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Advances in CAR-T cell therapy for hematologic and solid malignancies: latest updates from 2024 ESMO Congress

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Abstract
Chimeric antigen receptor (CAR)-T cell therapy has emerged as one of the most rapidly evolving modalities of immunotherapy, with substantial success in the treatment of hematological malignancies and encouraging outcomes in solid tumors. Yet, the efficacy of CAR-T therapy is hindered by challenges such as suboptimal expansion and persistence, adverse events, a scarcity of ideal targets, high immunosuppression, and insufficient infiltration due to the intricate tumor microenvironment, all of which limit its application. The 2024 European Society for Medical Oncology (ESMO) Congress presented novel CAR-T cell therapies for hematologic and solid malignancies, focusing on strategies such as cytokine modulation, innovative targets, allogeneic development, mRNA vaccine synergy, in vivo delivery and conditional activation to surmount these challenges.

Keywords CAR-T, Hematological malignancy, Solid tumor

To the editor

Chimeric antigen receptor (CAR)-T cell therapy has achieved substantial success in the treatment of cancers, particularly hematological malignancies [1]. However, prolonging remission and reducing the recurrence of hematological malignancies and the complex tumor microenvironment (TME) of solid tumors are challenges for CAR-T therapy [2]. We summarized the latest reports on novel CAR-T cell therapies for hematologic and solid malignancies from the 2024 European Society for Medical Oncology (ESMO) Congress and showcased these exciting advances.

Updates in hematological malignancies

ssCART-19, a novel autologous CD19-specific CAR-T therapy that incorporates shRNA technology to silence IL-6, demonstrated a favorable safety profile in a phase I trial of relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia. Among the 17 patients (58.8% with more than 50% blasts) followed up for a median of 19.6

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months, no grade≥4 cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or related deaths were observed. ssCART-19 achieved an 87.5% overall response rate (ORR) within 3 months, including 62.5% complete response (CR), with a 6-month duration of response of 100.0%, 80.0% and 0.0% for dose level 1 (DL1), DL2 and DL3, respectively, and an undetermined median overall survival (OS), while also successfully treating a patient with grade 2 central nervous system infiltration without developing ICANS [3].

Interim results from a phase Ib trial of NT-I7 (a long-acting IL-7 designed to induce CAR-T expansion following CD19 CAR-T therapy) in advanced diffuse large B-cell lymphoma suggested that NT-I7 at 60–480 μg/kg was well tolerated in 11 patients (mean age 67, 81.8% III-IV stage), with no CRS or ICANS. The ORR was 81.1%, including 63.6% CR. The median OS and progression-free survival (PFS) were 363 d and 92 d, respectively. NT-I7 administered on day 21 post-infusion enhanced CAR-T expansion, persistence and stemness [4].

A real-world study from the French DESCAR-T registry confirmed previous efficacy data from the pivotal ELARA trial, showing that with a median follow-up of 9.8 months, CD19 CAR-T therapy with tisagenlecleucel in 129 cases of R/R follicular lymphoma achieved a 98.2% ORR, including 85.8% best CR, with only 1.8% experiencing progression as the best response, 12-month PFS and OS rates of 62.6% and 84.9%, respectively (both medians were not reached), and <1% grade 3–4 CRS and/or ICANS [5].

The largest real-world comparison demonstrated that B-cell maturation antigen (BCMA) CAR-T therapies, especially ciltacabtagene autoleucel, improved OS in R/R multiple myeloma patients, with a higher CRS rate but a similar ICANS incidence to that of the bispecifics teclistamab. Older (age≥70) and transplant-ineligible individuals especially benefited [6].

Updates in solid tumors

A phase I trial of the intrathecal injection of QH104, an allogeneic B7H3-targeting CAR-γδT therapy for recurrent glioblastoma, achieved a 42.9% ORR and a 100% disease control rate (DCR) in 7 patients (2 females, 5 males, median age 60) with a median observation time of 6.5 months, without any dose-limiting toxicity, severe CRS, ICANS, or graft-versus-host disease [7].

BRG01, a first-in-class autologous CAR-T therapy targeting the Epstein-Barr virus envelope glycoprotein Gp350, exhibited dose-dependent antiviral and antitumor efficacy in a phase I trial involving 11 patients with advanced metastatic nasopharyngeal cancer (exhibiting 60-100% Gp350 expression), with tumor shrinkage rates of 75% (including complete remission) and PFSs of over six months for all subjects, which is superior to standard therapies and checkpoint inhibitors. No dose-limiting toxicity, grade≥2 CRS, ICANS, or treatment-related deaths occurred [8].

The oncofetal antigen CLDN6 is undetectable in healthy somatic tissue and is highly expressed in various solid cancers. The phase I BNT211-01 trial updated the results for automated process manufactured CLDN6 CAR-T cells±CLDN6-encoding mRNA vaccine (CARVac) in R/R CLDN6^{+} solid tumors, yielding a 38% ORR and a 69% DCR in 59 patients (median age 48, 56% male, median 4 prior treatment lines). Higher dose levels (DL2 or DL3) of CLDN6 CAR-T cells±CARVac increased the ORR to 55% and the DCR to 86%. CLDN6 CAR-T cells±CARVac showed safety signals, with 64% grade 3–4 treatment-related adverse events (AEs) and 39% serious related AEs [9].

Two pioneering CAR-T therapies are currently enrolling in multicenter phase I trials. MT-302, the first-in-class in vivo CAR therapy with an mRNA-lipid nanoparticle targeting TROP2, is being used to treat adults with advanced epithelial tumors (MYE Symphony study). This in vivo approach allows for dose and schedule optimization without conditioning, aiming at infiltrating the TME and initiating a broad antitumor immune response [10]. EU307, a fourth-generation autologous CAR-T therapy targeting GPC3 in advanced hepatocellular carcinoma, incorporates genetic engineering to secrete IL-18, thereby enhancing CAR-T cell persistence and function and reprogramming the immunosuppressive TME into an environment conducive to tumor eradication [11].

BTRP003L is a conditionally activated armored CAR-T therapy that targets epithelial glycoprotein-1 in gastrointestinal tumors. It is modified with various hypoxia-responsive elements and armed with the dominant-negative TGFβRII to increase activation and cytokine release in the hypoxic TME while minimizing its impact on normal tissues. The promising preclinical results support its potential for clinical development [12].

In conclusion, as detailed in Tables 1 and 2, these updates from the 2024 ESMO Congress underscore the continuous innovation and advances in CAR-T cell therapy for hematologic and solid malignancies, bringing new optimism to patients battling various cancers.

Table 1 Advances in CAR-T cell therapy for hematologic malignancies from ESMO2024

Agent	Drug type	Study type	Disease	Accrual	Median follow-up duration	Efficacy	Major AEs	References
ssCART-19	Autologous IL-6-knockdown CD19 CAR-T	Phase I trial (NCT04825496)	R/R B-cell ALL	17 (58.8% having over 50% blasts)	19.6 m	ORR 87.5% (CR 62.5%, CRi 25.0%) within 3 m; 6-m DOR at 100% for DL1, 80% for DL2, 0% for DL3; median OS not reached	No grade ≥ 4 CRS, ICANS or related deaths	[3]
NT-I7	Long-acting IL-7 following CD19 CAR-T	Phase Ib trial (NCT05075603)	Advanced DLBCL	11 (mean age 67, 81.8% III-IV stage)	N/A	ORR 81.1% (CR 63.6%); median OS 363 d; median PFS 92 d; dosed at day 21 after CAR-T infusion enhanced expansion, persistence and stemness	No CRS or ICANS	[4]
Tisagenlecleucel	Autologous CD19 CAR-T	Real-world study	R/R FL	129 (66.7% male, median age 63.7, median 3 prior treatment lines, 78.0% refractory, 75.0% relapsed in 6 m)	9.8 m	ORR 98.2% (best CR 85.8%); 1.8% progression as best response; 12-m PFS 62.6%, 12-m OS 84.9%, both medians not reached	< 1% grade 3–4 CRS and/or ICANS; no adverse drug reactions led to death	[5]
Idecabtagene vicleucel/ ciltacabtagene autoleucel vs. teclistamab	Autologous BCMA CAR-T vs. bispecifics	Real-world study	R/R MM	391 (277 idecabtagene vicleucel, 114 ciltacabtagene autoleucel) vs. 458 (mean age 66, 54% male)	N/A	Better OS in CAR-T; older (age ≥ 70) and transplant-ineligible patients benefited more from CAR-T	More CRS in CAR-T but similar ICANS	[6]

Abbreviations CAR, chimeric antigen receptor; AE, adverse event; R/R, relapsed/refractory; ALL, acute lymphoblastic leukemia; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate; CR, complete response; CRi, complete response with incomplete hematologic recovery; DOR, duration of response; DL, dose level; OS, overall survival; DLBCL, diffuse large B-cell lymphoma; N/A, not applicable or not available; PFS, progression-free survival; FL, follicular lymphoma; BCMA, B-cell maturation antigen; MM, multiple myeloma

Table 2 Advances in CAR-T cell therapy for solid tumors from ESMO2024

Agent	Drug type	Study type	Disease	Accrual	Median follow-up duration	Efficacy	Major AEs	References
QH104	Allogeneic B7H3 CAR-γδT	Phase I trial (NCT06018363)	Recurrent GBM	7 (2 females, 5 males, median age 60)	6.5 m	ORR 42.9%, DCR 100%	No DLT, grade ≥ 3 CRS, ICANS, or GvHD	[7]
BRG01	Autologous EBV Gp350 CAR-T	Phase I trial (NCT05864924)	Advanced metastatic NPC	11 (exhibiting 60-100% Gp350 expression)	N/A	Tumor shrinkage rates 75% (including CR); all PFSs > 6 m	No DLT, grade ≥ 2 CRS, ICANS, or treatment-related deaths	[8]
BNT211-01	Autologous CLDN6 CAR-T ± mRNA vaccine	Phase I trial (NCT04503278)	R/R CLDN6^{+} solid tumor	59 (median age 48, 56% male; median 4 prior treatment lines)	N/A	ORR 38%, DCR 69%	64% grade 3–4 treatment-related AEs, 39% serious related AEs	[9]
MT-302	in vivo TROP2 CAR-T (mRNA)	Phase I trial (NCT05969041)	Advanced epithelial tumor	N/A	N/A	N/A	N/A	[10]
EU307	Autologous IL-18-secreting GPC3 CAR-T	Phase I trial (NCT05783570)	GPC3^{+} advanced HCC	N/A	N/A	N/A	N/A	[11]
BTRP003L	Autologous hypoxia-regulated and dnTGFβRII-armored EGP-1 CAR-T	Preclinical study	Gastrointestinal tumor	N/A	N/A	Enhanced CAR-T expression and cytokine release in a hypoxic environment but lower activation levels under normoxic conditions	No observable AEs	[12]

Abbreviations CAR, chimeric antigen receptor; AE, adverse event; GBM, glioblastoma; DCR, disease control rate; DLT, dose-limiting toxicity; ICANS, immune effector cell-associated neurotoxicity syndrome; GvHD, graft-versus-host disease; NPC, nasopharyngeal cancer; N/A, not applicable or not available; CR, complete response; PFS, progression-free survival; EBV, Epstein-Barr virus; R/R, relapsed/refractory; HCC, hepatocellular carcinoma

Abbreviations

AE	Adverse event
BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
CR	Complete response
CRS	Cytokine release syndrome
DCR	Disease control rate
DL	Dose level
ESMO	European Society for Medical Oncology
ICANS	Immune effector cell-associated neurotoxicity syndrome
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
R/R	Relapsed/refractory
TME	Tumor microenvironment

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Data availability
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Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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