

What Is CAR-T Cell Therapy? Mechanism, Approved Indications, and Key Evidence

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CAR-T cell therapy engineers a patient's own T lymphocytes to express chimeric antigen receptors (CARs) that recognise and destroy tumour-specific targets. Six products are now FDA- and EMA-approved across haematological malignancies. This article explains the manufacturing process, approved indications, landmark efficacy data, and the clinical management of cytokine release syndrome and neurotoxicity.

KEY TAKEAWAYS

- CAR-T therapy uses a patient's own T cells, genetically engineered with a CAR construct targeting a tumour antigen, expanded ex vivo, and reinfused
- Six FDA/EMA-approved products target CD19 (B-cell malignancies) or BCMA (multiple myeloma); no solid tumour products are currently approved
- ZUMA-1 showed 58% CR in relapsed/refractory DLBCL; CARTITUDE-1 showed 97.9% ORR in heavily pre-treated multiple myeloma
- CRS affects 70-95% of patients; Grade 3+ managed with tocilizumab and corticosteroids within the first 14 days
- Referral to a CAR-T-certified centre is required for manufacturing logistics and specialised toxicity monitoring

What Is CAR-T Cell Therapy?

CAR-T cell therapy is a form of adoptive cell immunotherapy in which a patient's own T lymphocytes are genetically engineered to express chimeric antigen receptors (CARs) targeting tumour-specific surface proteins.⁴ The modified cells are expanded ex vivo and reinfused into the patient, where they mount a directed anti-tumour response. Unlike conventional chemotherapy or checkpoint inhibitors, CAR-T therapy delivers a living drug that can persist and proliferate in the body.

The manufacturing process involves 3 steps: leukapheresis to collect T cells from peripheral blood, transduction using a viral vector (typically lentiviral or retroviral) to insert the CAR gene, and ex vivo expansion before infusion.¹ The CAR construct consists of an extracellular antigen-binding domain derived from a monoclonal antibody, a transmembrane linker, and intracellular co-stimulatory and activation domains (CD28 or 4-1BB, plus CD3-zeta). Upon binding to the target antigen, the CAR activates the T cell and triggers cytotoxic killing. Effective adoptive T cell therapy comprises the killing of cancer cells through the therapeutic use of transferred T cells.⁷ CAR T cells mediate MHC-unrestricted tumor cell killing by enabling T cells to bind target cell surface antigens through a single-chain variable fragment recognition

domain.⁷ Upon engagement, CAR T cells form a non-classical immune synapse required for their effector function.⁷ These cells then mediate their anti-tumoral effects through the perforin and granzyme axis, the Fas and Fas ligand axis, as well as the release of cytokines to sensitize the tumor stroma.⁷ Before infusion, patients receive lymphodepleting chemotherapy, typically fludarabine plus cyclophosphamide, to reduce regulatory T cells, create cytokine space, and improve CAR-T engraftment.³

This mechanistic understanding does not establish universal efficacy across all tumour types. The persistence in the host and functional outputs are tightly dependent on the receptor's individual components, including the single-chain variable fragment, spacer domain, and costimulatory domains.⁷ Current models of the immune synapse and cytotoxic pathways rely heavily on in vitro observations and do not fully capture the complexities of the human tumour microenvironment. The reliance on specific antigen recognition means that tumours can evade detection by downregulating the target protein.

Clinicians must view CAR-T cells as complex biological systems rather than simple targeted agents. The success of the therapy depends on how component functions converge to augment CAR T cell performance.⁷ You should prepare patients for a multi-step process that requires significant time between leukapheresis and infusion. The living nature of the drug means that its pharmacokinetics are entirely different from traditional molecules, requiring specialized monitoring for expansion and persistence.

Approved Indications and Efficacy Data

As of 2026, 6 CAR-T products have received regulatory approval from the FDA and/or EMA, all targeting haematological malignancies:

Product	Target	Approved Indication
Tisagenlecleucel (Kymriah)	CD19	Paediatric/young adult ALL; DLBCL
Axicabtagene ciloleucel (Yescarta)	CD19	DLBCL, follicular lymphoma, PMBCL
Brexucabtagene autoleucel (Tecartus)	CD19	Mantle cell lymphoma; B-ALL
Lisocabtagene maraleucel (Breyanzi)	CD19	DLBCL; CLL/SLL
Idecabtagene vicleucel (Abecma)	BCMA	Relapsed/refractory multiple myeloma
Ciltacabtagene autoleucel (Carvykti)	BCMA	Relapsed/refractory multiple myeloma

No CAR-T products are currently approved for solid tumours, though trials are ongoing in glioblastoma, pancreatic cancer, and non-small cell lung cancer.

For large B-cell lymphoma, axicabtagene ciloleucel (ZUMA-1) demonstrated a complete response rate of 58% at median follow-up of 15.4 months, establishing CAR-T as a viable third-line option.¹ The ZUMA-7 trial demonstrated superiority over standard second-line chemoimmunotherapy in early-relapsed DLBCL, with event-free survival of 8.3 months versus 2.0 months.² For multiple myeloma, ciltacabtagene autoleucel (CARTITUDE-1) showed an overall response rate of 97.9% in heavily pre-treated patients, with a complete response rate of 78.6% at median follow-up of 27.7 months.³ In a systematic review of 448 patients receiving CD19-specific CAR-T therapy for relapsed or refractory B-cell acute lymphoblastic leukemia in the pediatric and young adult population, the incidence rate of complete remission was 82%.¹⁰ The cumulative incidence of relapse after CD19-specific CAR-T therapy is 36%.¹⁰ Subgroup analysis shows

the incidence rate of minimal residual negative complete remission was 69% with the CD28z costimulatory domain, 81% with the 4-1BB domain, and 77% with fourth-generation CD19-specific CAR-T therapy.¹⁰

These response rates do not guarantee long-term cures for all patients. Resistance to CAR-T cell therapies occurs in most patients.⁶ The data from these trials reflect highly selected populations and do not establish efficacy in patients with significant comorbidities or rapidly progressing disease who cannot wait for manufacturing. Resistance mechanisms include CAR-T cell dysfunction, intrinsic tumour resistance, and the immunosuppressive tumour microenvironment.⁶ The systematic review data for pediatric acute lymphoblastic leukemia relies on a cumulative sample of 446 evaluable patients aged 0 to 30 years, which does not translate to older adult populations.¹⁰

CAR-T cell therapy offers durable remissions in patients with relapsed or refractory haematological malignancies who have exhausted conventional options. You must identify eligible patients early to account for the manufacturing time. Current research strategies to overcome multiple resistance mechanisms include optimization of the CAR design, improvement of in vivo T cell function and persistence, modulation of the immunosuppressive tumour microenvironment, and synergistic combination strategies.⁶ Referral to a CAR-T-certified treatment centre is required in most jurisdictions due to the complexity of manufacturing logistics and specialised toxicity management protocols.

Safety Profiles and Clinical Challenges

The safety profile of CAR-T cell therapy is defined by severe, immune-mediated toxicities that require specialized management protocols. The two most clinically significant toxicities are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).⁵ Cancer immunotherapies lead to unique toxicity profiles distinct from the toxicities of other cancer therapies, depending on their mechanism of action.⁸

CRS occurs in 70 to 95% of patients across approved products. Grade 3 or higher CRS occurs in approximately 10 to 30% of cases and is managed with tocilizumab and corticosteroids. ICANS affects approximately 30 to 60% of patients and can manifest as encephalopathy, aphasia, or cerebral oedema in severe cases. Both toxicities typically occur within the first 14 days after infusion and are manageable at experienced centres. In the pediatric and young adult population receiving CD19-specific CAR-T therapy, the incidence rates of grade 3 or higher adverse events of neutropenia, thrombocytopenia, neurotoxicity, infections, and cytokine release syndrome were 38%, 23%, 18%, 29%, and 19%, respectively.¹⁰ The FDA has also reported cases of T-cell malignancies, including CAR-positive lymphomas, in patients receiving BCMA- or CD19-targeted autologous CAR-T cell immunotherapy.⁹

The current safety data do not establish the long-term risks of these living therapies. The reports of secondary T-cell cancers were derived from clinical trials and post-marketing adverse event data, leaving the exact incidence and definitive causality unclear.⁹ It is essential to explore the potential mechanisms by which chimeric antigen receptor-T cell therapy triggers secondary T-cell cancers to further guarantee safety.⁹ The management guidelines for CRS and ICANS are based on consensus rather than randomized trials comparing different intervention thresholds.⁸ The high cost of therapy, which can exceed \$400,000 per patient, poses a substantial burden on healthcare systems and limits broad accessibility.

You must monitor patients intensely during the first 14 days post-infusion. These toxicities often require specific management, which can include steroids and immune-modulating therapy and for which consensus guidelines have been published.⁸ Efforts are underway to reduce manufacturing costs and streamline the production process, including the development of allogeneic off-the-shelf CAR-T products derived from healthy donors. While research aims to mitigate toxicities through novel CAR designs or prophylactic interventions, clinicians must balance the immediate life-saving potential of the therapy against the severe acute risks and the emerging reports of secondary malignancies.

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