

PRECISION / the cell &
ADVANCE / gene therapy
collective™

Delivering on the
Promise of Cell Therapy:
Challenges and Trends

PRECISION
for medicine

Delivering on the Promise of Cell Therapy: Challenges and Trends

The historic August 2017 approval of the first chimeric antigen receptor (CAR) T-cell therapy put cell therapy into the spotlight, ushering in a new approach to the treatment of cancer. Now cell therapies are considered one of the most powerful tools in oncology and one of the most-studied investigative products. According to the Alliance for Regenerative Medicine, as of the first quarter of 2019, there were 642 cell therapy clinical trials under way worldwide—including cell therapy and gene-modified cell therapy trials across all phases.¹ Due to the currently high cost of CAR T-cell therapy (CAR-T), there is significant patient interest in gaining access to these treatments through clinical trials, adding a layer of competition to the already challenging process of product development.

In this white paper, we explore the current landscape of cell therapy, with an emphasis on CAR-T products, highlighting the key challenges and opportunities sponsors face as they endeavor to translate these treatments from the bench to the bedside.

Navigating the Regulatory Environment

US Regulations

The regulatory landscape for cell therapy is continually evolving to keep pace with technological advances. Since the issuance of its first guidance on cell therapy in 1998, the US Food and Drug Administration (FDA) has published a number of other guidance documents (see Table 1).

Another FDA guidance document that may be useful for sponsors of cell therapy products is Expedited Programs for Regenerative Medicine Therapies for Serious Conditions. Published in November 2017, the guidance offers recommendations on the expedited development and review of regenerative medicine therapies for serious or life-threatening diseases or conditions. It also provides information on the use of the accelerated approval pathway for therapies that have been granted the regenerative medicine advanced therapies (RMATs) designation.⁶

Table 1: **FDA Guidance on Cell Therapy**

Preclinical Assessment of Investigational Cellular and Gene Therapy Products	Provides recommendations on the preclinical information needed to support clinical trials for investigational cellular therapies, gene therapies, and therapeutic vaccines ²
Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products	Offers insight into the Agency's thinking on early-phase clinical trials of investigational cellular therapy and gene therapy products ³
Evaluation of Devices Used With Regenerative Medicine Advanced Therapies	Provides recommendations on the evaluation of devices used in the recovery, isolation or delivery of RMATs ⁴
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use	Clarifies how regulatory criteria apply to human cells, tissues, and cellular and tissue-based products ⁵

EU Regulations

In July 2018, the European Medicines Agency (EMA) released a draft revision of its guideline on quality, nonclinical and clinical aspects of medicinal products containing genetically modified cells (GMOs).⁷ The intent of the revision, which was in public consultation until July 31, 2019, was to take into account the evolution of scientific and regulatory experience with an emphasis on starting materials, comparability and validation, as well as to supplement the guideline with current thinking on the requirements for nonclinical and clinical studies. Of note, the guideline includes specific sections on the scientific principles and clinical aspects specific to CAR-T products.

Another nuance of the EU regulatory landscape is the existence of two different risk classifications for GMOs—contained use (Directive 2009/31/EC) and deliberate release (Directive 2001/18/EC)—which may impact the development of cell therapy products. Contained use is defined as any activity with GMOs for which specific containment measures are used to limit their contact with the environment.⁸ Deliberate release refers to any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment.⁹ Sponsors must decide which category the cell therapy falls under and make justification for that decision, keeping in mind that in some EU member states any GMO is considered deliberate release by default, even in the context of a clinical trial.

5 Key Challenges

Development of a cell therapy product is a substantial undertaking that requires a focus on quality and sustainability to ensure both the safety and efficacy of the treatment and its accessibility to the patients. Here we explore 5 key challenges that sponsors face:

1. Manufacturing

Sponsors are under pressure to optimize manufacturing prior to commercial launch, which is difficult when transforming a complex, individualized treatment into a customized commercial product. Following the initial launch of Kymriah® (tisagenlecleucel) for adult lymphoblastic leukemia, Novartis publicly struggled with production issues. Even after securing approval of a second indication for Kymriah, the pharmaceutical giant was still delivering the CAR-T treatment for free to some patients, as the product was suitable for investigational use, but did not meet the stricter label specifications established for commercial use.¹⁰

Clinical testing of early-stage cell therapies is often performed on platforms that are not commercially viable. As such, the manufacturing platform must evolve, in many cases from a single center or investigator initiated trial to a scalable, multi-site manufacturing process. Each manufacturing change has the potential to alter the product in a meaningful way, as raw material collection specifications may need to be updated to accommodate manufacturing of product for both multicenter trials and ultimately commercial launch. Logistics are also a factor, as products that require shipment and storage will require additional validation. All aspects of the chain of custody—from ordering, apheresis, handling, shipping, manufacturing, return shipping and infusion—must be tracked and managed in a highly controlled manner (see Figure 2). Currently, the manufacturing technologies underlying the cell therapy sector are evolving, with greater investment and utilization of digital technologies. This includes exploring ways to integrate and analyze data from online sensors that allow manufacturers to monitor conditions of a product batch in real time.¹¹

Figure 1: Chain of Custody for Cell Therapy

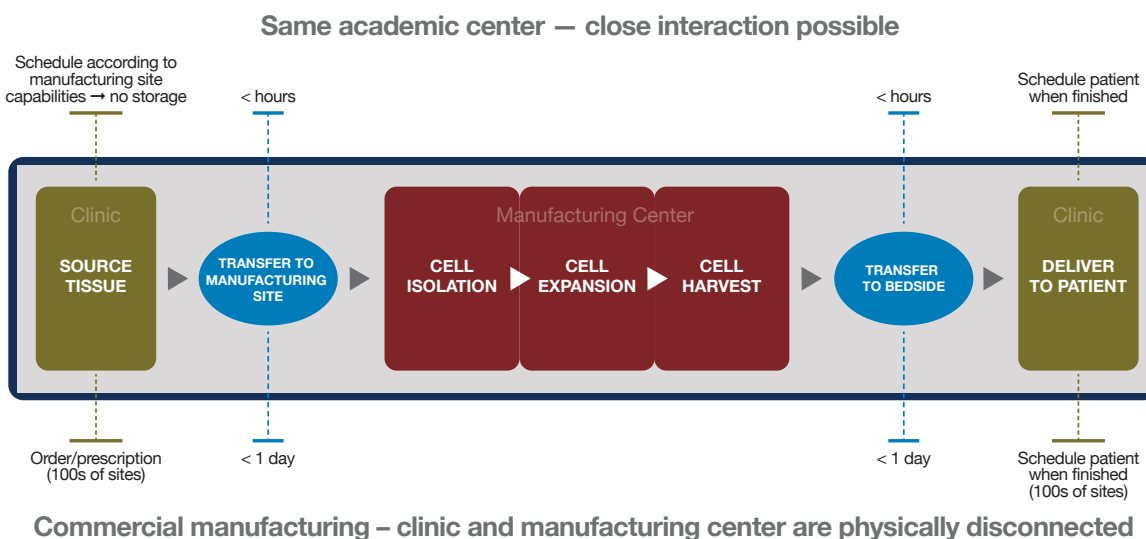


Figure 1: Chain of Custody for Cell Therapy¹² Adapted from Levine BL, Miskin J, Wonnacott K, Keir C. Global manufacturing of CAR-T cell therapy. *Mol Ther Methods Clin Dev.* 2016;4:92-101.

2. Immunogenicity and adverse events

One major potential side effect of CAR-T and other cellular therapy products is their ability to induce significant and potentially undesirable host immune responses. Risk factors for induction of immunogenicity have been shown to be associated with the presence of nonhuman or partially human sequences in the CAR construct, suicide domain or other components of the CAR-T, as well as with proteins utilized in the gene-editing step of manufacturing. Immunogenicity induction can impact CAR-T expansion and persistence, potentially affecting the safety and efficacy of treatment. Strategies being explored for mitigating the negative effects of the immune response against CAR-T therapies include humanization of the CAR construct, lymphodepletion chemotherapy, and immunosuppressive pretreatment.¹³

Side effects such as cytokine release syndrome (CRS) and neurologic toxicities are not uncommon following administration of some cellular therapies, most notably CAR-T therapy, and can be life-threatening. Other adverse events associated with cell therapies include serious infections, hypotension, hypoxia, acute renal failure, and hematologic abnormalities. Due to risk of CRS and neurologic events, both Kymriah and Yescarta® (axicabtagene ciloleucel) are approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). Hospitals and their associated clinics that dispense these therapies must be certified and trained to recognize and manage adverse events.

Figure 2: Potential Anti-CAR-T Immune Response Risk Factors

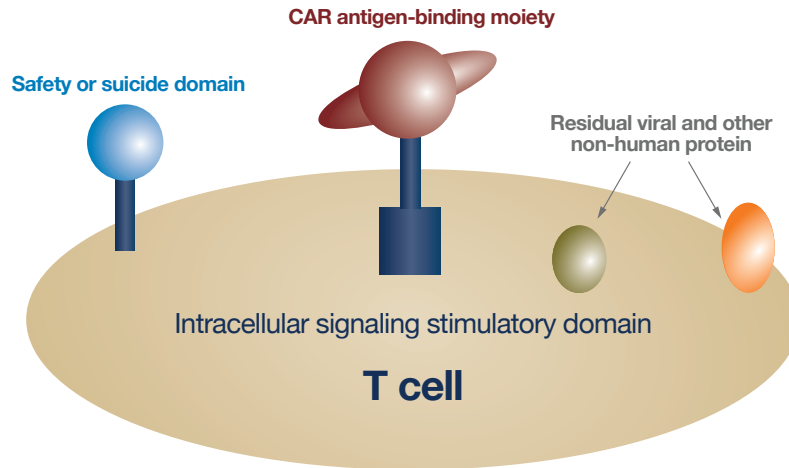


Figure 2: Potential Anti-CAR-T Immune Response Risk Factors¹³ Adapted from Gorovits B, Koren E. Immunogenicity of Chimeric Antigen Receptor T-Cell Therapeutics. *BioDrugs*. 2019;33(3):275-284.

3. Resistance

The first challenge in developing a cell therapy product is finding one with sufficient biological activity that leads to a meaningful clinical benefit. Selection of the antigen target is critical, and a CAR-T must be developed to selectively target cancer cells while sparing healthy tissue. As we have seen with Kymriah, which demonstrated an 83% complete remission rate within 3 months of treatment, the clinical benefit can be dramatic.¹⁴ However, longer follow-up has revealed that a significant percentage of these remissions may not be durable.¹⁵ To date, it is unclear whether this is due to poor persistence of CAR-T cells after infusion or secondary to antigen loss of the target receptor. Strategies for preventing relapse will be critical for optimizing the long-term success of CAR-T.

Figure 3: Barriers to Durable Remission After CAR-T Therapy

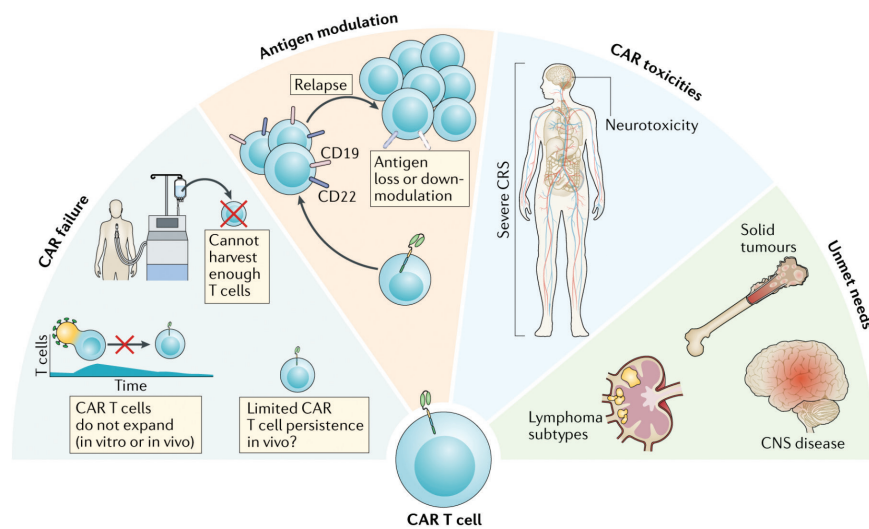


Figure 3: Barriers to Durable Remission After CAR-T Therapy¹⁵ Adapted from Shah N, Fry TJ. Mechanisms of resistance to CAR T cell therapy. *Nat Rev Clin Oncol*. 2019;16(6):372-385.

4. Reimbursement

The introduction of high cost therapies that have potential long-term clinical benefit also creates unique challenges for payers. While national health insurance programs will likely apply economically positive analysis of the long-term benefit of cell therapies because national health systems provide “lifelong” coverage for a patient, a private health insurance company may not see the benefit of this therapy because of higher member turnover and shorter coverage windows. So, what might seem as an obvious economic benefit may not actually prove to be true.

- Reimbursement can also be an issue during the clinical development process. Careful consideration should be given to potential costs that patients may incur from participating in cell therapy clinical trials as these studies can be procedurally intensive and it may be difficult to clearly delineate standard of care from trial procedures. As such, patients may be responsible for out of pocket costs associated with any procedures that are considered standard of care, limiting trial participation to those who can afford it.

5. Logistics of going global

Planning for global cell therapy studies must take into account that the regulatory environment in the EU is not harmonized. Indeed, certain countries, as well as individual sites within those countries, may have requirements beyond standard regulatory and ethical review.¹⁶

Moreover, with the growing number of cell therapy clinical trials across both solid and hematological malignancies, sponsors may face competition for both study participants and sites. Several institutions that are well-established in the conduct of cellular therapy trials are conducting investigator-initiated trials, which may take precedence over industry-based trials in terms of staff resourcing and patient enrollment. In addition, with increasing utilization of internal committees and reviews, sites have become more selective about the cell therapy studies they are willing to participate in and may decline participation in new studies. Even when sites do agree to participate, sponsors may face obstacles in integrating their processes into a site’s standard process, which will vary from institution to institution. Additionally, global manufacturing adds significant manufacturing challenges that can risk quality and safety.

Currently, the majority of approved cell therapies are only commercially available on a regional basis. Global launches are expected to present a variety of issues ranging from logistics, import/export requirements, reimbursement, regulatory approvals, market variability and differences in clinical adoption.¹⁷ Further, given the inherent differences in how each product is manufactured and how those differences can impact product quality and efficacy, sponsors need to proactively plan for institutional variations in how the raw material is collected and processed, as well as how the final product is received and manipulated prior to administration to the patient.

Overcoming Obstacles

Incorporating Scalable Solutions

Faced with all these challenges, sponsors may benefit from beginning with the end in mind and incorporating scalable solutions at the earliest stages of development. For instance, begin by identifying a commercially viable manufacturing system and then deconstructing it for use in early research to smooth the transition from clinical trials to commercial launch.¹⁸ Another example includes designing a manufacturing process that allows not only for site variability in collection and processing, but also sufficient processing times to facilitate logistics management. Yet another example would be setting up courier brokerages to facilitate product shipment, not just for conducting multicenter clinical trials, but also for scaling at commercial launch.

Building Safety Into the Fabric of Clinical Trials

Anticipating, preventing and proactively managing toxicity is critical to the success of CAR-T clinical trials. Adverse events following CAR-T therapy may vary widely in severity, time of onset and duration. On occasion, the toxicities may persist for the lifespan of the modified T cell.¹⁹ As such, the safety considerations related to CAR-T cells may impact both study design and trial management. Sponsors may want to refer to the recommendations released by the CAR-T-cell-therapy-associated TOXicity (CARTOX) Working Group in 2018 for monitoring, grading, and managing CAR-T-related toxicities to ensure some level of consistency across clinical trials.

Trends in Cell Therapy

As we gain a deeper understanding of T-cell biology and CAR-T cell function, we are seeing trends in cell therapy focused on improving long-term efficacy, minimizing or optimizing the management of toxicity, and expanding the pool of patients eligible for these customized treatments:

- 1. Optimizing CAR design and manufacturing.** One approach to optimizing CAR-T is designing constructs that target multiple antigens (bispecific CARs) in an effort to mitigate antigen loss. There are several ongoing clinical trials targeting both CD19 and CD22 in hematologic malignancies.²⁰ Researchers are also exploring application of gene-editing technologies for enhancing the efficacy of CAR T-cell therapies, as well as use of “off-the-shelf” CAR-Ts developed from allogeneic T cells to simplify and accelerate manufacturing.
- 2. Developing biomarker strategies to monitor patient response and/or persistence of the modified T cells within the body.** Researchers are also investigating predictive biomarkers that may be able to identify patients at risk for severe CRS and/or neurotoxicity during CAR T-cell therapies.²¹
- 3. Integrating ‘suicide switches’ or other genetic constructs as a way to help limit toxicity.** Suicide switches and elimination genes can be activated to trigger CAR T-cell death if toxicities develop, while remote-controlled CARs include inducible systems that control expression.

Suicide switches or elimination genes would allow the selective destruction of CAR T cells upon the administration of a nontoxic prodrug. Remote-controlled CARs would require new architectures that include a molecular “on-off” switch that enables precise regulation of the locations, duration, and intensity of the modified cells’ therapeutic behavior.²²

4. Targeting solid tumors to broaden indications. To date, cell therapies have exhibited limited success in solid malignancies, which present new challenges such as tumor heterogeneity, delivery, and the immunosuppressive tumor microenvironment. Solid tumors may also require multiple rounds of CAR T injections, which may increase the potential for serious toxicities. Neo-antigens represent an opportunity for solid tumor cell therapies, as they are truly cancer-specific targets found nowhere else in the body. Increasing the persistence of adoptively transferred T cells may be one of the keys to increasing efficacy in solid tumors, and multiple strategies ranging from pretreatment with cytoreductive chemotherapy and ablative therapies (such as radiation) to novel genetic engineering techniques are currently being studied to enhance persistence.²³

5. Exploring combination therapies to combat resistance. The interactions between cancer and the immune system are complex and dynamic. Combination therapies that target different mechanisms of tumor escape—whether it’s drug combinations or CAR-Ts that secrete immuno-stimulating agents (so-called “armored CARs”)—may help to reduce or eliminate resistance. A combination already being tested in clinical trials of solid tumors is a CAR-T alongside a checkpoint inhibitor.²⁴

Table 2: CAR-T Therapy: Hematologic Malignancies vs Solid Tumors

	HEMATOLOGIC MALIGNANCIES	SOLID TUMORS
Target Antigen	With the currently approved CAR-T therapies, the target antigen (CD19) is present on all malignant cells, but is also present on normal B cells	Tumors are heterogeneous, and malignant cells do not all present the same mix of antigens
Tumor Microenvironment	CAR T cells expand readily in the blood, but can lead to an immune overreaction	Tumors produce immunosuppressive agents that may facilitate immune escape
Delivery to Tumor	CAR-T infusion into the blood provides easy access to malignant cells	It may be difficult for CAR T cells to infiltrate the myriad layers of cells in these tumors

Table 2: CAR-T Therapy: Hematologic Malignancies vs Solid Tumors¹⁵ Adapted from *The Scientist, The Next Frontier of CAR T-Cell Therapy: Solid Tumors*, April 1, 2019.

Partnering With the Right People

Cell therapies hold great promise, offering the tantalizing possibility of individualized treatment for patients who may have no other options. However, these products are complex, and the process of translating and scaling them from the academic site to the commercial arena remains a challenge. Engaging with highly trained experts with the right skill sets is integral to the advancement of this powerful, potentially curative treatment modality. The complexity involved in the execution of a cell therapy development program requires experience that goes beyond the science to include the patient eligibility requirements and logistical challenges of both clinical and commercial success. Finding the right partners with the necessary expertise can help sponsors create a cell therapy product development roadmap, including an appropriate biomarker strategy, that optimizes the likelihood of clinical and commercial success.

References: **1.** Q1 2019 Data Report. Alliance for Regenerative Medicine website. <https://alliancerm.org/publication/q1-2019-data-report/>. Accessed August 29, 2019. **2.** Preclinical assessment of investigational cellular and gene therapy products - Guidance for industry. US Food and Drug Administration website. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf>. Accessed August 29, 2019. **3.** Considerations for the design of early-phase clinical trials of cellular and gene therapy products - Guidance for industry. US Food and Drug Administration website. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf>. Accessed August 29, 2019. **4.** Evaluation of devices used with regenerative medicine advanced therapies - Draft guidance for industry. US Food and Drug Administration website. <https://www.fda.gov/media/120266/download>. Accessed August 29, 2019. **5.** Regulatory considerations for human cells, tissues, and cellular and tissue-based products: minimal manipulation and homologous use. US Food and Drug Administration website. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf>. Accessed August 29, 2019. **6.** Expedited programs for regenerative medicine therapies for serious conditions - Draft guidance for industry. US Food and Drug Administration website. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf>. Accessed August 29, 2019. **7.** Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. European Medicines Agency website. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-aspects-medicinal-products-containing-genetically_en.pdf. Accessed August 29, 2019. **8.** Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast) (Text with EEA relevance). EUR-Lex website. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32009L0041>. Accessed August 29, 2019. **9.** Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration. EUR-Lex website. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32001L0018>. Accessed August 29, 2019. **10.** Pagliarulo N. In CAR-T, manufacturing a hurdle Novartis has yet to clear. Biopharma Dive website. <https://www.biopharmadive.com/news/in-car-t-manufacturing-a-hurdle-novartis-has-yet-to-clear/543624/>. Accessed August 29, 2019. **11.** Hargreaves N. How to solve a problem like Kymriah. Biopharma-Reporter.com website. <https://www.biopharma-reporter.com/Article/2019/02/22/Novartis-and-digital-manufacturing-transformation>. Accessed August 29, 2019. **12.** Levine BL, Miskin J, Wonnacott K, Keir C. Global manufacturing of CAR T cell therapy. *Mol Ther Methods Clin Dev.* 2016;4:92-101. **13.** Gorovits B, Koren E. Immunogenicity of chimeric antigen receptor T-cell therapeutics. *BioDrugs.* 2019;33(3):275-284. **14.** FDA approval brings first gene therapy to the United States. US Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states>. Published August 30, 2017. Accessed August 30, 2019. **15.** Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. *Nat Rev Clin Oncol.* 2019;16(6):372-385. **16.** Hartmann J, Schüßler-Lenz M, Bondanza A, et al. Clinical development of CAR T-cells—challenges and opportunities in translating novel innovative treatment concepts. *EMBO Mol Med.* 2017;9(9):1183-1197. **17.** Buckler L. 9 Challenges keeping cell and gene therapy executives up at night. *Cell & Gene* website. <https://www.cellandgene.com/doc/challenges-keeping-cell-and-gene-therapy-executives-up-at-night-0001>. Accessed August 30, 2019. **18.** Peshwa M. With cell therapies hurtling toward the market, it's time to prepare for the future. <https://www.gelifsciences.com/en/us/news-center/with-cell-therapies-hurling-toward-the-market-its-time-to-prepare-for-the-future-10001>. GE Healthcare website. Accessed August 30, 2019. **19.** Bonifant CL, et al. Toxicity and management in CAR T-cell therapy. *Mol Ther Oncolytics.* 2016;2:16011. **20.** ClinicalTrials.gov. Search parameters CD19+CD22. <https://clinicaltrials.gov/ct2/results?cond=&term=cd19%2Bcd22&cntry=&state=&city=&dist=>. Accessed September 6, 2019. **21.** Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomarker Research.* 2018;6:4. **22.** Sun S, Hao H, Yang G, et al. Immunotherapy with CAR-modified T cells: toxicities and overcoming strategies. *J Immunol Res.* 2018;2386187. **23.** DeRenzo C, Gottschalk S. Genetic modification strategies to enhance CAR T cell persistence for patients with solid tumors. *Front Immunol.* 2019;10:218. **24.** Grens K. The next frontier of CAR T-cell therapy: solid tumors. *The Scientist* website. <https://www.the-scientist.com/features/the-next-frontier-of-car-t-cell-therapy--solid-tumors-65612>. Published April 1, 2019. Accessed August 30, 2019.

PRECISION
ADVANCE the cell & gene therapy collective™

PRECISION
for medicine

PROJECT FARMA

PRECISION
value & health

Precision ADVANCE, a collection of interconnected services and complementary teams, uniquely focuses on the complexities of clinical, regulatory, manufacturing, and commercial needs to successfully bring cell or gene therapies to market.

Connect with one of our experts. Contact us at precisionadvance@precisionmedicinegrp.com.
To learn more about Precision ADVANCE, visit precisionmedicinegrp.com/advance.

PRECISION
for medicine

2 Bethesda Metro Center, Suite 850
Bethesda, MD 20814
precisionformedicine.com

© 2021 Precision Medicine Group. All rights reserved.

Rev. 03