Role of cell therapy product characteristics in patient response to TAK-940 (CD19(T2)28z1XX chimeric antigen receptor (CAR) T): biomarker analyses from a Phase 1 study

Varsha Sundaresan,[1] Brigitte Senechal,[2] Xiuyan Wang,[2] Shubhra Kashyap,[1] Erica Tong,[1] Faye Zhao,[1] Adarsh Joshi,[1] Ajeeta Dash,[1] Leopold Sellner,[1] Sharon Chen,[1] Devin McAvoy,[2] Kinga K Hosszu,[2] Devanjan S Sikder,[2] Isabelle Riviere,[1] Michel Sadelain,[2] Jae H. Park,[2] Reshma Singh[1]

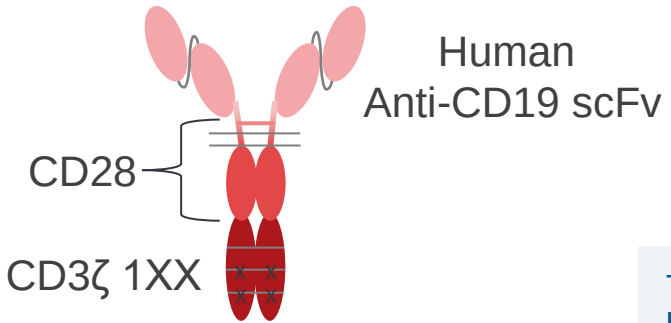
[1]Takeda Development Center Americas, Inc., MA, USA; [2]Memorial Sloan Kettering Cancer Center, NY, USA

TAK-940: Autologous anti-CD19 1XX CAR T

TAK-940 consists of **autologous T cells** that have been genetically modified using a retroviral vector to express a CAR targeting the TAA **CD19**, linked to the **costimulatory intracellular signaling domains** of CD28 and the ζ chain of the TCR/CD3 complex (CD3ζ)[1]

CD19 1XX CAR T cells include a 1928ζ mutant, 1XX, inactivating 2 of the 3 immunoreceptor tyrosine-based activation motifs (iTAMs) in the CD3ζ chain[1]

1928ζ 1XX construct



CD19 1XX CAR T cells specifically recognize and bind to CD19-expressing tumor cells, resulting in T-cell–mediated tumor cell lysis[1]

The development of TAK-940 is part of a broader collaboration with MSKCC[2]

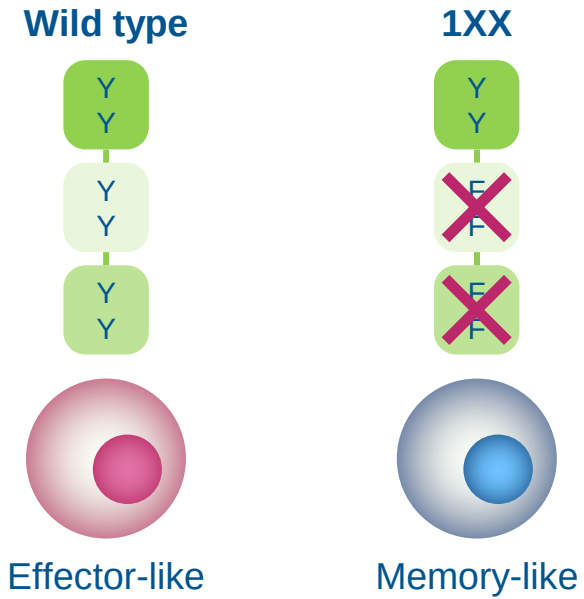
TAK-940 (also referred to as 1928ζ 1XX) is an investigational therapy. The MoA is based on preclinical data.

CAR, chimeric antigen receptor; CD, cluster of differentiation; MoA, mechanism of action; MSKCC, Memorial Sloan Kettering Cancer Center; scFv, single-chain variable fragment; TAA, tumor-associated antigen; TCR, T-cell receptor

1. Feucht J, et al. *Nat Med* 2019;25:82–8; 2. Takeda. News release. https://www.takeda.com/newsroom/newsreleases/2019/takeda-announces-multiple-cell-therapy-collaborations-to-advance-the-companys-novel-immuno-oncology-portfolio2/ (accessed Sep 11, 2023);

1XX CAR T cells are highly potent and more memory-like

- 1XX CAR T cells demonstrated a higher percentage of central memory T cells and a decrease in the fraction of terminally differentiated effector T cells
- 1XX design endowed the cells with enhanced ability to develop into highly functional, less differentiated & long-lived memory T cells with increased antitumor potency
- Increased potency observed preclinically supported evaluation of 1XX CAR T in the clinic at low starting doses



Feucht J et al. *Nature Med* 2019;25:82-88

A phase 1 study of CD19-targeted 19(T2)28z1XX CAR T cells in adult patients with relapsed or refractory B-cell malignancies

28 patients enrolled

Key eligibility criteria
- Age ≥ 18 years
- Histologically confirmed DLBCL and large B-cell lymphoma
- Chemotherapy refractory disease within 6 months to the last therapy

- OR -

Disease progression or recurrence ≤12 months from prior autologous stem cell transplant

- OR -

Relapsed disease after ≥2 prior chemo-immunotherapies with at least 1 containing an anthracycline and CD20-directed therapy

Escalation phase (n=16)
19(T2)28z1XX CAR T-cell dose

- **Dose Level 1** — 25 x 10^6
- **Dose Level 2** — 50 x 10^6
- **Dose Level 3** — 100 x 10^6
- **Dose Level 4** — 200 x 10^6

Expansion phase (n=12)

- **Dose Level 1** — 25 x 10^6

Key objectives

Primary:
- Safety and tolerability
- Identify RP2D

Secondary included:
- Efficacy
- In vivo persistence

Exploratory included:
- T-cell immunophenotyping
- Cytokine analysis

ClinicalTrials.gov identifier: NCT04464200

DLBCL, diffuse large B-cell lymphoma; RP2D, recommended Phase 2 dose.

Summary of clinical outcome

- A total of 28 patients were enrolled and treated in the dose escalation and expansion cohorts, achieving 82% ORR and 71% CR rate. Similar responses were observed across all dose levels, $25x10^6$ to $200x10^6$
- Among the 16 patients receiving $25x10^6$ cells, ORR was 88% and CR 75%
- A favorable safety profile was observed:
  - One dose-limiting toxicity, grade 3 ICANS in dose escalation
  - One patient experienced grade 3 CRS and ICANS in dose expansion

Presentation on the clinical data by Jae H. Park, MD
Session: 704 (# 892), Monday, Dec 11; 3:30 PM

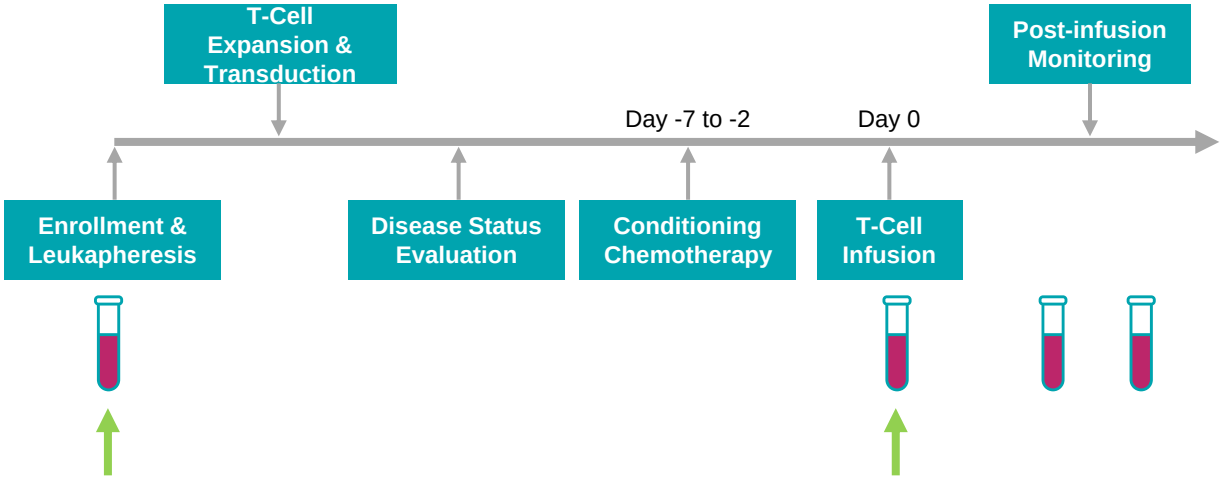
CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate.

Key biological/translational questions

- Does TAK-940 (CD19 1XX CAR-T) demonstrate altered composition of T-cell immunophenotypes as compared to the apheresis material?
  - Does the immune profile support the preclinical observation of increased memory T cells?

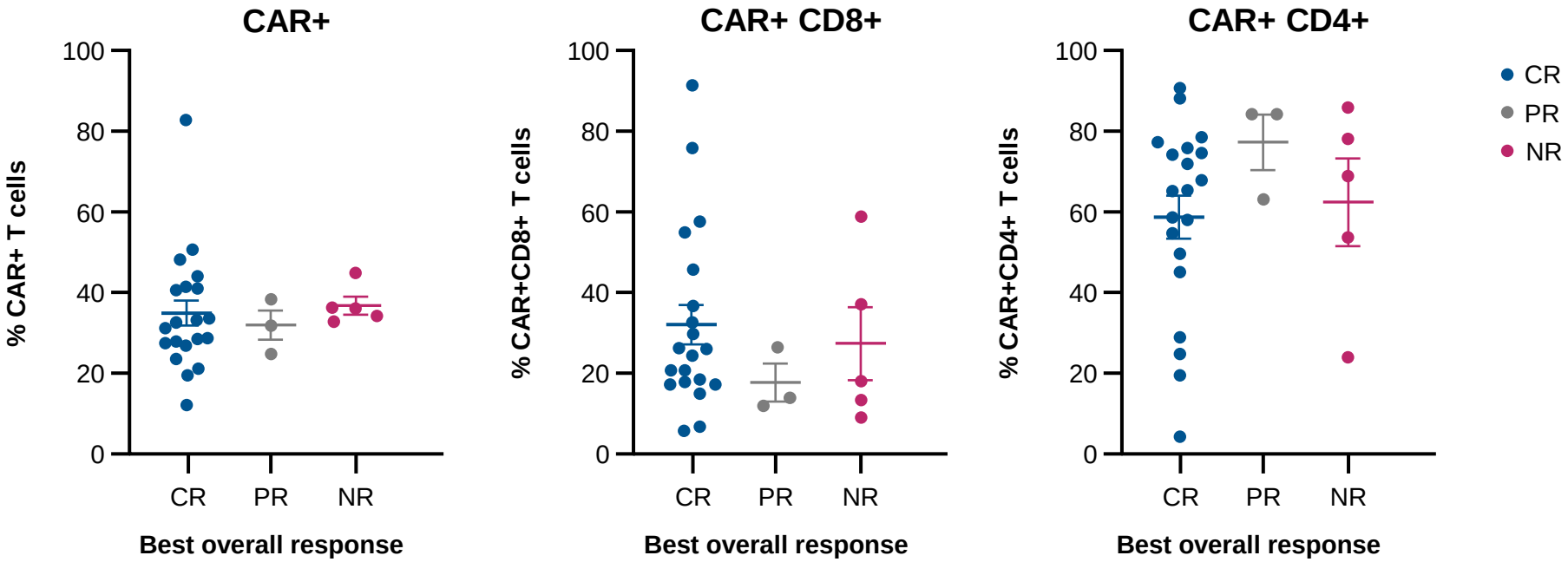
- Do CAR T immunophenotypes differentiate responders vs nonresponders?
  - Is there an impact of % CAR T cells infused on patient response?
  - Are there specific T-cell immunophenotypes enriched that associate with patient response?

Methodology



- Immunophenotyping was performed by flow cytometry on apheresis material, final infusion product, and patient samples collected post-infusion
- Flow cytometry panel consisted of markers for T-cell lineage/subsets (naïve, memory, effector), activation, senescence, and exhaustion

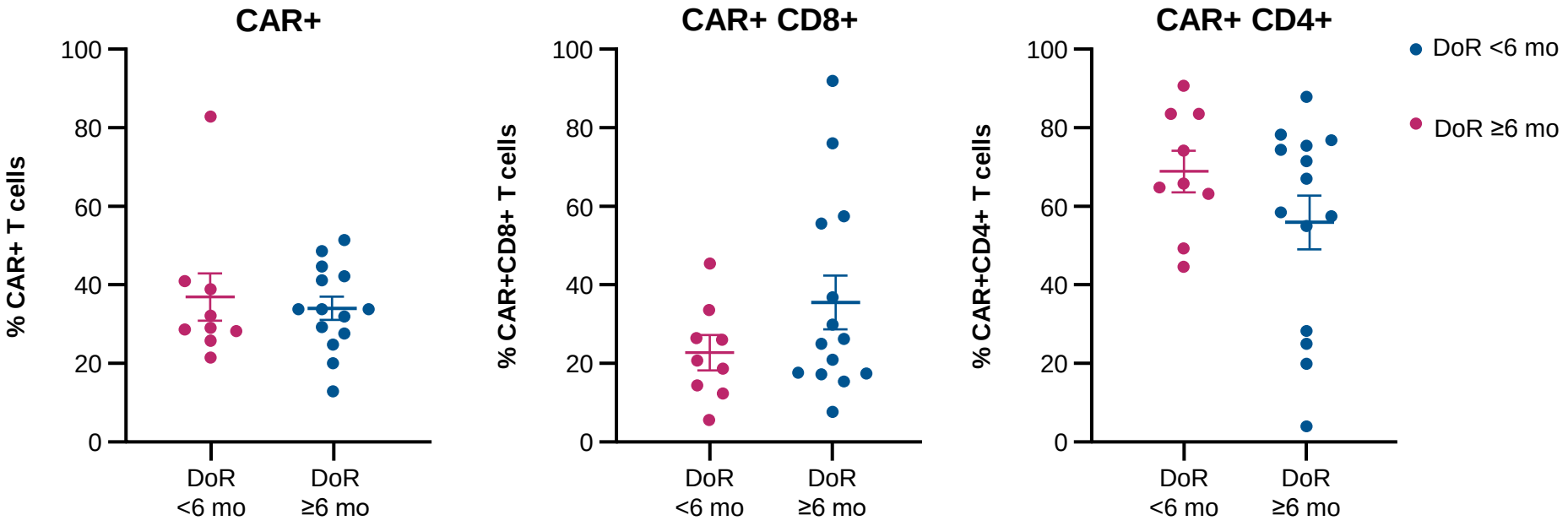
% CAR population in TAK-940 (CD19 1XX CAR-T) and association with best overall response



No association observed between % CAR and best overall response

CR, complete response; NR, no response; PR, partial response.

% CAR population in TAK-940 (CD19 1XX CAR-T) and association with duration of response

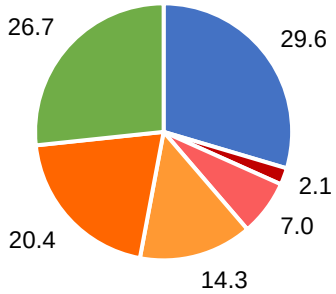


No association observed between % CAR and duration of response

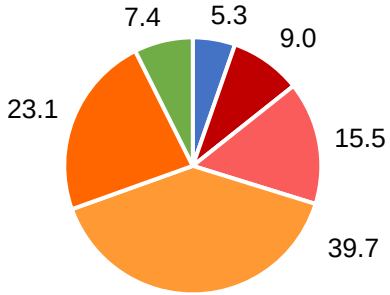
DoR, duration of response.

Comparison of T cell subsets in the apheresis material and TAK-940 (CD19 1XX CAR-T)

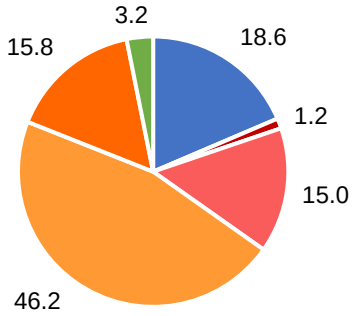
Apheresis material CD8+



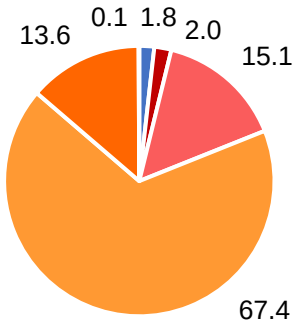
TAK-940 CAR+ CD8+



Apheresis material CD4+



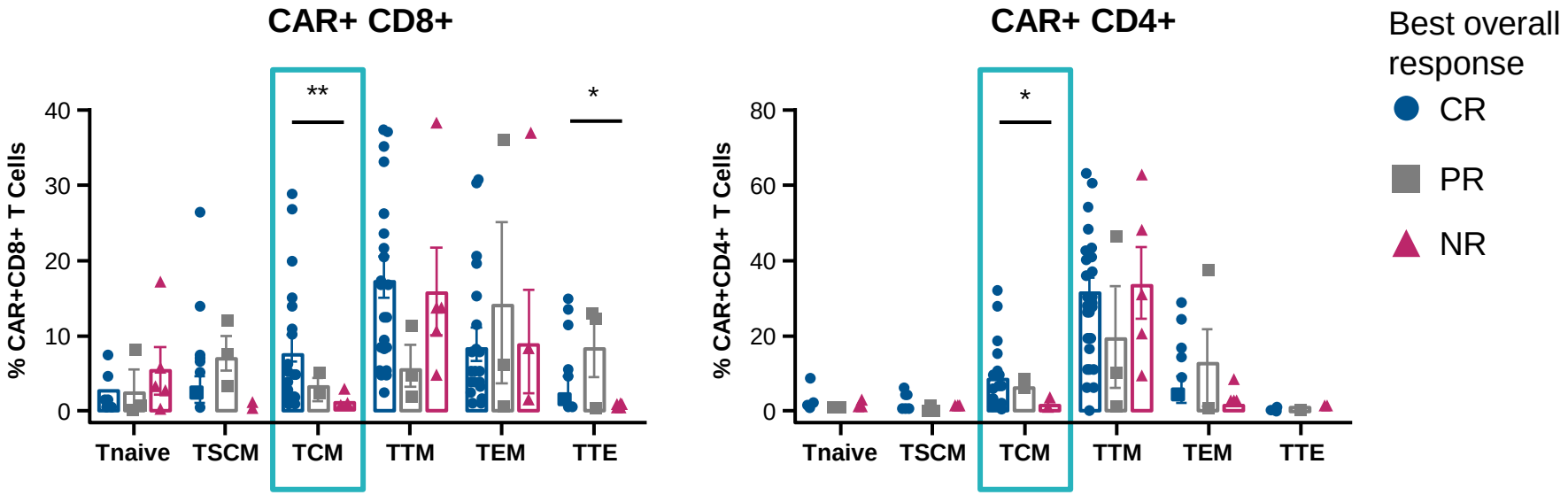
TAK-940 CAR+ CD4+



- Tnaive – naïve T cell
- TSCM – stem cell memory T cell
- TCM – central memory T cell
- TTM – transitional memory T cell
- TEM – effector memory T cell
- TTE – terminal effector T cell

Consistent with the preclinical observation, higher proportion of memory T cells and decrease in fraction of terminal effector T cells was observed in TAK-940 compared to apheresis material

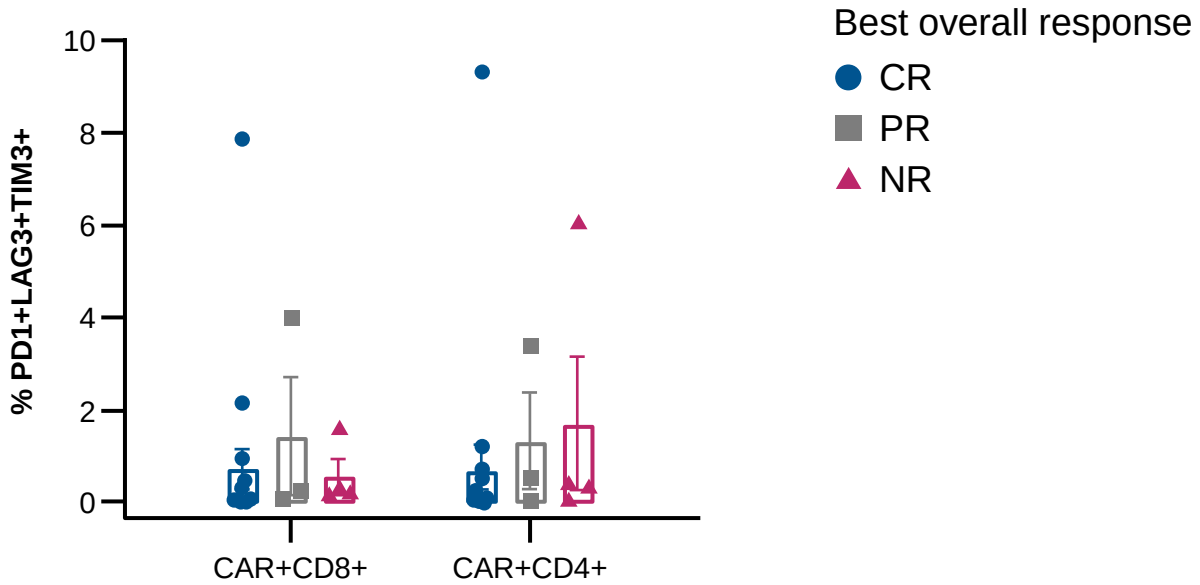
Memory T cell subsets in TAK-940 (CD19 1XX CAR-T) from responders and nonresponders



Significantly higher proportion of central memory T cells observed in complete responders compared with nonresponders

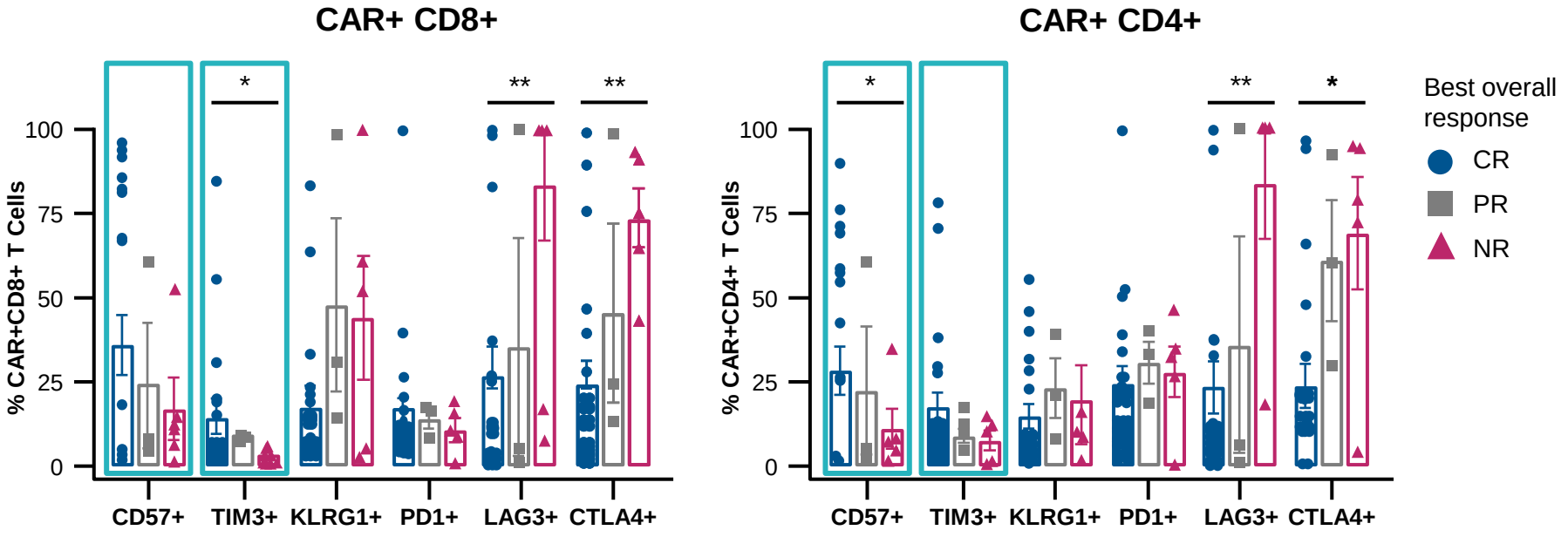
*p<0.05; **p<0.01.

Exhausted T cells in TAK-940 (CD19 1XX CAR-T) from responders and nonresponders



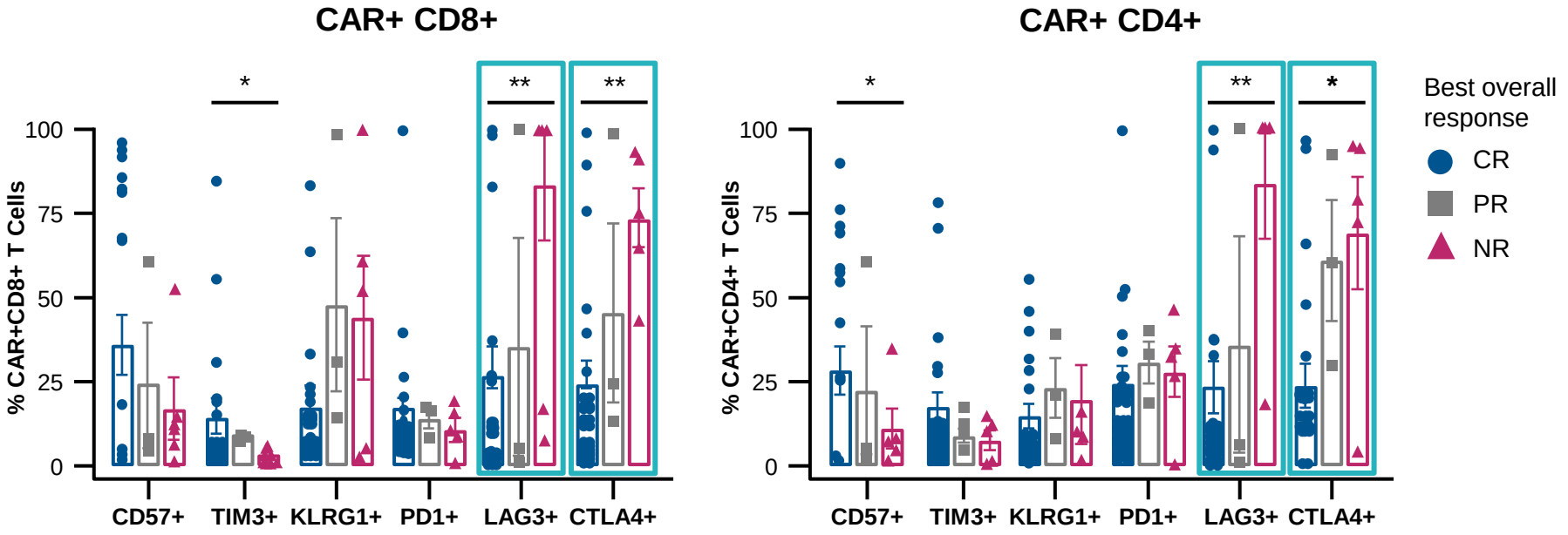
Low numbers of exhausted T cells in both responders and nonresponders

Activation and inhibitory markers in TAK-940 (CD19 1XX CAR-T) from responders and nonresponders



*p<0.05; **p<0.01.

Activation and inhibitory markers in TAK-940 (CD19 1XX CAR-T) from responders and nonresponders



Higher CD57+ and TIM3+, and lower CTLA4+ and LAG3+ CAR+ T cells observed in complete responders compared with nonresponders

*p<0.05; **p<0.01.

Conclusions

- TAK-940 leveraging the 1XX CAR design has demonstrated high potency in first-in-human Phase 1 study
  - Robust clinical responses observed with doses as low as $25x10^6$ CAR T cells

- TAK-940 (CD19 1XX CAR-T) contained a high proportion of memory T cells and low levels of exhausted T cells
  - Significantly higher proportion of CAR+ TCM subset was observed in TAK-940 product from complete responders compared with nonresponders

- The correlation of CD57, TIM3, LAG3, and CTLA4 expression on CAR+ T cells with increased potency of TAK-940 warrants further investigation

Acknowledgments

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- This study was funded by Takeda Development Center Americas, Inc., Lexington, MA, USA