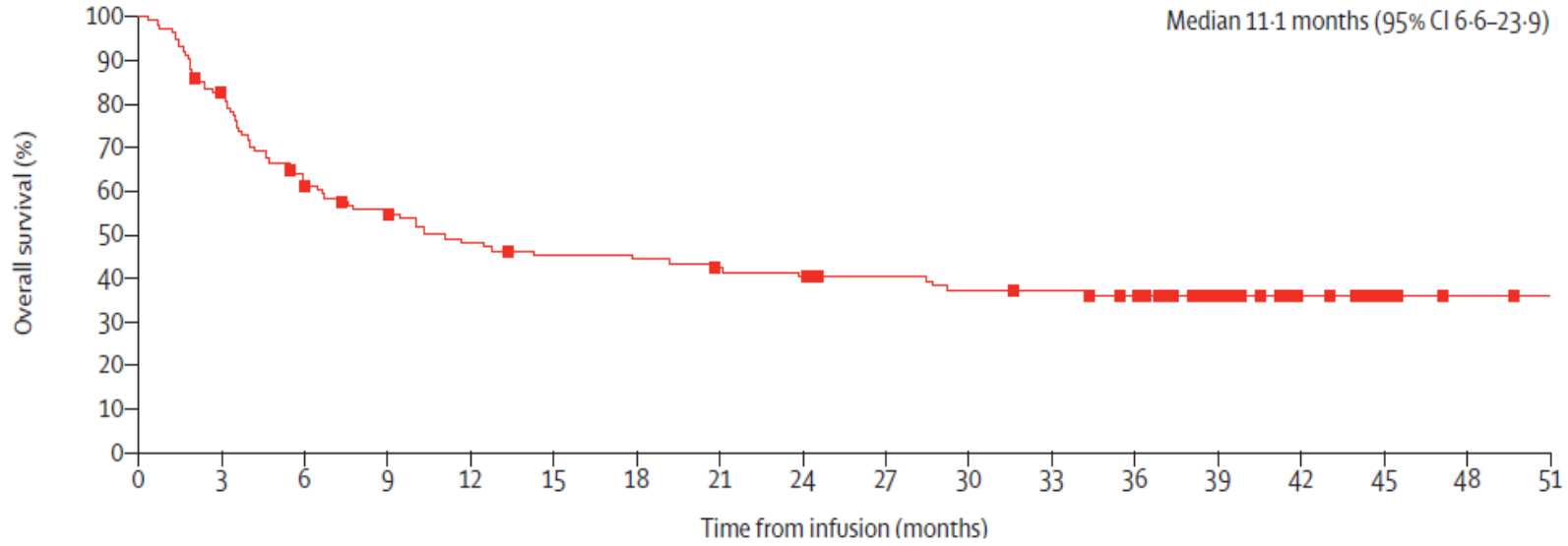
93 patients with DLBCL
median follow-up of 14 months
ORR 52%; CR 40%
Median PFS: NR

Schuster, NEJM 2017

Update Juliet

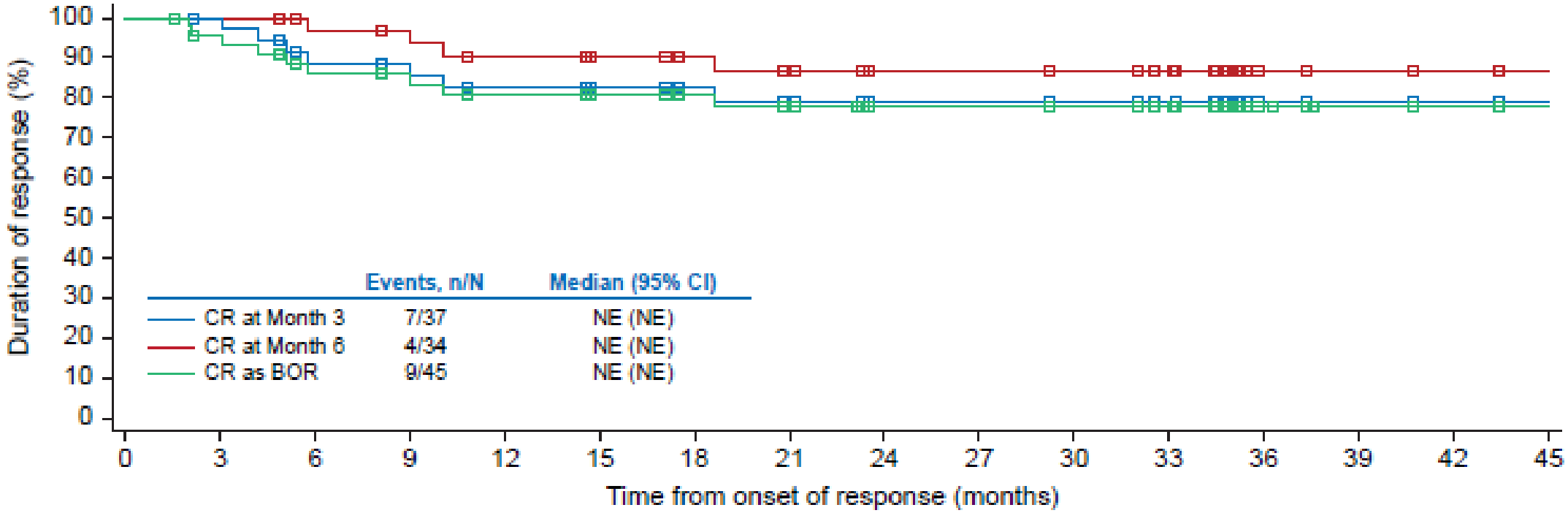
Median FUP 43 months





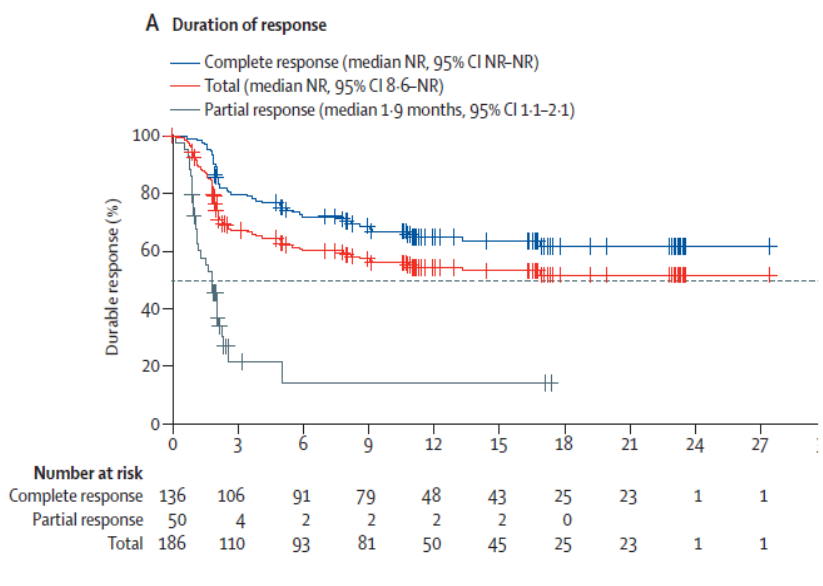
Schuster, Lancet Oncol 2021

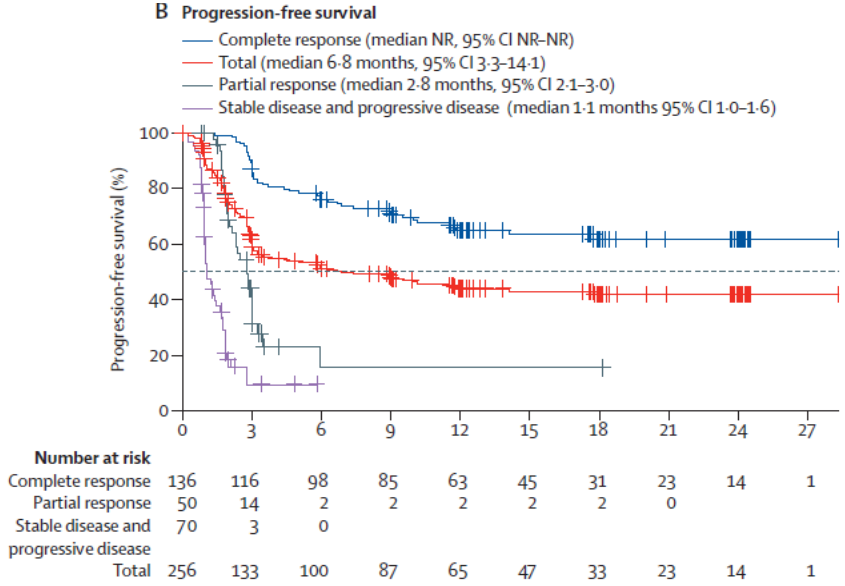
Update Juliet

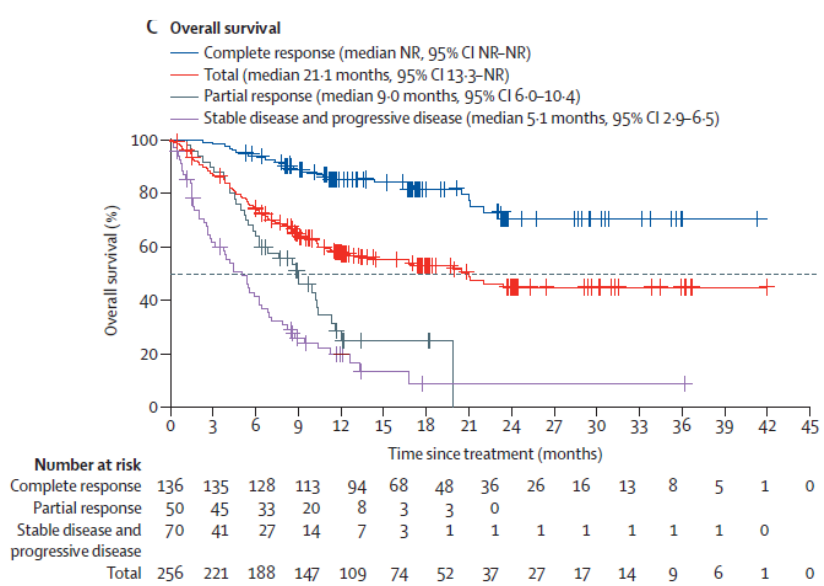


Schuster, Lancet Oncol 2021

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







294 patients with DLBCL
median follow-up of 18.8 months
ORR 73%; CR 53%
Median PFS: 6.8 months

Abramson, Lancet 2020

Update TRANSCEND

Median FUP 24 months

Median PFS, mo	6.8
95% CI[b]	3.3–12.7
Median (95% CI) follow-up, mo[c]	23.9 (23.7–24.0)
Probability (95% CI) of PFS at 2 years, %[b]	40.6 (34.0–47.2)
Median OS, mo	27.3[d]
95% CI[b]	16.2–45.6
Median (95% CI) follow-up, mo[c]	29.3 (26.2–30.4)
Probability (95% CI) of OS at 2 years, %[b]	50.5 (44.1–56.5)
Median DOR in pts who achieved CR, mo	26.1
95% CI[b]	23.1–not reached
Median (95% CI) follow-up, mo[c]	23.1 (23.0–23.2)
Probability (95% CI) of continued response at 2 years, %[b]	58.5 (49.2–66.7)

Abramson, Blood 2021

CAR-T cells in R/R DLBCL as 2nd line

ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

Bishop, NEJM 2021

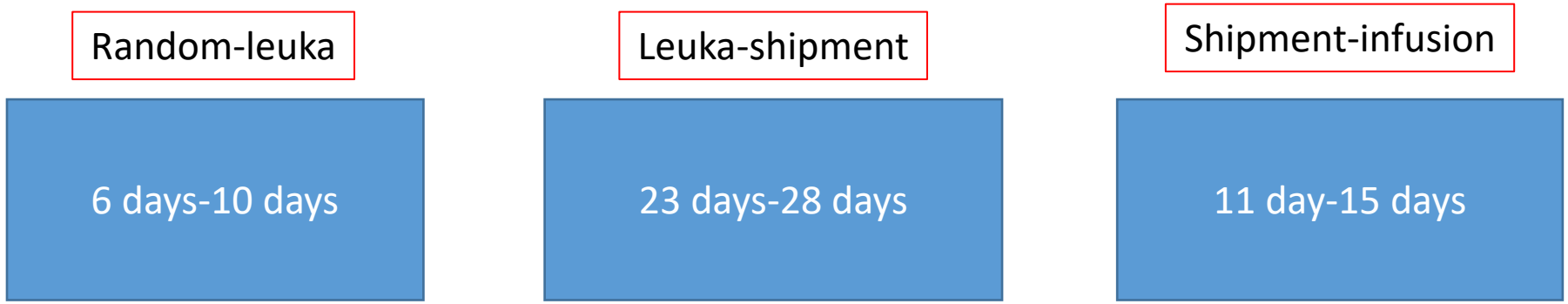
Results

- **155/162 (95.7%) received tisa-cel** at a median dose of 2.9×10^8 cells (range, 0.4 to 5.9)
- Tisa-cel group: no bridging therapy (BT)= 16,7%, 1 cycle BT= 35%, 2 cycles BT 47%

- 155/160 (96.9%) in the SOC group received at least 2 chemotherapy cycles, including 86 (53.8%) who received at least 2 regimens
- **52 patients (32.5%) received autologous HSCT** in the SOC group

Bishop, NEJM 2021

Results



- The median time from leukapheresis to tisa-cel infusion group was:
  - **52 days (range, 31 to 135) in the overall population**
  - 41 days (range, 31 to 91) in U.S. patients,
  - 57 days (range, 38 to 135) in non-U.S. patients;
  - 44 days (range, 34 to 76) in patients who received no bridging therapy
  - 47 days (range, 31 to 79) in those who received 1 cycle

Bishop, NEJM 2021

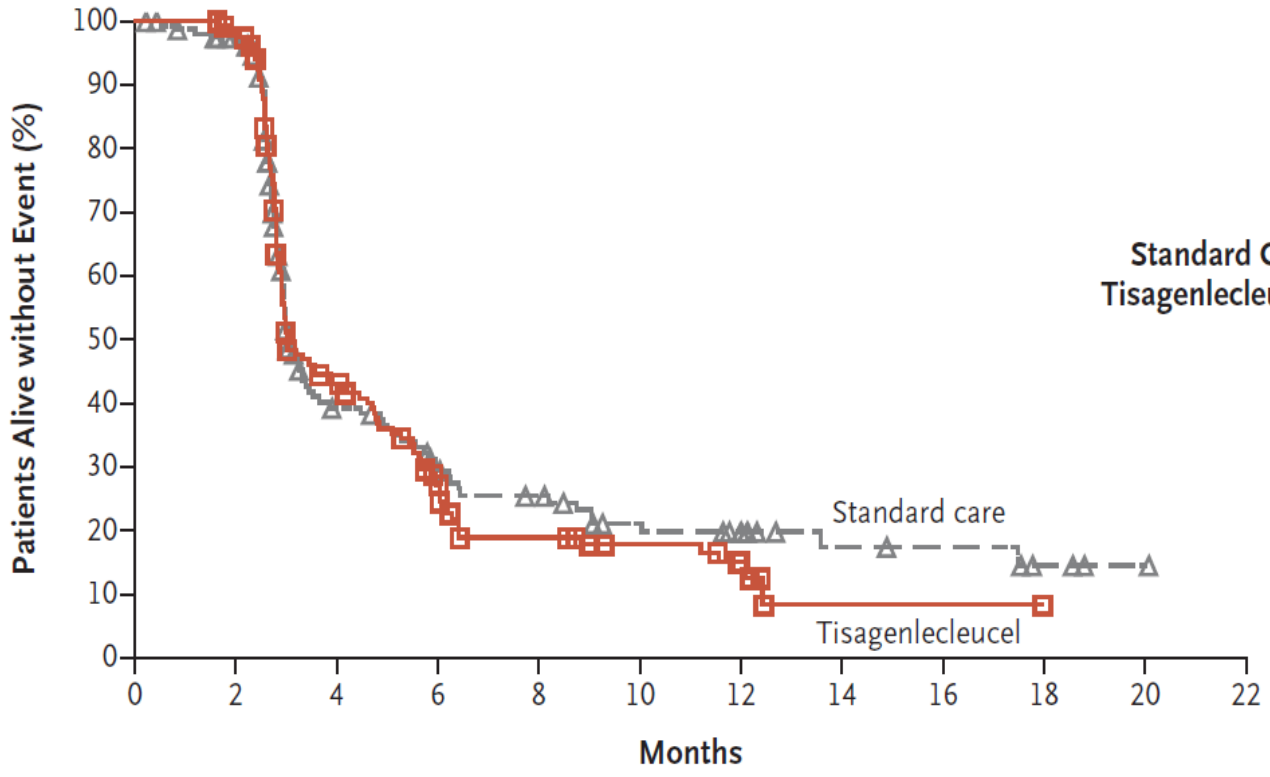
Results

Table 2. Overall Response at Week 6 Assessment and Best Overall Response.*

Response	Week 6 Assessment†		Best Overall Response at or after Week 12 Assessment‡	
	Tisagenlecleucel Group (N=162)	Standard-Care Group (N=160)	Tisagenlecleucel Group (N=162)	Standard-Care Group (N=160)
Best overall response — no. (%)				
Complete response	18 (11.1)	31 (19.4)	46 (28.4)	44 (27.5)
Partial response	44 (27.2)	55 (34.4)	29 (17.9)	24 (15.0)
Stable disease	48 (29.6)	46 (28.8)	19 (11.7)	22 (13.8)
Progressive disease	42 (25.9)	22 (13.8)	50 (30.9)	46 (28.8)
Unknown§	10 (6.2)	6 (3.8)	18 (11.1)	24 (15.0)
Complete or partial response				
No. of patients	62	86	75	68
Percent (95% CI)¶	38.3 (30.8–46.2)	53.8 (45.7–61.7)	46.3 (38.4–54.3)	42.5 (34.7–50.6)

Bishop, NEJM 2021

Results



	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

No. at Risk

Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

Bishop, NEJM 2021

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

Locke, NEJM 2021

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Axi-cel (N = 180)	Standard Care (N = 179)	Total (N = 359)
Age			
Median (range) — yr	58 (21–80)	60 (26–81)	59 (21–81)
≥65 yr — no. (%)	51 (28)	58 (32)	109 (30)
Male sex — no. (%)	110 (61)	127 (71)	237 (66)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	1 (1)	1 (<1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group — no. (%)†			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance-status score of 1 — no. (%)‡	85 (47)	79 (44)	164 (46)
Disease stage — no. (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
Second-line age-adjusted IPI of 2 or 3 — no. (%)§	82 (46)	79 (44)	161 (45)
Molecular subgroup according to central laboratory — no. (%)¶			
Germinal center B-cell–like	109 (61)	99 (55)	208 (58)
Activated B-cell–like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to first-line therapy at randomization — no. (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse at ≤12 mo after the initiation or completion of first-line therapy	47 (26)	48 (27)	95 (26)
Disease type according to central laboratory — no. (%)			
Diffuse large B-cell lymphoma‖	126 (70)	120 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0	1(1)	1 (<1)
High-grade B-cell lymphoma, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator — no. (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell– or histiocyte–rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein–Barr virus–positive diffuse large B-cell lymphoma	2 (1)	0	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)

Table 1. (Continued.)

Characteristic	Axi-cel (N = 180)	Standard Care (N = 179)	Total (N = 359)
High-grade B-cell lymphoma, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	43 (24)	27 (15)	70 (19)
Primary cutaneous diffuse large B-cell lymphoma, leg type	1 (1)	0	1 (<1)
Other	0	3 (2)	3 (1)
Prognostic marker according to central laboratory — no. (%)			
High-grade B-cell lymphoma, double- or triple-hit	31 (17)	25 (14)	56 (16)
Double-expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Not applicable	74 (41)	70 (39)	144 (40)
Missing data	3 (2)	15 (8)	18 (5)
CD19+ status on immunohistochemical testing — no. (%)**	144 (80)	134 (75)	278 (77)
Bone marrow involvement — no. (%)††	17 (9)	15 (8)	32 (9)
Elevated lactate dehydrogenase level — no. (%)‡‡	101 (56)	94 (53)	195 (54)
Median tumor burden (range) — mm^2§§	2123 (181–22,538)	2069 (252–20,117)	2118 (181–22,538)

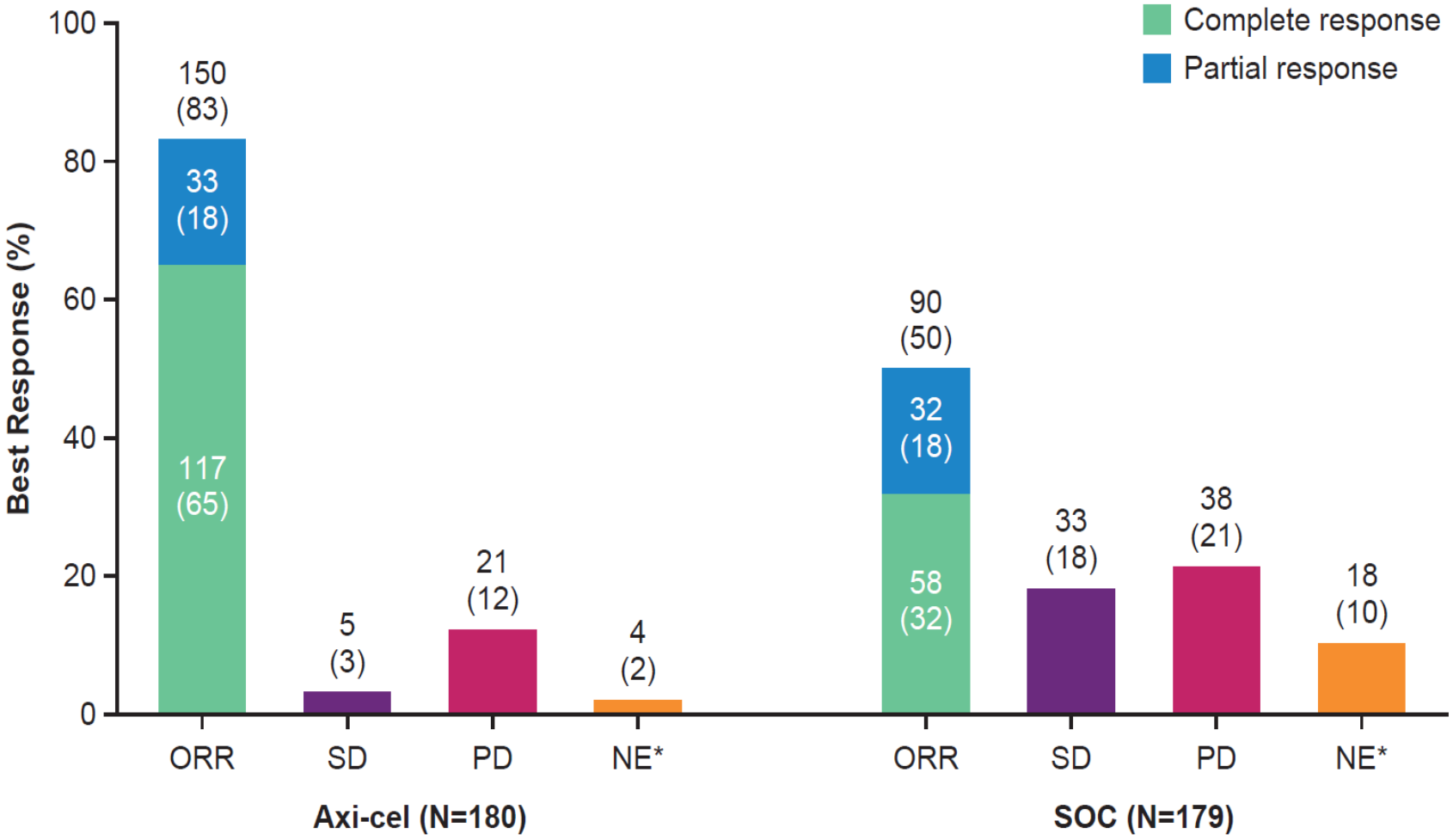
Locke, NEJM 2021

Results

- Median time follow-up 25M
- 170/180 **(94%) received axi-cel**
- The median time from leukapheresis to product release was **13 days**.
- 64/179 patients (**36%) received HDCT**

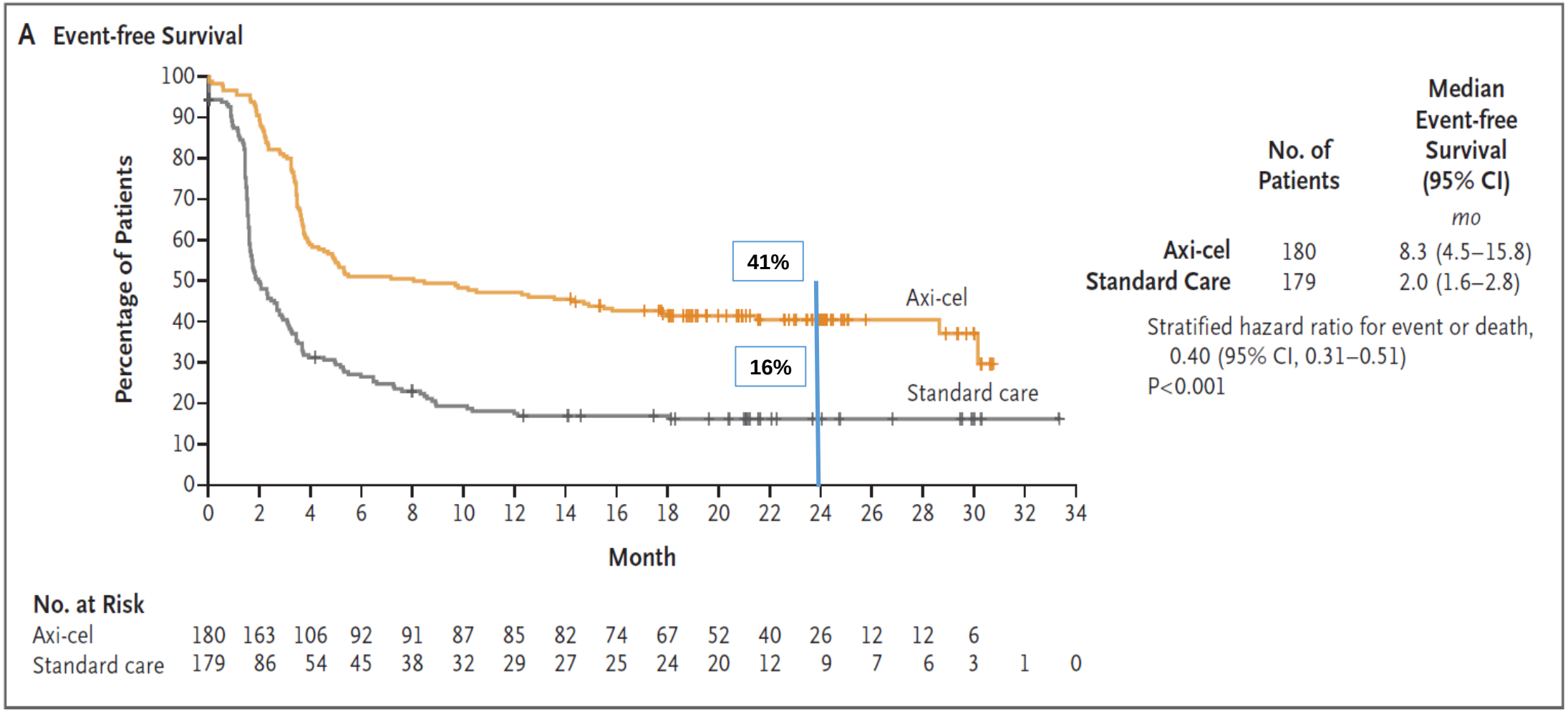
Locke, NEJM 2021

Results



Locke, NEJM 2021

Results

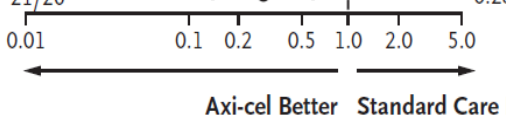


Locke, NEJM 2021

Results

B Subgroup Analysis

Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



Locke, NEJM 2021

Lisocabtagene maraleucel 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 (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

Kamdar, Lancet 2022
Kamdar, Lancet 2022

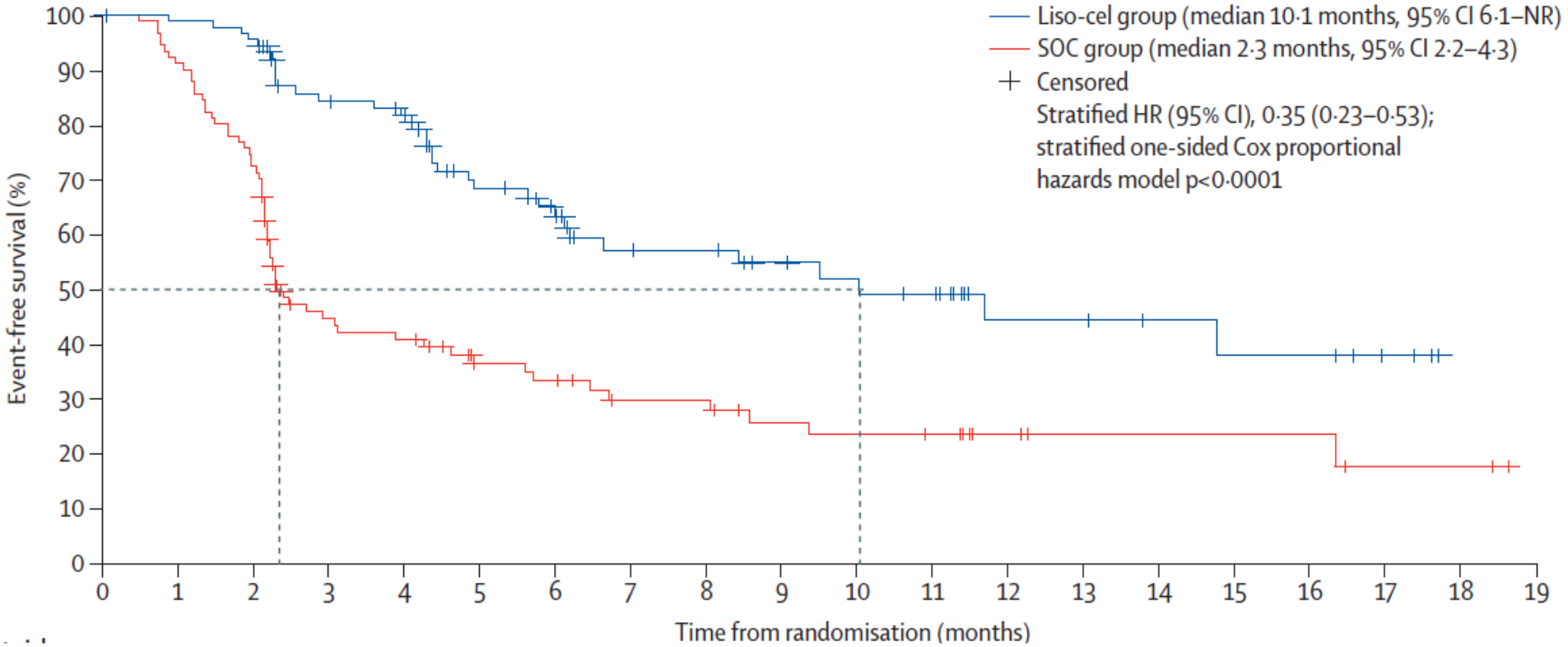
Results

- Median time follow-up 6M
- 89/92 **(97%) received liso-cel**
- The median time from leukapheresis to product release was **26 days**.
- 43/91 patients (**46%) received HDCT**

Results

	Liso-cel group (n=92)	Standard-of-care group (n=92)	Stratified HR (95% CI)*	p value
Overall response rate (secondary endpoint)				
n (%, 95% CI)	79 (86%; 77–92)	44 (48%; 37–59)	..	..
Best response since randomisation				
Complete response	61 (66%)	36 (39%)	..	..
Partial response	18 (20%)	8 (9%)	..	..
Stable disease	4 (4%)	21 (23%)	..	..
Progressive disease	6 (7%)	24 (26%)	..	..
Not evaluable	3 (3%)	3 (3%)	..	..

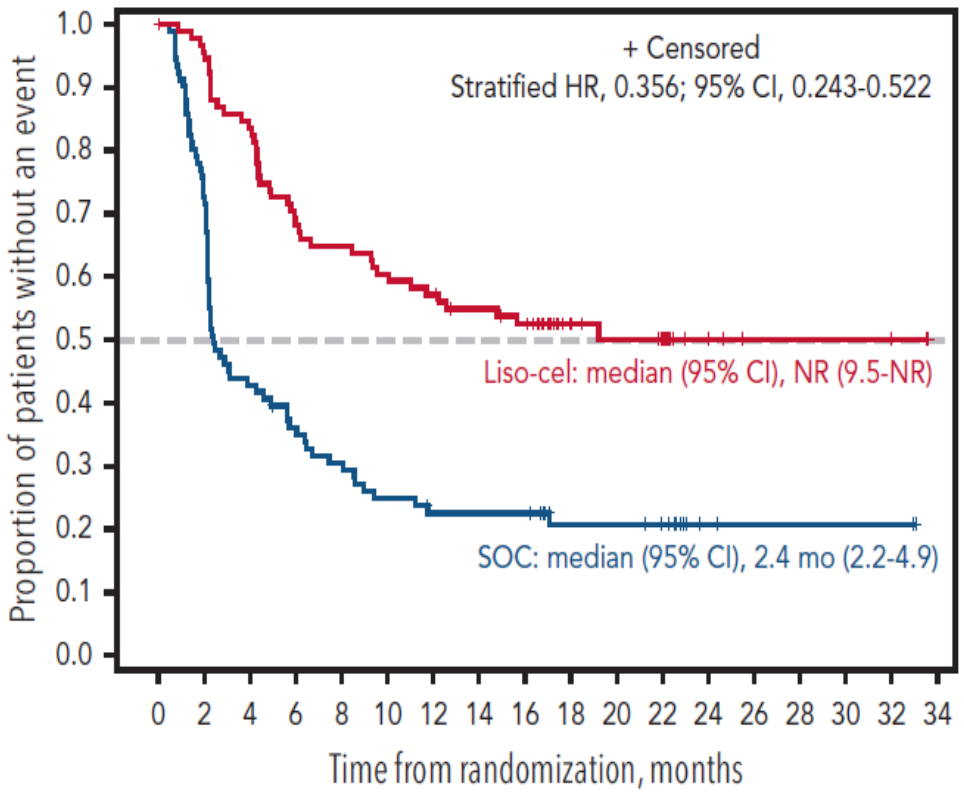
Results

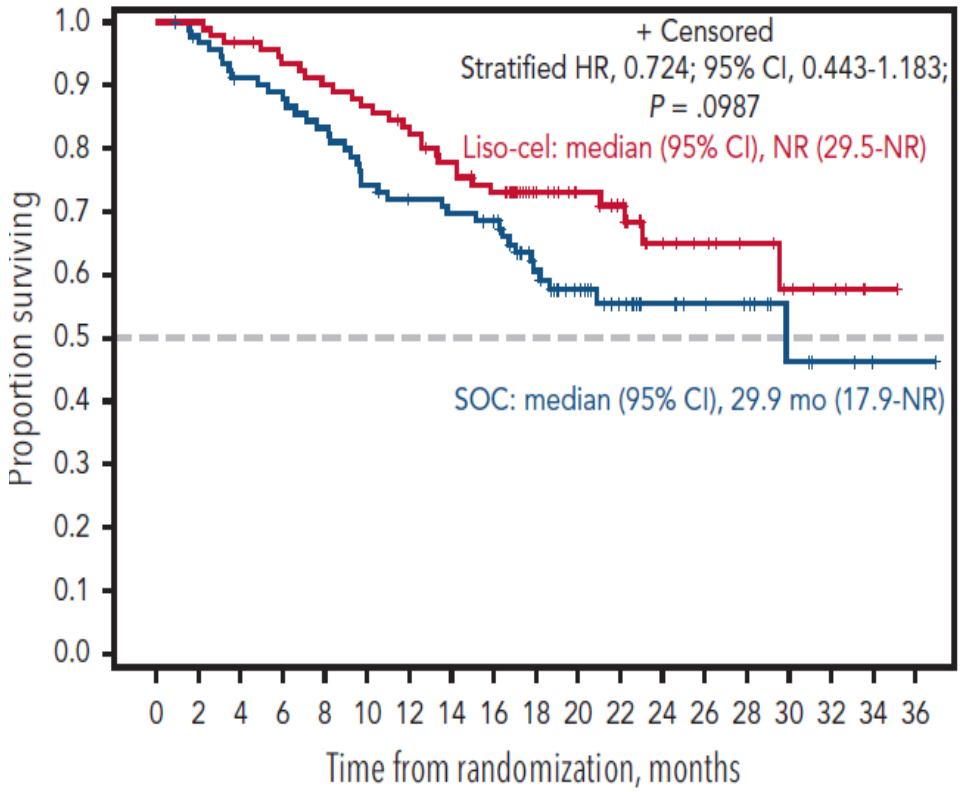


Kamdar, Lancet 2022

CLINICAL TRIALS AND OBSERVATIONS

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study





Median FUP 17.5 months

Abramson, Blood 2023

Comparison between Belinda and ZUMA7 (CAR-T arm)

	ZUMA7	Belinda	TRANSCEND
Bridging therapy	No	Yes (even 2 lines)	Yes
COO ABC	9%	32%	23%
DH/TH DLBCL	24%	19%	24%
Median time leuka-infusion CAR-T	13 days	52 days	26 days
CR/PR	83%	46% (12w)	79%
EFS	41%	15%	52%
Median EFS	8M	3M	NR

Grazie per l’attenzione