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Efficacy and Safety of TAK-007, Cord Blood-Derived CD19 CAR-NK Cells, in Adult Patients With Relapsed/Refractory B-cell Non-Hodgkin Lymphoma

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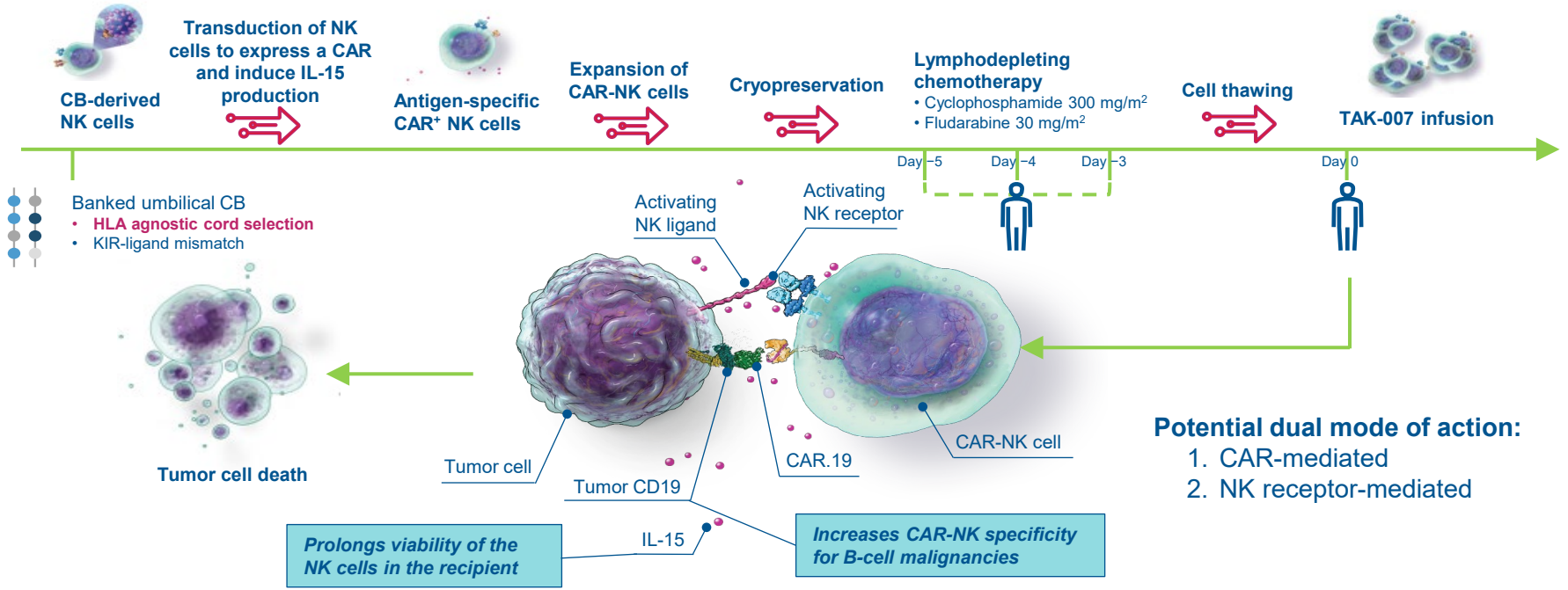
CAR-T therapies offer curative benefits for patients with B-cell malignancies, but have clinical and operational limitations

- CAR-T therapies have shown sustainable and curative benefits for leukemia and B-cell lymphoma, but have limitations[1-3]
  - Lengthy and complex production process due to autologous, customized nature[2]
  - Possibility of manufacturing failures because of insufficient amounts of T-cells due to disease-related cytopenia or T-cell dysfunction[4]
  - Risk of severe life-threatening toxicities such as high-grade CRS and ICANS[5]
- Allogenic CAR-T therapies may offer potential advantages such as off-the-shelf availability and scalability, but present challenges such as risk of GvHD and allo-rejection[6]
- CAR-NK cells have the potential to overcome these limitations, and early clinical trial data have shown their administration is not associated with the development of CRS, ICANS, or GvHD[7]

CAR, chimeric antigen receptor; CAR-T, CAR T-cell; CRS, cytokine release syndrome; GvHD, graft versus host disease; ICANS, immune effector cell-associated neurotoxicity syndrome; NK, natural killer.

1. Zhang X, et al. *Front Immunol*. 2022;13:927153
2. Mitra A, et al. *Front Immunol*. 2023;14:1188049
3. Cappell KM, Kochenderfer JN. *Nat Rev Clin Oncol*. 2023;20:359–7
4. Rafiq S, et al. *Nat Rev Clin Oncol*. 2020;17:147–67
5. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45–55
6. Lonez C, Breman E. *Cells*. 2024;13:146
7. Liu E, et al. *N Engl J Med*. 2020;382:545–53

TAK-007 are off-the-shelf, allogeneic, cryopreserved, umbilical cord blood-derived, CD19-targeting CAR-NK cells



Potential dual mode of action:

1. CAR-mediated
2. NK receptor-mediated

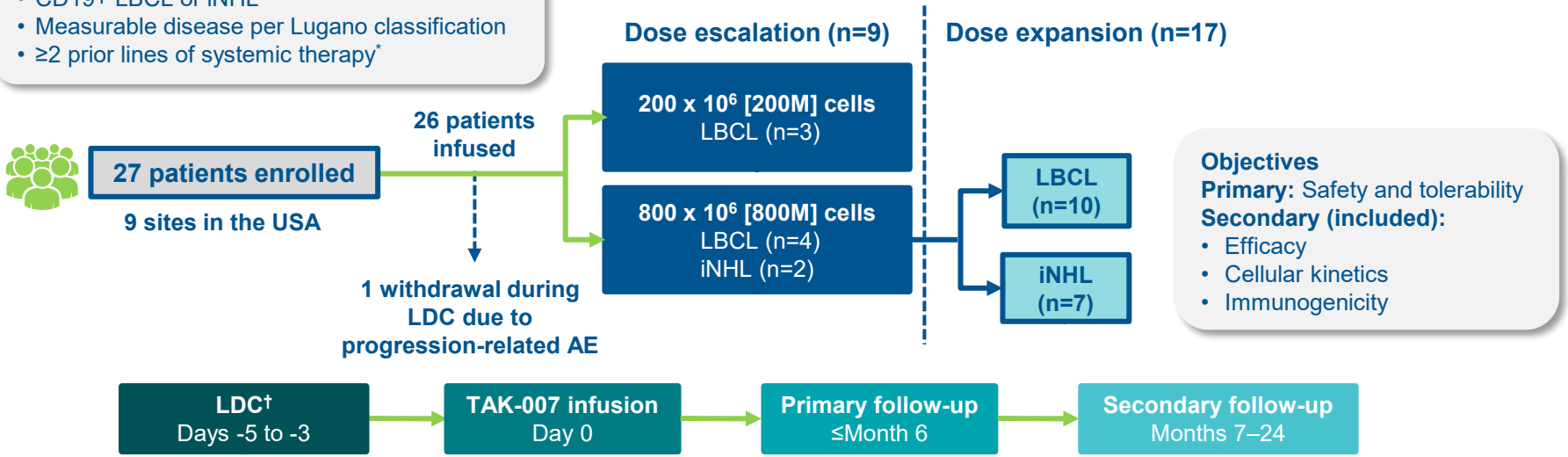
CB, cord blood; HLA, human leukocyte antigen; IL, interleukin; KIR, killer cell immunoglobulin-like receptor.

1. Liu E, et al. *N Engl J Med*. 2020;382:545–53
2. Marin D, et al. *Nat Med*. 2024;30:772–84
3. Liu E, et al. *Leukemia*. 2018;32:520–31

Open-label, multi-center phase 2 trial of TAK-007 in patients with relapsed/refractory LBCL or iNHL

ClinicalTrials.gov identifier: NCT05020015
Status: ongoing, patient enrollment closed

Key eligibility criteria
- CD19+ LBCL or iNHL
- Measurable disease per Lugano classification
- ≥2 prior lines of systemic therapy*



Data cutoff date: Jul 1, 2024.
*Patients with LBCL must have received an anti-CD20 mAb and an anthracycline-containing chemotherapy regimen and have failed or been ineligible for high-dose chemotherapy and ASCT; patients with iNHL must have received an anti-CD20 mAb and an alkylating agent.
†Cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2.
AE, adverse event; ASCT, autologous stem cell transplant; iNHL, indolent non-Hodgkin's lymphoma; LBCL, large B-cell lymphoma; LDC, lymphodepleting chemotherapy; mAb, monoclonal antibody.

Median age was 64 years, and most patients were male and White

Characteristic	200M escalation cohort	800M escalation and expansion cohorts		All patients (N=26)
	LBCL (n=3)	LBCL (n=14)	iNHL (n=9)	
Median age, years (range)	61 (59–69)	65 (38–82)	64 (49–83)	64 (38–83)
Male sex, n (%)	2 (67)	12 (86)	4 (44)	18 (69)
Race, n (%):				
White	3 (100)	11 (79)	9 (100)	23 (88)
Black or African American	0	1 (7)	0	1 (4)
Asian	0	1 (7)	0	1 (4)
Multiple	0	1 (7)	0	1 (4)
Ethnicity, n (%)				
Hispanic or Latino	0	0	1 (11)	1 (4)
Not Hispanic or Latino	3 (100)	13 (93)	8 (89)	24 (92)
Not reported	0	1 (7)	0	1 (4)

Patients were heavily pretreated and approximately half had received prior anti-CD19 therapies

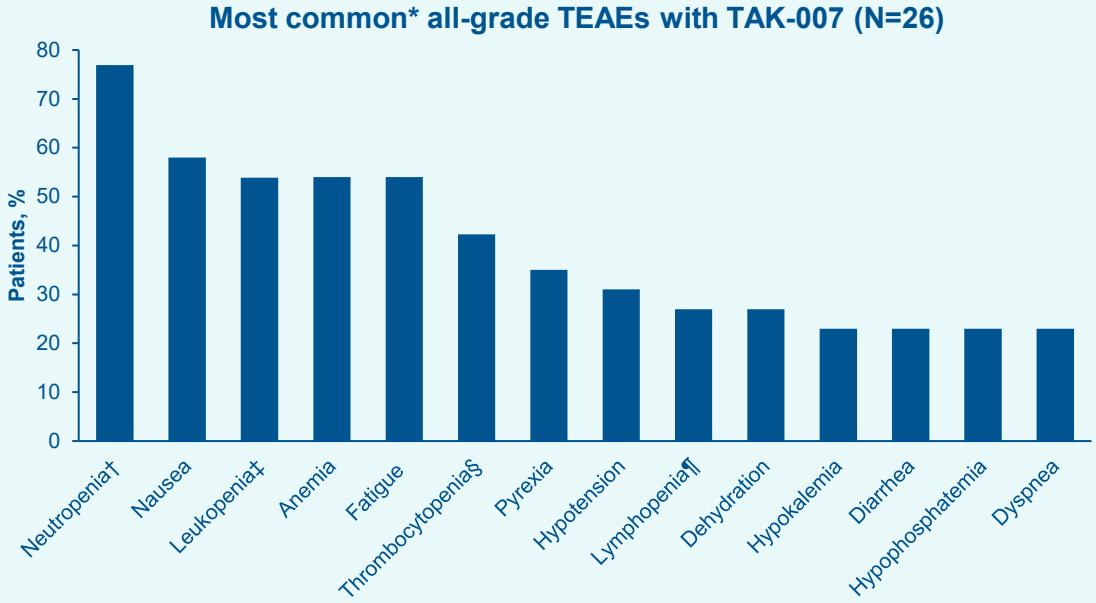
Characteristic	200M escalation cohort	800M escalation and expansion cohorts		All patients (N=26)
	LBCL (n=3)	LBCL (n=14)	iNHL (n=9)	
Disease subtype at study entry, n (%)				
LBCL NOS	2 (67)	6 (43)*	0	8 (31)
LBCL arising from iNHL (FL or MZL)	1 (33)	6 (43)	0	7 (27)
HGBL with MYC/BCL2/BLC6 rearrangement	0	2 (14)	0	2 (8)
FL	0	0	8 (89)	8 (31)
Splenic MZL	0	0	1 (11)	1 (4)
Prior number of lines of therapy, median (range)	6 (5–6)	4.5 (2–11)	5 (2–9)	5 (2–11)
Patients with prior anti-CD19 therapies, n (%)	2 (67)	7 (50)	2 (22)	11 (42)
Prior CAR-T therapy	2 (67)	6 (43)	1 (11)	9 (35)
Response to last line of therapy, n (%)				
Refractory†	1 (33)	8 (57)	2 (22)	11 (42)
Relapsed‡	1 (33)	5 (36)	6 (67)	12 (46)
Unknown	1 (33)	1 (7)	1 (11)	3 (12)

*Includes one patient with Epstein-Barr virus-positive DLBCL NOS.
†Defined as patients who had disease progression as best response to last line of therapy or stable disease for <6 months after last line of therapy.
‡Defined as patients who had a partial or complete response at last line of therapy and relapsed prior to the study.
DLBCL NOS, diffuse LBCL; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified.

TEAEs were generally manageable; CRS were all grade 1–2 and occurred in only 3 patients

- All 26 patients had TEAEs
- No DLTs were observed
- At baseline, 21 (81%) patients had grade ≥2 cytopenia
- 77% of non-hematologic TEAEs were grade 1–2
- The most common non-hematologic TEAEs were nausea in 15 (58%) patients, and fatigue in 14 (54%)
- IRR occurred in 1 patient following TAK-007 administration
- TAK-007-related CRS was observed in 3 patients (grade 1, n=2; grade 2, n=1)
- No TAK-007-related ICANS occurred
- There were no reports of GvHD

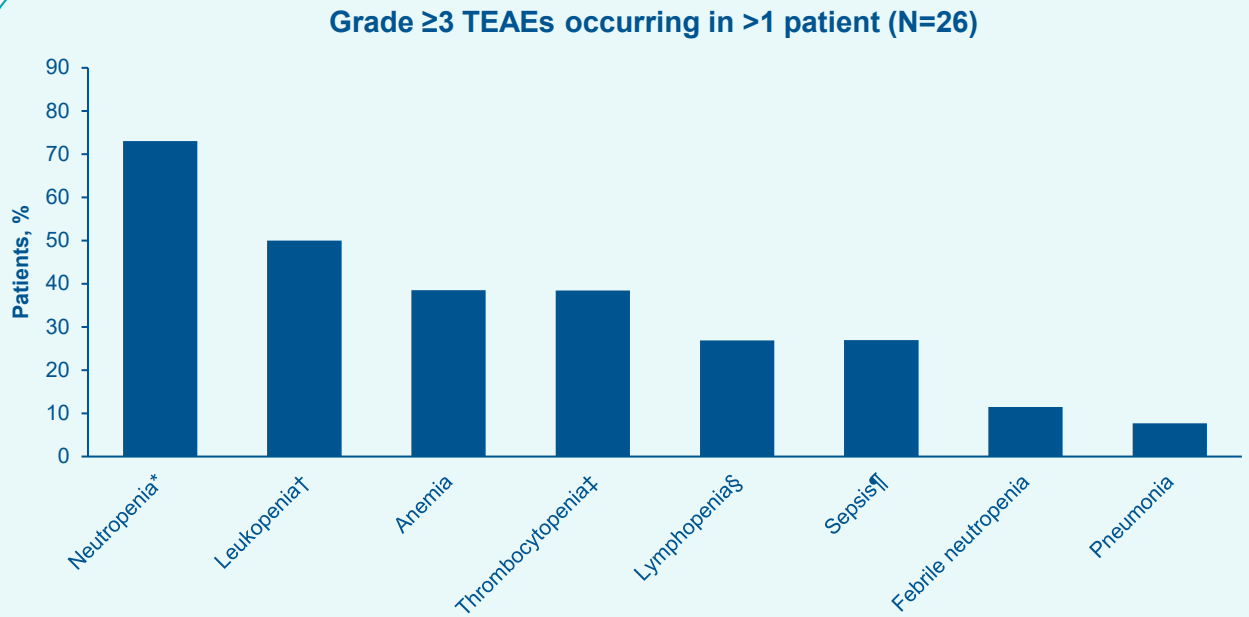
DLT, dose-limiting toxicity; IRR, infusion-related reaction; PT, MedDRA preferred term; TEAE, treatment-emergent AE.



*All-grade non-hematological TEAEs reported in >20% of patients. †Includes PTs 'neutropenia' and 'neutrophil count decreased'. ‡Includes PTs 'leukopenia' and 'white blood cell count decreased'. § Includes PTs 'thrombocytopenia' and 'platelet count decreased'. ¶Includes PT 'lymphocyte count decreased'.

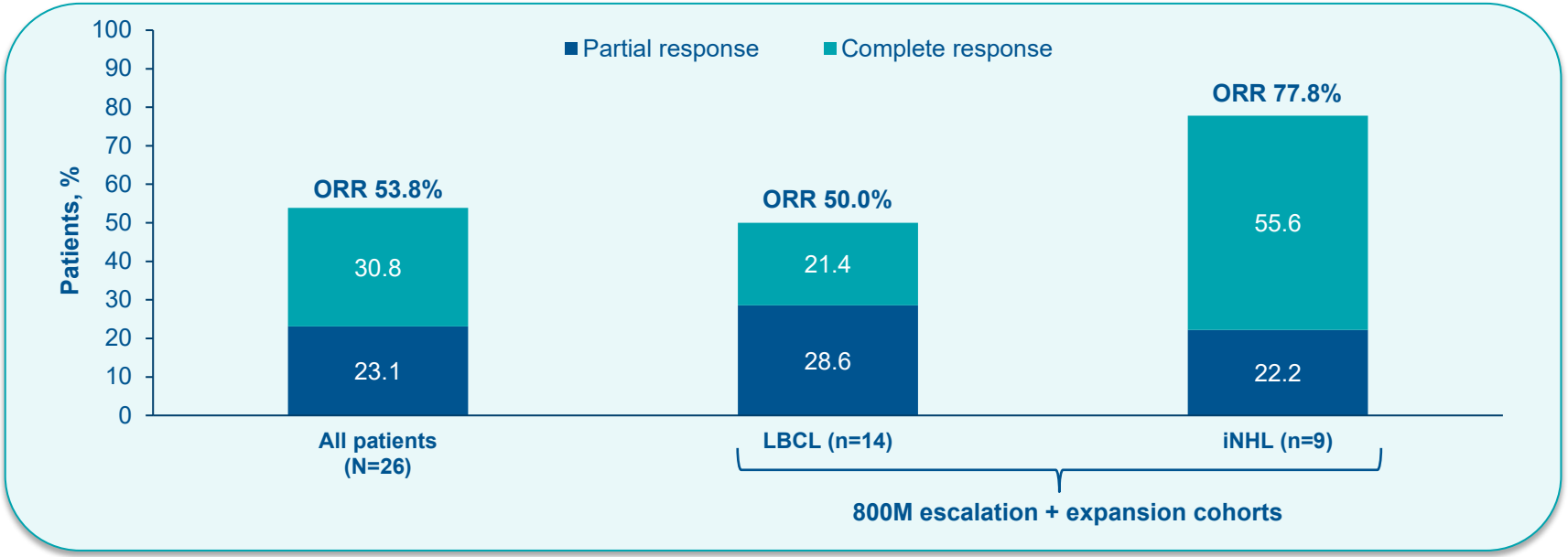
Grade ≥3 TEAEs were mostly hematologic

- Overall, 24 (92%) patients had grade ≥3 TEAEs
- Most common grade ≥3 TEAEs were neutropenia in 19 (73%) patients and leukopenia in 13 (50%) patients
- Serious TEAEs were reported in 20 (77%) patients, but were not attributed to TAK-007 or LDC in 14 (54%) patients (including 7 patients who died due to underlying lymphoma)



*Includes PTs 'neutropenia' and 'neutrophil count decreased'. †Includes PTs 'leukopenia' and 'white blood cell count decreased'. ‡Includes PTs 'thrombocytopenia' and 'platelet count decreased'. § Includes PT 'lymphocyte count decreased'. ¶Includes PTs 'sepsis', 'bacterial sepsis', 'enterococcal sepsis', 'klebsiella sepsis', and 'pseudomonal sepsis'.

Responses were observed in 14 of 23 patients (61%) treated with 800M TAK-007

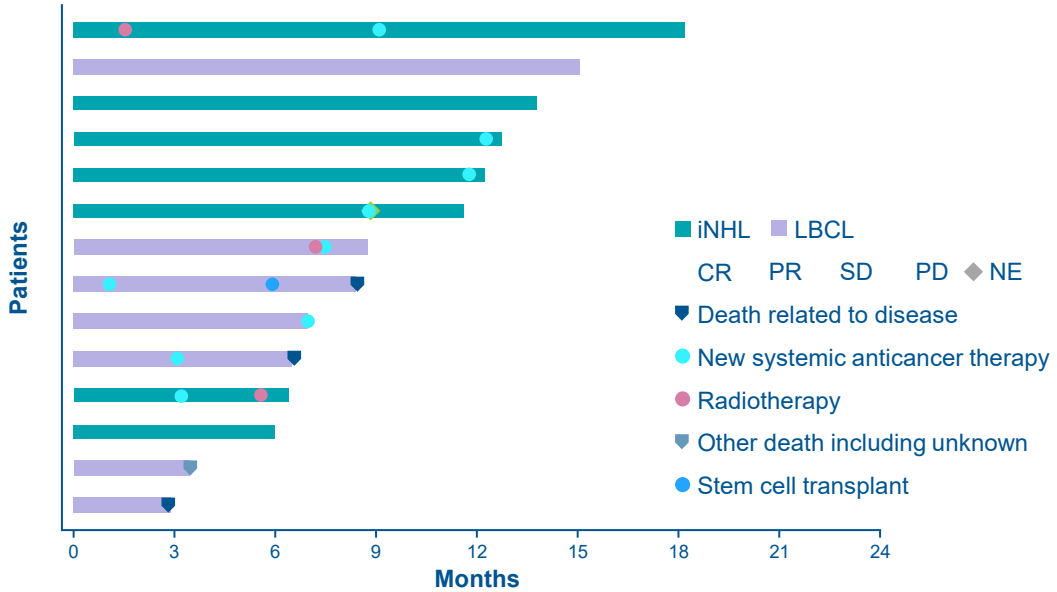


- ORR was 42.9% and 68.8% among patients in the 800M cohorts with and without prior CD19 CAR-T treatment, respectively

Percentages may not sum due to rounding.
ORR, overall response rate.

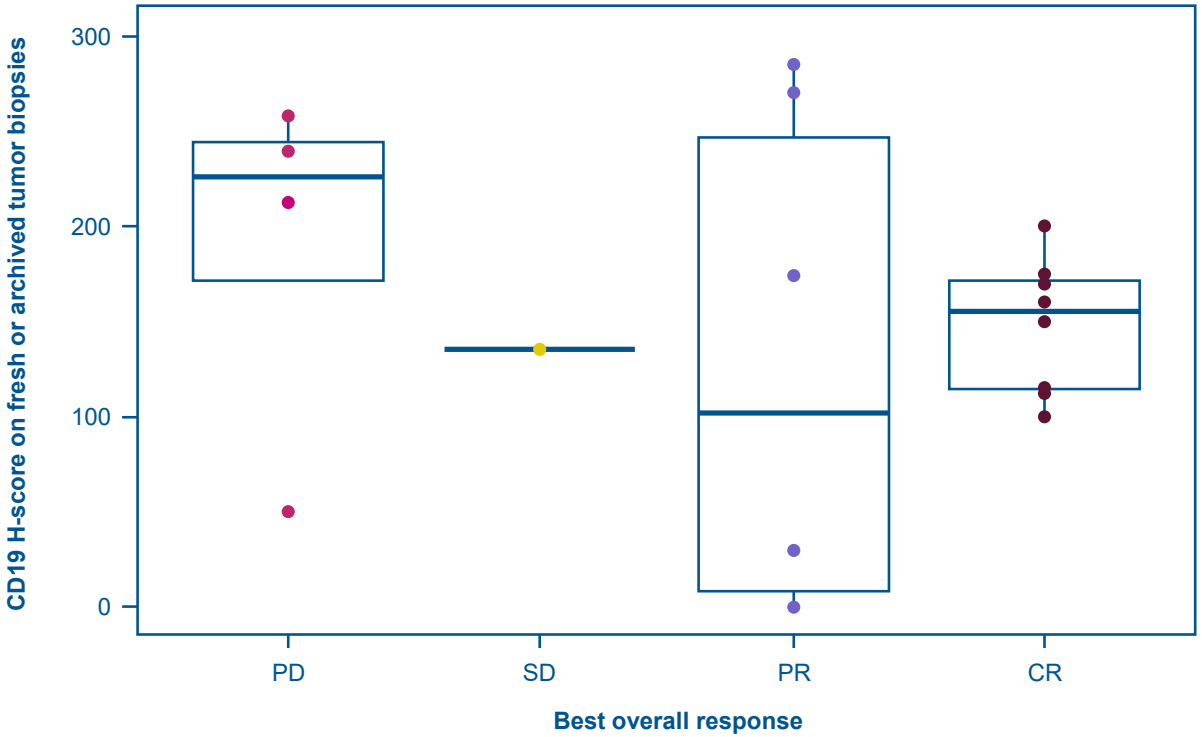
Responses were seen in patients with LBCL and iNHL, but long-term remissions were limited

- Median duration of response was 2.6 months in the LBCL cohorts and 4.9 months in the iNHL cohorts



CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

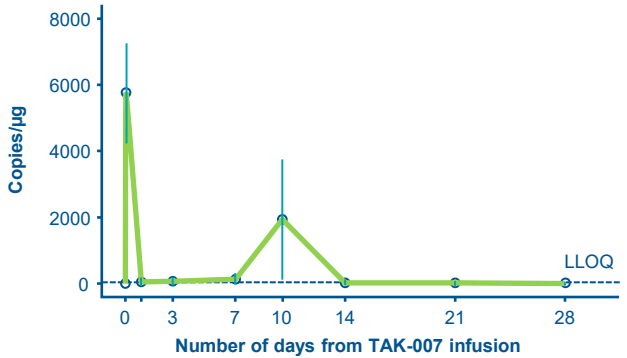
Clinical responses were seen across a range of CD19 antigen densities on pre-treatment biopsies



There was a positive correlation between higher exposures and probability of a response

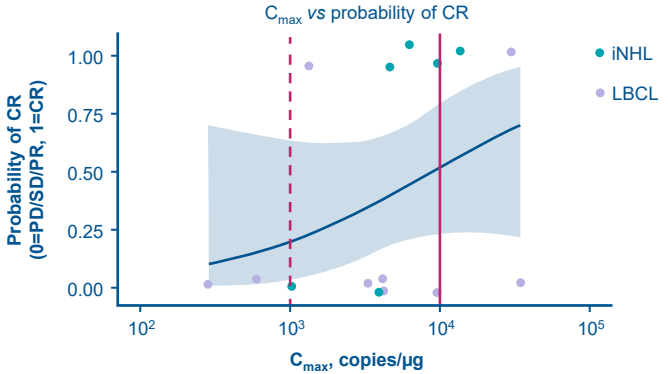
- Cellular kinetics exhibited a multiphasic disposition, representing an initial cellular contraction followed by cellular expansion
- Peak serum levels were observed on Days 7–10 post-TAK-007 infusion, which were followed by a terminal elimination phase with decreasing levels on Days 10–28

Average cellular kinetics profile* in patients receiving a single dose of TAK-007 (800M)



- The exposure-response analysis indicated a positive correlation between higher exposures to TAK-007 (C_{max}) and response (CR and ORR) to treatment

Exposure-response relationship: logistic regression of the probability of CR



- There were no reports of treatment-emergent humoral immunogenicity specific to donor HLA or the extracellular domain of CAR molecules on TAK-007

*Cellular kinetics profile presented as mean ± standard error.
C_{max}, maximum serum concentration; LLOQ, lower limit of quantification (using droplet digital polymerase chain reaction assay).

Summary and conclusions

- **TAK-007 is an allogeneic, off-the-shelf CD19 CAR-NK cell therapy offering potential clinical and operational advantages versus traditional CAR-T therapies**
- **TAK-007 at 800M demonstrated early efficacy and a favorable safety profile in a heavily pretreated patient population**
  - Low rates of IRRs and CRS were reported, with no cases of ICANS or GvHD
  - ORR was 53.8% with responses seen in patients with LBCL and iNHL
    - Patients with less aggressive disease (iNHL vs LBCL) were more likely to respond to TAK-007 treatment
    - Responses were observed independent of baseline CD19 expression
    - Long-term remissions were limited
  - Peak serum levels were observed on Days 7–10 post-TAK-007 infusion
  - Treatment-emergent humoral immunogenicity was not observed in this allogeneic HLA-agnostic setting
- **The use of >1 dose of TAK-007 at 800M may further increase efficacy and durability of response**

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