CAR-Team

L'uso precoce delle CAR-T nei linfomi diffusi a grandi cellule in prima recidiva o chemio-refrattari

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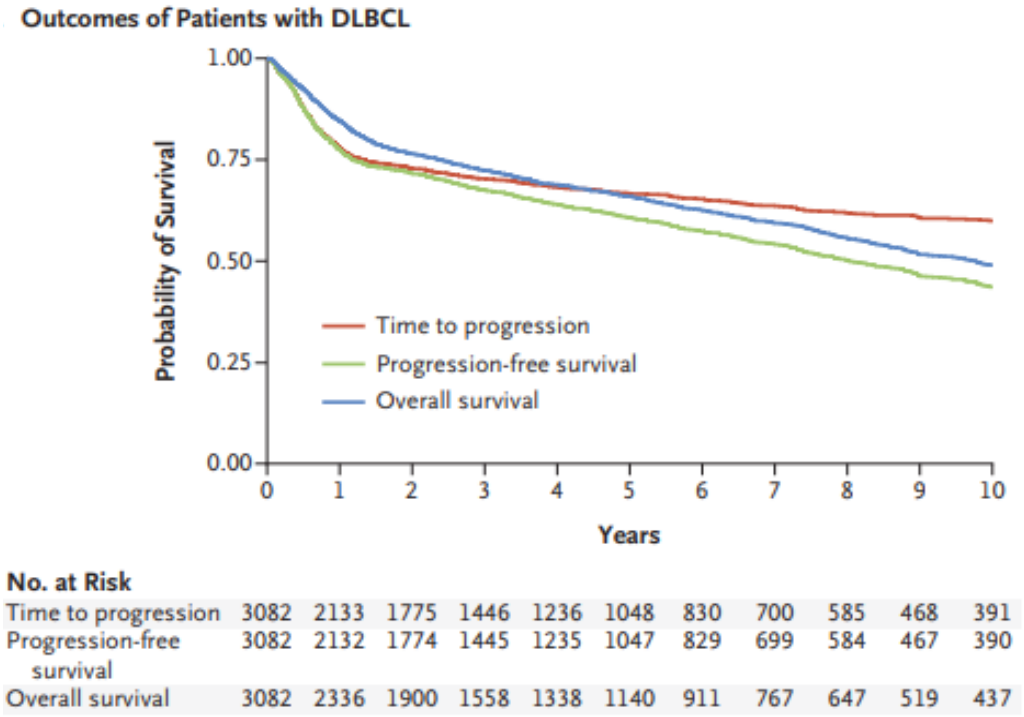
Relapsed/refractory DLBCL: the size of the issue



No. at Risk

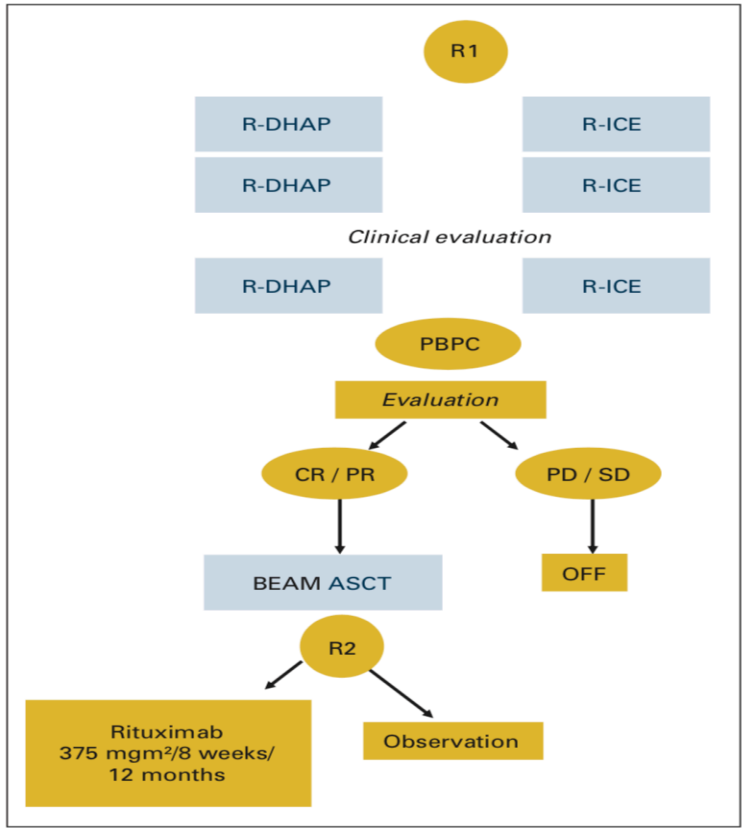
Time to progression	3082	2133	1775	1446	1236	1048	830	700	585	468	391
Progression-free survival	3082	2132	1774	1445	1235	1047	829	699	584	467	390
Overall survival	3082	2336	1900	1558	1338	1140	911	767	647	519	437

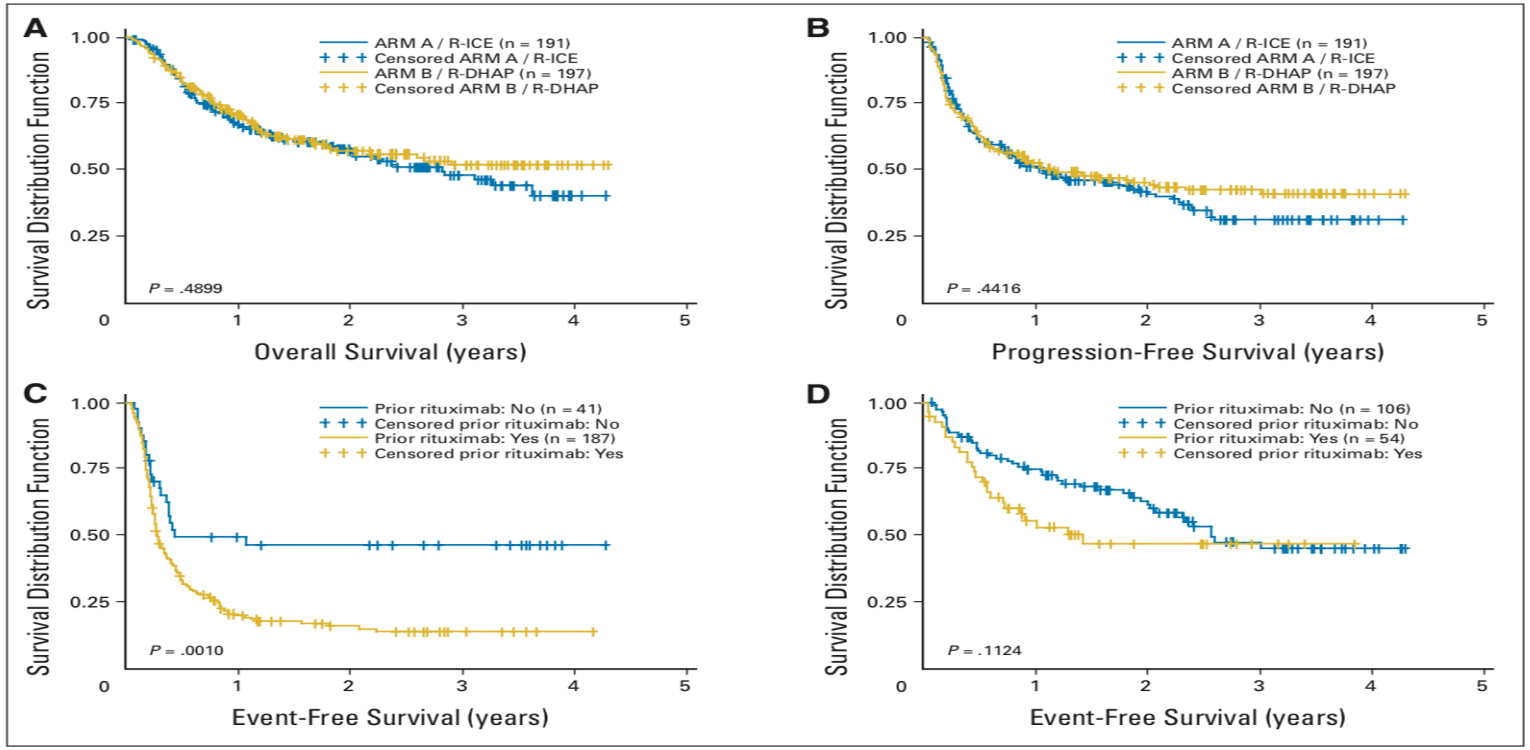
- **35-40% failures after R-CHOP first line therapy**
- **Most of them within 12 months after the end of RCHOP**

Sehn LH and Salles G. N Engl J Med 2021; 384:842-858.

Relapsed/refractory disease: transplant elegible

CORAL Trial (400)

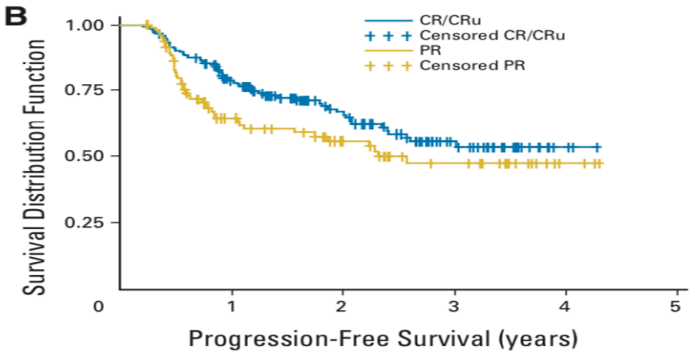




3 yrs-PFS 37% (95% CI, 31-42%)
3 yrs-OS 49% (95% CI, 43-55%)

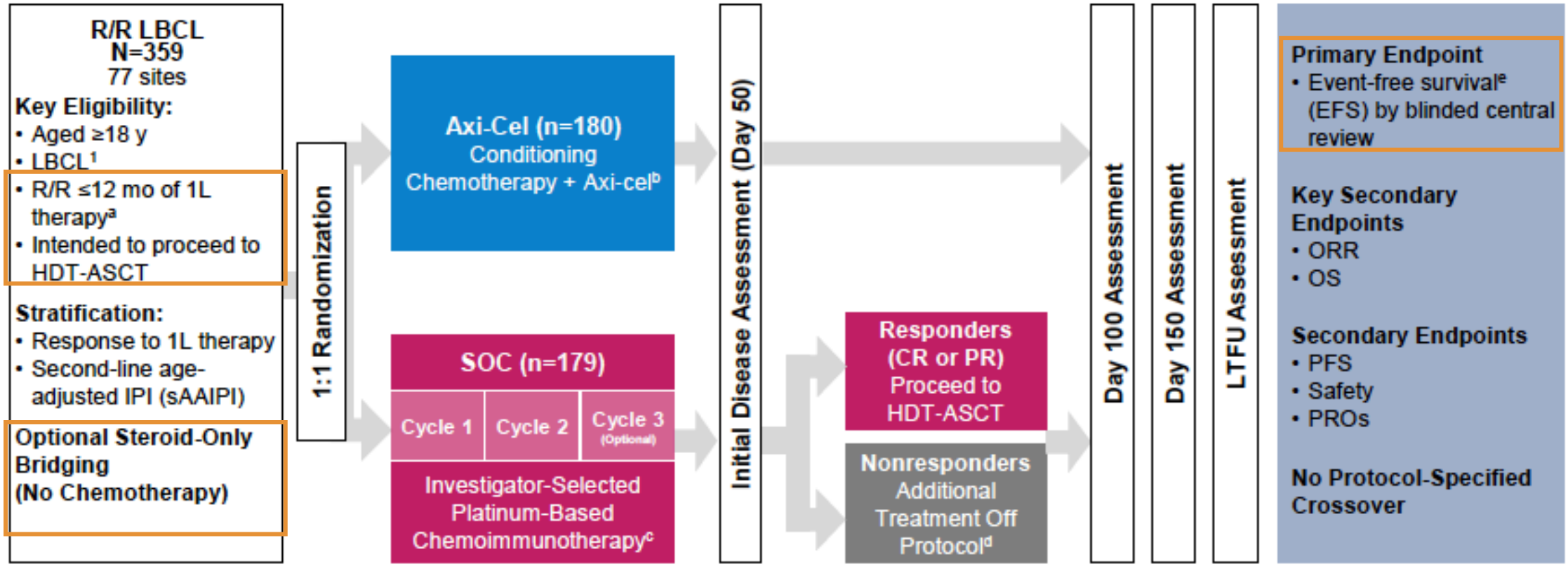
Prognostic factors:

- Prior rituximab treatment
- Pre-ASCT response
- IPI score



Gisselbrecht C, et al. J Clin Oncol. 2010; 28:4184-4190.

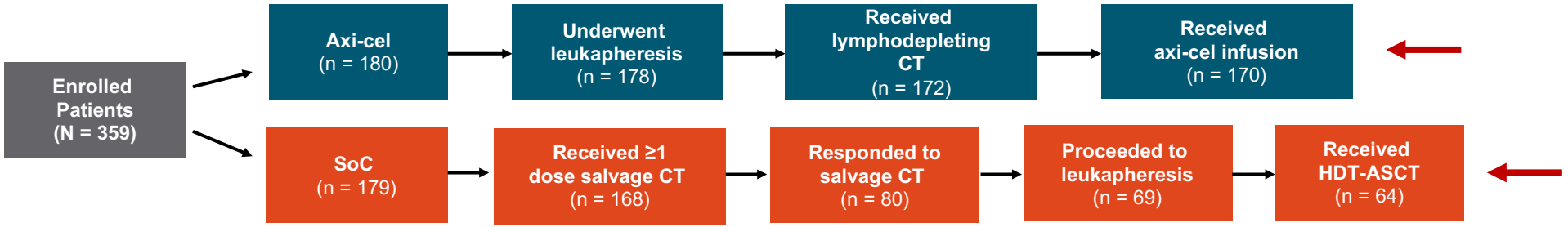
Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel Versus Standard-Of-Care (SOC)Therapy in Patients With Relapsed/Refractory DLBCL



Locke FL, et al. New Engl J Med 2022;386:640-654.

Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel Versus Standard-Of-Care (SOC)Therapy in Patients With Relapsed/Refractory DLBCL

94% of patients received axi-cel, whereas 36% of patients received HDT-ASCT



Characteristic	Axi-cel (n = 180)	SoC (n = 179)	Overall (N = 359)
Median age, yr (range)	58 (21-80)	60 (26-81)	59 (21-81)
▪ ≥65 yr, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
2L age-adjusted IPI 2-3, n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy, n (%)			
▪ Primary refractory	133 (74)	131 (73)	264 (74)
▪ Relapse within 12 mo	47 (26)	48 (27)	95 (26)
Prognostic marker per central lab, n (%)			
▪ HGBL (including double/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)
Elevated LDH, n (%)	101 (56)	94 (53)	195 (54)

Axi-cel: ORR= 83%; CR=65%

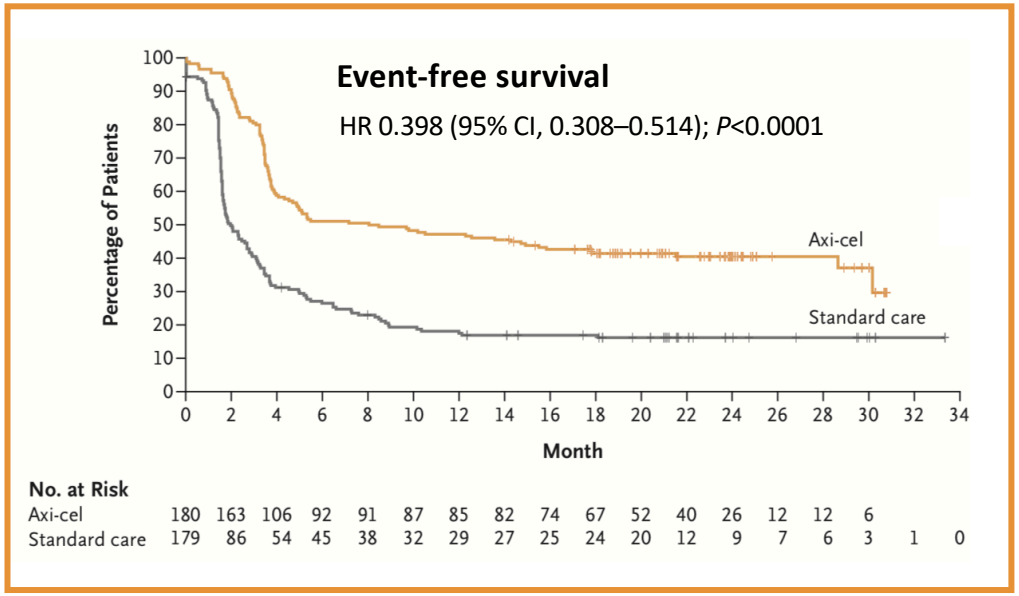
SOC: ORR= 50%; CR=32%

Odds Ratio, 5.31 (95% CI, 3.1–8.9); *P*<0.0001

Median time from enrollment and Axi-cell infusion 29 days

Locke FL, et al. New Engl J Med 2022;386:640-654.

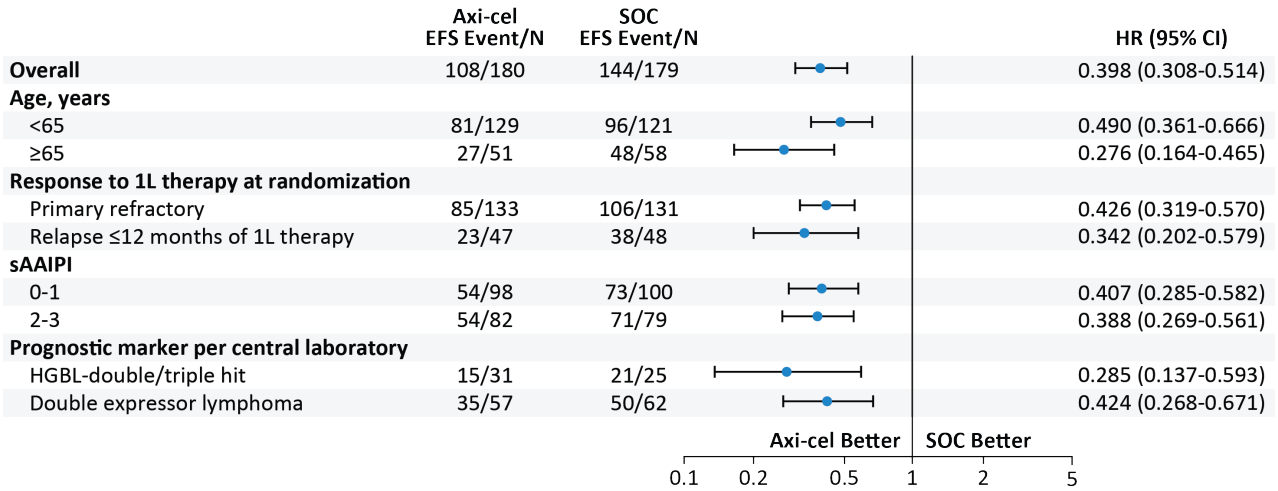
Results



Median Follow up 24.9 months

	Median EFS (95% CI), months	24-mo EFS (95% CI), %
Axi-cel (N=180)	8.3 (4.5–15.8)	40.5% (33.2–47.7)
SOC (N=179)	2.0 (1.6–2.8)	16.3% (11.1–22.2)

Subgroup analysis



Secondary End points

- ORR: 83% vs. 50%, p < 0.001
- CR: 65% vs. 32%, p < 0.001

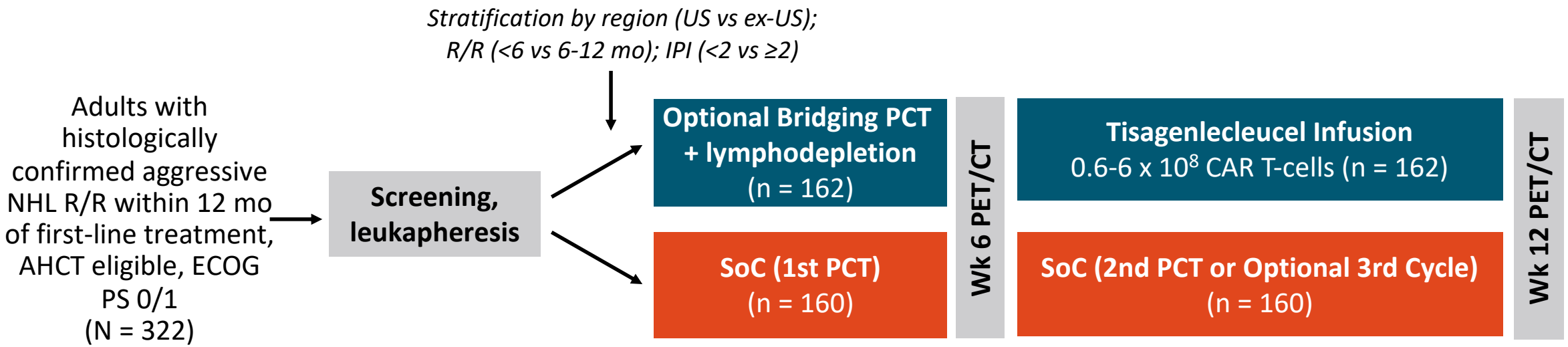
Odds Ratio, 5.31 (95% CI, 3.1–8.9); *P*<0.0001

- Median OS mediana: not reached vs. 35.1 months*, p = 0.054

*56% of the patients who failed standard arm was treated with CAR-T

Locke FL, et al. New Engl J Med 2022;386:640-654.

Phase III BELINDA Trial: Tisagenlecleucel vs Standard of Care (SOC) as Second-line Treatment for R/R Aggressive B-Cell Non-Hodgkin Lymphom



SoC arm received first PCT + AHCT for responders or second PCT for nonresponders, based on Wk 6 assessment. Crossover to tisagenlecleucel permitted for SoC at Wk 12 for nonresponders. Patients assessed at Wk 6 and 12, then 3-monthly to Mo 12, 6-monthly to Mo 24, and yearly to Mo 60.

Bishop MR et al. New Eng J Med 2022; 386:629-639.

Phase III BELINDA Trial: Tisagenlecleucel vs Standard of Care (SOC) as Second-line Treatment for R/R Aggressive B-Cell Non-Hodgkin Lymphom

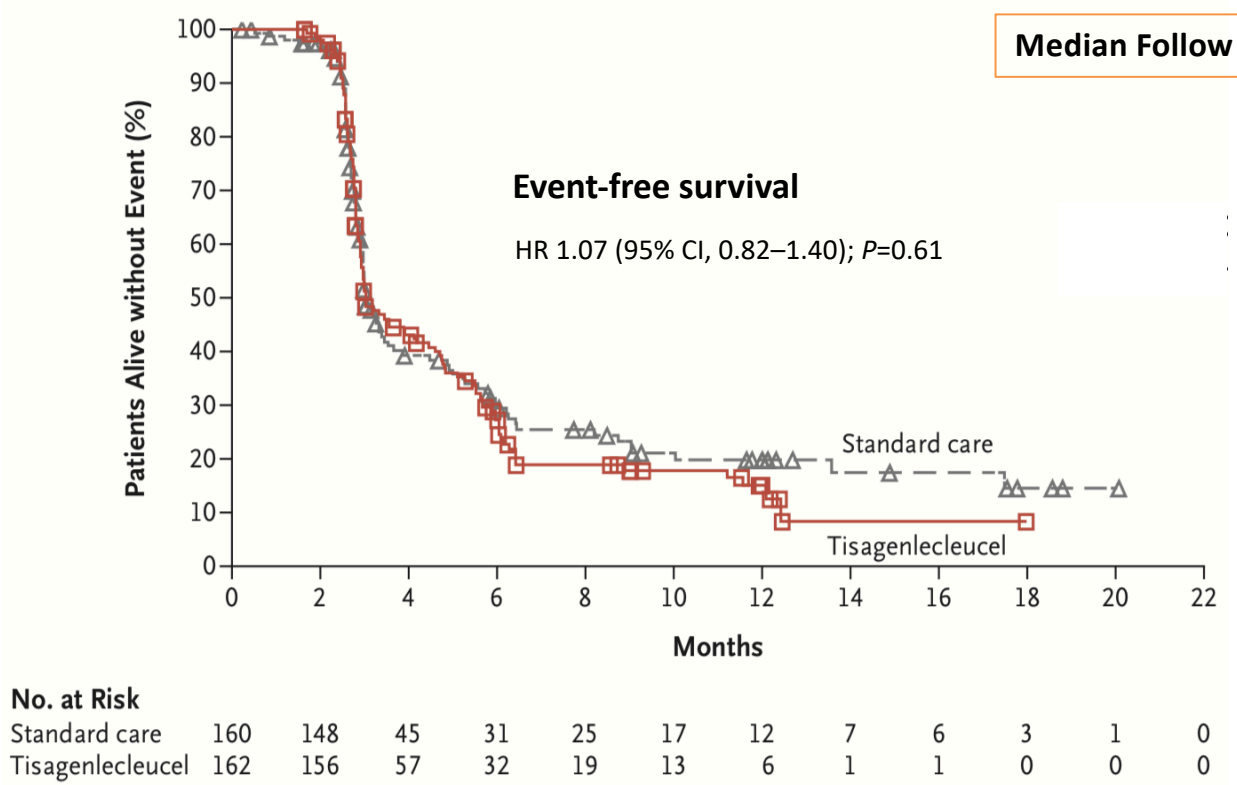
Characteristic, n (%)	Tisagenlecleucel (n = 162)	SoC (n = 160)
Age ≥65 yr	54 (33.3)	46 (28.8)
Male	103 (63.6)	98 (61.3)
US region	48 (29.6)	47 (29.4)
Race		
▪ White	128 (79.0)	128 (80.0)
▪ Asian	20 (12.3)	22 (13.8)
▪ Black	8 (4.9)	3 (1.9)
▪ Other/unknown	6 (3.7)	7 (4.4)
Hispanic/Latinx	12 (7.4)	13 (8.1)
Disease subtypes		
▪ DLBCL-NOS	101 (62.3)	112 (70.0)
▪ HGBL with *MYC* and *BCL2* and/or *BCL6*	32 (19.8)	19 (11.9)
▪ HGBL-NOS	7 (4.3)	8 (5.0)
▪ PMBCL	12 (7.4)	13 (8.1)
▪ FL grade 3B	5 (3.1)	1 (0.6)
▪ Other	5 (3.1)	7 (4.4)

Characteristic, n (%)	Tisagenlecleucel (n = 162)	SoC (n = 160)
Remission duration		
▪ Refractory	107 (66.0)	107 (66.9)
▪ Relapsed <6 mo	30 (18.5)	32 (20.0)
▪ Relapsed 6-12 mo	25 (15.4)	21 (13.1)
ECOG PS 1	70 (43.2)	65 (40.6)
IPI ≥2	106 (65.4)	92 (57.5)
Stage at time of study entry		
▪ I/IE and II/IIE/II bulky	55 (34.0)	62 (38.8)
▪ III and IV	107 (66.0)	98 (61.3)

- Median time from initial diagnosis to randomization:
  - 8.4 mo (tisagenlecleucel) vs 8.2 mo (SoC)
- Median time from most recent relapse/PD to randomization:
  - 1.4 mo (tisagenlecleucel) vs 1.1 mo (SoC)

Bishop MR et al. New Eng J Med 2022; 386:629-639.

Results



	Median EFS (95% CI), months
Tisa-cel (N=160)	3.0 (3.0–3.5)
SOC (N=162)	3.0 (2.9–4.2)

End point secondari

- ORR (week12): 46.3% vs. 42.5%
- CR (week12): 28.4% vs. 27.5%,
- OS :non valutabile per brevità di follow up

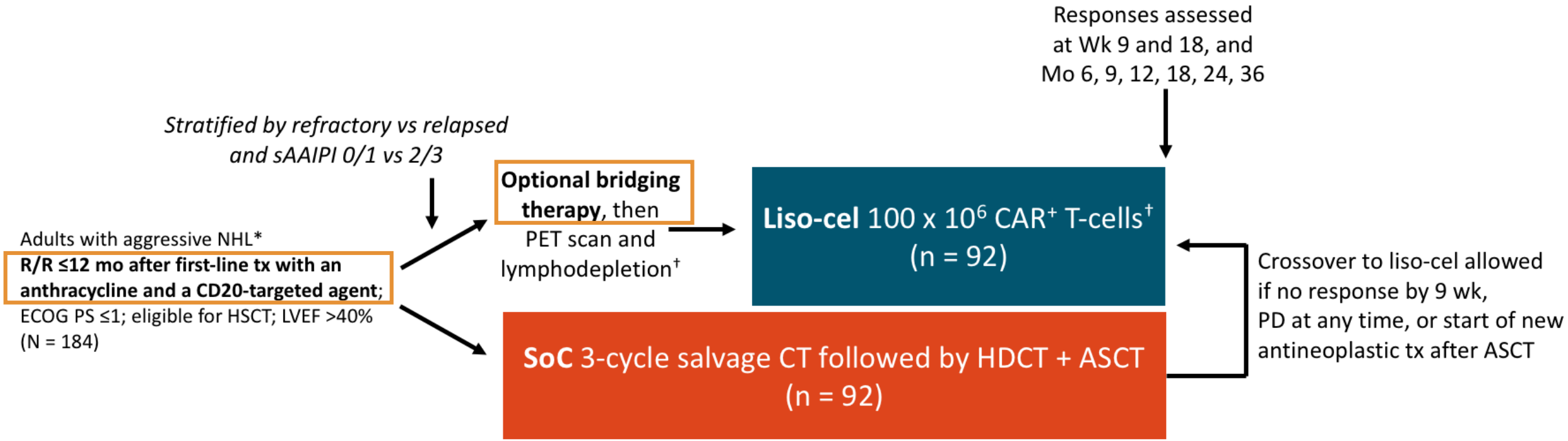
Median time from lymphocytopheresi and CART infusion 52 days (31-135)

Bishop MR et al. New Eng J Med 2022; 386:629-639.

Clinical and biological characteristics of ZUMA 7 and BELINDA trial

	ZUMA 7 Axi cell group	BELINDA Tisagenlecleucel	ZUMA 7 SOC	BELINDA SOC
Primary end point	EFS	EFS after 12 weeks	EFS	EFS after 12 weeks
No patients	180	162	179	160
Disease status	**RR < 12 mo no impeding organ comprimise**	**RR < 12 mo ASCT eligible**	**RR < 12 mo non impeding organ comprimise**	**RR < 12 mo ASCT eligible**
Bridging therapy	**Only glucorticoids**	**Yes Chemotherapy**	**NA**	**NA**
DLBCL **DLBCL-DH**	126(70) 31(17)	101(62) 32(20)	120(67) 25(14)	112(70) 19 (12)
ABC type	**16 (9)**	**52(32)**	**9(5)**	**42 (26)**
Progressive disease prior CART	**2(1)**	**42(26)**	NA	NA
Received CART infusion	170(94)	155(96)	NA	NA
Received ASCT on study	NA	NA	**64(36)**	**52(32)**
M. days from enrollment to CART infus.	**29**	**52**	NA	NA
M.Time days to CART release	**13**	**23 U.S, 28 non US**	NA	NA
Complete response (CR) %	**65**	**28**	32	28

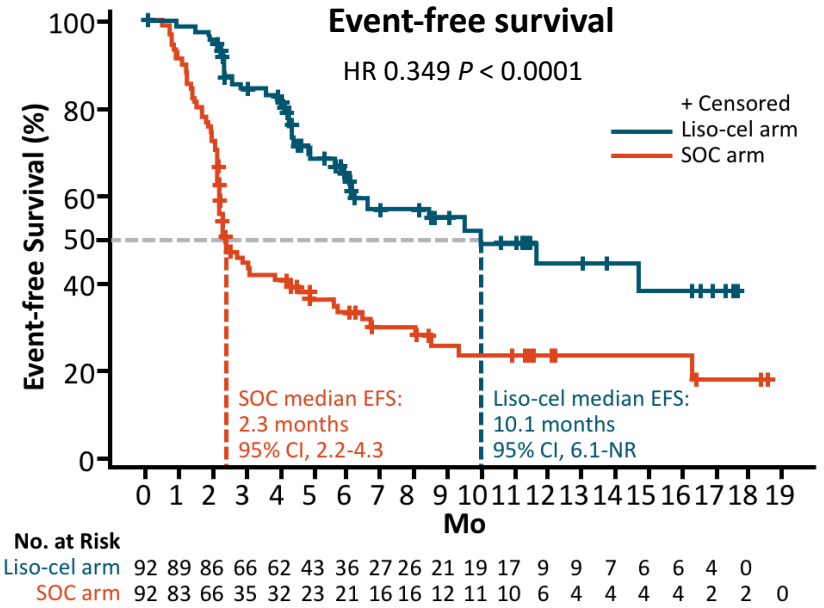
TRANSFORM: study design



*DLBCL NOS, HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL.
†Fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 x 3 days.

- **Primary endpoint: EFS per IRC**

Results



Analisi esplorativa dei sottogruppi

Subgroup		Stratified HR (95% CI)	Liso-Cel (n/N)	SoC (n/N)	Stratified HR
sAAIPI	▪ 0/1		16/56	32/55	0.298
	▪ 2/3		19/36	31/37	0.404
Previous response	▪ Refractory		30/67	52/68	0.350
	▪ Relapsed		5/25	11/24	0.343
Age group, yr	▪ <65, n (%)		17/56	46/67	0.277
	▪ ≥65 to <75, n (%)		18/36	15/23	0.301
Sex	▪ Male		19/44	44/61	0.331
	▪ Female		16/48	19/31	0.346
ECOG PS (at screening)	▪ 0		18/48	36/57	0.420
	▪ 1		17/44	27/35	0.201
SPD	▪ >50 cm²		3/10	9/10	0.099
	▪ ≤50 cm²		29/77	53/76	0.366
LDH	▪ <500 µ/L		30/79	53/81	0.350
	▪ ≥500 µ/L		4/10	10/11	0.460
Prior CT response	▪ Chemorefractory (PD/SD)		15/25	16/18	0.338
	▪ Chemosensitive (PR/CR)		20/67	47/74	0.320
NHL type	▪ DLBCL		21/60	36/57	0.357
	▪ HGBCL		14/22	19/21	0.413
DLBCL subtype	▪ DLBCL NOS de novo		19/53	30/49	0.395
	▪ DLBCL transformed from NHL		2/7	6/8	0.218
DLBCL subtype based on cell of origin	▪ GCB		21/45	29/40	0.348
	▪ ABC/non-GCB		7/21	22/29	0.477

0.125 0.5 1 2 4 8
Favor Liso-cel Favor SOC

Median Follow up 6.2 months

	EFS mediana (95% CI), mesi
Liso-cel (N=92)	**10.1 (6.1–non raggiunta)**
SOC (N=92)	2.3 (2.2–4.3)

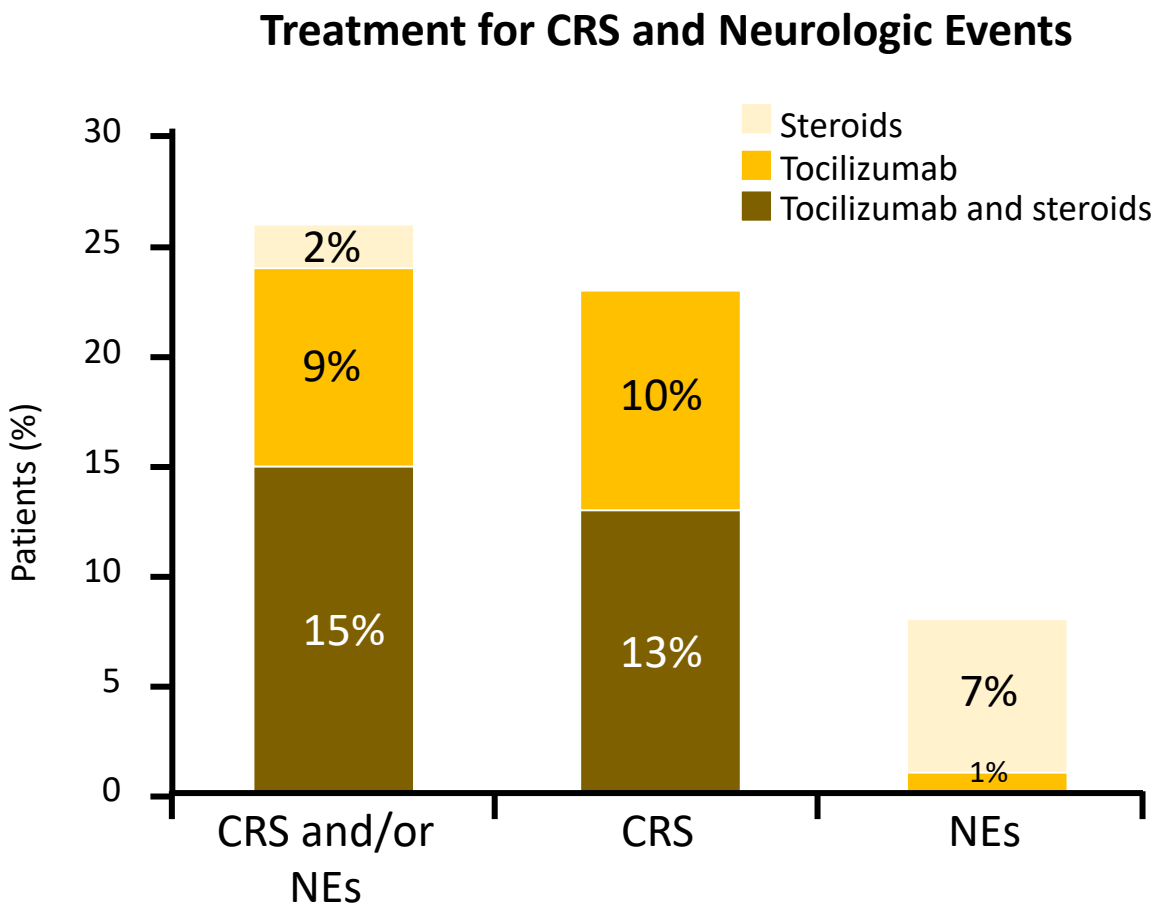
End point secondari:

- ORR: 86% vs. 48% $p < 0.0001$
- CR: 66% vs. 39%, $p < 0.0001$
- OS : not evaluable yet

Kamdar M et al. (Abstr 91. Oral presentation) ASH meeting 2021.

TRANSFORM: TEAEs of Special Interest

TEAEs of Special Interest, n (%)	Liso-Cel (n = 92)
CRS, any grade*	45 (49)
▪ Grade 1	34 (37)
▪ Grade 2	10 (11)
▪ Grade 3	1 (1)
▪ Grade 4/5	0
▪ Median time to onset, days (range)	5 (1-63)
▪ Median time to resolution, days (range)	4 (1-16)
Neurologic events, any grade‡	11 (12)
▪ Grade 1	5 (5)
▪ Grade 2	2 (2)
▪ Grade 3	4 (4)
▪ Grade 4/5	0
▪ Median time to onset, days (range)	11 (7-25)
▪ Median time to resolution, days (range)	6 (1-30)
Prolonged cytopenia	40 (43)
Grade ≥3 infection	14 (15)



*Graded according to Lee 2014 criteria. †Hypertransaminasemia, which resolved after 2 days. ‡Graded according to NCI CTCAE. §Grade ≥3 anemia, neutropenia, or thrombocytopenia at 35 days after liso-cel infusion for liso-cel arm or 35 days after start of last CT for SoC arm.

Kamdar M et al. (Abstr 91. Oral presentation) ASH meeting 2021.

Conclusions

- The prognosis of R/R DLBCL chemorefractory or early relapse after R-CHOP is dismal
- 2/3 trials with early use of CART were successful leading to a better outcome than ASCT. This means that the role of HDC and ASCT should be redefined and is still an option in late relapse or may be in chemosensitive patients only.
- We do not know if rapidly progressive patients after R-CHOP may benefit from CART because underrepresented in the studies. We will see in the clinical practice.
- Other treatments as bispecific antibodies are on the scene now and could be an alternative or a complementary tool to CART.