Enhanced CAR T-cell Expansion and Durable Complete Responses with NKTR-255 Plus Lisocabtagene Maraleucel in Relapsed/Refractory Large B-cell Lymphoma

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Introduction

- CD19-targeted CAR T-cell therapy has transformed the treatment landscape for patients with R/R LBCL. However, durable responses remain limited, with an estimated 3-year PFS of 44 to 51% in the second-line setting.[1,2]

- Limited *in vivo* CAR T-cell proliferation and survival are key causes of failure.

- NKTR-255 is an investigational polymer-conjugated IL-15 agonist that enhanced the efficacy of subtherapeutic CD19 CAR T-cell doses in a xenograft lymphoma model.[3]

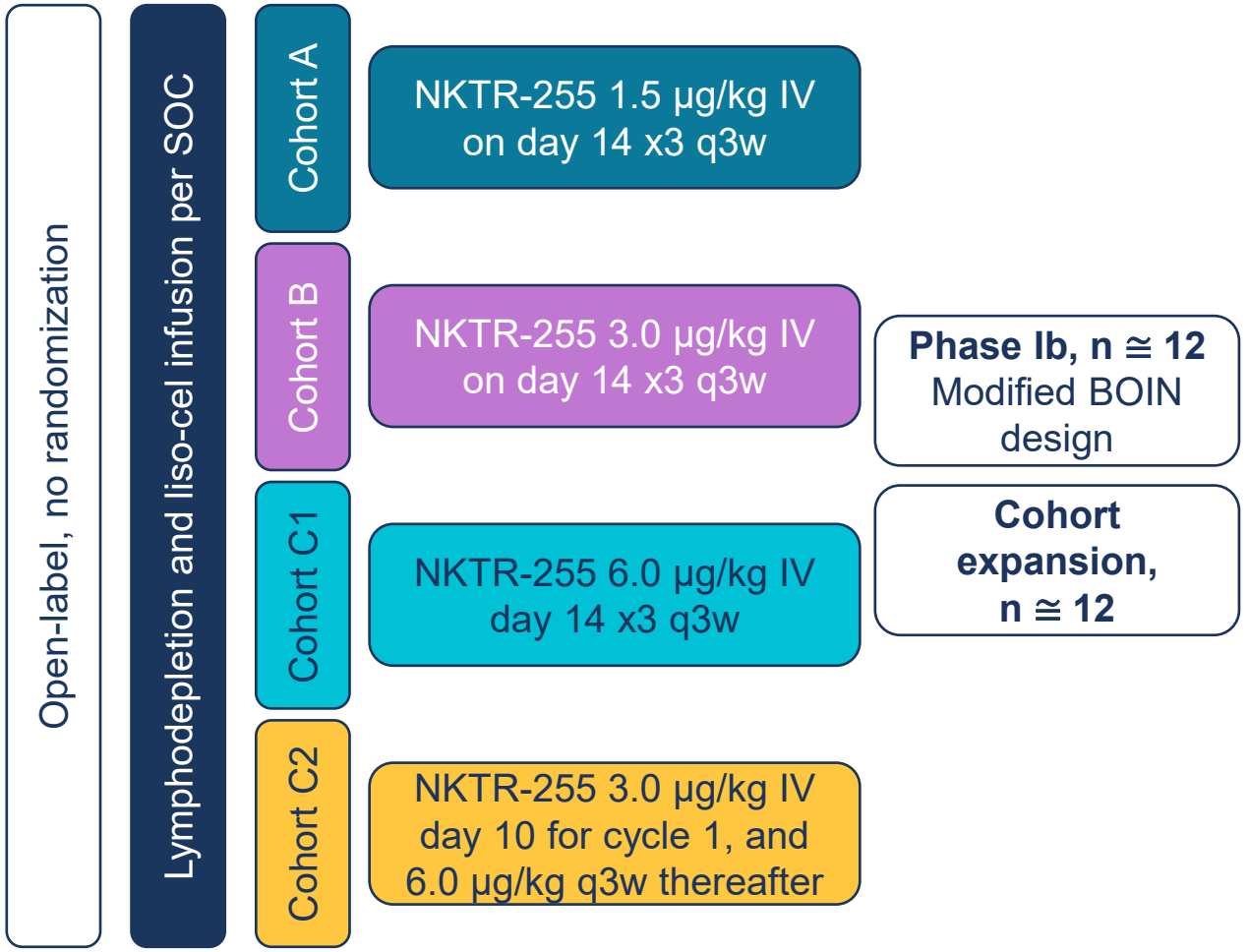
- Here, we present results from a phase 1b clinical trial evaluating NKTR-255 in combination with liso-cel in R/R LBCL.

LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; PFS, progression-free survival; R/R, relapsed/refractory.

1. Westin JR, *et al*. *N Engl J Med* 2023; 2. Kamdar MK, *et al*. *ASCO* 2024 (Abstract #7013); 3. Hirayama AV, *et al*. *Blood Adv* 2023.

Study Design

Key Eligibility Criteria
- Age ≥ 18 years of age
- LBCL with an FDA-approved indication for treatment with lisocabtagene maraleucel
- FDG-avid disease
- Karnofsky performance status ≥ 60%
- Active parenchymal CNS involvement excluded



Primary Endpoints
- Safety and tolerability
- Optimal biological regimen
- CR rate at 3 months

Key Secondary Endpoints
- CR rate and ORR at 6 months
- DOR, PFS, and OS

ClinicalTrials.gov: NCT05359211

BOIN, Bayesian Optimal Interval Design; CNS, central nervous system; CR, complete response; DOR, duration of response; LBCL, large B-cell lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

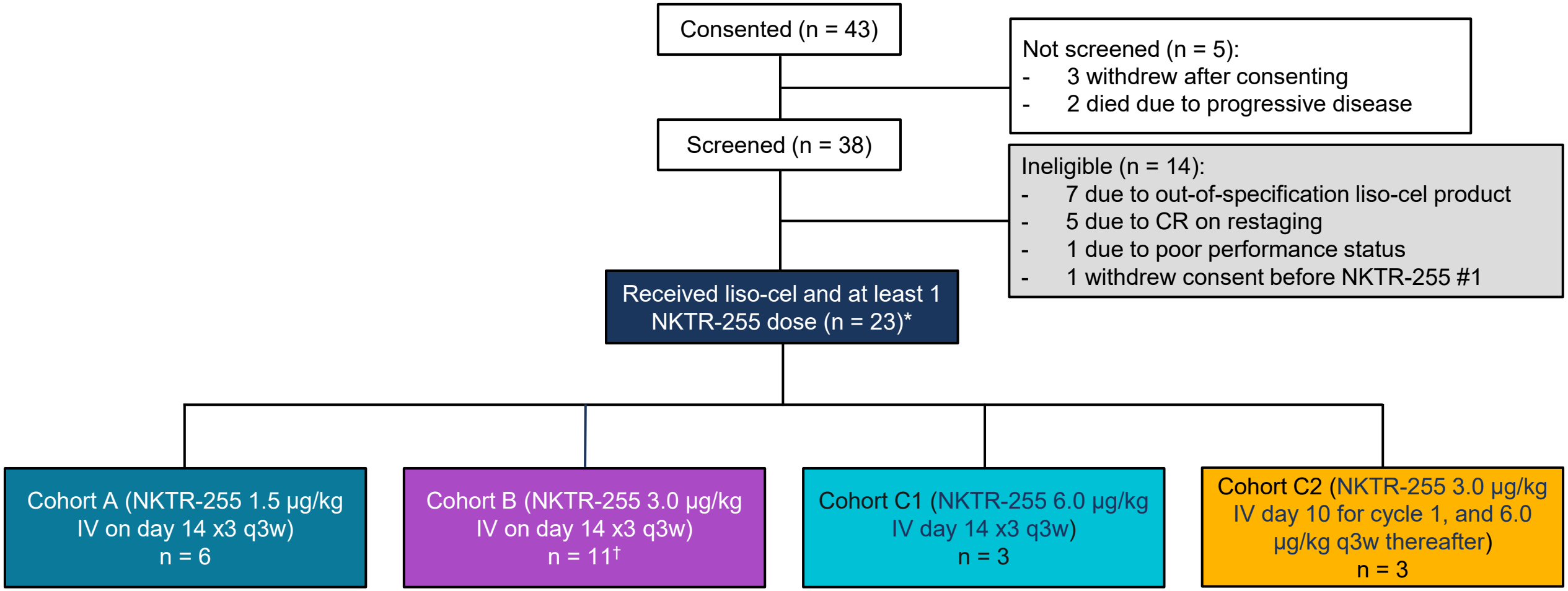
Key Eligibility for Study Drug Infusion

Patients were assessed before each NKTR-255 infusion to determine if they fulfilled the following eligibility criteria:

- No grade ≥ 3 CRS within 72 hours of the planned study drug infusion.
- No fever ≥ 38.0°C/grade ≥ 1 CRS within 24 hours of the planned study drug infusion.
- No previous grade ≥ 3 ICANS of > 72 hours duration.
- No grade ≥ 2 ICANS within 24 hours of the planned study drug infusion.
- No tocilizumab and/or dexamethasone within 48 hours preceding the study drug infusion.
- No previous grade 4 infusion-related reaction to the study drug.

CRS and ICANS were graded per ASTCT criteria.

Patient Disposition



*One patient waiting for treatment; †Only 1 patient did not receive all 3 planned NKTR-255 infusions.

Baseline Characteristics

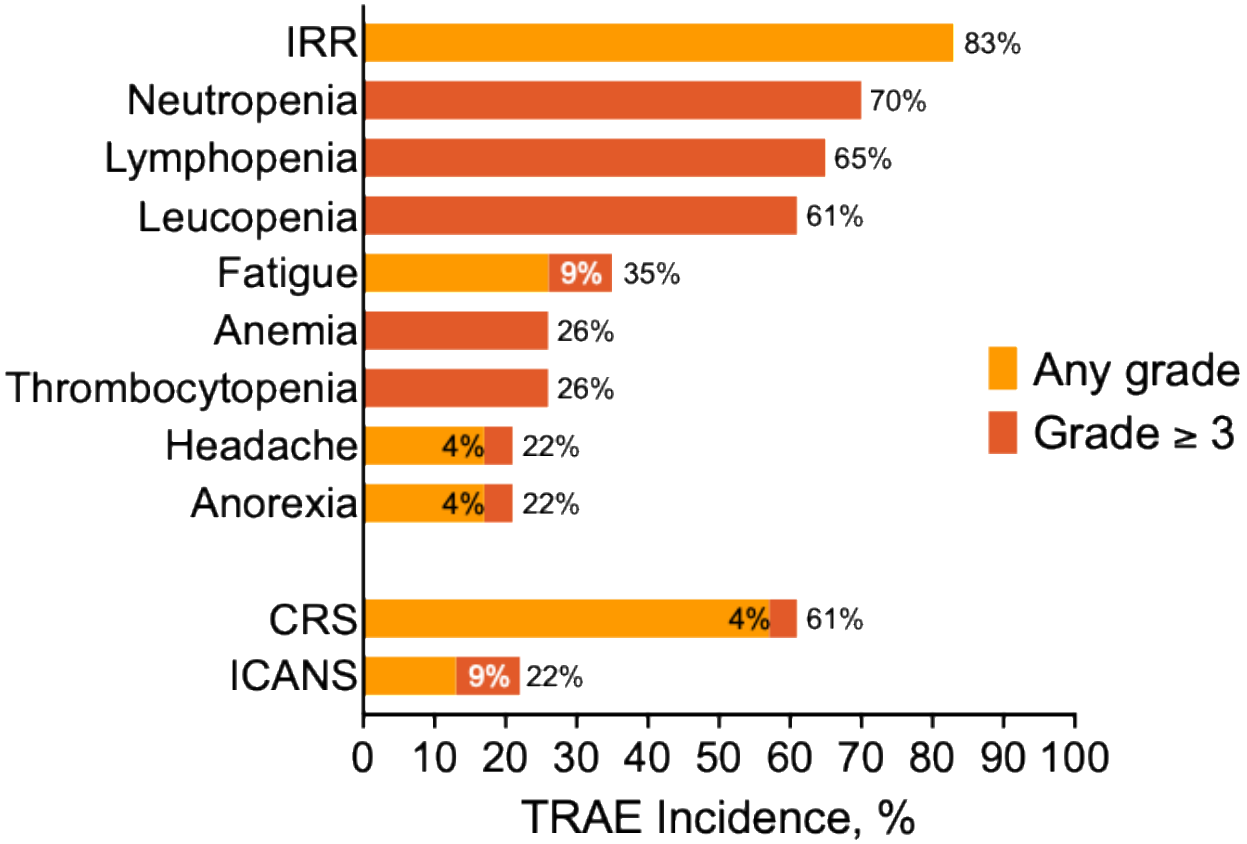
Characteristic	Cohort A (n = 6)	Cohort B (n = 11)	Cohort C1 (n = 3)	Cohort C2 (n = 3)	Overall population (n = 23)
Age					
Median (IQR), years	67 (43-79)	67 (45-74)	62 (51-70)	64 (60-70)	66 (56-73)
≥ 65 years, n (%)	4 (66)	7 (64)	1 (33)	1 (33)	13 (57)
Male sex, n (%)	5 (83)	9 (82)	3 (100)	1 (33)	18 (78)
ECOG performance score ≥ 1, n (%)	6 (100)	6 (55)	3 (100)	3 (100)	18 (78)
Disease histology, n (%)					
DLBCL, NOS	4 (66)	2 (18)	0	0	6 (26)
DLBCL transformed from FL	0	2 (18)	2 (67)	1 (33)	5 (22)
HGBL	2 (33)	3 (27)	1 (33)	2 (67)	8 (35)
Other*	0	4 (36)	0	0	4 (17)
Cell of origin (Hans algorithm), n (%)					
Germinal-center B-cell phenotype	4 (66)	7 (64)	2 (67)	3 (100)	16 (70)
Non-germinal center B-cell phenotype	2 (33)	4 (36)	1 (33)	0	7 (30)
Ann Arbor stage III or IV, n (%)	5 (83)	11 (100)	3 (100)	3 (100)	22 (96)
Extranodal disease, n (%)	3 (50)	11 (100)	3 (100)	3 (100)	20 (87)
Lactate dehydrogenase (LDH)					
Median (IQR), U/L	177 (131-246)	202 (13-247)	171 (132-215)	308 (134-354)	202 (134-247)
Elevated, n (%)	1 (17)	6 (55)	1 (33)	2 (67)	10 (43)
SPD – median (IQR), cm^2†	16.1 (5.8-31.0)	16.5 (2.7-30.2)	3.8 (1.4-7.3)‡	31.8 (0-38.1)	13.9 (2.7-30.2)
Primary refractory/early relapsed, n (%)	4 (66)	9 (82)	3 (100)	2 (67)	18 (78)
Number of prior therapies – median (range)	2 (2-3)	2 (1-3)	2 (1-3)	3 (2-3)	2 (1-3)
Bridging therapy after apheresis, n (%)	4 (66)	7 (64)	2 (67)	3 (100)	16 (70)

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements; IQR, interquartile range.

*Two patients with high-grade B-cell lymphoma with 11q aberrations, one patient with primary mediastinal B-cell lymphoma, and one with T-cell/histiocyte-rich large B-cell lymphoma; †Sum of the product of the perpendicular diameters of up to 6 target measurable nodes and extranodal sites. ‡Two subjects with predominantly nonmeasurable disease.

Treatment-related Adverse Events (TRAEs) in ≥ 15%

TRAEs are defined as AEs related to liso-cel therapy and/or NKTR-255



- Only 3 patients (13%) experienced a delay in the first NKTR-255 infusion due to liso-cel-associated toxicities.
- The most common NKTR-255-related AE was IRRs in 19 patients (83%).
  - Distinguished from grade 1 CRS, as they occurred shortly after NKTR-255 infusion and resolved within 24 hours with supportive care alone.
- The most common grade ≥ 3 TRAE were cytopenias.
- CRS and ICANS before NKTR-255 infusion were as expected with liso-cel alone.
- Only 1 patient (4%) did not receive all 3 planned NKTR-255 infusions.
  - Guttate psoriasis diagnosed after liso-cel infusion and exacerbated after NKTR-255 #1 and #2 in a subject in cohort B.
- No DLT or grade 5 TRAEs were observed.

CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ICANS, immune effector cell-associated neurotoxicity syndrome; IRR, infusion-related reaction.

Adverse Events of Special Interest

	Cohort A (n = 6)	Cohort B (n = 11)	Cohort C1 (n = 3)	Cohort C2 (n = 3)	Overall population (n = 23)
CRS					
Any grade, n (%)	4 (67)	6 (55)	1 (33)	3 (100)	14 (61)
Grade ≥ 3, n (%)	0	1 (9)	0	0	1 (4)
Median time to onset, days (range)	2 (1-8)	2 (1-3)	4	3 (1-10)	2 (1-10)
Median duration, days (range)	3 (2-5)	4 (1-7)	1	2 (2-6)	3 (1-7)
ICANS					
Any grade, n (%)	1 (17)	2 (18)	0	2 (67)	5 (22)
Grade ≥ 3, n (%)	1 (17)	1 (9)	0	0	2 (9)
Median time to onset, days (range)	3	(7-9)	NA	(3-10)	7 (3-10)
Median duration, days (range)	4	(4-8)	NA	(2-4)	4 (2-4)
Treatment for CRS and ICANS					
Tocilizumab, n (%)	3 (50)	4 (36)	0	2 (67)	9 (39)
Steroids, n (%)	2 (33)	4 (36)	0	2 (67)	8 (35)
Anakinra, n (%)	0	1 (9)	0	0	1 (4)
Cytopenias after day 28*					
Anemia, n (%)	0	3 (27)	0	2 (67)	5 (22)
Neutropenia, n (%)	2 (33)	5 (45)	3 (100)	3 (100)	13 (57)
Thrombocytopenia, n (%)	0	5 (45)	0	1 (33)	6 (26)

Only 2 patients (9%) developed CRS and/or ICANS following NKTR-255 infusion:

- Recurrent ICANS (grade 3) with ~24 hours duration in a subject in cohort B.
- Grade 1 CRS and grade 2 ICANS starting on the day of the first NKTR-255 infusion in a subject in cohort C2.

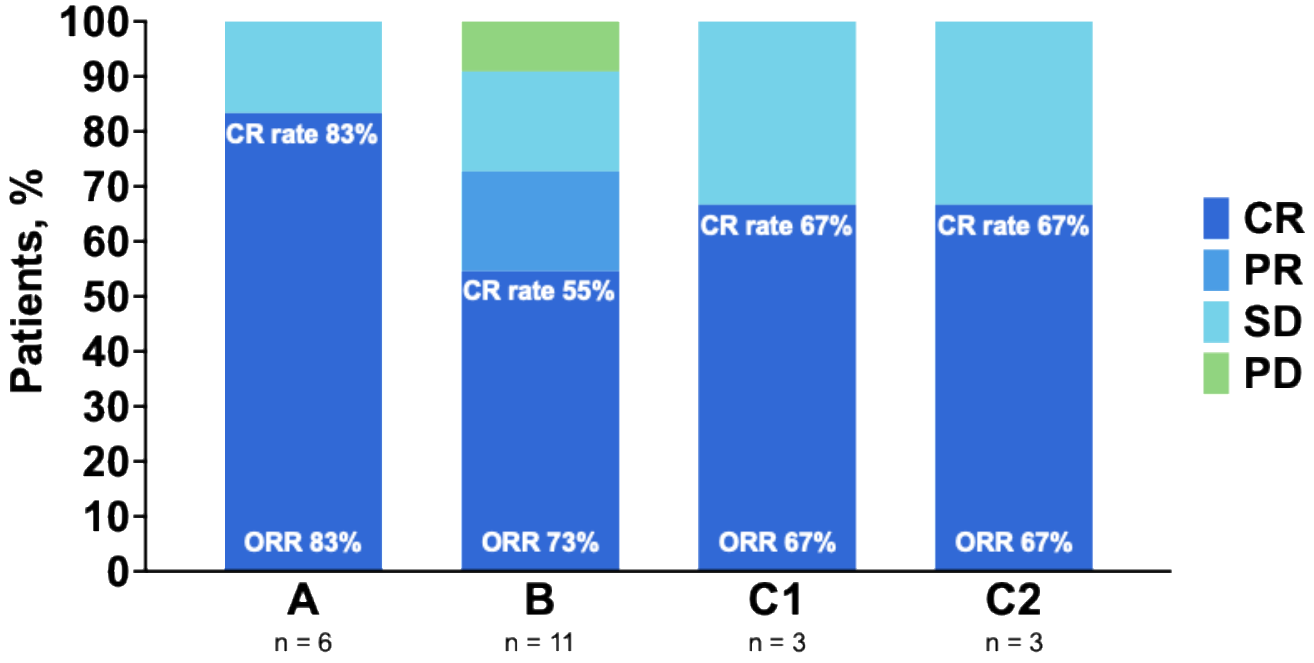
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

*Defined as CTCAE v5.0 grade ≥ 3 cytopenias occurring after day 28 post-CAR T-cell infusion.

High ORR and CR Rate After Liso-cel Plus NKTR-255

Five of 13 subjects (38%) who achieved a PR at first restaging later converted to CR—1 in cohort B and 2 each in cohorts C1 and C2

Best response across Cohorts



Consistently high response rates compared to pivotal and real-world data

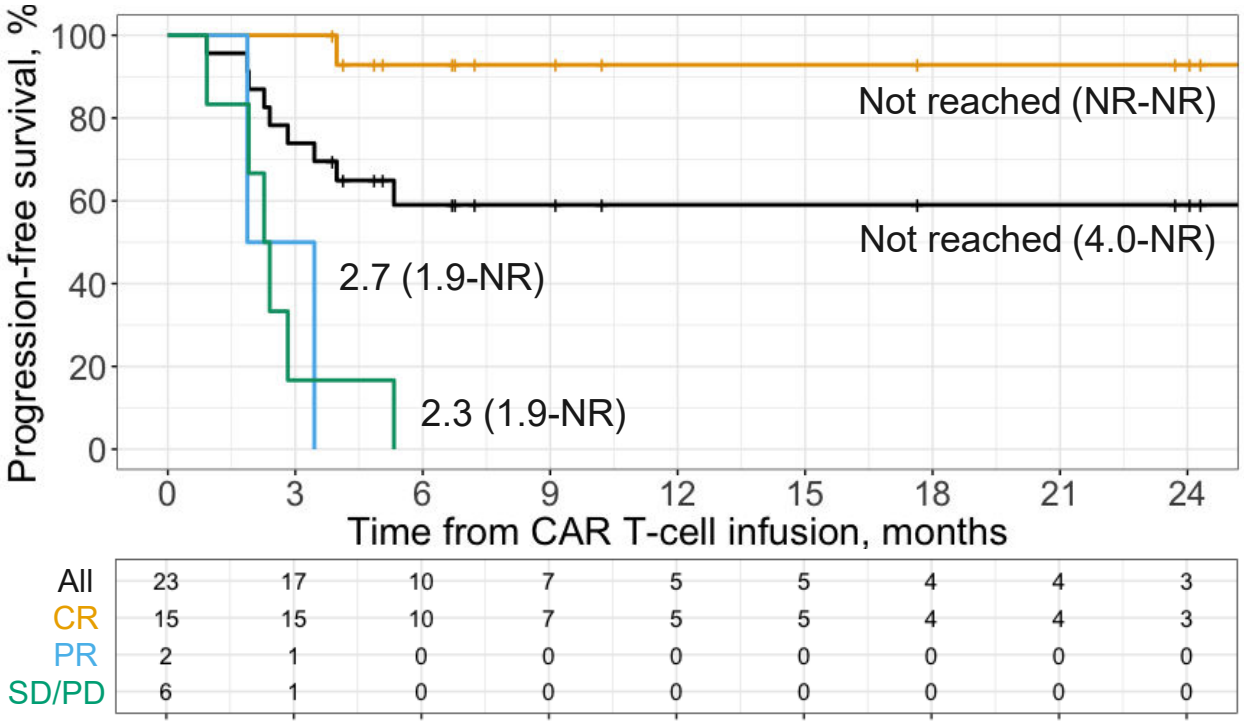
	ORR (95% CI)	CR rate (95% CI)
Liso-cel + NKTR-255 (n = 23)	**74%** (53.5-87.5)*	**65%** (44.9-81.2)*
TRANSCEND NHL 001[1] (n = 256)	**73%** (66.8-78.0)†	**53%** (46.8-59.4)†
Liso-cel in real-world[2] (n = 48)	**73%** (57.9-84.3)*	**42%** (27.9-56.7)*

*Two-sided 95% Wilson/Brown confidence intervals; †Two-sided 95% Copper-Pearson confidence intervals.

1. Abramson JS, *et al*. *The Lancet* 2020; 2. Portuguese AJ, *et al*. *Haematologica* 2025.

Durable CR After Liso-cel Plus NKTR-255

PFS in Liso-cel + NKTR-255



Median follow-up (95% CI)*: 9.1 months (5.1-23.7)

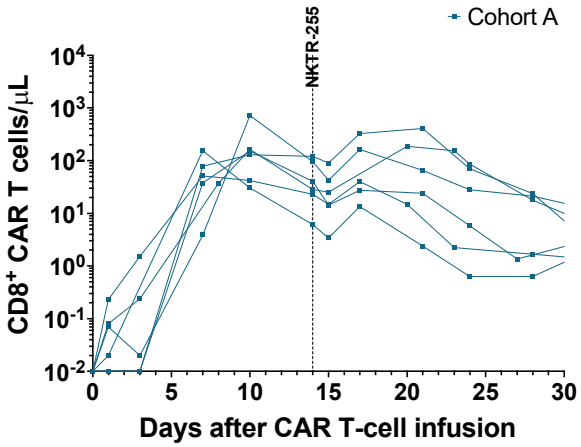
Favorable PFS in patients who achieved CR after Liso-cel + NKTR-255

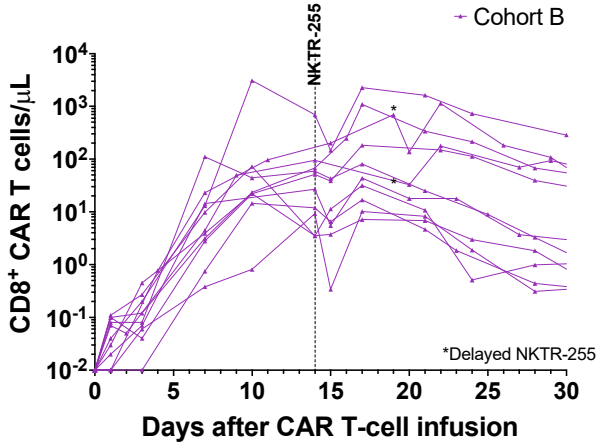
	12-month PFS estimate (95% CI)†	
	All	**Patients with CR**
Liso-cel + NKTR-255 (n = 23)	**59.0%** (41.4-84.2)	**92.3%** (80.3-100.0)
TRANSCEND NHL 001[1] (n = 256)	**44.1%** (37.3-50.7)	**65.1%** (56.1-72.7)
Liso-cel in real-world[2] (n = 58)	**40.2%** (29.3-55.4)	**No data**

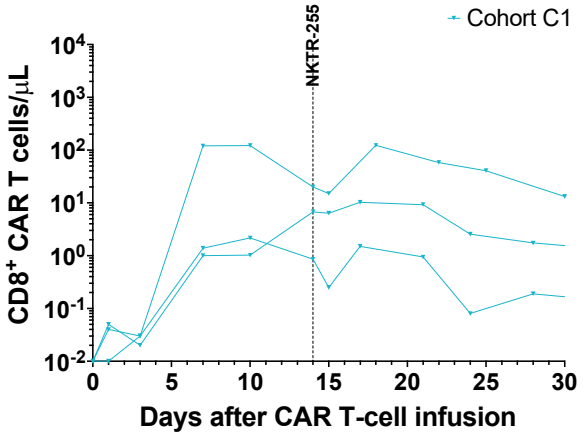
*Reverse Kaplan-Meier method was used to obtain median follow-up, and its 95% CI; †Kaplan-Meier method was used to obtain 2-sided 95% CI intervals.

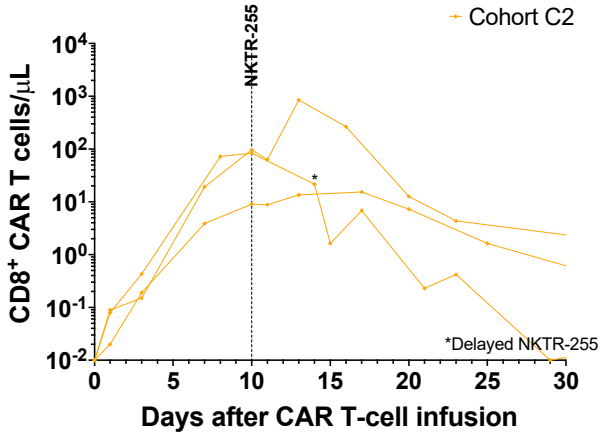
1. Abramson JS, *et al*. *The Lancet* 2020; 2. Portuguese AJ, *et al*. *Haematologica* 2025.

Liso-cel Kinetics in Combination with NKTR-255

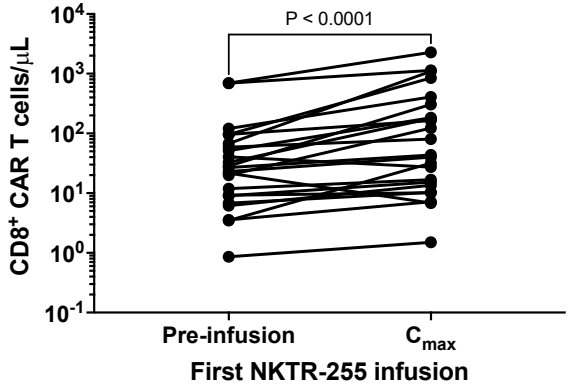




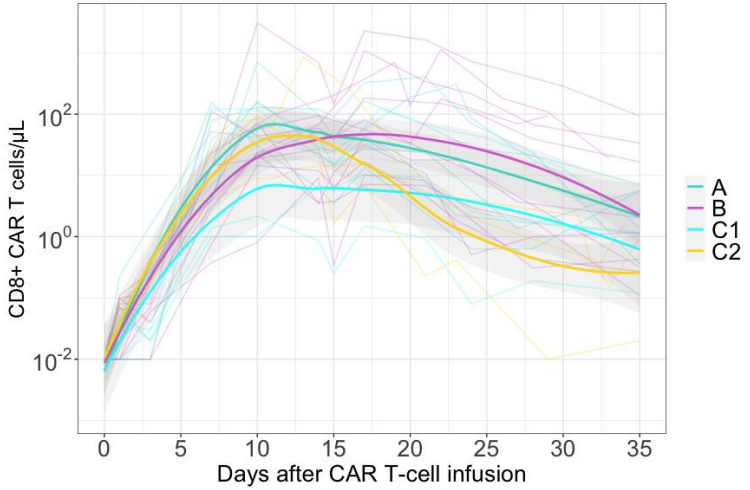




- CAR T cells re-expanded following NKTR-255 infusion, particularly CD8⁺ CAR T cells after the first dose.
  - Median CD8⁺ CAR T-cell fold change of 1.7 (range, 0.3-16.2).



- Better CAR T-cell expansion and persistence in cohorts A and B.

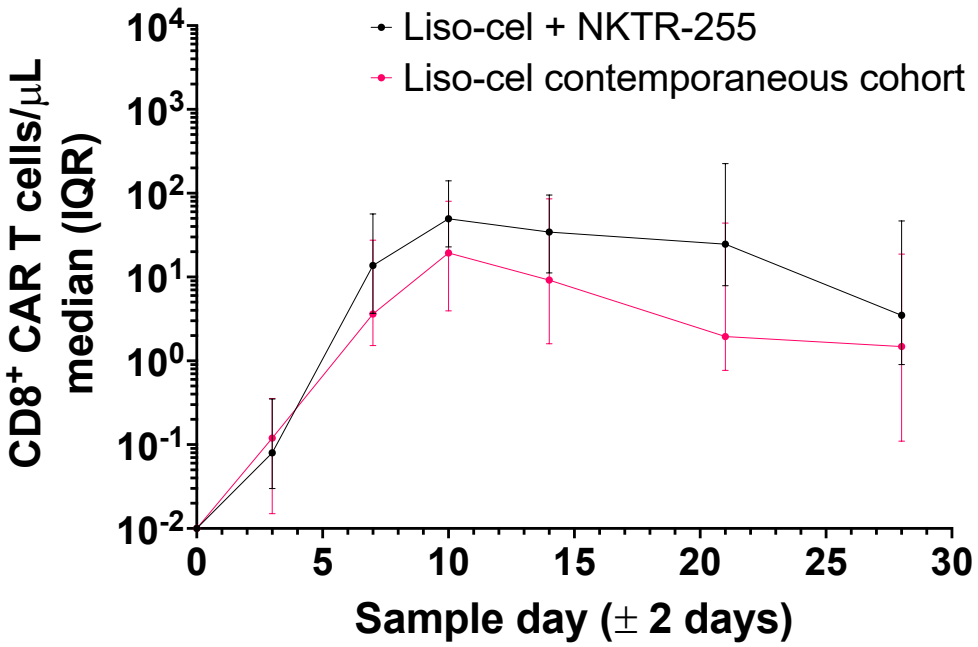


The OBR was identified as NKTR-255 infusion on day ≥14 at 1.5-3.0 µg/kg

OBR, optimal biological regimen.

Better CAR T-cell Kinetics Compared to Liso-cel Alone

CAR T-cell kinetics in patients who received liso-cel + NKTR-255 at the OBR compared to an unselected contemporaneous cohort treated with liso-cel alone



	Liso-cel + NKTR-255 (n = 18)*	Liso-cel alone (n = 13)	*P* value
LDH			
Median (IQR), U/L	203 (134-254)	181 (137-202)	0.38†
Elevated, n (%)	7 (39)	2 (15)	0.24‡

†*P* value per Wilcoxon rank-sum test (two-sided); ‡*P* value per Fisher's exact test (two-sided)

Median (IQR)	Liso-cel + NKTR-255 (n = 18)*	Liso-cel alone (n = 13)	*P* value
CD3⁺ CAR T cells by FC			
C_{max}, cells/µL	191.1 (63.8-510.0)	48.9 (17.8-248.3)	0.05
AUC_{0-28}, days x cells/µL	1445.0 (537.5-3951.0)	315.4 (173.7-2272.0)	0.03
CD4⁺ CAR T cells by FC			
C_{max}, cells/µL	14.9 (7.0-39.0)	6.8 (3.2-12.9)	0.07
AUC_{0-28}, days x cells/µL	106.0 (73.8-269.7)	63.4 (21.9-135.9)	0.04
CD8⁺ CAR T cells by FC			
C_{max}, cells/µL	150.7 (49.2-485.0)	41.3 (11.2-207.1)	0.03
AUC_{0-28}, days x cells/µL	1051.0 (444.5-3737.0)	211.4 (153.3-2101.0)	0.04

P values per Wilcoxon rank-sum test (two-sided)

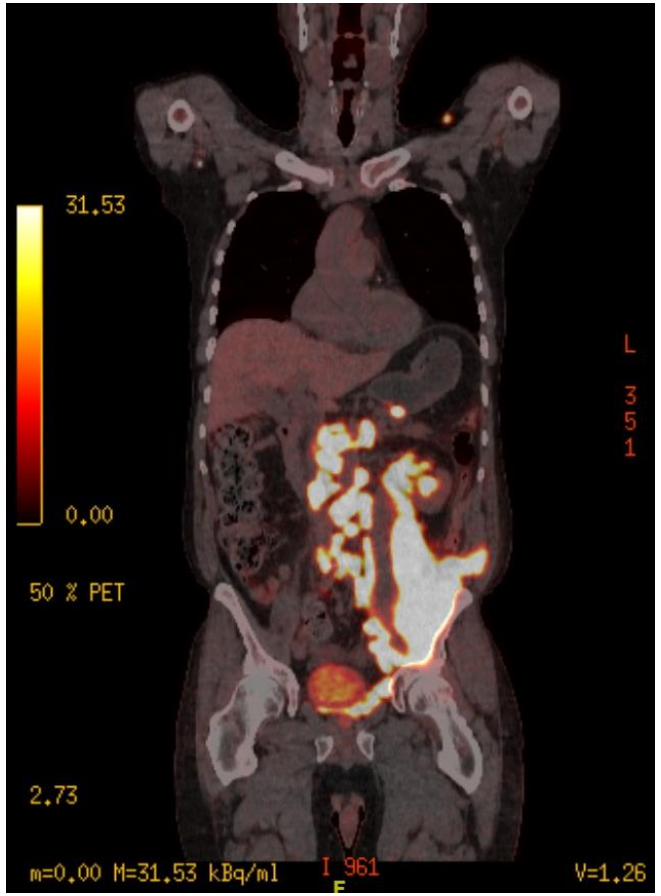
AUC_{0-28}, area under the curve for CAR T-cell absolute counts from 0 to 28 days after infusion; C_{max}, maximum CAR T-cell absolute counts; FC, flow cytometry; LDH, lactate dehydrogenase; OBR, optimal biological regimen.

*Including 1 patient in Cohort C2 whose first NKTR-255 infusion was delayed from Day 10 to Day 14.

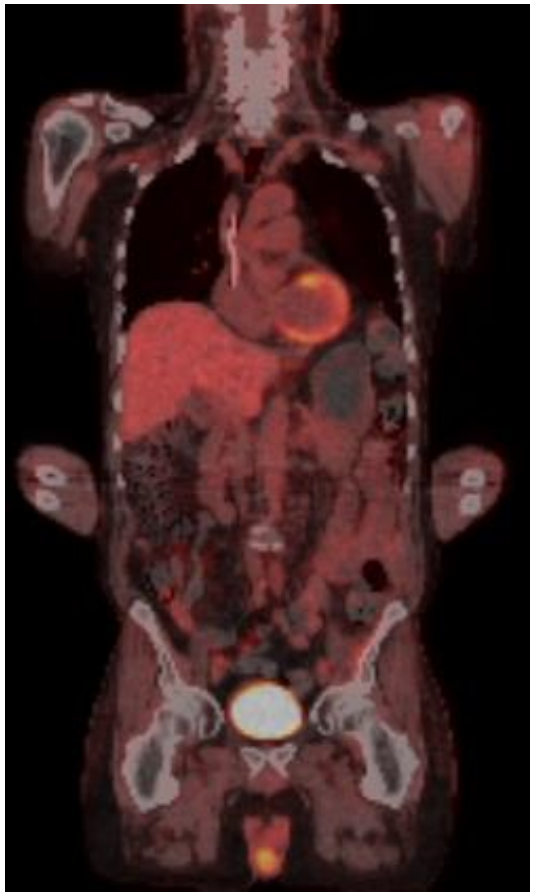
Examples of Responses Following Liso-cel Plus NKTR-255

Subject with “triple-hit” lymphoma in Cohort B

Pretreatment PET/CT

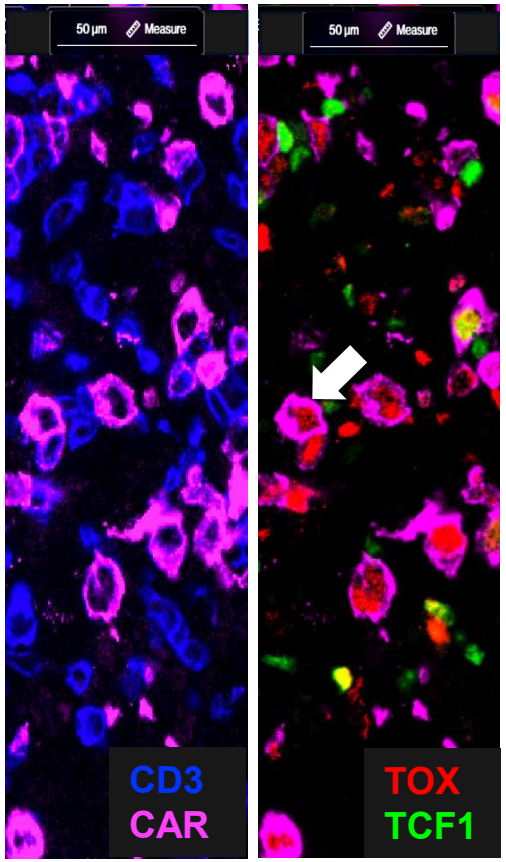


Restaging PET/CT ~day 28: CR, Deauville 1

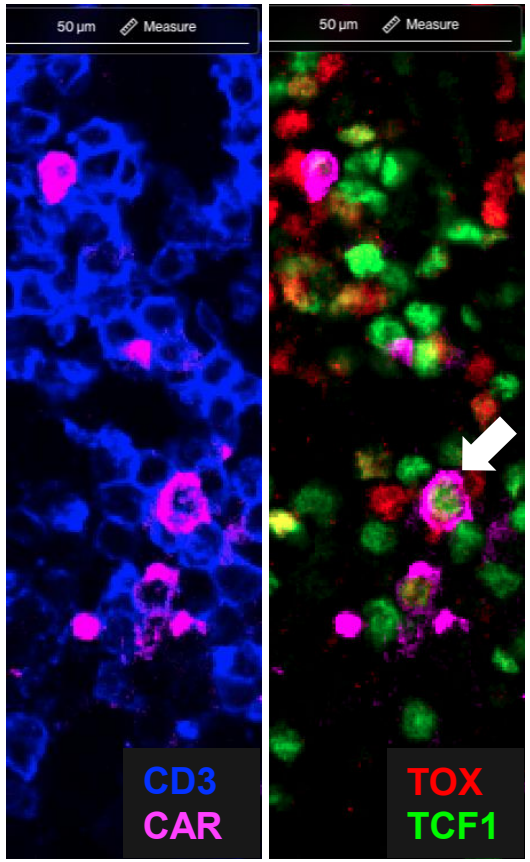


Change in T-cell/ CAR T-cell phenotype in the TME

Day 8 following liso-cel infusion



Day 20 following liso-cel infusion and day 6 after NKTR-255 #1



TME, tumor microenvironment.

Summary

- The combination of liso-cel and NKTR-255 in patients with R/R LBCL was well tolerated and safe.
  - CRS and ICANS before NKTR-255 infusion were as expected with liso-cel alone.
  - Only 2 patients (9%) developed CRS and/or ICANS following NKTR-255 infusion.
- Treatment with liso-cel plus NKTR-255 resulted in a high rate of durable CRs.
  - 12-month PFS of 59% with only one relapse in 15 patients achieving CR.
- CAR T cells re-expanded following NKTR-255 infusion.
  - $CD8^+$ CAR T-cell re-expansion in 91% of patients.
- Higher CAR T-cell expansion and $AUC_{0\text{-}28}$ were observed in patients treated with NKTR-255 infusion on day ≥14 at 1.5-3.0 µg/kg compared to liso-cel alone.
- These results support ongoing and future studies combining NKTR-255 and CAR T-cell therapy.

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UW Medicine