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# CAR T cell therapy for T cell leukemia and lymphoma: latest updates from 2022 ASH Annual Meeting

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**Abstract**

Due to the concern of fratricide, clinical development of CAR T cells for the therapy of T cell malignancies lags behind that for B cell malignancies. Attempts are being made to revise T cell biomarkers so that the re-engineered CAR T cells can target T cell malignancies. CD3 and CD7 are the two pan-T cell surface biomarkers that have been either knocked out or knocked down through genome base- editing technology or by protein expression blockers so that the re-engineered T cells can target T cells without fratricide. We summarized several latest reports on the CAR T cells for the therapy of T cell leukemia /lymphoma from the 2022 ASH Annual Meeting, with latest updates on clinical trials of TvT CAR7, RD-13-01, and CD7 CART.

**Keywords** CAR T, CD3, CD7, T cell leukemia, Lymphoma

To the editor

Attempts are being made to revise T cell biomarkers so that the re-engineered CAR T cells can target T cell malignancies without fratricide [1]. CD3 and CD7 are the two pan-T cell surface biomarkers that have been either knocked out or knocked down through genome base-editing technology or by protein expression blockers so that the re-engineered T cells can target T cells without fratricide [2, 3]. We summarized several latest reports on the CAR T cells for the therapy of T cell leukemia / lymphoma (TCLL) from the 2022 ASH Annual Meeting (ASH2022).

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## CD7 targeted CAR T cells by genome editing

The abstract 2001 reported a targeted base- editing (BE) technology that can mediate precise C→U→T conversion using CRISPR guided cytidine deamination [4] (Table 1). The BE-edited allogeneic CAR T cells have disruptions of TCR, CD7 and CD52 (BE-CAR7). Early data from the clinical trial, TvT CAR7 study, were reported at ASH2022 [4]. This phase I study was planned for children with relapsed /refractory (R/R) CD7 + T-ALL. The BE-CAR7 cells were used to induce negative measurable residual disease (MRD) prior to allogeneic hematopoietic stem cell transplant (alloHSCT) at day + 28 (Table 2). The first highly refractory T ALL subject treated had grade 2 cytokine release syndrome (CRS), grade I immune effector cell-associated neurotoxicity syndrome (ICANS). The patient (pt) successfully achieved MRD negativity, had no graft-vs-host disease (GVHD), and received alloHSCT.

Another study reported data on a different CD7-genome edited alloCAR T cell product, RD13-01, in 10 patients with R/R TCLL [5]. On day 28, 8 pts reached complete remission (CR), and 7 of them had negative MRD. 6 patients in CR (including 1 MRD + CR)

**Table 1** Properties of CAR T cells targeting T cell malignancies

| Product | Genome editing | PEBL | Target | T cells | References |
|---|---|---|---|---|---|
| BE-CAR7 | + | – | CD7 | Off-the-shelf | [4] |
| RD-13-01 | + | – | CD7 | Off-the-shelf | [5] |
| PCART7 | – | +CD7 | CD7 | Donor | [6] |
| CD3PEBL | – | +CD3 | CD3 | Off-the-shelf | [8] |
| CD3/7PEBL | – | +CD3/7 | CD7 | Off-the-shelf | [7] |

*PEBL* protein expression blocker

proceeded to alloHSCT. Among the 10 subjects, 4 had durable CR, 4 died, 2 had no response. Nine of the 10 pts had grade I and 1 with grade 3 CRS, 1 had ICANS. GVHD was not reported.

## CD7 targeted CAR T cells by protein expression blocking

By employing an IntraBlock technology that can retain CD7 intracellularly, thereby leading to downregulation of surface CD7 expression, CD7-targeted CAR T cells from either stem cell donors or new donors were engineered and infused to patients with R/R TCLL [3]. In a recent report of phase 2 data with a 11 -month median follow-up [6], the objective response rate (ORR) remained at 90% 3 months post-infusion for the 20 enrolled pts. The rate for one-year progressive-free survival was 62.3%, and overall survival rate at 1 year was 60.0% (95% CI, 38.5–81.5). There was 10% grade 3 or higher CRS. Grade 1–2 GVHD was at 40%.

CD7 protein expression blocker (PEBL) binds and anchors CD7 in the ER and Golgi apparatus, resulting in CD7 degradation, thus leading to downregulation of surface CD7 expression. One group constructed a dual CD3/CD7 PEBL to block both CD3 and CD7 expression, together with anti-CD7 CAR, the CAR T cells, PCART7, specifically targeted CD7 + T cells in vitro and in vivo [7]. Due to lack of TCR activation secondary to CD3 downregulation, GVHD was not observed. This approach avoids genome editing, though clinical trials are needed to verify the applicability in human.

## CD3 targeted CAR T cells by protein expression blocking

By using the CD3 PEBL mentioned above, anti-CD3 PEBL-CAR T cells were generated that have been shown to have potent and specific cytotoxicity against CD3 + target cells in both in vitro and in vivo models [8]. Again, GVHD was much reduced in the mouse model treated with the anti-CD3 PEBL-CAR T cells. These features make this novel anti-CD3 CAR-T cells suitable for the treatment of TCLL.

In summary, by genome knockout or by blocking protein expression of surface CD3 and /or CD7, it is feasible to avoid fratricide and target T cell malignancies through CAR T cells.

**Table 2** Outcomes of clinical trials of CAR T cells targeting T cell malignancies

| Product | BE-CAR7 | RD-13–01 | PCART7 |
|---|---|---|---|
| Patients | 1 | 10 | 20 |
| Conditioning regimen | Fludarabine (150 mg/ $m^2$), cyclophosphamide (120 mg/kg) and alemtuzumab (1 mg/kg) | Fludarabine (25–30 mg/$m^2$/d), cyclophosphamide (300 mg/$m^2$/d) and etoposide (100 mg/$m^2$/d) on Day -6 to Day -3 | |
| ORR/CR | 1/1 MRD negative on day 28 | 8/10 (80%) CR on day 28 | 18/20 (90%) ORR at 3 months |
| PFS | | 4/6(66.7%) 315-day PFS | 62.3% 1-year PFS |
| OS | | | 60% 1-year OS |
| GVHD | 0/1 | | 8/20 (40%) grade 1–2 GvHD |
| CRS/ICANS | 1/1 grade 2 CRS 1/1 grade 1 ICANS | 9/10 (90%) grade 1 CRS, 1/10 (10%) grade 3CRS | 2/20 (10%) grade 3 or higher CRS |
| Clinical trial number | ISRCTN15323014 | NCT04620655 | NCT04689659 |
| References | [4] | [5] | [6] |

*CAR* chimeric antigen receptor, *CRS* cytokine release syndrome, *CR* complete response, *GVHD* graft vs host disease, *ICANS* Immune effector cell-associated neurotoxicity syndrome, *MRD* measurable residual disease, *ORR* overall response rate, *PFS* progression free survival, *OS* overall survival

**Abbreviations**

| | |
|---|---|
| ASH | American Society of Hematology |
| ALL | Acute lymphoblastic leukemia |
| CAR | Chimeric antigen receptor |
| CRS | Cytokine release syndrome |
| ICANS | Immune effector cell-associated neurotoxicity syndrome |
| CR | Complete response |
| GvHD | Graft vs host disease |
| ORR | Overall response rate |
| PFS | Progression free survival |
| OS | Overall survival |

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**Author contributions**
DL designed the study. DL and XZ drafted the manuscript. QH prepared the tables. All authors participated in the process of drafting and revising the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
The material supporting the conclusion of this study has been included within the article.

## Declarations

**Ethics approval and consent to participate**
This is not applicable for this summary.

**Consent for publication**
This is not applicable for this summary.

**Competing interests**
The authors declare no competing interests.

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