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Dual-targeted CAR T-cell immunotherapies for hematological malignancies: latest updates from the 2023 ASH annual meeting

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Abstract

Over the past few years, dual-targeted chimeric antigen receptor (CAR) T-cell therapy has been employed in the management of hematological malignancies to mitigate treatment failure, particularly in cases of antigen escape. The most widely used approaches include CD19/CD20, CD20/CD22, and BCMA/CD19 CAR T-cells. Alternative immune cells, including natural killer T cells and invariant natural killer T cells, exhibit innate anti-tumor activity and reduced toxicity. This review summarizes several recent clinical trial reports and preclinical studies from the 2023 American Society of Hematology (ASH) annual meeting on dual-targeted CAR T-cell immunotherapy for hematological malignancies.

Keywords Chimeric antigen receptor, Dual-targeted, Hematological malignancy, Clinical trial

To the editor

Although single-targeted chimeric antigen receptor (CAR) T cells have achieved remarkable success in treating hematological malignancies, relapse remains a major obstacle to achieving long-term survival [1]. CAR T cells targeting multiple antigens have been demonstrated to be an effective strategy to overcome antigen escape [2]. Here, we summarize the latest reports on dual-targeted CAR T-cell immunotherapy for hematological malignancies from the 2023 American Society of Hematology (ASH) annual meeting.

Dual-targeted CAR T-cell therapies for B-NHL

Three trials reported the outcomes of CD19/CD20 CAR T-cell therapy for relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL) [3–5]. Eleven r/r B-NHL patients (pts) received CART19/20 therapy derived from autologous naïve/memory T cells (Table 1) [3]. The overall objective rate (ORR) was 90.9% and the complete response (CR) rate was 72.7% (Table 2). With a median follow-up (mFU) of 32.3 months, the median progression-free survival (mPFS) and median overall survival (mOS) were not reached. Six pts experienced grade 1 cytokine release syndrome (CRS). No immune effector cell-associated neurotoxicity syndrome (ICANS) occurred.

LV20.19 CAR T cells, which also target CD20/CD19, are enriched for stem cell-like memory and central memory T cells (Table 1) [4]. A total of 17 pts with r/r mantle cell lymphoma (MCL) were enrolled, resulting in 100%

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Table 1 The properties of dual-targeted CAR T cells :

Product	Targets	Costimulatory domain	CAR generation	Transduction	Source of T cells	Refs.
CART19/20	CD19/CD20	4-1BB	Second	Lentiviral	Autologous $T_{N/MEM}$ cells	[3]
LV20.19	CD19/CD20	4-1BB	Second	Lentiviral	Autologous T cells with T_{SCM} and T_{CM} phenotype	[4]
C-CAR039	CD19/CD20	4-1BB	Second	NA	Autologous T cells	[5]
ATA3431	CD19/CD20	NA	NA	NA	Allogeneic T cells from healthy donor with T_{CM} phenotype	[6]
API-192	CD19/CD20	NA	Fourth, armored with IL-15	NA	Human cord blood CD34 hematopoietic stem and progenitor cell-derived NKT cells	[7]
UCART20×22	CD20/CD22	NA	NA	Lentiviral	Allogeneic T cells from healthy donor	[8]
CD19/CD70 CAR T cells	CD19/CD70	CD28/CD27	Third	Lentiviral	Autologous T cells	[9]
CD19/CD133 CAR T cells	CD19/CD133	CD19: CD28 CD133: 4-1BB	Second	NA	Allogeneic iNKT cells from healthy donor	[10]
GC012F	BCMA/CD19	NA	NA	NA	Autologous T cells	[11]
TIM3/CLEC12a CAR T cells	TIM3/CLEC12a	CD28/4-1BB	Third	Retroviral	Autologous T cells	[12]

$T_{N/MEM}$, naïve/memory T; T_{SCM}, stem cell-like memory T; T_{CM}, central memory T; NKT, natural killer T; iNKT, invariant natural killer T; NA, not available

ORR and 76% CR (Table 2). Two pts relapsed at 8 and 24 months, respectively. The 1-year PFS rate was 77%, and the 1-year OS rate was 84%. Two pts developed grade 3 ICANS. No severe CRS (grade ≥ 3) was observed.

C-CAR039, an autologous CD19/CD20 CAR T-cell therapy, was administered to r/r B-NHL pts resistant to CD20 antibody (Table 1) [5]. In total 91.5% of pts (43/47) achieved ORR, with 85.1% (40/47) achieving CR (Table 2). With a mFU of 23.9 months, the estimated 2-year PFS and OS were 66.0% and 77.9%, respectively. Only one patient experienced grade 3 CRS. No severe ICANS occurred.

ATA3431, an allogeneic CD19/CD20 CAR T-cell product, demonstrated enhanced persistence and superior anti-tumor activity in a mouse model of Burkitt's lymphoma (Table 1) [6].

API-192, targeting CD19 and CD20, is a cord blood CD34 hematopoietic stem and progenitor cell-derived natural killer T (NKT) cell product armored with IL-15 (Table 1) [7]. API-192 exhibited robust expansion and serial tumor killing against Raji and Nalm6 cells.

UCART20×22 is the first human allogeneic CD20/CD22 CAR T-cell product (Table 1) [8]. All three r/r B-NHL pts treated with UCART20×22 demonstrated an objective response with two achieving CR. No ICANS, graft-versus-host disease (GvHD) or severe CRS occurred (Table 2).

Eight pts with r/r diffuse large B-cell lymphoma (DLBCL) were enrolled in the treatment of CD19/CD70 CAR T-cell therapy (Table 1) [9]. ORR was achieved in 87.5% of pts, with 75.0% evaluated as CR (Table 2). With a mFU of 19.9 months, three pts relapsed. The median disease-free survival (mDFS) was 10.5 months. Severe CRS or ICANS was not observed.

Dual-targeted CAR T-cell therapies for ALL

Invariant natural killer T (iNKT) cells possess the ability to safeguard against GvHD without TCR deletion (Table 1). Allogeneic CD19/CD133 CAR iNKT-cell therapy exhibited remarkable efficacy in treating MLL-rearranged acute lymphoblastic leukemia (ALL), while also potentially preventing immune escape, leptomeningeal disease, and lineage switch [10].

Dual-targeted CAR T-cell therapies for MM

A phase I clinical trial reported updated results of BCMA/CD19 CAR T-cell therapy (GC012F) for pts with newly diagnosed multiple myeloma (MM) (Table 1) [11]. The ORR was 100% and the stringent CR rate was 95.5% (Table 2). The mOS and mPFS were not reached with a mFU of 13.6 months. No ICANS or severe CRS was reported.

Dual-targeted CAR T-cell therapies for AML

CLEC12a/TIM3 CAR T cells demonstrated potent anti-leukemic efficacy and exhibited prolonged persistence in the blood for 20 weeks following administration in an acute myeloid leukemia (AML) mouse model [12].

In summary, dual-targeted CAR T-cell immunotherapies have shown promising outcomes. Severe CRS or ICANS have not been reported in most clinical trials. Larger phase II trials with extended follow-up are necessary to determine whether these approaches can mitigate the risk of antigen loss/dim, relapse, and enhance the duration of response (DOR). Furthermore, dual-targeted immunotherapies derived from allogeneic NKT or iNKT cells have demonstrated the feasibility, potency, and safety necessary for further clinical validation.

Table 2 Outcomes of clinical trials of dual-targeted CAR T-cell immunotherapies in hematological malignancies from ASH 2023

Product	CART19/20	LV20.19	C-CAR039	UCART20×22	CD19/CD70 CAR T-cell therapy	GC012F
Disease	r/r B-NHL	r/r MCL	r/r B-NHL	r/r B-NHL	r/r DLBCL	NDMM
Clinical trial phase	I	I/II	Ib/II	I/IIa	I/II	I
Targets	CD19/CD20	CD19/CD20	CD19/CD20	CD20/CD22	CD19/CD70	BCMA/CD19
Dosage	$50\times10^6\pm30\%$ cells $200\times10^6\pm30\%$ cells	2.5×10^6cells/kg	$1.0–5.0\times10^6$cells/kg	50×10^6 cells	NA	1×10^5 cells/kg 2×10^5 cells/kg 3×10^5 cells/kg
Patients (n)	11	17	48	3	8	22
ORR	90.9%	100% at day 28 100% at day 90	91.5%	100.0%	87.5%	100.0%
CR	72.7%	76% at day 28 92% at day 90	85.10%	66.7%	75.0%	95.5%
mFU (months)	32.3	14	23.9	NA	19.9	13.6
Relapse	NA	2 pts	NA	NA	3 pts	NA
Survival	mPFS: NR mOS: NR	PFS: 77% at 1-year OS: 84% at 1-year DOR: 92% at 1-year	PFS: 66.0% at 2-year OS: 77.9% at 2-year	NA	mDFS: 10.5 months mOS: NR	mPFS: NR mDOR: NR
CRS	54.50%	94.1%	93.80%	100%	37.50%	27.30%
Grade 1–2	54.50%	94.1%	91.70%	100%	37.50%	27.30%
Grade 3–4	0%	0%	2.10%	0%	0%	0%
ICANS	0%	17.60%	6.30%	0%	0%	0%
Grade 1–2	0%	5.90%	6.30%	0%	0%	0%
Grade 3–4	0%	11.80%	0%	0%	0%	0%
Clinical trial number	NCT04007029	NCT04186520	NCT04693676	NCT05607420	NCT05436496	NCT04935580
References	[3]	[4]	[5]	[8]	[9]	[11]

ORR, overall objective rate; CR, complete response; mFU, median follow-up; mDFS, median disease-free survival; mPFS, median progression-free survival; mOS, median overall survival; mDOR, median duration of response;CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; r/r, relapsed or refractory; B-NHL, B-cell non-Hodgkin lymphoma; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ND, newly diagnosed; MM, multiple myeloma; pts, patients; NR, not reached; NA, not available

Abbreviations

ASH	American Society of Hematology
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
B-NHL	B-cell non-Hodgkin lymphoma
CAR	Chimeric antigen receptor
CR	Complete response
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
GvHD	Graft-versus-host disease
ICANS	Immune effector cell-associated neurotoxicity syndrome
iNKT	Invariant natural killer T
MCL	Mantle cell lymphoma
MM	Multiple myeloma
mDFS	Median disease-free survival
mFU	Median follow-up
mOS	Median overall survival
mPFS	Median progression-free survival
NA	Not available
ND	Newly diagnosed
NKT	Natural killer T
NR	Not reached
ORR	Overall objective rate
pts	Patients
r/r	Relapsed or refractory
T_{CM}	Central memory T
$T_{N/MEM}$	Naïve/memory T
T_{SCM}	Stem cell-like memory T

Author contributions

ZKS and SYP designed this study. YJY wrote the original manuscript. GH and HL prepared tables. All the authors participated in evaluating and editing the manuscript. The final manuscript has been read and approved by all the authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable for this summary.

Consent for publication

Not applicable for this summary.

Competing interests

The authors declare no competing interests.

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References

1. Zhang P, Zhang G, Wan X. Challenges and new technologies in adoptive cell therapy. J Hematol Oncol. 2023;16(1):97.
2. Ma Y, Dai H, Cui Q, Liu S, Kang L, Lian X, et al. Decitabine in combination with fludarabine and cyclophosphamide as a lymphodepletion regimen followed by CD19/CD22 bispecific targeted CAR T-cell therapy significantly improves survival in relapsed/refractory B-ALL patients. Exp Hematol Oncol. 2023;12(1):36.
3. Puliafito BR, Walthers CM, Ji B, Ghafouri SN, Naparstek J, Trent J, et al. Updated follow-up of a phase 1 trial of Bispecific CART19/20 cells for relapsed or refractory Non-hodgkin Lymphoma. Blood. 2023;142(Supplement 1):3490.
4. Shah NN, Furqan F, Szabo A, Kearl T, Zamora A, Neumann J, et al. Adaptive Manufacturing of LV20.19 CAR T-Cells for relapsed, Refractory Mantle Cell Lymphoma. Blood. 2023;142(Supplement 1):1024.
5. Li P, Yu WJ, Zhou LL, Yang M, Ye SG, Zhu J, et al. C-CAR039, a Novel Anti-CD20/CD19 bi-specific CAR T-Cell therapy shows deep and durable clinical benefits in patients with relapsed or refractory (r/r) B-Cell Non-hodgkin Lymphoma (B-NHL) in Long Term follow up. Blood. 2023;142(Supplement 1):1025.
6. Cha S, Charbonneau M, Brito A, Habibi A, Pham C, Nguyen C, et al. ATA3431: allogeneic CD19/CD20 bispecific CAR EBV T cells for the treatment of B-Cell malignancies. Blood. 2023;142(Supplement 1):4800.
7. Gov L, Yu JJ, Qubain M, Pompura SL, Allen SD, Christopher MA, et al. API-192, an allogeneic CD19/20 CAR-NKT cell product derived from Cord Blood CD34 + HSPCs for the treatment of B-Cell malignancies. Blood. 2023;142(Supplement 1):4801.
8. Abramson JS, Ramakrishnan A, Pierola AA, Braunschweig I, Cartron G, Thieblemont C, et al. Preliminary Results of Nathali-01: A First-in-Human Phase I/IIa Study of UCART20x22, a Dual Allogeneic CAR-T Cell Product Targeting CD20 and CD22, in Relapsed or Refractory (R/R) Non-Hodgkin Lymphoma (NHL). Blood. 2023;142(Supplement 1):2110.
9. Tu SF, Zhou LJ, Huang R, Zhou X, Yang JL, Li MF, et al. Efficacy and Safety of Chimeric Antigen Receptor T Cells Therapy Strategy with Dual Targeting of CD19 and CD70 to treat Relapsed/Refractory diffuse large B-Cell lymphoma. Blood. 2023;142(Supplement 1):3492.
10. Ren HW, Elliott N, Phil BM, Cross J, Field L, Ponnusamy K, et al. Bispecific CAR-iNKT immunotherapy for high risk MLL-Rearranged Acute Lymphoblastic Leukemia. Blood. 2023;142(Supplement 1):766.
11. Du J, Qiang WT, LU J, Jia YC, He HY, Liu J, et al. Updated results of a phase I open-label single-arm study of dual Targeting BCMA and CD19 Fastcar-T cells (GC012F) as first-line therapy for transplant-eligible newly diagnosed high-risk multiple myeloma. Blood. 2023;142(Supplement 1):1022.
12. Van Der Schans JJ, Vishwasrao P, Gils NV, Hosny M, Wang ZY, Arkel JV, et al. Dual Split-Signaling TIM3 + CLEC12a targeting CAR T-Cells with Optimized Signaling as a safe potential therapy for Acute myeloid leukemia. Blood. 2023;142(Supplement 1):883.

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