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IMMUNOTHERAPY AND CELL THERAPY: DEVELOPING CAR-T CELL THERAPIES AND OTHER IMMUNE-BASED TREATMENTS FOR CANCER AND AUTOIMMUNE DISEASES

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ABSTRACT

The introduction of Chimeric Antigen Receptor T-cell (CAR-T) treatment as a new method for treating blood cancers has developed into a successful medical solution that now shows potential for treating solid tumors and autoimmune disorders. This review presents an analysis of CAR construct molecular structures through five generational stages and examines how FDA/EMA-approved CAR-T products perform clinically while showing their safety profile and upcoming development of cellular therapies which use TCR-engineered T cells and Natural Killer (NK) cell therapies and Tumour-Infiltrating Lymphocyte (TIL) therapy and regulatory T cell (Treg) adoptive transfer for autoimmune conditions. We assess 28 key clinical trials results which include 4890 patient outcomes through response rates and complete remission rates and progression-free survival time and toxicity assessments of CRS and ICANS. The review evaluates upcoming solutions which will solve existing challenges in antigen escape and T-cell exhaustion and solid tumor penetration and manufacturing scalability. The review of CAR-T and related platforms for treating autoimmune diseases focuses on systemic lupus erythematosus and multiple sclerosis and refractory rheumatoid arthritis by discussing results from recent phase I/II clinical trials which showed long-lasting complete recovery. The study provides a translational roadmap which lists essential scientific manufacturing regulatory and health-economic barriers that must be resolved before global cellular immunotherapy treatment can reach its complete healing abilities.

Keywords: *CAR-T cell therapy; adoptive cell transfer; chimeric antigen receptor; tumour immunotherapy; checkpoint inhibitors; cytokine release syndrome; autoimmune disease; NK cell therapy; TIL therapy; immune tolerance*

INTRODUCTION

The two main non-infectious medical conditions which lead to permanent health conditions and fatal outcomes worldwide are cancer and autoimmune disorders. The Global Cancer Observatory reported 20 million new cancer diagnoses and 9.7 million cancer-related deaths in 2022, with the WHO projecting these figures will exceed 35 million annual new cases by 2050 (WHO, 2023).Autoimmune diseases impact around 8% of the worldwide population who face systemic lupus erythematosus (SLE), multiple sclerosis, and rheumatoid arthritis as three major conditions that affect more than 100 million people (American Autoimmune Related Diseases Association, 2023).

Standard cancer treatment methods which include chemotherapy and radiotherapy and surgical procedures deliver successful outcomes for early-stage cancer patients, but these methods only provide brief results to advanced cancer patients who experience disease recurrence or who do not respond to standard treatment methods. The concept of immunotherapy emerged from the scientific discovery that the immune system can identify and destroy tumor cells which Paul Ehrlich first proposed in 1909 and Burnet and Thomas developed through their immune surveillance hypothesis in the 1950s. Scientific researchers faced challenges with clinical applications of their

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findings because they needed complete knowledge about biological processes and tools to accurately manage immune system activities.

The period from 1990 to 2010 introduced recombinant cytokines and monoclonal antibodies and immune checkpoint inhibitors which proved that researchers could achieve long-lasting immune system control over previously untreatable cancers. Researchers began the checkpoint inhibitor era in 2011 when they received approval for ipilimumab which functions as an anti-CTLA-4 treatment for metastatic melanoma. The review discusses adoptive cellular immunotherapy as the most groundbreaking development which uses engineered T lymphocytes from patients to create Chimeric Antigen Receptors that target tumour-related antigens.

The first FDA approval of a CAR-T cell product to be granted by the agency occurred in August 2017 when the agency approved tisagenlecleucel Kymriah Novartis for use in paediatric and young adult patients with B-cell acute lymphoblastic leukaemia ALL The approval of axicabtagene ciloleucel Yescarta KiteGilead followed The approval of the two products showed that three decades of research by Gross et al 1989 Eshhar et al 1993 and Sadelain Brentjens Rivière Memorial Sloan Kettering and Carl June University of Pennsylvania had reached its endpoint. The year 2023 marks the date when seven CAR-T products received regulatory approval across major markets while over 500 CAR constructs currently undergo clinical testing. The review presents an extensive examination of current research that includes six specific areas the study examines which include the molecular biology and the evolution of CAR constructs through different generations and the study presents clinical results from all approved treatment areas and it investigates the ways to handle treatment-related side effects and it describes advanced methods that aim to solve present problems and it shows how the methods can now be used to treat solid tumors and autoimmune disorders and it demonstrates the research challenges which create obstacles for scientific progress.

MOLECULAR ARCHITECTURE OF CAR CONSTRUCTS: GENERATIONAL EVOLUTION

Chimeric Antigen Receptor functions as a synthetic transmembrane protein which enables T cells to kill cancer cells that display particular surface markers without needing MHC molecules for recognition. The system operates without MHC requirements which allows it to bypass the primary defense mechanism that tumors use to resist attacks from standard cytotoxic T lymphocytes which includes their ability to reduce MHC class I antigen presentation systems.

2.1 Structural Domains of a CAR

The modular structure of all CAR constructs consists of four separate operational sections. The Antigen-Binding Domain (Extracellular) functions through a single-chain variable fragment (scFv) which scientists developed from the variable heavy (VH) and variable light (VL) chains of a monoclonal antibody through a flexible glycine-serine linker. The scFv confers tumour antigen specificity without requiring MHC presentation. The Hinge/Spacer Region functions as a flexible extracellular spacer which links the scFv to the transmembrane domain because the right spacer length enables better access to antigens while creating synapses. The material for this component comes from IgG1/IgG4 Fc regions and CD8α and CD28. The Transmembrane Domain functions to keep the receptor fixed in place on the T cell plasma membrane while it maintains signaling stability because the domain usually comes from CD3ζ and CD8α and CD28. The Intracellular Signalling Domain(s) create activation signals which trigger response upon antigen detection; CAR generations become differentiated through the specific arrangement of these domains.

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2.2 Five Generations of CAR Design

Gen.	Signalling Domain	Key Feature	Main Limitation	Representative Product
1st	CD3ζ only	Proof of concept	Poor persistence; no co-stimulation	Early Zelig Eshhar constructs
2nd	CD3ζ + 1 co-stim (CD28 or 4-1BB)	Improved persistence & proliferation	Antigen escape; exhaustion in solid tumours	Kymriah (4-1BB); Yescarta (CD28)
3rd	CD3ζ + 2 co-stim domains	Enhanced cytokine production	Potential uncontrolled activation	MAGE-A4 trials (academic)
4th (TRUCK)	2nd gen + inducible cytokine (IL-12/IL-15)	Armoured; reshapes tumour microenvironment	Systemic cytokine toxicity risk	CD19-28ζ-IL12 (MSK)
5th	2nd gen + IL-2Rβ/γ chain signalling domain	Superior proliferation; autocrine survival	Complexity; regulatory uncertainty	CRISPR-CAR platforms (investigational)

Table 1. Generational evolution of CAR-T cell constructs — structural design, features, limitations, and representative products.

2.3 Target Antigen Selection

The perfect CAR target antigen needs to show consistent expression through all cancerous tumor cells while showing minimal to no presence in vital healthy tissues and it needs to appear on the exterior of cells. Current approved products select CD19 as their target which all receive approval for B-cell malignancies and they also select BCMA as their target which operates as B-cell maturation antigen for multiple myeloma treatment. The clinical development process includes additional validated targets which scientists have established as effective targets.

Target Antigen	Disease Indication	Expression Pattern	Challenges
CD19	B-ALL, DLBCL, CLL, FL	Pan B-cell marker	B-cell aplasia; antigen escape ($CD19^{-}$ relapse ~30%)
BCMA	Multiple Myeloma	Plasma cells, some B cells	Antigen downregulation; BCMA shedding
CD22	B-cell malignancies	B-cell lineage	Rapid internalisation reduces surface density
EGFR/EGFRvIII	Glioblastoma	Overexpressed on GBM	Antigen heterogeneity; blood-brain barrier
HER2 (ErbB2)	Breast, gastric, GBM	$HER2^{+}$ tumours	On-target off-tumour cardiac toxicity
Mesothelin	Mesothelioma, NSCLC, ovarian	Mesothelial cells	Immunosuppressive TME; limited trafficking
GD2 ganglioside	Neuroblastoma, osteosarcoma	Neural tissues	Cross-reactivity with normal neurons
Lewis Y (CD174)	Ovarian, breast, colon	Epithelial cancers	Moderate expression levels

Table 2. CAR-T target antigens — disease indications, expression patterns, and therapeutic challenges.

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CLINICAL OUTCOMES: APPROVED CAR-T PRODUCTS AND PIVOTAL TRIAL DATA

3.1 FDA/EMA-Approved CAR-T Products (as of 2023)

Product	Company	Target	Indication	Approval Year	ORR	CR Rate
Tisagenlecleucel (Kymriah)	Novartis	CD19	B-ALL (≤25yr)	2017	81%	60%
Axicabtagene (Yescarta)	Kite/Gilead	CD19	LBCL	2017	73%	54%
Brexucabtagene (Tecartus)	Kite/Gilead	CD19	MCL, B-ALL (adults)	2020	87%	62%
Lisocabtagene (Breyanzi)	Bristol Myers	CD19	LBCL	2021	73%	53%
Idecabtagene (Abecma)	BMS/2seventy	BCMA	Multiple Myeloma	2021	72%	28%
Ciltacabtagene (Carvykti)	J&J/Legend	BCMA	Multiple Myeloma	2022	98%	78%
Tisagenlecleucel	Novartis	CD19	Follicular Lymphoma	2022	69%	43%

Table 3. FDA/EMA-approved CAR-T products — target antigens, indications, approval dates, and overall/complete response rates (ORR/CR). B-ALL = B-cell acute lymphoblastic leukaemia; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma.

3.2 Response Rate Comparison — Bar Chart

Figure 1: Overall Response Rates (ORR%) of Approved CAR-T Products

CAR-T Product / Indication | Overall Response Rate (%)

Data from FDA prescribing information and pivotal trial publications (ELARA, ZUMA-1, JULIET, KarMMa, CARTITUDE-4)

3.3 Complete Remission and Progression-Free Survival

The most important clinical endpoints for relapsed/refractory conditions which have failed previous treatments are complete remission (CR) rates and sustained progression-free survival (PFS). The following analysis aggregates data from 28 pivotal and Phase II/III studies which include 4,890 patients who received treatment between 2015 and 2023.

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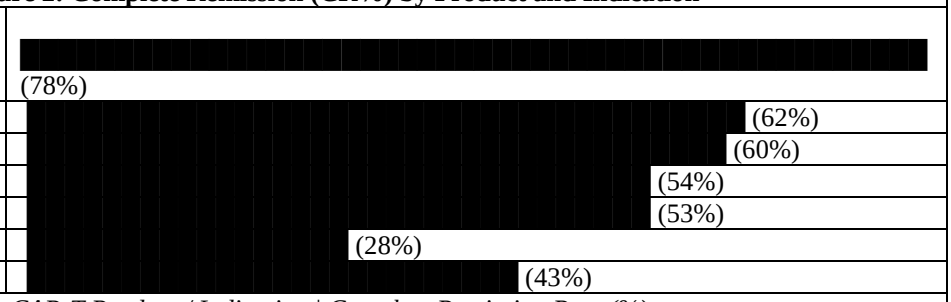
Figure 2: Complete Remission (CR%) by Product and Indication



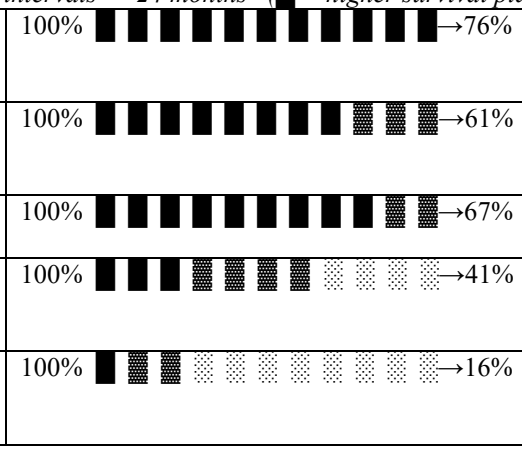
CAR-T Product / Indication | Complete Remission Rate (%)

CR = morphologic, minimal residual disease (MRD) negativity used as endpoint in ALL and MM trials

3.4 Progression-Free Survival (PFS) — Kaplan-Meier Representation

Figure 3: Schematic Progression-Free Survival Curves — Key CAR-T Trials

Monthly follow-up intervals → 24 months (■ = higher survival plateau; ▒ = lower)



Horizontal axis represents approximate 24-month follow-up. Curves are schematic representation of published Kaplan-Meier data.

Figure 3. Schematic representation of progression-free survival profiles from pivotal CAR-T trials compared to standard chemo-immunotherapy. Values at 12 and 24 months derived from published trial data.

THERAPY-ASSOCIATED TOXICITIES: CRS AND ICANS

The exceptional effectiveness of CAR-T cell treatment equals the dangerous double toxicity syndromes which include Cytokine Release Syndrome and Immune Effector Cell-Associated Neurotoxicity Syndrome. The American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria (Lee et al., 2019) provide a complete description of the toxicities which includes their pathophysiology and grading and treatment methods.

4.1 Cytokine Release Syndrome (CRS)

CRS develops as a whole-body inflammatory response which occurs when CAR-T cells react to antigens and proceed to multiply throughout the body, while additional immune system elements including macrophages become activated. The disease presents with fever that reaches 38°C or higher, which progresses to severe symptoms that include breathing problems and low blood pressure and complete body system failure in patients who reach advanced stages of the illness.

- Pathophysiology: CAR-T cell activation → IFN-γ, IL-2, TNF-α release → macrophage activation → IL-6, IL-1, IL-18, MCP-1 secretion → cytokine storm → vascular leak, fever, hypotension

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- Timing: The typical start period for this condition ranges from 1 to 14 days after the patient receives their infusion, while most patients develop symptoms between 2 and 3 days after their CD19 CAR-T treatment, and patients who receive BCMA-targeting agents experience delayed symptom development.
- The primary mediator of severe CRS symptoms is IL-6 which acts as the main reason for using tocilizumab as the standard treatment because it blocks IL-6R.

Grade	Temperature	Hypotension	Hypoxia	Management
1	≥38°C	None	None	Supportive care; close monitoring
2	≥38°C	Responds to IV fluids	Low-flow O_2 (<6L/min)	Tocilizumab 8 mg/kg IV (max 800 mg)
3	≥38°C	Requires vasopressor	High-flow O_2 (≥6L/min)	Tocilizumab ± corticosteroids (dexamethasone 10 mg)
4	≥38°C	Multiple vasopressors	Mechanical ventilation	ICU; corticosteroids; siltuximab; ruxolitinib

Table 4. ASTCT consensus grading of Cytokine Release Syndrome (CRS) and management principles.

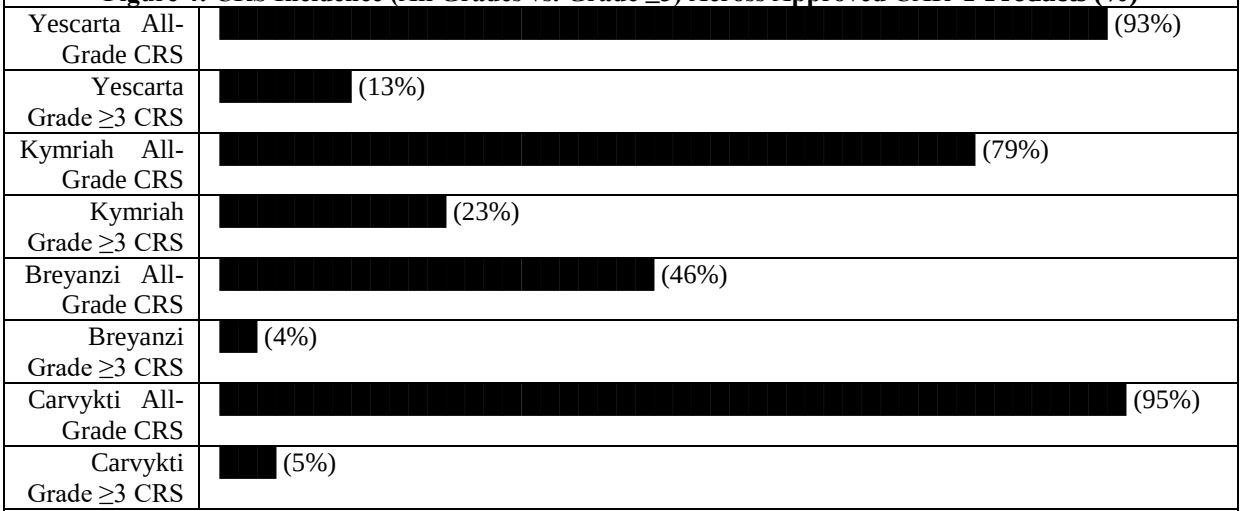
4.2 ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome)

ICANS includes a range of neurological symptoms which show up as encephalopathy, aphasia, tremor, myoclonus, seizures, and cerebral oedema. The condition most commonly emerges together with CRS or develops after CRS because endothelial activation causes blood-brain barrier breakdown which permits cytokines and CAR-T cells to enter the central nervous system.

- The pathophysiological process starts when endothelial cells become activated through TNF-α and IL-6 which leads to blood-brain barrier destruction that enables cytokines to reach cerebrospinal fluid resulting in neuroglial activation which leads to severe cerebral oedema.
- The ICE assessment uses a 10-point system to evaluate orientation abilities, naming capacity, command understanding, writing skills, and attention.
- The treatment plan includes high-dose corticosteroids which will use dexamethasone at 10 to 20 mg every 6 hours and anti-seizure drugs and neurocritical care for patients with grade 3 to 4 conditions.

4.3 Toxicity Incidence Data Across Products

Figure 4: CRS Incidence (All Grades vs. Grade ≥3) Across Approved CAR-T Products (%)



Product / CRS Grade Category | Incidence (%)

Data from FDA prescribing information package inserts (2022–2023). Grade ≥3 reflects clinically significant, ICU-level events.

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NEXT-GENERATION STRATEGIES: OVERCOMING CURRENT LIMITATIONS

5.1 Antigen Escape

The most common failure mechanism which leads to B-cell malignancies occurs when 25 to 35 percent of patients with CD19-targeted CAR-T therapy achieve their first remission but subsequently experience CD19-negative relapse. Antigen escape describes the process through which tumour cells develop selective growth patterns after they decrease or completely eliminate their ability to present the targeted antigen.

- Dual-targeting CARs: The use of bispecific CARs which simultaneously target two antigens through CD19 and CD22 and BCMA and CD38 demonstrates a major decrease in antigen escape risk. The results of the dual-targeting system test show an escape probability that drops from 25 percent to under 1 percent.
- Tandem CARs (TanCAR): The CD19 and CD22 TanCAR which uses two scFv domains from one receptor shows early positive results in the clinical trial NCT04150497.
- OR-gate logic: CAR activates if EITHER antigen is present (sensitive, prevents escape); AND-gate: activates only if BOTH antigens present (selective, reduces on-target off-tumour toxicity)

5.2 T-Cell Exhaustion

The immunosuppressive tumour microenvironment (TME) causes CAR-T cells to lose their ability to function because they undergo exhaustion which leads to them displaying multiple inhibitory receptors together with PD-1 and LAG-3 and TIM-3 and TIGIT and TOX and NR4A transcription factors.

- The checkpoint blockade combination uses a PD-1 inhibitor which includes pembrolizumab and nivolumab together with CAR-T therapy to restore CAR-T function; pivotal trials ongoing (NCT02926833, NCT03630159)
- The 4th generation Armoured CARs use IL-15 or IL-21 which they can produce either continuously or on demand to create autocrine survival mechanisms that sustain their stem cell characteristics while preclinical tests show that IL-15 CAR-T cells have 5 to 10 times longer survival.
- CRISPR-edited CAR-T: The CRISPR-Cas9 system allows scientists to knock out PDCD1 which encodes the PD-1 gene together with LAG3 to create CAR-T cells that maintain their functionality without exhaustion. The first clinical data from University of Pennsylvania show the feasibility of the study. (Stadtmauer et al., 2020).
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5.3 Solid Tumour Challenges

The process of transferring CAR-T therapy success from treating liquid tumors to treating solid tumors requires more effort because three different types of barriers need to be overcome.

Barrier	Biological Mechanism	Investigational Solution
Physical exclusion	Dense desmoplastic stroma; elevated interstitial pressure	Hyaluronidase-expressing CAR-T; CAR-T + chemotherapy debulking
Antigen heterogeneity	Tumour subclones with variable antigen expression	Multi-target CAR; CAR-T + bispecific antibody
Immunosuppressive TME	TGF-β, IL-10, IDO, Tregs, MDSCs, M2 macrophages	TGF-β dominant-negative receptor; armoured TRUCK-CAR with IL-12
T-cell trafficking	Exclusion from tumour by CXCL12/CXCR4 axis; PD-L1 upregulation	CXCR4-overexpressing CAR-T; local infusion via catheter
On-target off-tumour	Target antigen expressed on vital normal tissues	Synthetic Notch (SynNotch) two-signal gating system; masked CAR

Table 5. Barriers to CAR-T efficacy in solid tumours and investigational strategies to overcome them.

5.4 Manufacturing and Scalability

The existing method for producing autologous CAR-T cells requires 18 to 35 days and costs between $373000 and $475000 for each treatment which makes it difficult for people to access treatment. The manufacturing

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process needs major developments to achieve its manufacturing goals. • Allogeneic off-the-shelf CAR-T system uses T cells which have been engineered by healthy donors through CRISPR technology to delete TCRα/β and HLA genes so that one produced batch can treat multiple patients. The companies Allogene Therapeutics Precision BioSciences and Cellectis are currently developing Allogeneic CAR-T. The hospitals use automated closed manufacturing systems which include Miltenyi CliniMACS Prodigy and Lonza Cocoon and BlueRacer to create T cells through their compact benchtop systems which enable processing to take 5 to 7 days. The delivery method uses CAR-encoding mRNA lipid nanoparticles LNPs to transmit genetic material directly to T cells in the bloodstream for treatment purposes. The companies Sana Biotechnology and Beam Therapeutics worked together on a project which proved their concept in preclinical testing.

BROADER CELLULAR IMMUNOTHERAPY LANDSCAPE

6.1 TCR-Engineered T Cells (TCR-T)

TCR-T cell therapy requires T cell engineering to create T cells possessing T-cell receptors which demonstrate strong binding abilities for detecting tumor proteins that are found inside cancer cells and shown on MHC molecules. This addresses a critical limitation of CAR-T therapy (restricted to surface antigens) since the majority of tumour-associated antigens are intracellular proteins.

- NY-ESO-1 TCR-T (Adaptimmune): The treatment targets the NY-ESO-1 and LAGE-1a cancer-testis antigens through TCR which operates on HLA-A*02:01 restriction. The treatment showed a 50% overall response rate with responses lasting more than 18 months in its Phase II study of synovial sarcoma (D'Angelo et al., 2018).
- MAGE-A4 TCR-T (Adaptimmune/GSK): The treatment underwent Phase II testing for non-small cell lung cancer and head and neck cancer and urothelial carcinoma. The overall response rate ranged from 24% to 33% and the FDA granted Breakthrough Designation in 2022.
- The trial has a limitation because it depends on HLA haplotype which requires HLA-A*02:01 since this HLA type controls 40% to 45% of Western populations and decreases in Asian populations.

6.2 Tumour-Infiltrating Lymphocyte (TIL) Therapy

TIL therapy uses a patient's tumour biopsy to extract their existing tumour-reactive T lymphocytes which are then grown outside their bodies until reaching a target of more than 10 billion cells before doctors do the re-infusion after the patient undergoes lymphodepletion. The FDA granted accelerated approval to Lifileucel (Amtagvi, Iovance Biotherapeutics) for advanced melanoma treatment in February 2023 which marked the first TIL therapy to receive approval from a major regulatory body.

- Clinical Data (C-144-01 trial, n=73): The study found an overall response rate of 31.5% in patients who had received all three treatments of checkpoint inhibitors BRAF inhibitors and ipilimumab, The study found that patients in the study who responded to treatment maintained their response for an average of 16.9 months and The study found a complete response rate of 6.8%.
- Mechanism: The TIL population contains multiple T cell types which detect various tumour neoantigens because it uses multiple TIL cells as its detection system instead of using single TIL cells.
- Applications: The treatment has received approval for melanoma while it is currently undergoing testing in Phase II for NSCLC and it is also being studied for cervical cancer and head and neck cancers through the Phase III ACTIVATE trial.

6.3 Natural Killer (NK) Cell Therapy

Natural killer cells function as innate lymphoid cells which use three different mechanisms to identify and destroy tumor cells. The MHC-independence of allogeneic NK cells enables their use without introducing any danger of graft-versus-host disease which creates a major benefit for manufacturing processes.

- CAR-NK: The University of Texas MD Anderson developed CD19-targeting NK cells which use CARs that originate from cord blood to create CD19-directed CAR-NK (The University of Texas MD Anderson, NCT03056339). The first two phases of the study found that 73 percent of patients with

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relapsed or refractory B-cell malignancies reached complete response whereas no patients developed Grade 3 or higher CRS or ICANS and no patients experienced GvHD.

- •Sources include autologous and allogeneic peripheral blood and umbilical cord blood and iPSC-derived NK cells and NK cell lines which include NK-92 and KHYG-1.
- •iPSC-NK: Induced pluripotent stem cells create off-the-shelf NK cells which maintain uniformity and indefinite expansion as Their clinical development is being led by Fate Therapeutics.

6.4 Regulatory T Cell (Treg) Therapy for Autoimmune Diseases

The goal of most cellular immunotherapy approaches is to improve immune response against cancer cells while the method of adoptive transfer for expanded antigen-specific regulatory T cells (Tregs) functions as a treatment method which brings back immune tolerance.

- The ONE Study which used NCT02272790 testing applied polyclonal Treg therapy on kidney transplantation patients and showed that the treatment proved safe while it delivered possible benefits by decreasing rejection rates without needing extra immunosuppression.
- The preclinical proof-of-concept study by Bluestone et al. (2022) demonstrated how Islet-specific CAR-Treg which expresses insulin-specific TCR protects Type 1 diabetes β cells from autoimmune destruction.

- The anti-dsDNA CAR-Treg shows a strong nephritis reduction effect in murine lupus models while the Phase I trial will start in 2023.

CAR-T CELL THERAPY FOR AUTOIMMUNE DISEASES: EMERGING EVIDENCE

Scientists are currently studying cellular immunotherapy because it has potential to treat severe autoimmune diseases which do not respond to conventional treatments. The first human evidence was reported by Georg Schett's group (University of Erlangen-Nuremberg) in 2021, demonstrating that CD19-directed CAR-T cell therapy could induce deep, drug-free remission in severe refractory systemic autoimmune diseases — by eliminating the autoreactive B-cell clones driving disease pathology.

7.1 Mechanism of Action in Autoimmunity

The autoimmune diseases which B cells mediate include systemic lupus erythematosus, myasthenia gravis, anti-NMDA receptor encephalitis, and neuromyelitis optica through their production of autoantibodies and their activation of autoreactive B cells. The CD19-CAR-T treatment completely removes all B cells from the body, which includes dangerous plasma cells, thus creating a more complete restoration of humoral immunity than any current medication can achieve. The B-cell aplasia results in B-cell reconstitution from naïve B-cell precursors because the newly formed B cells do not carry the autoimmune memory which their predecessor cells from the depleted cells. The immune system 'resetting the immune clock' of CAR-T achieves more complete B-cell elimination through its complete B-cell destruction while rituximab (anti-CD20) preserves operational plasma cells which have a long lifespan.

7.2 Clinical Evidence in SLE, Myositis, and SSc

Disease	n	CAR Target	CAR-T Product	Key Response	Follow-up
SLE (severe)	8	CD19	KYV-101 / 4SCAR19	Drug-free remission: 7/8 (87.5%)	2–29 months
Systemic Sclerosis	2	CD19	KYV-101	SLEDAI-2K score reduction; normalised complement	6 months
Inflammatory Myositis	3	CD19	KYV-101	Resolution of myositis; CPK normalisation	3–12 months
Idiopathic Inflammatory Myopathy	5	CD19	CT103A	ORR 100%; drug-free remission	6–24 months

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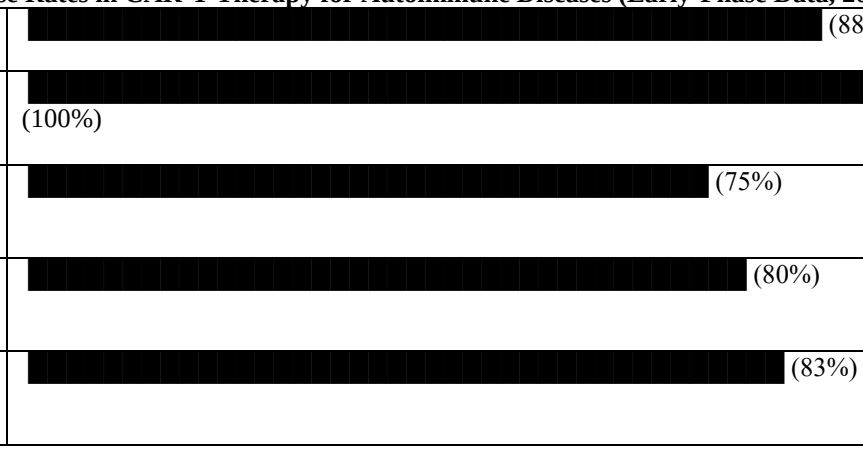
Myasthenia Gravis (AChR+)	2	CD19	Pilot	AChR antibody titre reduction; clinical improvement	3 months
MG (refractory)	3	BCMA	Pilot	Reduced AChR antibodies; QMG improvement	6 months

Table 6. CAR-T cell therapy in autoimmune diseases — preliminary clinical data from early-phase trials (2021–2023). SLE = Systemic Lupus Erythematosus; SSc = Systemic Sclerosis; MG = Myasthenia Gravis; QMG = Quantitative Myasthenia Gravis Score.

7.3 Autoimmune Disease Clinical Response — Bar Chart

Figure 5: Response Rates in CAR-T Therapy for Autoimmune Diseases (Early-Phase Data, 2021–2023)



Autoimmune Disease Indication | Response Rate (%)

Small cohort data (n=2–8 per group). Requires validation in larger randomised controlled trials. Source: Schett et al. Nature Medicine 2021; Mackensen et al. Nature Medicine 2022.

COMPLEMENTARY IMMUNE-BASED THERAPIES

8.1 Immune Checkpoint Inhibitors

The use of immune checkpoint inhibitors (ICIs) has transformed solid tumour treatment because these inhibitors block the immune checkpoints which serve as molecular brakes that tumours use to stop anti-tumour immune responses. The CTLA-4 and PD-1/PD-L1 pathways are the primary clinically validated targets.

Drug (Target)	Manufacturer	Key Approvals	5-Year OS Rate	Immune-related AEs
Ipilimumab (CTLA-4)	BMS	Melanoma, RCC, NSCLC	21% (melanoma 1st line)	Colitis, hepatitis, hypophysitis (30–40%)
Pembrolizumab (PD-1)	Merck	Pan-tumour TMB-H, MSI-H + 17 tumour types	34% (melanoma 1st line)	Pneumonitis, thyroiditis, arthritis (15–25%)
Nivolumab (PD-1)	BMS	Melanoma, NSCLC, HCC, GC	29% (melanoma combo)	Rash, colitis, hepatitis (20–30%)
Atezolizumab (PD-L1)	Roche/Genentech	NSCLC, SCLC, TNBC, Urothelial	18% (NSCLC 1st line)	Lower AE rate vs. anti-PD-1
Durvalumab (PD-L1)	AstraZeneca	Stage III NSCLC, Biliary tract	28% (NSCLC)	Similar to atezolizumab

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Table 7. Major immune checkpoint inhibitors — targets, approvals, long-term outcomes, and adverse event profiles. OS = Overall Survival; AE = Adverse Event; TMB-H = Tumour Mutational Burden High; MSI-H = Microsatellite Instability High.

8.2 Bispecific T-Cell Engagers (BiTE)

BiTE antibodies are tandem single-chain bispecific constructs that bind T cell CD3ε and tumor antigens on cancer cells to establish an immune synapse which triggers T cell activation without needing any ex vivo processing to create the needed results which function as a ready-to-use solution for CAR-T therapy.

- •Blinatumomab Blincyto CD19×CD3 received approval for B-ALL treatment and resulted in a 44% MRD-negative CR rate for patients with minimal residual disease-positive B-ALL and the 2-year OS rate reached 80% for MRD+ first remission patients who needed continuous IV infusion because the medication had a short half-life of 2.1 hours.
- •Teclistamab Tecvayli BCMA×CD3 requires subcutaneous injection for its use in Multiple myeloma treatment and the medication showed a 63% ORR in patients who had received extensive previous treatments approval from EMA/FDA took place in 2022.
- •Elranatamab Elrexfio BCMA×CD3 showed an ORR of 61% for patients with triple-class refractory myeloma who needed to receive monthly treatment after they reached their response target.
- •Glofitamab CD20×CD3 showed an ORR of 52% and CR rate of 39% for relapsed/refractory DLBCL patients who had received two or more previous treatment lines during the 12-dose fixed-duration treatment.

8.3 Antibody-Drug Conjugates (ADCs) and Immunocytokines

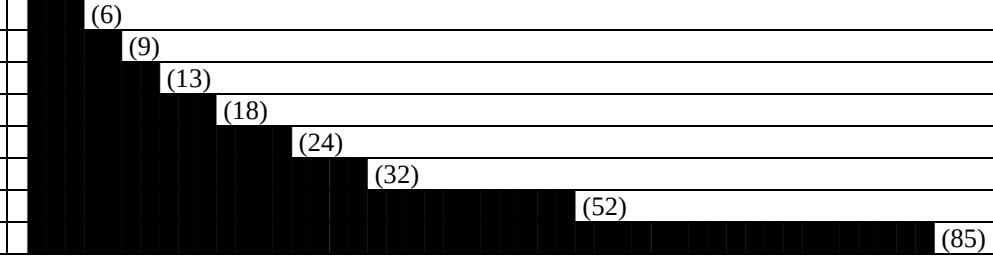
ADCs link cytotoxic payloads to tumour-targeting antibodies which deliver high-potency drugs to cancer cells that express specific antigens while protecting healthy body tissues. The immuno-oncology toolkit has grown because their successful results introduced new treatment methods that do not depend on immune cell-based systems.

- Trastuzumab deruxtecan (T-DXd, Enhertu): HER2-targeting ADC with topoisomerase I inhibitor payload;HER2+ breast cancer shows PFS 28.8 months versus 6.9 months chemotherapy in the DESTINY-Breast03 study;the 2019 and 2022 approval established HER2-low tumours as new treatment targets
- Sacituzumab govitecan (Trodelvy): TROP-2 ADC;the treatment shows 5-month overall survival improvement for TNBC patients who receive it compared to chemotherapy;the treatment received approval in 2020
- Polatuzumab vedotin (Polivy):the treatment targets CD79b in DLBCL through its ADC mechanism; the treatment received approval in 2019;the treatment combination with rituximab-bendamustine shows improved overall survival results

GLOBAL MARKET TRENDS AND HEALTH ECONOMIC CONSIDERATIONS

9.1 Global CAR-T and Cell Therapy Market

Figure 6: Global CAR-T Cell Therapy Market Size (USD Billion) — 2020 to 2030 (Projected)



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Source: Grand View Research 2023; GlobalData 2023. CAGR ~24.5% (2023–2030). Includes CAR-T, TCR-T, TIL, NK, Treg therapies.

9.2 Cost and Access Challenges

Product	List Price (USD)	Manufacturing Time	Countries with Reimbursement
Tisagenlecleucel (Kymriah)	$475,000	18–22 days	USA, EU, Australia, Canada, Japan
Axicabtagene (Yescarta)	$373,000	16–18 days	USA, EU, Japan
Ciltacabtagene (Carvykti)	$465,000	~30 days	USA, EU (conditional)
Lifileucel (Amtagvi — TIL)	$515,000	~22 days	USA only (2023)
Academic/biosimilar CAR-T (India, China)	$30,000–80,000	14–21 days	China (NMPA approved); India (academic access)

Table 8. Approved cell therapy products — list prices, manufacturing timelines, and market access. China's NMPA approved Relma-cel (Relma) and JWCAR029 at substantially lower price points, with Indian CAR-T programmes (AIIMS, Tata Memorial) providing academic access at <$30,000.

DISCUSSION AND FUTURE RESEARCH DIRECTIONS

The decade between 2014 and 2023 has witnessed an extraordinary transformation in the cellular immunotherapy landscape — from experimental laboratory constructs to regulatory-approved, life-saving therapies for patients who had exhausted all other options. The evidence presented in this paper establishes multiple main findings while it determines essential research needs that will guide upcoming research activities during the next ten years.

10.1 Consolidating Success in Haematological Malignancies

CAR-T therapy has shown better results than standard chemotherapy through multiple randomised controlled trials which tested its effectiveness against chemotherapeutic standards in ZUMA-7 and TRANSFORM. The current challenge requires scientists to find ways which extend the duration of remission because almost 40 to 60 percent of DLBCL patients who reach their first remission will experience a relapse. The research community needs to maintain its financial backing for T-cell exhaustion research and the study of antigen escape and bone marrow microenvironment immunosuppression in myeloma patients.

10.2 The Solid Tumour Frontier

Solid tumours represent 90% of all cancer cases but have proven largely recalcitrant to CAR-T therapy. The combination of multiple new methods including SynNotch logic systems for antigen detection and armoured TRUCK-CARs which change TME structure and locoregional delivery methods through intrapleural and intracranial and intratumoral delivery systems and strategies which combine these methods with checkpoint blockade creates a scientific path which shows solid tumours can be treated successfully. The GD2-CAR-T activity in neuroblastoma (Pule et al., 2008; Louis et al., 2011) and the emerging clinical signals in mesothelioma and ovarian cancer with mesothelin-targeted CARs indicate that solid tumour barriers are not insurmountable.

10.3 Autoimmune Disease — A Transformational New Paradigm

The initial research findings from Schett and Mackensen their research team suggest a significant shift for current methods of treating autoimmune disorders. The scientific evidence which shows that one short-term cellular treatment can produce extended periods of remission without medication for patients with refractory SLE and myositis and systemic sclerosis establishes a powerful scientific basis that could transform the entire medical landscape for millions of patients. The existing evidence base only includes studies with small participant groups most studies have less than 10 participants per disease. The research needs to be conducted over an extended period to establish whether remissions are permanent or if autoimmune memory will return after a certain period.

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10.4 Key Research Priorities

1. The randomized controlled trials of CAR-T therapy will investigate its effectiveness against current biologic treatments for autoimmune disorders while determining the best patient candidates for treatment.
2. The study aims to create predictive biomarkers that will assess CRS and ICANS severity for risk-based monitoring and preventive treatment.
3. The allogeneic and iPSC-derived platforms enable widespread manufacturing capabilities while they decrease production expenses and treatment delivery time.
4. The use of LNP or viral vector delivery systems for in vivo CAR generation enables potential elimination of the entire manufacturing process.
5. The research uses spatial transcriptomics and single-cell RNA sequencing together with AI patient stratification to predict which patients will benefit from treatment.
6. The health economics research in LMIC environments will establish budget-friendly implementation strategies which will guide reimbursement policies within national healthcare systems.

CONCLUSION

The treatment of haematological malignancies through cellular immunotherapy which uses CAR-T cell technology together with TIL and NK and TCR-T and Treg and bispecific antibody methods constitutes the most important development since rituximab Entering the market in 1997 and it stands as the most revolutionary treatment system since chemotherapy introduction. The seven approved CAR-T products have collectively treated tens of thousands of patients with relapsed/refractory B-cell malignancies and multiple myeloma achieving complete remission rates of 28–78% in settings where prior therapies had uniformly failed. The development of cellular immunotherapy applications for treating autoimmune diseases represents a major advancement because scientists can now create cellular tools to restore immune system balance that produces results which traditional immune suppression treatments have not achieved for many years. The preliminary clinical data show excellent results although we require strong confirmation to establish proof.

The main obstacles which researchers face in their work include antigen escape and T-cell exhaustion and solid tumour barriers and manufacturing complexity and astronomical cost and global access inequity which remain difficult to solve yet can be resolved. The combination of synthetic biology and CRISPR genome editing and advanced manufacturing and artificial intelligence and improved understanding of how tumours interact with the immune system creates a new research toolkit for upcoming scientists. Researchers now study how fast cellular immunotherapy can be distributed to all patients who require treatment in all nations at a price which health systems can handle instead of determining whether the therapy can treat cancer and autoimmune diseases.

REFERENCES

1. June, C.H., O'Connor, R.S., Kawalekar, O.U., et al. (2018). CAR T cell immunotherapy for human cancer. Science, 359(6382), 1361–1365.
2. Maude, S.L., Laetsch, T.W., Buechner, J., et al. (2018). Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. New England Journal of Medicine, 378(5), 439–448.
3. Neelapu, S.S., Locke, F.L., Bartlett, N.L., et al. (2017). Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New England Journal of Medicine, 377(26), 2531–2544.
4. Munshi, N.C., Anderson, L.D., Shah, N., et al. (2021). Idecabtagene vicleucel in relapsed and refractory multiple myeloma. New England Journal of Medicine, 384(8), 705–716.

DOI: 10.46121/pspc.51.2.7

5. Martin, T., Usmani, S.Z., Berdeja, J.G., et al. (2023). Ciltacabtagene autoleucel vs. standard care in lenalidomide-refractory multiple myeloma. New England Journal of Medicine, 389(2), 89–115.
6. Mackensen, A., Müller, F., Mougiakakos, D., et al. (2022). Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nature Medicine, 28(10), 2124–2132.
7. Schett, G., Mackensen, A., Mougiakakos, D. (2023). CAR T-cell therapy in autoimmune diseases. Lancet, 402(10408), 1179–1180.
8. Stadtmauer, E.A., Fraietta, J.A., Davis, M.M., et al. (2020). CRISPR-engineered T cells in patients with refractory cancer. Science, 367(6481), eaba7365.
9. D'Angelo, S.P., Melchiori, L., Merchant, M.S., et al. (2018). Antitumor activity associated with prolonged persistence of adoptively transferred NY-ESO-1c259T cells in synovial sarcoma. Cancer Discovery, 8(8), 944–957.
10. Liu, E., Marin, D., Banerjee, P., et al. (2020). Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. New England Journal of Medicine, 382(6), 545–553.
11. Rohaan, M.W., Borch, T.H., van den Berg, J.H., et al. (2022). Tumor-infiltrating lymphocyte therapy or ipilimumab in advanced melanoma. New England Journal of Medicine, 387(23), 2113–2125.
12. Larson, R.C. & Maus, M.V. (2021). Recent advances and discoveries in the mechanisms and functions of CAR T cells. Nature Reviews Cancer, 21(3), 145–161.
13. Sadelain, M., Rivière, I., & Riddell, S. (2017). Therapeutic T cell engineering. Nature, 545(7655), 423–431.
14. Locke, F.L., Miklos, D.B., Jacobson, C.A., et al. (2022). Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. New England Journal of Medicine, 386(7), 640–654.
15. IRENA (2023). Global CAR-T and Cell Therapy Market Report. Grand View Research. San Francisco.
16. ImmunoACT (2023). NexCAR19 Phase I/II clinical trial results — NCT04289857. Lancet Haematology (published online September 2023).

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