White Paper

Self-Driving CAR: The Promise of In Vivo CAR-T Therapy for Hematologic Malignancies

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Introduction

Global burden of hematologic malignancies

Hematologic malignancies (HMs) represent a significant portion of the global cancer burden. This white paper focuses on in vivo-engineered T-cell therapy for three major HM subtypes of the B lineage: acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM).

Over recent decades, the global incidence of HMs has steadily increased, while age-adjusted mortality rates have declined, largely due to advances in treatment.[1,2] In 2019, an estimated 1.34 million new cases of HMs were diagnosed worldwide[1]. Among these, leukemia had the highest global incidence, with around 643,580 cases reported. ALL accounts for a fraction of leukemia cases (~153,320 new cases in 2019) and is more common in children than in adults.[1] Diffuse large B-cell lymphoma (DLBCL) is the most common NHL subtype, comprising approximately 30%–40% of NHL cases, with incidence rising with age.[3] The global incidence of MM is also rising (155,690 cases in 2019),[1] particularly in developed regions such as North America, where incidence rates are about 4.7 per 100,000 compared with approximately 0.8 per 100,000 in West Africa.[4] Standard treatments differ between HMs but may include chemotherapy, radiotherapy, therapeutic antibodies, small-molecule drugs, and cellular therapies such as chimeric antigen receptor (CAR)-modified T cells (CAR-Ts) and autologous and allogeneic hematopoietic stem-cell transplantation (HSCT).[5] However, primary resistance, relapse, and adverse effects have led to treatment failure in many patients.[5,6]

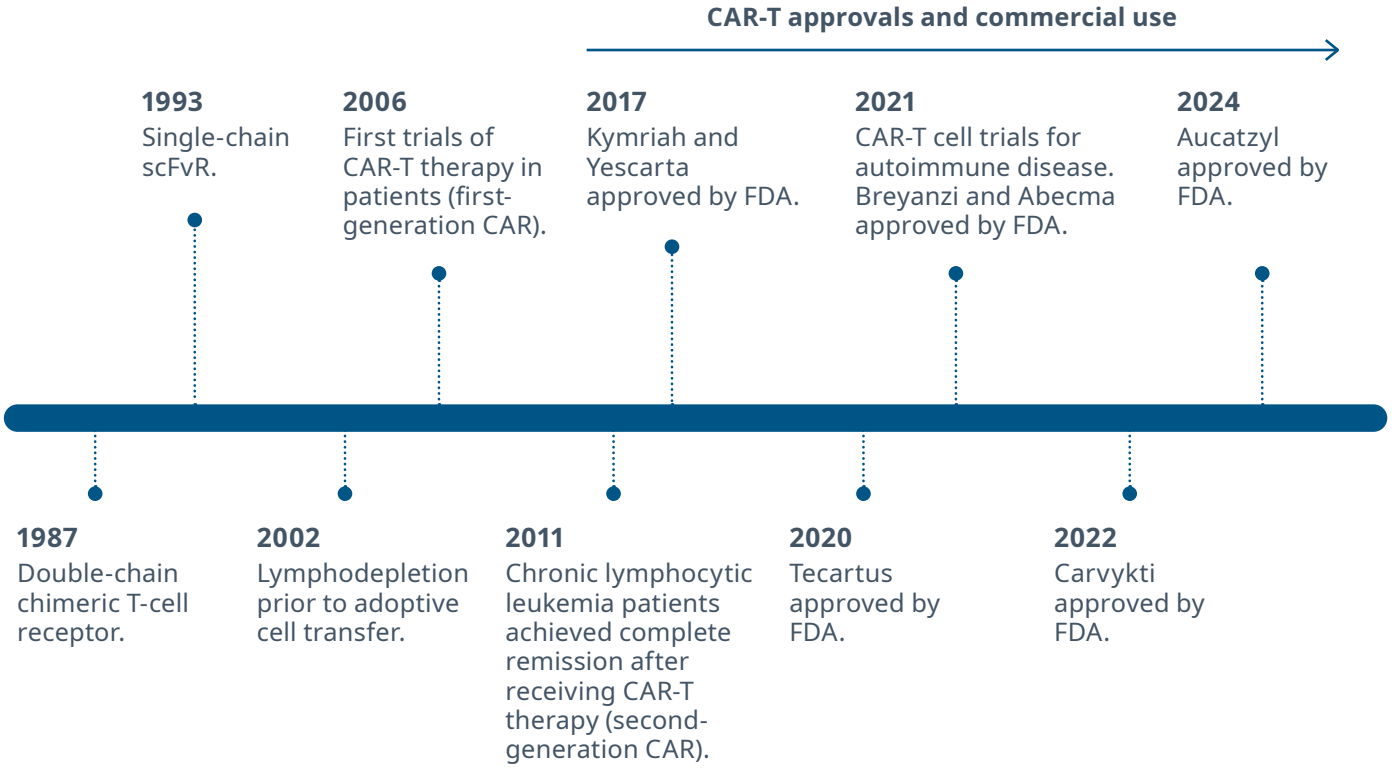
Transformative impact of ex vivo autologous CAR-T therapies

In response to the growing global burden of HMs, innovative therapies such as CAR-T treatments have emerged. Ex vivo autologous CAR-T therapies have revolutionized the treatment landscape for a subset of HMs by establishing a targeted immune response against tumor cells.[7] A CAR is a synthetically designed receptor that—when introduced into a T cell—enables the engineered CAR-T to recognize the target antigen of the CAR.[8] In autologous CAR-T therapy, T cells are harvested from a patient and genetically engineered in a laboratory to express the CAR. The patient receives the CAR-Ts shortly after completion of a short course of lymphodepletion chemotherapy, which is administered to promote CAR-T engraftment.[9] The therapeutic efficacy of CAR-T therapy is—in part—governed by the qualities of a patient's T cells and the structural design of the CAR. These receptors comprise four principal domains: an extracellular segment responsible for antigen binding—typically a single-chain variable fragment (scFv); a hinge region; a transmembrane domain facilitating membrane anchorage; and intracellular signaling modules that mediate T-cell activation and target killing upon antigen engagement.[8]

CAR-T therapy is the result of decades of immunological and bioengineering research (Figure 1). The design of the first generation of CARs, published in 1993 by Zelig Eshhar, combined an scFv from a monoclonal antibody with the CD3ζ signaling chain.[10-12] Subsequent generations added one (second-generation) or more (third-generation) co-stimulatory domains in the CAR construct,[13] along with other modifications to enhance efficacy and/or control of the CAR-Ts.[13, 14] Second-generation CARs that incorporate a single CD28 or 4-1BB co-stimulatory domain form the backbones of all currently approved CAR-T products (Table 1).[15-21]

CAR-T therapies have demonstrated robust efficacy in subsets of relapsed/refractory (R/R) HMs (Table 1) in both global and Asia-Pacific (APAC) clinical trials and real-world settings.[22] The first United States Food and Drug Administration (US FDA) approval of a CAR-T product was granted in 2017. Since then, multiple products have been approved for a range of HMs (Table 1).

Figure 1: Historical development milestones of CAR-T therapy



CAR-T, chimeric antigen receptor T cell;
FDA, Food and Drug Administration;
scFvR, single-chain variable fragment receptor.

Table 1: FDA-approved CAR-T therapies

PRODUCT NAME	GENERIC NAME	YEAR FIRST APPROVED	TARGET ANTIGEN BINDING DOMAIN	DISEASE(S)	STUDY	STUDY, YEAR OF PUBLICATION	OVERALL RESPONSE, COMPLETE RESPONSE	SURVIVAL OUTCOMES	ORIGINATING COMPANY*
Kymriah	Tisagenlecleucel-t	2017	CD19	ALL	ELIANA	Maude et al 2018[15]; Laetsch et al 2023[23]	OR: 81% CR: 60%	mEFS: 24 mos	Novartis
				DLBCL	JULIET	Schuster et al 2021[24]	OR: 53% CR: 39%	mPFS: 2.9 mos mEFS: 2.8 mos	
				FL	ELARA	Fowler et al 2021[25]; Dreyling et al 2022[26]	OR: 86% CR: 68%	PFS: 57.4% at 24 mos	
Yescarta	axicabtagene ciloleucel	2017	CD19	LBCL	ZUMA-1	Neelapu et al 2017[27]; Jacobson et al 2021[19];	OR: 82% CR: 54%;	mEFS: 5.7 months, with 24-month EFS of 38%;	Kite Pharma (Gilead)
					ZUMA-7	Locke et al 2022[28]; Westin et al 2023[29];	OR: 83% CR: 65%;	mPFS: 14.7 mos;	
					ALYCANTE	Houot et al 2023[30]	OR: 90% CR: 79%	mPFS: 11.8 mos	
				FL	ZUMA-5	Jacobson et al 2022[31]	OR: 92% CR: 74%	PFS: 64.8% at 18 mos	
Tecartus	brexucabtagene autoleucel	2020	CD19	MCL	ZUMA-2	Wang et al 2022[32]	OR:91% CR: 68%	mPFS: 25.8 mos	Kite Pharma (Gilead)
				B-ALL	ZUMA-3	Shah et al 2021[33]	OR: 71% CR: 56%	mRFS: 11.6 mos	
Breyanzi	lisocabtagene maraleucel	2021	CD19	LBCL	TRANSCEND NHL 001	Abramson et al 2024[34];	OR: 73% CR: 53%	mPFS: 6.8 mos	Juno (Bristol Myers Squibb)
					TRANSFORM	Abramson et al 2023[35];	OR: 87% CR: 74%	PFS: 58.2% at 18 mos	
					PILOT	Sehgal et al 2025[36]	OR: 80% CR: 54%	PFS: 43% at 18 mos	
				FL	TRANSCEND FL	Morschhauser et al 2024[37]	OR: 97% CR: 94%	PFS: 83% at 12 mos	
				CLL	TRANSCEND CLL 004	Siddiqi et al 2023[38]	OR: 47% CR: 18%	mPFS: 17.9 mos	
				MCL	TRANSCEND MCL	Wang et al 2024[39]	OR: 83% CR: 72%	mPFS: 15.3 mos	
Abecma	idecabtagene	2021	BCMA	MM	KarMMa	Munshi et al 2021[40]	OR: 73% CR: 33%	mPFS: 8.8 mos	Bluebird Bio (Bristol Myers Squibb)
Carvykti	ciltacabtagene autoleucel	2022	BCMA	MM	CARTITUDE-1	Martin et al 2022[41]	OR: 97.9% CR: 82.5%	PFS: 54.9% at 27 mos	Janssen Biotech and Legend Biotech
Aucatzyl	obecabtagene autoleucel	2024	CD19	B-ALL	FELIX	Roddie et al 2024[42]	OR: 77% CR: 55%	median EFS: 11.9 mos	Autolus Therapeutics

ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; CD19 , cluster of differentiation 19; CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; mEFS, median event-free survival; mPFS, median progression-free survival; mRFS, median relapse-free survival; mos, months; OR, objective response rate; PFS, progression-free survival.
*Originating company: company that led to submission of FDA application.

CAR-T landscape in APAC countries

The CAR-T landscape in APAC is evolving rapidly, driven by an expanding portfolio of therapies and diverse country-level approaches to market access and funding. Approved CAR-T therapies in the region include Kymriah, Yescarta, Breyanzi, Abecma, and Carvykti[43, 44] (Table 2). To better understand regional differences, APAC countries are categorized into three archetypes based on infrastructure, regulatory maturity, and funding mechanisms (Table 2; see IQVIA WP Private Market Opportunity for CAR-T cell Therapy in Asia Pacific for further details).[43]

Limitations of conventional ex vivo CAR-T approaches

Ex vivo CAR-T therapies, although rapidly evolving, face multifaceted challenges that hinder their widespread adoption. High manufacturing costs significantly contribute to the high price of pharmaceutical CAR-T products, which serves as a major barrier to equitable access.[44] While certain countries facilitate access to CAR-T treatment through patient access and reimbursement programs, others lacking such provisions require individuals to bear the full cost out of pocket — a financial burden that can significantly limit access to the treatment.[43]

Table 2: APAC countries: The three archetypes

ARCHETYPE	ACCESS MODEL	COUNTRIES	FUNDING/REIMBURSEMENT STATUS	APPROVED/ REIMBURSED THERAPIES
Innovative	Publicly funded; administered via designated hospitals	Australia	Varies by product, state, and treatment setting	Kymriah
				Yescarta
			TGA-approved, MSAC-recommended, but no pricing agreement yet	Carvykti
		Japan	Partial	Kymriah
				Yescarta
				Breyanzi
				Abecma
				Carvykti
		Korea	Partial	Kymriah
				Yescarta
Advancing	Partial insurance coverage; expanding via public–private partnerships	China	Limited	Yescarta
				Carteyva
		Singapore	Limited	Kymriah
				Yescarta
		Taiwan	Partial	Kymriah
Initializing	Limited access via clinical trials, compassionate use, or medical tourism	India, Malaysia, Thailand, Vietnam, Philippines, Indonesia	None	No formal approvals; access is experimental or indirect

MSAC, Medical Services Advisory Committee;
TGA, Therapeutic Goods Administration.

Autologous CAR-T production is labor-intensive and prone to variability due to patient-specific factors.[45] Manufacturing failures occur relatively infrequently, but can increase the complexity of delivery of cellular immunotherapies.[8, 46] Manufacturing time presents a significant bottleneck. Conventional ex vivo autologous CAR-T production can take several weeks, with cell expansion alone requiring 1–2 weeks, and sterility testing adding further time, potentially delaying treatment for patients with aggressive disease.[45] The extended waiting period can lead to the requirement for bridging treatment and may cause clinical deterioration or disease progression prior to infusion.[45]

The patient journey — from referral and apheresis to cell reprogramming, infusion, and long-term monitoring — is inherently intricate, requiring complex logistical coordination that further amplifies challenges.[43] This added complexity is primarily attributable to the substantial infrastructural requirements and the need for highly trained personnel, both of which are frequently limited in emerging health care markets.[43]

Off-the-shelf approaches, including allogeneic CAR-T therapy derived from healthy donors or induced pluripotent stem cells (iPSCs), and direct in vivo engineering, offer promising alternatives to mitigate manufacturing and economic challenges of single-patient autologous CAR-T therapies.[45]

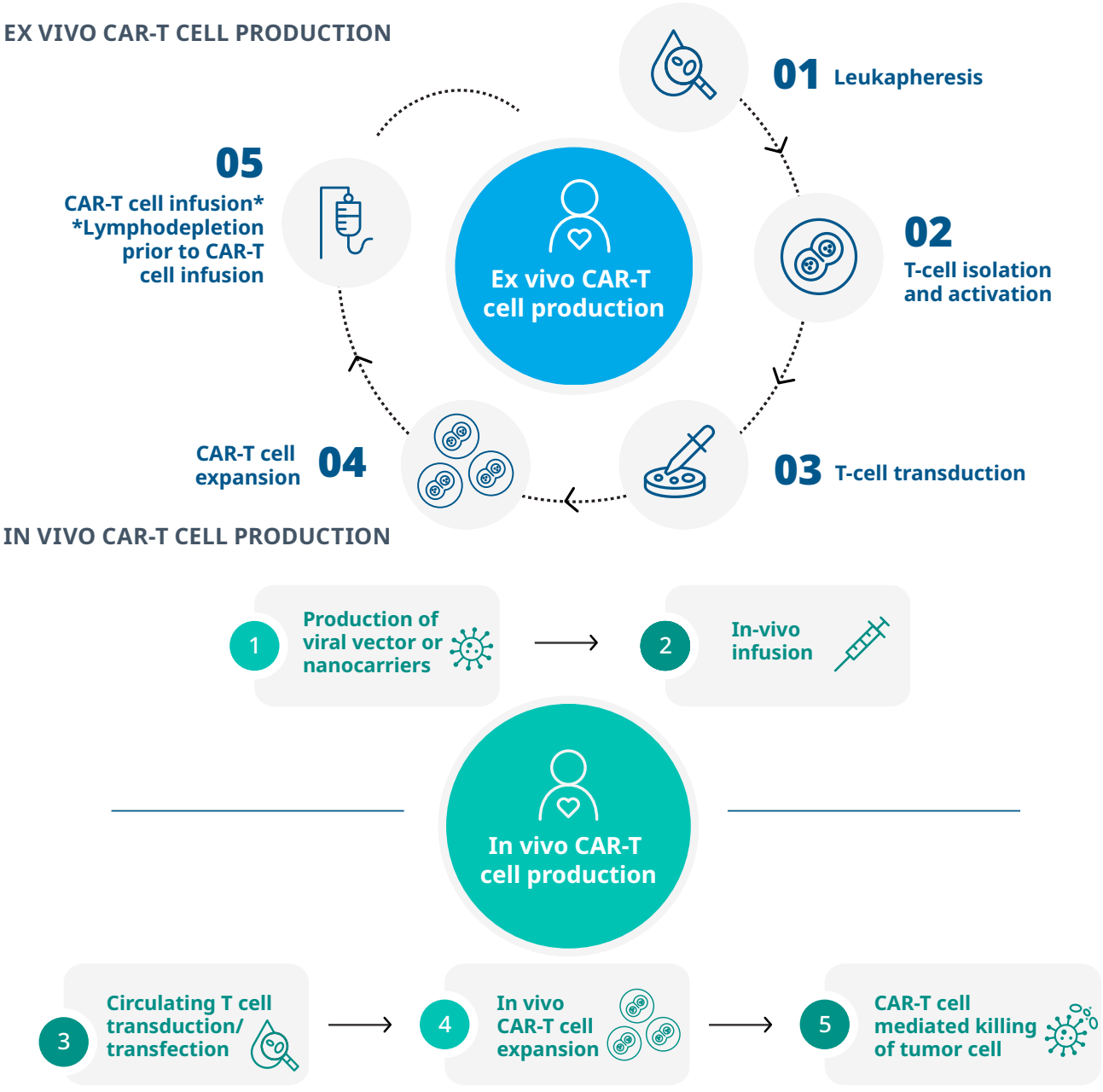
Allogeneic CAR-T therapy can reduce costs and manufacturing time through centralized production and economies of scale, although the response and survival rates and risks associated with adverse effects such as graft-versus-host disease are yet to be fully characterized.[45] In vivo engineering eliminates the need for individualized cell processing and may offer a pathway to faster, more scalable therapeutic production.[45]

Introduction to in vivo CAR-T therapy

Conventional CAR-T cells are generated ex vivo for each patient, requiring leukapheresis, T-cell activation, genetic modification, and culture in a suitably equipped and regulated facility. Prior to infusion, lymphodepleting chemotherapy using agents such as fludarabine and cyclophosphamide is needed to enhance engraftment of the infused CAR-Ts.

The entire process is labor-intensive, costly, and time-consuming.[13] In contrast, in vivo CAR-T generation (Figure 2) bypasses these steps by delivering CAR constructs directly into the patient's body using viral vectors or nanocarriers, allowing T cells to be reprogrammed in situ.[47] This approach eliminates the need for cell harvesting and manipulation outside the body, offering a streamlined alternative to conventional manufacturing.[13]

Figure 2: Ex vivo vs. in vivo CAR-T therapies



Adapted from Pinto et al. Journal of Translational Medicine
CAR-T, chimeric antigen receptor T cell.

The transition from ex vivo to in vivo CAR-T therapy represents a paradigm shift with the potential to improve accessibility, reduce costs, and enhance scalability.[47] As discussed earlier, ex vivo CAR-T therapies are associated with high costs, requiring weeks of processing, making them inaccessible to many regions, especially in resource-limited settings.[45] In contrast, in vivo approaches eliminate the need for centralized cell manufacturing and personalized cell handling, thus markedly reducing manufacturing time and enabling off-the-shelf solutions that can be administered rapidly and potentially more broadly.[13] This modified form of CAR-T therapy could significantly reduce logistical burdens, including the transportation and storage of patient-derived cells, thus improving cost-effectiveness. Unlike ex vivo therapies, in vivo CAR-T therapies can be administered more efficiently, offering timely intervention for patients with aggressive malignancies who require immediate care.[47] Moreover, in vivo CAR-T therapies are not typically expected to require the use of — or be compatible with — lymphodepleting chemotherapy,[47] easing the pre-treatment burden of care on patients. Preclinical studies have demonstrated successful in vivo CAR-T generation with potential for reduced systemic toxicity, such as cytokine release syndrome and neurotoxicity,[48, 49] and simplified protocols,[50] suggesting a potentially safer and more scalable option for a broader patient group, with shorter inpatient stays.[13] The outcomes of current clinical trials of in vivo CAR-Ts are awaited. Table 3 demonstrates differences between in vivo and ex vivo CAR-T therapies.

Table 3: Comparison of ex vivo and in vivo CAR-T therapies

FEATURES	EX VIVO CAR-T THERAPY	IN VIVO CAR-T THERAPY
Manufacturing process/location	Outside the body (cells are extracted, modified, and reinfused)	Inside the body (cells are genetically modified directly within the patient)
Time to treatment	Several weeks (due to cell processing and logistics)	Potentially same-day; off-the-shelf
Cost	High	Potentially lower
Clinical care infrastructure	Requires complex infrastructures, logistics, and specialized personnel	Simplified logistics; potentially more outpatient administration
Personalization	Personalized treatment (autologous cells)	Less personalized; standardized vectors for broad use
Immune conditioning	Requires lymphodepletion chemotherapy	May avoid lymphodepletion chemotherapy, thereby reducing toxicity
Safety profile	Risk of CRS, ICANS, and other toxicities; well-characterized kinetics for approved products	Kinetics of toxicities have not been determined; risks of off-target effects
Control over modification	Limited variability of cell dose	More limited control of genetic modification
Clinical maturity	FDA approved for hematologic malignancies	Mostly in preclinical or early clinical trial stages. Very limited data to demonstrate efficacy in humans
Scalability	Challenging due to individualized processing	More scalable; potentially suitable for broader patient populations
Regulatory pathways	Commercial products are handled/disposed of in the same manner as blood products/biologicals, under section 32 of TGA	Are GMOs and handled as such in all clinical environments; handled as prescription medicines under section 23 of TGA

CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; FDA, Food and Drug Administration; GMO, genetically modified organism; TGA, Therapeutic Goods Administration.

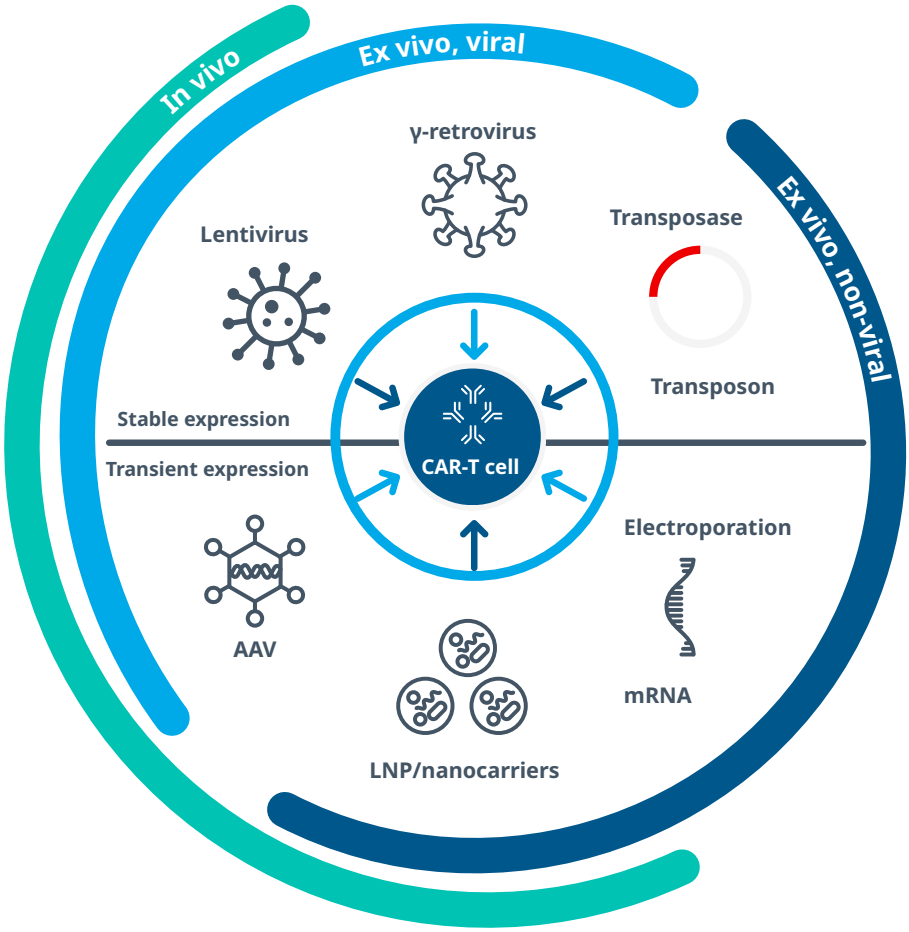
In vivo CAR-T paradigm

Numerous strategies for in vivo engineering of T cells are under development. Among these, the two most advanced approaches that have reached preclinical and clinical trials are lentiviral vectors (LVs) and nucleic acid encapsulated lipid nanoparticles (LNPs).[51,52] These platforms enable in situ reprogramming of circulating T cells by delivering CAR constructs directly into the body, bypassing the need for ex vivo T-cell manipulation[52] (Figure 3). Among these platforms, LNPs mainly utilize conventional transient, non-integrating mRNA technology, wherein ionizable lipids encapsulate mRNA, which facilitates endosomal escape,[51, 52] thereby enabling transient CAR expression. The transient nature of expression may be beneficial for limiting toxicity, but may come at the cost of reduced duration of effector function from each infusion.[52] The composition of the LNP can be modified to alter the efficiency of T-cell engineering; however, the low specificity and risks of non-T-cell transfection remain. Nevertheless, this approach supports efficient, scalable production.[52]

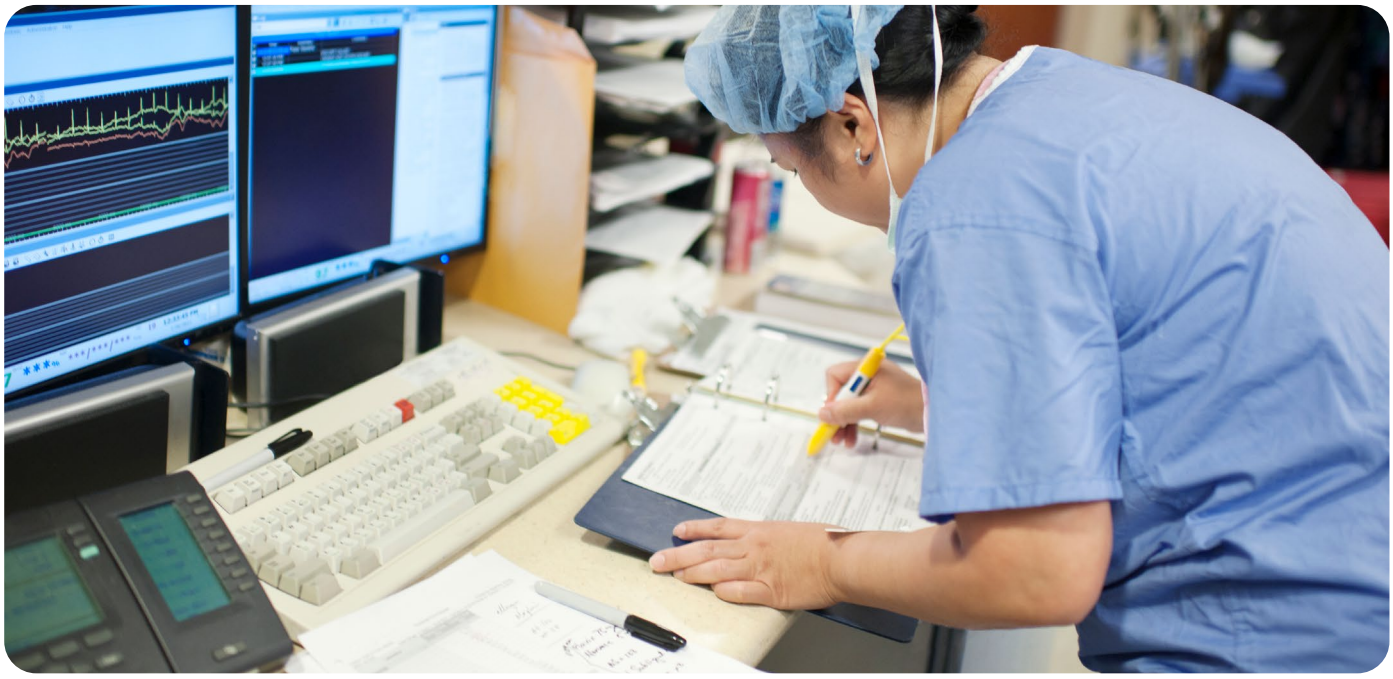
Viral vectors (especially LV) enable durable genomic integration, ensuring prolonged CAR expression.[52,53] Notably, LV vectors pseudotyped with CD3-specific ligands have demonstrated high selectivity and efficiency in transducing $CD3^+$ T cells in vivo.[47] However, they may also introduce potential risks, such as insertional mutagenesis and off-target effects, with potential integration into bystander T cells, raising safety concerns.[52, 53]

Emerging engineering strategies aim to enhance in vivo CAR-T therapy efficacy by improving their trafficking to tumor sites and modulating the tumor microenvironment to support sustained immune activity.[13] Technologies such as VivoVec™ and CD5-targeted LNPs exemplify innovations in targeted delivery systems, enabling robust in vivo T-cell activation and efficient CAR expression.[47, 54,55] The VivoVec™ system employs lentiviral particles engineered to display a stimulatory multidomain fusion protein on their surface and deliver a CD19-specific CAR transgene and a rapamycin-activated cytokine receptor for selective generation of functional CAR-T cells without lymphodepletion.[47] The RACR system improves CAR-T persistence, augments IL-15 delivery, extends T-cell survival, and increases CAR expression in mice and macaques.[56] Use of tissue-specific promoters in the integrated construct — among other strategies — is being actively explored to enhance cell-type specificity. These advancements collectively represent a significant leap forward in efforts to design safer, more effective in vivo CAR-T therapies.

Figure 3: An illustration of ex vivo and in vivo delivery systems



Adapted from Rossie, Breman. Frontiers in Immunology et al
CAR-T, chimeric antigen receptor T cell; mRNA, messenger ribonucleic acid.



Clinical advances and trials

Recent advances in in vivo CAR-T therapies (Table 4) are redefining the global clinical trial landscape for HMs. Several pharmaceutical companies are leading this paradigm shift using LV vectors targeting B-cell malignancies such as NHL and MM.[56] In 2024, Interius BioTherapeutics initiated a multicenter Phase I trial for INT2104 for B-cell cancers.[56] INT2104 is a CD7-targeted lentiviral vector designed to deliver a CAR20 transgene, encoding an anti-CD20 CAR construct, for the treatment of B-cell malignancies. Recently, Interius has received regulatory approval for expanding its Phase I studies of INT2104 to Europe.[57] Concurrently, Umoja Biopharma, in collaboration with AbbVie, has launched Phase I trials in the USA of UB-VV111 for B-cell cancers.[56] Further expanding its pipeline, Umoja and IASO Biotherapeutics initiated trials for UB-VV400/410, a VivoVec-based CD22 CAR-T therapy with RACR, in 2024;[56] and UB-VV300/310, a CD20 CAR-T therapy expected to enter trials in 2026.[56] Novartis and Vyriad announced a collaboration in late 2024 to develop active-targeting LV vectors for oncology indications.[56]

With respect to LNP platforms, Orna Therapeutics is set to initiate trials for ORN-145 and ORN-328 (panCAR™ technology), targeting CD19 in B-cell cancers and BCMA in MM, respectively.[56] ORN-145 and ORN-328 are circular RNAs delivered to T cells via LNPs. RNA remains episomal (in the cytoplasm) and does not integrate into the host genome.[56] Other notable LNP-based developments include AbbVie/Capstan's CPTX2309 (target CD19), a CD8 antibody-directed therapy using non-integrating mRNA delivered via LNPs, with Phase I readout expected in 2026. Tessera is also developing LNP-delivered RNA targeting CD19/CD20 for oncology indications[56] (Table 4).

In the APAC region, clinical development of in vivo CAR-T therapies for HMs is gaining momentum, driven by regional biotech firms and multinational collaborations. AbbVie and Capstan Therapeutics initiated a Phase 1 trial of CPTX-2309, an mRNA-LNP, in healthy volunteers in Australia in 2024.[58] This study (NCT06917742) aims to assess the safety, tolerability, and pharmacodynamics of this novel in vivo CAR-T approach for autoimmune diseases, with future oncology applications anticipated.[59]

Interius BioTherapeutics also launched a Phase 1 trial of INT2104 (INVISE trial), an LV-vector-based CD20 CAR therapy, in Australia for patients with R/R B-cell NHL (NCT06539338).[60] Preclinical data demonstrated robust B-cell depletion and favorable safety profiles, supporting clinical translation.[60] Kelonia Therapeutics is conducting a Phase 1 trial of KLN-1010 (inMMyCAR trial), a CD3 antibody-directed lentiviral vector targeting BCMA in MM, also in Australia (NCT07075185), evaluating safety, tolerability, pharmacology, and preliminary efficacy following a single dose.[61] In addition, Umoja Biopharma and AbbVie have launched a Phase I trial in Australia of UB-VV111, targeting CD19 in LBCL and CLL (NCT06528301)[56] (Table 4).

In China, AstraZeneca and EsoBiotec initiated a Phase 1 trial of ESO-T01 in 2024, a nanobody-targeted immune-shielded LV vector encoding a humanized BCMA single-domain-antibody CAR for R/R MM, in Wuhan, China (NCT06691685) (Table 4). Preliminary clinical data published in The Lancet reported manageable toxicity and early signs of CAR expression and BCMA engagement.[62]

Collectively, these APAC-based trials underscore the region's growing role in pioneering in vivo CAR-T platforms. While efficacy data remain preliminary, early safety signals are encouraging.[60, 62] The inclusion of both healthy volunteers and R/R patient cohorts provides a robust foundation for broader therapeutic applications.

Table 4: Selected list of companies involved in in vivo CAR-T development

COMPANY	ASSET	MECHANISM TO TARGET SPECIFIC CELLS FOR IN VIVO MODIFICATION	STAGE	TARGET ANTIGEN/ DISEASE	TRIAL SITES	PLATFORM	CLINICAL TRIALS. GOV NUMBER	NOTES
Interius Biotherapeutics / Gilead	INT2104	Anti-CD7 scFv	Phase I	CAR-T cells targeting CD20 on malignant B cells	Europe/ Australia	Integrating Lentiviral vector	NCT06539338	Gilead to acquire Interius for $350 m. First Phase I data expected late 2025/ early 2026
Umoja / IASO Biotherapeutics	UB-VV400	CD3 scFv, CD80 and CD58)	Phase I	CD22 in NHL/ Autoimmune	China	Integrating Lentiviral vector	NCT06743503	$100 m series C completed in Jan 2025
Umoja Biotherapeutics / AbbVie	UB-VV111	CD3 scFv, CD80 and CD58	Phase I	CD19 in Large B-cell lymphoma and chronic lymphocytic leukemia	USA/ Australia	Integrating Lentiviral vector	NCT06528301	Partnership worth up to $1.4 bn announced Jan 2024
Umoja Biopharma	UB-VV300/310	CD3 scFv, CD80 and CD58	Planned	CD20 in NHL	USA	Integrating Lentiviral vector	N/A	Planned in 2026
AbbVie / Capstan Therapeutics	CPTX2309	CD8 antibody	Phase I	CD19 in autoimmune diseases	Australia	Non-integrating mRNA delivered via LNP	NCT06917742	AbbVie to acquire Capstan for up to $2.1 bn. Phase I readout expected H1 2026
AstraZeneca / EsoBiotec	ESO-T01	Single VHH-directed BCMA-targeted CAR-T	Phase I	BCMA in MM	China	Non-replicating self-inactivating lentiviral vector	NCT06791681 and NCT06691685	Acquired in March via $425 m upfront and up to $575m in milestones
Legend	Undisclosed	Undisclosed	Phase I	CD19/CD20 in NHL	-	Viral vector	N/A	-
Tessera	Undisclosed	Undisclosed	Preclinical	CD19/CD20 in oncology	-	LNP delivery of an RNA gene writer	N/A	Preclinical results presented at ASGCT meeting, May 2025
Novartis / Vyriad	Undisclosed	Undisclosed	Preclinical	Undisclosed	-	Active-targeting lentiviral vector	N/A	Partnership announced Nov 2024
Kelonia Therapeutics / Astellas	KLN-1010	CD3 antibody	Phase I	BCMA in MM	Australia	Lentiviral vector	NCT07075185	Astellas partnership unveiled March 2024
Everest Medicines	Undisclosed	Undisclosed	Preclinical	Cancer/ Autoimmune	-	mRNA/LNP	N/A	-
Orna Therapeutics	ORN-145	LNP containing immunotropic lipids	Planned	CD19 in B-cell cancers	USA	Circular RNA /LNP (non-integrating)	N/A	Planned
Orna Therapeutics	ORN-328	LNP containing immunotropic lipids	N/A	BCMA in MM	USA	Circular RNA /LNP (non-integrating)	N/A	Planned in 2026

ASGCT, American Society of Gene and Cell Therapy; BCMA, B-cell maturation antigen; bn, Billion; CAR-T, chimeric antigen receptor T cell; CD3, cluster of differentiation 3; CD7, cluster of differentiation 7; CD8, cluster of differentiation 8; CD19, cluster of differentiation 19; CD20, cluster of differentiation 20; CD22, cluster of differentiation 22; CD58, cluster of differentiation 58; CD80, cluster of differentiation 80; LNP, lipid nanoparticle; MM, multiple myeloma; mRNA, messenger ribonucleic acid; N/A, not applicable; NHL, non-Hodgkin lymphoma; scFv, single-chain Variable fragment; RNA, ribonucleic acid; USA, United States of America; VHH, variable domain of the heavy chain.

Challenges and considerations

Safety concerns and delivery

In vivo CAR-T therapy offers a scalable alternative to ex vivo approaches but faces safety and delivery challenges. A major challenge is the efficient and selective delivery of CAR transgenes to T cells within the body.[63] Viral vectors, such as lentiviruses, remain the most efficient for transgene integration; however, their use raises concerns of insertional mutagenesis and oncogenic transformation due to random genomic integration.[52, 53, 64] Although large-cohort follow-up studies show no excess secondary malignancy risk with approved viral systems used in ex vivo CAR-T platforms, stringent testing for purity, stability, and off-target effects of in vivo delivered LVs is mandated.[47] Additionally, viral vectors can trigger immune responses and inflammatory cascades, complicating safety profiles.[47] Engineering strategies — such as incorporating T-cell-specific ligands or surface modifications — aim to improve targeting and reduce systemic exposure.[47] Yet these modifications require rigorous validation to avoid unintended immunogenicity.

Conversely, non-viral nanocarriers, particularly LNPs, may offer a safer alternative by eliminating risks of genomic integration and enabling transient CAR expression.[65] Their advantages include lower immunogenicity and scalable manufacturing; however, LNPs face challenges of endosomal entrapment and degradation, limiting transfection efficiency.[65] Moreover, cationic lipid components can induce cytotoxicity and genotoxicity if not optimized, and accumulation in healthy tissues raises concerns for systemic toxicity.[65] Advanced designs — such as pH-responsive carriers, antibody-conjugated LNPs, and pore-forming proteins/peptides — are being explored to enhance cytosolic delivery and minimize off-target effects.[47]

The kinetics of CAR-T generation and maintenance of CAR-T cell functionality and persistence are other key challenges,[47] prompting efforts to optimize CAR design through co-stimulatory domains and enhance memory T-cell formation to mitigate exhaustion.[66] Strategies to prevent T-cell exhaustion, such as checkpoint inhibitors or cytokine support, are also being investigated.[67] Lastly, CRS and ICANS pose significant risks, although standardized management protocols are currently in place to mitigate their impact.[56] A recent Phase I study published in *The Lancet*, involving four adult patients with R/R MM treated with the lowest dose of ESO-T01, demonstrated that all patients experienced CRS shortly after infusion, with grade 3 CRS in three and grade 1 in one patient.[62] ICANS was observed in only one patient, who presented with grade 1 ICANS on Day 8. In this study, both CRS and ICANS were effectively managed with glucocorticoids.[62]

In summary, although in vivo CAR-T therapy demonstrates significant potential as a scalable, off-the-shelf strategy for cancer treatment, addressing safety concerns and optimizing delivery methods remain essential for its effective clinical implementation. Notably, multiple trial readouts anticipated by 2026 are expected to provide further validation of these platforms and may accelerate their path toward broader clinical adoption.[56]

Regulatory considerations

In vivo CAR-T therapies are regulated as prescription medicines in Australia.[68, 69] The Australian Therapeutic Goods Administration (TGA) classifies in vivo gene therapies, including those delivered via viral vectors, under "prescription medicine" governed by Section 23 of the Therapeutic Goods Act 1989.[70] In addition to TGA approval, any gene therapies, including viral vector in vivo CAR-T therapies, are considered Genetically Modified Organisms (GMOs) and must secure clearance from the Office of the Gene Technology Regulator (OGTR) in Australia, which assesses environmental and human health risks.[71] OGTR approval is mandatory prior to or concurrent with TGA registration.[71]

Like Australia, New Zealand governs cell and gene therapies under the Medicines Act 1981, requiring Health Research Council review and MEDSAFE approval prior to trial initiation.[71] Clinical trials involving gene

therapies are specifically reviewed by the Gene Technology Advisory Committee, which assesses safety and ethical considerations of these interventions.[71] GMOs require Environmental Protection Authority approval under the Hazardous Substances and New Organisms Act (HSNO) 1996 for importation, development, or release.[71]

Australia is a strategic APAC trial hub, providing streamlined regulations and access to diverse patient populations. Countries such as New Zealand, Japan, South Korea, Taiwan, and Singapore further add to the patient pool, enhancing feasibility for later-phase studies.[69] Partnering with an established contract research organization (CRO) is pivotal for seamless trial execution. CROs can offer end-to-end support, including supporting sponsors in navigating regulatory pathways, site selection, investigator engagement, site training, patient recruitment and retention, data management, pharmacovigilance, and multiregional trial coordination. Their expertise in navigating submissions to MEDSAFE, the Pharmaceuticals and Medical Devices Agency, the Ministry of Food and Drug Safety, the Taiwan Food and Drug Administration, and the Health Sciences Authority can enable sponsors to expand trials across APAC efficiently.[69] As a trusted CRO partner, IQVIA combines unmatched regulatory expertise and deep local insights with global capabilities to simplify regulatory navigation, accelerate clinical development, and unlock commercialization opportunities for advanced therapies such as CAR-T in APAC.

To sum up, in vivo CAR-T therapies encounter intricate regulatory requirements throughout the APAC region. However, Australia distinguishes itself by providing a streamlined, internationally harmonized framework, bolstered by robust clinical infrastructure, experienced CROs, and a diverse patient base. Collaborating strategically with CROs helps companies efficiently manage regulatory procedures, choose appropriate trial sites, and conduct trials across multiple countries, which ultimately supports wider commercialization efforts.

Future directions

After establishment of efficacy and safety of in vivo CAR-T therapies in suitably designed clinical trials, the next frontier lies in strategic integration with other immunomodulatory treatment approaches — such as checkpoint inhibitors and cytokine modulators — to boost anti-tumor responses and address immune resistance. Beyond HMs, there is growing interest in extending these therapies to solid tumors and autoimmune diseases, where localized, durable immune modulation could offer significant outcomes. A key future innovation will be the development of off-the-shelf, programmable CAR-T therapies that may be delivered in clinical settings without extensive infrastructure, enabling broader accessibility and scalability. Importantly, with appropriate pre-medication protocols, these therapies may become more accessible and cost-effective, with the potential to reduce the duration of hospitalization or be administered in outpatient settings. Advances in CAR design, delivery vectors (eg, LNPs, viral platforms), and precision patient selection will be critical to optimize therapeutic performance and safety across diverse clinical settings.

Conclusion

In vivo CAR-T therapies represent a paradigm shift in immuno-oncology, offering a promising approach toward scalable, accessible, and cost-effective treatment for HMs. In vivo CAR-T platforms eliminate the need for complex cell harvesting and manufacturing, potentially broadening patient access and reducing logistical burdens. As these therapies advance, their transformative potential in HMs becomes increasingly evident, with early data suggesting robust efficacy and safety.

Realizing the full clinical and commercial potential of in vivo CAR-T therapies requires sustained investment in research, collaboration, and adaptive regulatory frameworks. IQVIA believes that strategic partnerships — particularly among sponsors, CROs, regulatory bodies, and clinical investigators — are critical in accelerating development timelines and availability of in vivo CAR-T therapies to patients while ensuring patient safety and regulatory compliance.

What next?

- Effective adoption and implementation of novel delivery systems — LNPs, viral vectors, and other innovative constructs.
- Streamline regulatory pathways, referral processes, and approval processes.
- Expand indications for complex HMs, solid tumors, and autoimmune diseases.
- Strengthen site capabilities and infrastructure to enable broader patient accessibility and support decentralized modalities.

With its global reach and integrated capabilities in clinical development, regulatory strategy, and real-world evidence, IQVIA is uniquely positioned to accelerate the advancement of in vivo CAR-T therapies. Through precise protocol development, strategic site selection, decentralized trial facilitation, and proactive pharmacovigilance, IQVIA offers data-driven solutions and specialized therapeutic knowledge to support stakeholders in successfully navigating a rapidly evolving environment.

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