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Novel CAR T-cell therapies for relapsed/refractory B-cell malignancies: latest updates from 2023 ASH annual meeting

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Abstract

Chimeric antigen receptors (CAR) are engineered fusion proteins that target T-cells to specific surface antigens of tumor cells to generate effective anti-tumor responses. CAR T-cell therapy is playing an increasingly important role in the treatment of relapsed/refractory B-cell malignancies (R/R BCM). Attempting to make CAR T-cells safer and more effective in treating R/R BCM, various novel engineered CAR T-cell agents are currently in the research and development or clinical trial stages. We have summarized here the latest reports on the novel CAR T-cell therapies for R/R BCM presented at the 2023 ASH Annual Meeting as well as the latest updates in related clinical trials.

Keywords CAR T-cell therapy, Relapsed/refractory B-cell malignancies, ASH 2023

To the editor

CAR T-cell therapy has become an effective treatment for relapsed/refractory B-cell malignancies (R/R BCM). However, due to serious adverse events and failure to control or eradicate malignancies, many patients still cannot benefit from CAR T-cell therapy [1]. How to make CAR T-cells produce durable, effective, and safe anti-tumor effects remains a key issue. For this purpose, new targets are being studied or screened, and CAR T-cells are also being redesigned and modified [2]. Variously engineered CAR T-cells are in clinical trials. We have summarized the latest reports on novel CAR T-cell therapies for R/R BCM from the 2023 ASH Annual Meeting (ASH 2023) as well as the latest updates related to clinical trials.

Novel modified CD19 targeted CAR T-cell therapy

CD19 CAR T-cells have always been the mainstay of CAR T-cell therapy for R/R BCM [3]. However, successful CAR T-cell therapy not only requires effective and durable clinical efficacy but also safe and tolerable toxicity [4]. At ASH 2023, several studies reported novel modified CD19 targeted CAR T-cell agents that not only ensure CAR T-cells efficacy but also alleviate adverse events such as severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Kang et al. reported novel CD19 targeted CAR T-cells incorporating a small hairpin RNA element to silence the interleukin-6 gene (ssCART-19), reducing the incidence of severe CRS and neurotoxicity in R/R B-cell

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acute lymphoblastic leukemia patients [5]. Compared with the control group the incidence of grade 3–4 CRS in the ssCART-19 group decreased by 22.61% and there was no occurrence of grade 3–4 ICANS. The complete response (CR) or CR with incomplete hematological recovery (CRi) rate of ssCART-19 treatment on day 28 was 91.49%. Another Phase 1 trial on a novel third generation CD19 directed CAR T-cells incorporating CD28 and Toll-like receptor 2 co-stimulatory domains mitigated the risk of CAR T-cell therapy related ICANS while maintaining therapeutic efficacy in R/R B-cell non-Hodgkin's lymphoma (NHL) [6]. There was no grade≥3 CRS or any grade ICANS during the treatment period, and there was still a 52% CR at month three. Park et al. created a novel CD19 CAR construct with calibrated CAR activation potential by mutating 2 out of 3 immunoreceptor tyrosine-based activation motifs, called 19(T2)28z1XX [7]. Patients with R/R diffuse large B-cell lymphomas (DLBCL) receiving 19(T2)28z1XX CAR T-cell therapy showed persistent remission, with an overall CR rate of 71%, and a low incidence of severe CRS (4%) and ICANS (7%). Zheng et al. reported the latest clinical data of non-viral programmed cell death protein-1 locus specifically integrated anti-CD19 CAR T-cells (BRL-201) generated using CRISPR-Cas9 for the treatment of R/R NHL, with a median follow-up period of 29 months [8]. BRL-201 provided a safe and effective clinical response with an objective response rate (ORR) of 100% and a CR rate of 85.7%, while no grade 3–4 CRS or ICANS were observed.

Novel CAR T-cell therapy targeting ROR-1, CD70 and dual antigens

Several studies reported the latest clinical trial data on CAR T-cells engineered to recognize new targets for the treatment of R/R BCM. Abramson et al. reported the preliminary results of UCART20×22, a dual allogeneic CAR T-cell product targeting CD20 and CD22 in R/R NHL [9]. All three enrolled patients responded with two CRs and one PR on day 28. Meanwhile, UCART20×22 exhibited good safety and acceptable toxicity. Tu et al. published the results of CD19/CD70 CAR T-cell therapy for R/R DLBCL [10]. The CR rate at 1 month reached 75.0%. After a median follow-up time of 19.9 months, 50% of patients still maintained CR, with a median disease-free survival of 10.5 months. No patients experienced a grade≥3 CRS or any grade ICANS. In addition, a bispecific anti-CD20/CD19 CAR T-cell agent, C-CAR039, demonstrated durable responses and good safety in R/R B-NHL therapy [11]. The ORR and CR rates were 91.5% and 85.1%. Meanwhile, only one patient (2.1%) experienced severe CRS and there was no occurrence of severe ICANS. Another ongoing phase 1/2 trial is evaluating the effectiveness and safety of ROR1-specific CAR T-cell therapy for R/R aggressive B-cell lymphoma, including LBCL and Mantle cell lymphoma [12]. This study consists of two stages: phase 1 is for dose escalation while phase 2 is for dose expansion.

In conclusion, ASH 2023 presented the prospects and progress of novel CAR T-cell therapies for the treatment of R/R BCM as summarized in Tables 1 and 2. At present, the failure of CAR T-cell therapy is usually attributed

Table 1 Novel CAR T-cell agents for relapsed/refractory B-cell malignancies

Product	Phase	Target	Reconstruction method	Indication	T cells	Clinical trial identifier	References
ssCART−19	I/II	CD19	shRNA-IL−6 gene silencing element	R/R B-ALL	Autologous	NCT03919240	[5]
WZTL−002	I	CD19	CD28 and TLR2 co-stimulatory domains	R/R B-NHL	Autologous	NCT04049513	[6]
19(T2)28z1XX	I	CD19	Mutating 2 of the 3 ITAMs	R/R DLBCL	Autologous	NCT04464200	[7]
BRL−201	I	CD19	Non-viral PD−1 locus specific integration via CRISPR-Cas9	R/R B-NHL	Autologous	NCT04213469	[8]
UCART20×22	I/IIa	CD20/CD22	N/A	R/R B-NHL	Donor	NCT05607420	[9]
CD19/CD70 CAR T-cells	I/II	CD19/CD70	N/A	R/R DLBCL	Autologous	NCT03125577	[10]
C-CAR039	I	CD20/CD19	N/A	R/R B-NHL	Autologous	NCT04693676/NCT04696432/NCT04655677/NCT04317885	[11]
ONCT−808	I/II	ROR1	N/A	R/R BCL	Autologous	NCT05588440	[12]

R/R: Relapsed/refractory, B-ALL: B-cell acute lymphoblastic leukemia, B-NHL: B-cell non-Hodgkin's lymphoma, DLBCL: Diffuse large B-cell lymphomas, BCL: B-cell Lymphoma, IL−6: Interleukin−6, TLR2: Toll-like receptor 2, ITAMs: Immunoreceptor tyrosine-based activation motifs, PD−1: Programmed cell death protein−1

Table 2 The efficacy and safety of novel CAR T-cells

Product	Patients	Conditioning regimen	CRS	ICANS	ORR/CR/CRi	PFS	OS	References
ssCART−19	47	Fludarabine at 30mg/m^2/day, cyclophosphamide at 300mg/m^2/day on D−5,−4, and−3	Grade 1–2 25/47 (53.20%) Grade 3–4 7/47 (14.89%)	Grade 1 2/47 (4.26%)	91.49% CR/CRi on day 28	mPFS 14.7 months	N/A	[5]
WZTL−002	21	Fludarabine (30 mg/m^2/day) and cyclophosphamide (500mg/m^2/day) on D−5,−4, and−3	Grade 1–2 13/21 (62%)	No ICANS of any grade	52% CR at 3 months	N/A	N/A	[6]
19(T2)28z1XX	28	Fludarabine and cyclophosphamide	Grade 1–2 24/28 (86%) Grade 3 1/28 (4%)	Grade 1–2 1/28 (4%) Grade 3 2/28 (7%)	82% ORR 71% CR	N/A	N/A	[7]
BRL−201	21	Cyclophosphamide (500mg/m^2, D−3 to−2) and fludarabine (30mg/m^2, D−4 to−2)	Grade 1–2 14/21 (66.7%)	Grade 1–2 4/21 (19.0%)	100% ORR 85.7% CR	mPFS 20.8 months	76.2% 12-month OS	[8]
UCART20×22	3	Fludarabine 30 mg/m^2 × 3d, cyclophosphamide 0.5 g/m^2 × 3d, alemtuzumab 12 mg on D1, 24 mg on D2, D3	Grade 1–2 3/3 (100%)	No ICANS of any grade	66.7% CR on day 28	N/A	N/A	[9]
CD19/CD70 CAR T-cells	8	Cyclophosphamide and fludarabine chemotherapy conditioning 1–2 days	Grade 1–2 3/8 (37.5%)	No ICANS of any grade	87.5% ORR 75.0% CR at 1 month	N/A	N/A	[10]
C-CAR039	48	Cyclophosphamide plus fludarabine chemotherapy conditioning 3 days	Grade 1–2 44/48 (91.7%) Grade 3 1/48 (2.1%)	Grade 1–2 3/48 (6.52%)	91.5% ORR 85.1% CR	66.0% 24-month PFS	77.9% 24-month OS	[11]
ONCT−808	N/A	Cyclophosphamide and fludarabine	N/A	N/A	N/A	N/A	N/A	[12]

CRS: Severe cytokine release syndrome, ICANS: Immune effector cell-associated neurotoxicity syndrome, ORR: Overall response rate, CR: Complete response, CRi: CR with incomplete hematological recovery, mPFS: Median progression free survival, OS: Overall survival

to the loss of target antigens or depletion of CAR T-cells, while dual antigen targeting and CAR T-cells modification are potential strategies to overcome treatment failure. Therefore, the emergence of novel CAR T-cell therapies will further improve the treatment safety and effectiveness of patients with R/R BCM.

Abbreviations

ASH	American Society of Hematology
CAR	Chimeric antigen receptor
R/R	Relapsed/refractory
BCM	B-cell malignancies
DLBCL	Diffuse large B-cell lymphomas
NHL	Non-Hodgkin's lymphoma
CRS	Cytokine release syndrome
ICANS	Immune effector cell-associated neurotoxicity syndrome
CR	Complete response
CRi	CR with incomplete hematological recovery
ORR	Objective response rate
PFS	Progression free survival
OS	Overall survival

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Author contributions
ZX and HL designed the study. WZ and SL drafted the manuscript. JL, SX and MW 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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Data availability
The material supporting the conclusion of this study has been included within the article.

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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