WHITE PAPER

From cancer to autoimmunity: Addressing clinical and operational hurdles in CAR T-cell therapy expansion

A KEY QUESTION

How can biotech sponsors overcome the challenges of expanding CAR T-cell therapy into autoimmune and other non-oncologic indications by improving patient recruitment, site readiness and trial success while managing cost and complexity?

KEYWORDS

CAR T-cell Therapy, Autoimmune Diseases, Patient Recruitment and Retention, Long-Term Follow-Up (LTFU), Decentralized Clinical Trials (DCT), Site

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Chimeric antigen receptor (CAR) T-cell therapy has revolutionized treatment paradigms in hematologic malignancies and is now broadening into autoimmune diseases and other non-oncologic indications.[1] Of the more than 1,500 active or planned CAR T-cell therapy clinical trials worldwide, a small percentage represent autoimmune and inflammation indications.[2, 3]

Based on previous successes with innovative CAR T treatments, biotech sponsors have the potential to address high unmet needs beyond hematological malignancies, but still face many hurdles in clinical development. To better understand how these groundbreaking advancements have evolved and help sponsors navigate the complexity of clinical trials, this white paper reviews CAR T fundamentals and discusses considerations for addressing common operational challenges.

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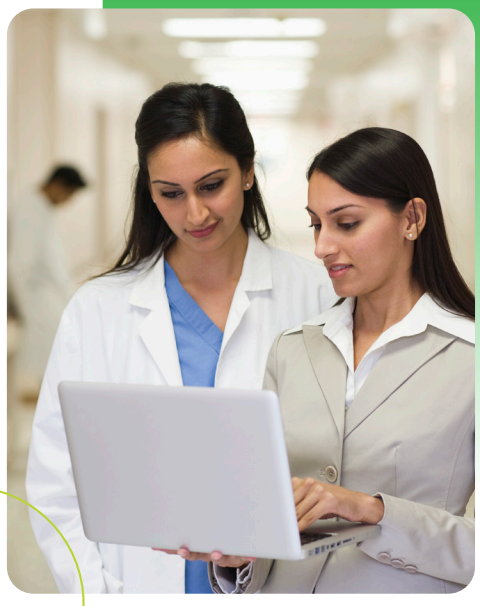
The evolution of CAR T therapies

The roots of immunotherapy have iteratively advanced since the study of vaccines and immune responses in the 1800s, eventually leading to the creation of the first-generation autologous CAR T constructs. While each CAR T generation has shown success, it has also revealed specific issues, which have driven researchers to refine methods, explore more advanced designs and develop novel manufacturing methods.[4]

- Early CAR T therapies employed patient-derived T-cells engineered *ex vivo* to express a single-target CAR with CD3ζ (intracellular signaling domain) to demonstrate antitumor activity
- Second-generation CAR T introduced co-stimulatory domains (e.g., CD28, 4-1BB), enhancing T-cell activation, proliferation and persistence
- Third-generation CARs utilize a combination of multiple costimulatory signaling domains within the endodomain
- Fourth-generation CAR T, known as T cells redirected for universal cytokine killing (TRUCKs), integrate inducible cytokine expression and include safety switches to modulate the tumor environment and control CAR T activity precisely
- Fifth generation CAR T constructs integrate logic-gate or switchable modules, multi-targeting capabilities, and cytokine-signaling motifs (e.g., IL-2) to provide precise activation, improved persistence and controlled activity, addressing shortcomings of earlier designs

Each generation continues to pave the way for safer, more effective clinical applications in oncology while also expanding the potential to treat non-cancerous chronic conditions, such as rheumatoid arthritis, lupus, diabetes and multiple sclerosis.



An innovative, individualized and targeted treatment

CAR T-cells can be designed to bypass the limitations of natural T-cell recognition as they:

- Target tumor-specific antigens, for example, in B-cell malignancies (such as multiple myeloma) and autoimmune diseases (like systemic lupus erythematosus)
- Activate cytotoxic pathways upon antigen binding, ultimately leading to a cascade of signals that induce cell death
- Persist in the body to provide long-term immune surveillance

The patient experience: CAR T-cell therapy manufacturing, infusion and monitoring

At a high level, the CAR T-cell therapy process involves cell collection, genetic modification and reinfusion. Through leukapheresis, T-cells are separated and collected from the patient's peripheral blood. A donor's blood can also be used for allogeneic, "off-the-shelf" approaches, a method that aims to reduce production time, complexity and cost.

The collected T-cells are genetically engineered in the lab to express the Chimeric Antigen Receptor (CAR) and undergo expansion. To create the optimal microenvironment for CAR T-cells, the patient may first undergo treatment with lymphodepleting drugs.[5] Once a quality check is performed on the product, CAR T-cells are infused into the patient's body, which then proliferate and infiltrate target cells.

After infusion, the patient is monitored for adverse effects, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which can impair patient outcomes and are challenging to treat.[6]

Late complications, such as infections, cytopenias and neurologic toxicities, are possible, stressing the need for long-term monitoring. Beyond monitoring for safety and efficacy over the long term, care teams play a crucial role in enhancing outcomes and improving the quality of life for patients treated with CAR T therapies.[7]

A focus on innovations in CAR T for autoimmune conditions

Autoimmune diseases remain an area of very high unmet medical need. Most autoimmune diseases lack disease-specific therapies and instead rely on broad immunosuppressants and monoclonal antibodies associated with significant risks such as infection, organ toxicity and long-term side effects.

Mechanistically, autoimmunity arises when autoantibodies and autoreactive cytotoxic T lymphocytes recognize self-antigens, triggering tissue destruction, widespread inflammation and progressive organ damage. CAR T-cell therapies offer a targeted approach by eliminating pathogenic B cells (e.g., anti-CD19 CAR T) or modulating T-cell responses, providing a potential "immune reset" for diseases such as systemic lupus erythematosus and rheumatoid arthritis. These constructs most commonly target CD19 or BCMA to deplete dysfunctional B cells producing autoantibodies.[8, 9, 10]

Patient recruitment and retention in CAR T studies

The ability to find, recruit and retain patients in cell therapy clinical studies is challenging for several reasons. For example:

- The protocol of a cell therapy study may limit the number of qualified patients
- The strict eligibility criteria may restrict enrollment of patients with relapsed or refractory disease reducing trial accrual rates, limiting the evidence base, hindering broader clinical adoption and reducing understanding of CAR T efficacy in earlier disease stages
- A cell therapy is likely to be a new and unknown treatment regimen for patients
- The requirement for an extensive long-term follow-up (LTFU) period may discourage patient enrollment

To reduce burden and promote recruitment, sponsors should consider the needs of the sites, the patients and caregivers by:

- Equipping sites with comprehensive educational tools for patients to understand how a cell therapy functions
- Offering adequate time for patients to review all materials and consult with their caregivers
- Discussing the LTFU commitment during initial discussions and again at the time of consent
- Sharing the time commitment required for inpatient hospitalization and outpatient visits to help coordinate support and options for scheduling
- Incorporating decentralized clinical trial (DCT) solutions to improve LTFU retention

Operational challenges and considerations in CAR T trials

While evolving medical science and technology has spurred development of these unique therapies, these advances have also presented significant operational complexities and challenges to clinical trials. Consider some of the following needs and potential solutions:

Coordinating complex processes	CAR T trials involve cross-department coordination to manage apheresis, administration and adverse event management. The multi-disciplinary clinical team must be experienced in both CAR T therapeutics and the particular disease.
Creating a regulatory strategy	A sponsor's submission strategy in the U.S. must be appropriate at the site level, individually considering regulatory framework, the requirements of the institutional biosafety committee (IRB) and institutional review board (IBC), and the availability of Chemistry, Manufacturing and Controls (CMC) documentation.
Mitigating risk	Sponsors must evaluate participating sites, external vendors involved, study materials required, the CAR T product pathway, among other factors, to perform risk mitigation and proactively to avoid delays in patient recruitment, treatment and dose escalation.
Evolving with changes	Early phase CAR T therapy studies often have several amendments per study as sponsor strategies evolve to incorporate new information. Flexibility is essential to avoid delays and meet both study and program goals.
Managing logistics	Apheresis and cell therapy processes have intense, time-critical product requirements for storage, transport, preparation and delivery to sites and require a high level of site and patient awareness.
Delivering timely, high-quality data	The study database must be as clean as possible at all times, especially during dose escalation. Frequent safety data review is necessary when generating a high load of data. Sponsors must recognize the intense burden on the sites, which can be reduced with specific data tracking and monitoring projection tools.

A focus on sites in CAR T trials

Selecting the sites that are sufficiently resourced to fully commit to a CAR T study is critical. Study sites must be capable of accommodating the complexity of the CAR T processes, have access to the required study population and be able to work seamlessly with an interdisciplinary, interdepartmental approach within a high operational burden. Site training, staffing and mentorship can help with training, especially if a sponsor's study is facing competition for site and investigator resources for studies competing for the same patient population.

Leading the next wave of CAR T breakthroughs

Pharma and biotech sponsors continue to pioneer CAR T innovations and explore transformative solutions beyond oncology. To support these efforts, Fortrea has been proud to advance more than 80 cell therapy studies across 865 sites, engaging more than 5,400 patients.

Our team at Fortrea is also building a Cell Therapy Site Network to map capabilities and establish additional site relationships. These efforts will enable us to quickly place cell therapy studies at qualified and competent sites.

Drawing on our experience working with hundreds of inflammatory and autoimmune trials, as well as all six of the FDA-approved oncology CAR T-cell therapies, we continue to minimize risks and promote predictability in the development journey.

Together, let's improve your odds of success and redefine treatment paradigms for autoimmune and inflammatory diseases, offering patients precise, effective and life-changing therapeutic options.

Learn more: https://www.fortrea.com/therapeutics/inflammatory-autoimmune

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