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Fees: There are no fees associated with participation in this activity.

Release date: September 10, 2018
Expiration date: September 10, 2019

Learning Objectives:

Following this activity, participants should be able to:

- Outline fundamental elements of chimeric antigen receptor (CAR) design and CAR T-cell therapy development
- Summarize key studies using CD19-targeted CAR T-cell therapy in relapsed/refractory B-cell malignancies and their outcomes
- Identify current and emerging management strategies for CAR T-cell therapy–associated toxicities
- Discuss preclinical and clinical strategies being developed for CAR T-cell therapy use in solid tumors
- Summarize recommended considerations for CAR T-cell persistence and disease surveillance
- Outline seminal components required to establish institutional CAR T-cell therapy programs
- Discuss current coverage/reimbursement structures and proposed reimbursement strategies for CAR T-cell therapy

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This activity is supported by educational grants from Kite Pharma and Novartis.

Chimeric Antigen Receptor T-Cell Therapy

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Abstract

Patients with relapsed or refractory (R/R) cancers have a poor prognosis and limited treatment options. The recent approval of 2 chimeric antigen receptor (CAR) autologous T-cell products for R/R B-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma treatment is setting the stage for what is possible in other diseases. However, there are important factors that must be considered, including patient selection, toxicity management, and costs associated with CAR T-cell therapy. To begin to address these issues, NCCN organized a task force consisting of a multidisciplinary panel of experts in oncology, cancer center administration, and health policy, which met for the first time in March 2018. This report describes the current state of CAR T-cell therapy and future strategies that should be considered as the application of this novel immunotherapy expands and evolves.

J Natl Compr Canc Netw 2018;16(9):1092–1106
doi: 10.6004/jnccn.2018.0073

Background

Chimeric antigen receptor (CAR) T cells are genetically engineered cells that represent a novel class of cancer immunotherapy.[1] The development of adoptive cellular therapy using CAR T cells spans almost 30 years, with the seminal study by Gross et al[2] laying the groundwork for the development of first-generation CAR T cells. CARs are rationally designed synthetic receptors that target surface antigens in their native conformation.[1,3] They are composed of a tumor targeting moiety, most often an antibody single-chain variable fragment, linked to a hinge region, a transmembrane domain, and an intracellular activation motif made up of the CD3 zeta (CD3ζ) chain of the T-cell receptor (TCR) complex.[4] Due to these molecular features, T cells expressing CARs are not major histocompatibility complex–restricted. In more recent clinical trials, second-generation CARs have been used, and these include one costimulatory signaling domain—typically either CD28 or 4-1BB—which have been shown to enhance T-cell proliferation and cytokine production.[4] Some studies suggest that 4-1BB-containing CARs have longer T-cell persistence.[5–7] Third-generation CARs, which have at least 2 costimulatory domains, have shown activity but need further evaluation in clinical studies to determine whether such constructs are superior to those containing a single costimulatory domain.[8,9]

In general, the process of autologous CAR T-cell therapy begins with collecting WBCs from the patient via leukapheresis, followed by TCR activation (eg, anti-CD3/anti-CD28 beads), and genetic engineering via retroviral or lentiviral transduction. After the CAR T

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Submitted August 10, 2018; accepted for publication August 14, 2018.

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cells are generated, they are expanded to clinically relevant numbers, undergo quality control testing, and are cryopreserved. Manufacturing of commercial CAR T-cell products occurs at a centralized facility, necessitating transfer of the apheresis product to the manufacturing site, and the final cryopreserved CAR T-cell product back to the treatment facility. Typically, the patient undergoes lymphodepleting chemotherapy to create a favorable immune environment for CAR T-cell activity prior to receiving a single intravenous infusion of the product.[10] Once the CAR T cells are infused, several factors may impact their efficacy and toxicity profile, including extent of previous treatments, intensity of the lymphodepleting chemotherapy regimen, and disease burden at the time of infusion. Other factors that may impact CAR T-cell activity and safety include immunogenicity, immunosuppressive components in the microenvironment, and on-target/off-tumor effects.[4] Several strategies are being explored to enhance CAR designs that will maximize functionality and minimize toxicity, and will be discussed later.[4,11,12]

CD19 CAR T-Cell Therapy and Disease Management

Leukemias

Prognosis and overall survival (OS) rates in adult and pediatric patients with relapsed and refractory (R/R) acute lymphoblastic leukemia (ALL) is poor.[13–15] However, recent advances in immunotherapy are expanding treatment options for these patients, including CD19/CD3 bispecific antibody blinatumomab, CD22 antibody-drug conjugate inotuzumab ozogamicin, and CD19 CAR T cells.[16] The initial phase I clinical evaluation by several institutions of anti-CD19 CARs, with either a CD28 or 4-1BB costimulatory domain in adult and pediatric R/R CD19-positive ALL, have demonstrated unprecedented clinical efficacy, with >70% to 90% of patients achieving a complete response (CR) within 28 days.[17–22] These clinical findings set the foundation for the development of tisagenlecleucel, a CAR platform initially established by a research group at the University of Pennsylvania (CTL019) and now commercialized. The phase I Pedi CART19 single-institution trial in pediatric patients with R/R ALL demonstrated minimal residual disease (MRD)–negative CR in 88% of patients 1 month after infusion.[23] Subsequent data from the ELIANA study, a global multicenter phase II trial evaluating the efficacy of tisagenlecleucel in pediatric and young adults with R/R ALL, confirmed these initial results, demonstrating an overall remission/response rate (ORR) of 81% within 3 months of infusion, and OS rates of 90% and 76% at 6 and 12 months, respectively.[24] Together, these data facilitated the accelerated FDA approval of tisagenlecleucel as a therapeutic option in patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or greater relapse.

Additional studies evaluating the efficacy of CD19 CAR T cells in the adult population are underway, with promising responses.[21,25,26] For instance, after infusion of anti-CD19 CAR with a CD28 domain (19-28z CAR T) in 53 adults with R/R ALL, complete remission was observed in 83% of patients, with a sustained impact on OS.[21] Similar data are emerging from an ongoing phase I trial of KTE-C19 (a different CD28-based anti-CD19 CAR T-cell product), wherein an 88% MRD-negative CR rate was observed.[17]

Although observed remissions in clinical trials are encouraging, several factors impact the durability of responses to CAR T-cell therapy. Disease relapses can occur and may involve multiple mechanisms, including suboptimal CAR T-cell expansion or persistence, disrupted antigen trafficking, and antigen escape through acquired mutations, splice variants, or leukemic lineage switching.[27–34] Some studies suggest that fludarabine and cyclophosphamide lymphodepletion may enhance CAR T-cell persistence,[18,22,35,36] whereas other studies suggest that T-cell subset selection may positively impact CAR T-cell efficacy[22,29,37]; however, further studies are warranted. To reduce the potential of antigen escape, alternative or multiple antigens could be targeted.[16,38,39] One alternative to CD19 is CD22, which is expressed in most cases of pre–B-cell ALL.[40] A novel anti–CD22-CAR demonstrated antileukemic activity in a phase I study involving pediatric and adult patients with ALL previously treated with CD19-directed immunotherapy.[29]

Other considerations for CAR T-cell use in R/R ALL therapy include whether it should be evaluated as a bridge to hematopoietic stem cell transplant (HSCT), or potentially as a replacement for HSCT, if long-term durable remissions can be achieved.[1] More clinical studies are needed to determine whether CAR T-cell therapy in ALL can be expanded for use in additional settings, such as after first re-

lapse, in first remission with persistent MRD, or even as initial induction or consolidation therapy. Future studies to determine the criteria that contribute to maximal therapeutic benefit will shed light on these considerations and optimize CAR T-cell therapy use.

Lymphomas

Patients with multiply relapsed diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma (NHL), have poor outcomes.[41–43] Multiple clinical studies evaluating anti-CD19 CAR T-cell therapy in refractory CD19-positive B-cell lymphomas have demonstrated promising antilymphoma activity.[44–48] These encouraging clinical outcomes have provided the rationale for efforts to seek FDA approval for CD19 CARs for the treatment of NHL, and the clinical results of the lead commercial CAR T-cell products are summarized in this section.

KTE-C19/axicabtagene ciloleucel (axi-cel) was the first CAR T-cell therapy to be FDA-approved for the treatment of NHL in October 2017. Axi-cel is an anti-CD19 CD3ζ/CD28-based CAR T-cell therapy, which was originally developed and clinically tested at the NCI and subsequently commercially developed. The multicenter phase I study, ZUMA-1, evaluated KTE-C19/axi-cel in 7 patients with refractory DLBCL[49]; the ORR was 71% (5/7) at 4 weeks postinfusion, with 3 of 7 patients still in remission at 24 months. In the phase II expansion of ZUMA-1, 101 of 111 enrolled patients with refractory DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma were treated with axi-cel.[46] The CR rate and ORR were 54% and 82%, respectively. After a median follow-up of 15.1 months, 40% of patients remained in CR. Of 34 patients with partial response at 1 month, 11 (32%) subsequently achieved CR without additional therapy.[50] In addition, landmark analysis of progression-free survival (PFS) determined that among the 60 patients with disease control (ie, stable disease or better) at 3 months, the 12-month PFS rate was 73%.[50] Subset analyses suggest that low-burden disease may be associated with a higher rate of durable responses. These data facilitated accelerated FDA approval of axi-cel in R/R DLBCL.

The second commercial product to be FDA-approved in May 2018 for the treatment of DLBCL was tisagenlecleucel. In the multicenter pivotal phase II JULIET study examining the efficacy of tisagenlecleucel in adults with R/R DLBCL, the best ORR was 53.1% among 81 infused patients.[47] In addition, 74% of patients who experienced a CR at 3 months continued to show ongoing remission at 6 months, suggesting that, as with axi-cel, long-term durable remissions may be observed in a substantial minority of patients.

Other CAR T-cell products being commercially developed for treatment of NHL include JCAR017/lisocabtagene maraleucel, a CD3ζ/4-1BB-based CD19 CAR evaluating a defined ratio of CD4 and CD8 T-cell subsets, which was originally developed and clinically tested at Fred Hutchinson Cancer Research Center. In the TRANSCEND study, the efficacy of lisocabtagene maraleucel was evaluated in R/R B-cell NHL.[44] The best overall response and CR rates were 75% and 56%, respectively, and 80% of patients experiencing CR at 3 months remained so at 6 months.[44] Similar to the ZUMA-1 study, patients with low-burden disease or relapse after transplant had improved ORR relative to patients with high tumor burden or primary refractory disease.[44]

On the Horizon

Given the results observed with CAR T-cell therapy in ALL and DLBCL, several studies are in progress to determine whether other tumors will respond and whether toxicities will differ.[51–58] Using CAR T cells to target the anti–B-cell maturation antigen (BCMA) in heavily treated R/R multiple myeloma (MM) has demonstrated encouraging preliminary responses.[51,52,59,60] In a multicenter phase I study examining the efficacy of bb2121, a second-generation anti-BCMA CAR, in 21 patients with R/R MM, the ORR for 18 evaluable patients in the group treated with at least 150 x 10^6 CAR T cells was 94%.[61] Emerging clinical studies have also demonstrated sustained remissions using anti-CD19 CARs in heavily pretreated patients with chronic lymphocytic leukemia.[54,55,57]

Overall, the data in hematologic malignancies suggest that some patients with R/R disease will experience sustained remissions with CAR T-cell therapy, and the duration of response may correlate with the persistence of CAR T cells. An important consideration for future clinical studies will be standardizing protocols so that any factors that contribute to improvements or differences in outcomes can be clarified.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- CAR T cells are a novel class of cancer immunotherapy with promising efficacy in R/R hematologic cancers.
- CD19 CAR T-cell therapy is now approved in pediatric and young adult R/R ALL, as well as adult R/R DLBCL, with further studies underway using alternative antigen targets across these and other hematologic malignancies.
- CAR persistence, efficacy, and safety are influenced by many features, including disease burden, conditioning chemotherapy, and perhaps CAR design.
- Where feasible, the task force recommends standardization of eligibility criteria across clinical trials to better inform clinical and disease features that may influence efficacy and toxicity.

Management of CAR T-Cell Associated Toxicities

Current Structures

Several toxicities are associated with CAR T-cell therapy, but 2 of the most common and well-described toxicities in patients with hematologic malignancies are cytokine release syndrome (CRS) and neurologic toxicity, also called CAR-related encephalopathy syndrome (CRES).[62,63] Ensuring that multidisciplinary clinical staff, including physicians and nurses who monitor patients for toxicity and oncology pharmacists, are trained and familiar with toxicity presentations and management strategies is key to providing timely care.[64] CRS onset typically begins within 24 to 48 hours after infusion, but may occur up to 1 week after infusion, with an average duration of 1 week. The first sign of CRS is usually fever, which can progress to hypotension and/or hypoxia; other signs and symptoms may include arrhythmias, coagulopathies, tachycardia, and other organ toxicities.[62,63] Management strategies have been refined by integrating multi-institutional experiences with CD19 CAR T cells. Low-grade CRS management involves supportive care, including antipyretics for fevers, and evaluation for alternative sources of fever, intravenous fluids for hydration, and antiemetics for nausea. Higher-grade toxicities may require intravenous fluid boluses and pressor support for hypotension, and high-flow oxygen for hypoxia, in addition to interleukin (IL)-6 antagonists (ie, tocilizumab or siltuximab) and/or corticosteroids.

Neurotoxicity/CRES, an extension of vascular dysfunction, typically begins within 4 to 6 days postinfusion and can last from 1 to several weeks. Symptoms include changes in speech and fluency, mild disorientation, confusion, and changes in wakefulness or somnolence.[62,63] Conducting a good baseline neurologic assessment is imperative for subtle changes to be detected on subsequent examinations. Crucial information may also be observed by the patient's caregiver. Management strategies for low-grade CRES include primarily corticosteroids, supportive care, and appropriate precautions. Higher-grade neurotoxicity may require antiepileptic therapy and corticosteroids.[62,63] If CRES treatment is indicated while the patient still has active CRS, tocilizumab is recommended; if this is not effective, siltuximab can be used. In patients with CRES alone, IL-6 antagonists are not effective. Pharmacists are also involved in supportive care and play a role in the administration of antimicrobial, antiviral, and antifungal prophylaxis and seizure prophylaxis medications.

Future Considerations

Several clinical studies have established toxicity grading criteria and management algorithms,[29,54,62,65,66] and institutions use varying algorithms for toxicity management. However, as the use of CAR T-cell therapy expands to treat multiple malignancies, there is a need for standardization in terms of management strategies, antimicrobial prophylaxis, and patient selection to minimize toxicities and maximize the efficacy of treatment. Given the efficacy of tocilizumab in treating CRS, there may be a potential benefit for earlier administration before the onset of severe CRS symptoms; prophylactic administration is currently being investigated.[67] Emerging preclinical and clinical studies suggest a role for potential alternatives to tocilizumab and corticosteroids for managing toxicities, including anakinra, ruxolitinib, and siltuximab,[65,68–72] although the mechanism of action and efficacy of these agents needs to be established. In addition, emerging studies are seeking to determine the prognostic utility of cytokine profiles or serum biochemical markers in predicting toxicity or response.[49,73–77]

Some studies suggest that certain factors may predict the severity of CRS and CRES symptoms. For instance, low disease burden at the time of infu-

sion may correlate with decreased incidence of CRS/CRES symptoms and improved survival.[21,44,78] Conversely, higher numbers of infused CAR T cells may increase a patient's likelihood of experiencing intermediate or severe levels of neurotoxicity.[18,79] Other toxicities associated with CAR T-cell therapy include prolonged cytopenias, hematophagocytic lymphohistiocytosis, disseminated intravascular coagulation, and macrophage activation syndrome,[48,63,72] all of which merit further study so that effective management strategies can be developed. Future studies will also need to determine whether existing comorbidities, including prior thrombosis, cardiac and respiratory dysfunction, venoocclusive disease, central nervous system disease, and autoimmune disease, affect the efficacy of CAR T cells and negatively impact patient outcomes. Considering that there are a myriad factors that impact response to CAR T-cell therapy, a clearer understanding of major factors will inform future management strategies and may help stratify toxicity management.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- Multidisciplinary team education and communication is essential for CAR T-cell–associated toxicity management.
- Tocilizumab and corticosteroids are the main options used to manage CRS and neurotoxicities.
- CAR T-cell–associated toxicities and effective management strategies need to be further investigated and defined.
- The task force recommends the development of standardized toxicity grading and management algorithms to optimize outcomes after CAR T-cell therapy.

Moving Beyond Hematologic Malignancies and Considerations for Follow-Up

Solid Tumors

With improvements in CAR designs and the development of more streamlined T-cell manufacturing processes, preclinical and clinical studies aim to expand the use of CAR T cells in solid tumors.[80–82] Indeed, treatment of solid tumors has proved highly challenging due to heterogeneous antigen expression, immunosuppressive networks in the tumor microenvironment limiting CAR T-cell function and persistence, and suboptimal trafficking to solid tumors.[83,84] The field is still in the early stages of defining the most promising tumor-associated antigens for eliminating malignant disease while maintaining patient safety. Although clinical trials to date have not observed high clinical response rates, they have demonstrated feasibility and safety and modest antitumor activity in a subset of patients. These initial data have provided insights for both the challenges that must be addressed and the therapeutic potential of CAR T cells in the setting of solid tumors.

Clinical experiences with CD19 T-cell trials demonstrating that CAR T cells accumulate in the cerebrospinal fluid (CSF) and reduce the incidence of metastatic leukemic disease in the brain[19,85] have raised enthusiasm for evaluating this therapy for malignant brain tumors. To date, most trials have focused on treatment of glioblastoma (GBM), but significant efforts are also being applied to pediatric brain tumors and tumors that metastasize to the brain. One of the first examples of CAR T-cell use in brain tumors targeted the glioma-associated protein IL-13 receptor alpha 2 (IL13Rα2).[86–88] Initial clinical findings demonstrate that local delivery of IL13Rα2-targeted CAR T cells into the tumor and/or CSF is safe[89] and, remarkably, has elicited a CR in a patient with recurrent multifocal GBM, including metastatic lesions in the spine.[80] Clinical trials have also demonstrated safety for targeting other GBM-associated antigens, including HER2 and EGFRvIII,[90,91] supporting the notion that even immune-specialized sites such as the brain will be amenable to CAR therapy.

One of the significant challenges for solid tumor CAR T-cell therapy is that many antigens are not restricted to tumor cells, and targeting such antigens risks on-target/off-tumor toxicities. In addition, tumor heterogeneity and the existence of several mechanisms that contribute to tumor escape, including tumor cell plasticity,[92] raises the concern that many antigens might need to be targeted to induce a durable response and overcome selecting clonal variants that are resistant to therapy. Use of mixed, dual, tandem, or transient CARs aims to address this concern and is currently being investigated.[93–95] Other studies have demonstrated the potential of affinity tuning CARs to induce antitumor effects only in the presence of amplified tumor-associated antigen ex-

pression.[96,97] Solid tumors are also heterogeneous in terms of composition, and immunosuppressive components of the microenvironment can impact CAR T-cell activity.[98,99] Approaches to mitigate immunosuppression include combining CAR T cells with inhibitors of immune checkpoints (eg, PD-1), use of cytokines to remodel the microenvironment, and preconditioning of patients.[100–108]

Another complex issue is effective delivery and trafficking of CAR T cells to the solid tumors. Although different routes of delivery present with advantages and disadvantages, preclinical studies using several tumor models suggest that locoregional delivery may be more effective than systemic delivery for solid tumors.[86,109–111] However, these findings will need to be refined in clinical trials.[80,89,112,113] In addition, some studies suggest that matching the tumor-derived chemokine profile with the chemokine receptors expressed on CAR T cells may improve trafficking to the tumor.[114–116] Once the CAR T cells reach the tumor site, their efficacy may be limited if sufficient numbers do not widely infiltrate the tumor. To address this barrier, some research groups are designing CAR T cells that target tumor stroma.[117–119]

Overall, there is active investigation into the potential of expanding CAR T-cell therapy to the treatment of solid tumors. As more light is shed on solid tumor features that impact T-cell biology, optimized CAR designs can be developed that effectively treat solid tumors.[120]

Virus-Specific Cellular Therapy

Infections and posttransplant lymphoproliferative disorder are complications that can occur after HSCT, and subsequently contribute to procedure-related mortality and morbidity.[121] Some studies have shown that matched donor-derived virus-specific T cells specific for Epstein-Barr virus (EBV), cytomegalovirus (CMV), or adenovirus are effective at managing viral infections in patients who have undergone transplantation.[122–126] However, some factors, including appropriate HLA-restricted donor availability, immune status of the patient, and time needed to generate the cell products (40–60 days), may limit use of this technology.[121,127] Strategies are being explored to address this issue, including developing banks of virus-specific T cells, which would significantly improve treatment feasibility.[121,127]

Surveillance

Data regarding long-term clinical effects of CAR T cells are currently sparse, and there is a need for follow-up and survivorship monitoring. Some known effects of CAR T-cell therapy in B-cell lineage–targeting are B-cell aplasia and hypogammaglobulinemia.[20,49,128] However, with frequent monitoring of immunoglobulin G (IgG) levels, hypogammaglobulinemia can be corrected with intravenous or subcutaneous IgG replacement therapy.[63] Patients should also be screened for hepatitis B and C and HIV prior to CAR T-cell infusion to prevent viral reactivation. Although no consensus exists on the impact of vaccination in patients with persistent CAR T cells against B-cell lineage, data show that CD19-negative plasma cells can retain B cell–independent humoral immunity despite persistent CD19 targeting and B-cell aplasia.[129]

Another issue that must be considered is the development of infections, both in the acute period following CAR T-cell infusions[130] and in long-term follow-up, where it has yet to be determined whether prolonged B-cell aplasia increases risk of infection. Routine surveillance for disease recurrence is also important, given uncertainty regarding the durability of remission, with some targets likely having curative potential in a subset of patients, and other targets only providing a limited period of remission.[28–30]

With initial gene therapy studies, there were reports of the development of lymphoproliferative disorders secondary to transgene insertional mutagenesis.[131] With more modern technologies, the risk of insertional mutagenesis is lower,[132] but monitoring in the follow-up period remains important. In clinical trials, patients undergo routine sampling during long-term follow-up to test for ongoing persistence of CAR T cells, and testing of clonality is included if clinically indicated. Although no reports of a lymphoproliferative disorder have been reported in CAR T-cell studies, a single case report described a patient in whom antigen-negative tumor cells expressed the CAR.[133] It was determined that during the culture for CAR T-cell manufacturing, an antigen-negative tumor cell was transduced by the vector and subsequently infused into the patient.[133] Such scenarios and their impact require further clinical investigation. To minimize the potential for inclusion of non-targeted leukemic cells taking up CAR vectors, it may be advantageous to deplete malignant cells from the starting apheresis product or to select for CD4/

CD8 T cells to enhance T-cell activity while minimizing risk of reinfusion of a malignant cell.[22]

An additional area of interest is monitoring for replication-competent lentivirus (RCL) or replication-competent retrovirus. Vectors used for transduction during CAR T-cell manufacturing are replication-incompetent, but there is a theoretical risk of vector rearrangement to create a replication-competent virus or potentially activate proto-oncogenes. In clinical trials, there have been no reports of RCL in patients who received CAR T-cell infusions using the vesicular stomatitis virus G protein as a marker.[134] For long-term analysis, the FDA requires that clinical study sponsors using investigational new drugs involving gene therapy test patient samples for replication-competent virus at 3, 6, and 12 months postinfusion in the first year and, if samples are negative, bank samples yearly through year 15 postinfusion. In clinical trials that used lentiviral vectors for transduction, there have been a few reports of false-positive HIV test results.[135–137] This test result is based on the amplification of HIV long terminal repeat sequence, and the result appeared to be assay-dependent in one report.[135] Based on these findings, it is important to educate treated patients that false-positive results for HIV may occur. The lack of standardized and commercially available tests to measure CAR T-cell persistence is a challenge.

As more patients are treated with CAR T-cell therapies, clinicians will need to counsel patients accordingly. The Foundation for the Accreditation of Cellular Therapy (FACT) has developed new standards specific to the use of immune effector cells (IECs), including gene-modified T cells, which outline guidelines for monitoring and reporting of patient outcomes.[138] Integration of such programs by study sponsors will provide more insight in this area.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- Solid tumors present many complex barriers to CAR T-cell therapy; however, this active area of investigation has the potential to develop novel strategies to overcome specific challenges in solid tumors.
- Emerging data suggest a role for donor-derived and off-the-shelf virus-specific T cells to manage viral infections.
- Standardized procedures for monitoring CAR T-cell persistence and disease surveillance are needed to determine potential long-term effects of CAR T-cell therapy. The task force recommends the following guidelines:
  - Frequency of follow-up: beginning on day 28 postinfusion of CAR T cells and assuming resolution of acute toxicities, patients should be monitored every 3 months for up to a year (or as clinically indicated). If the patient is fit and in remission, bearing in mind the FDA requirement of at least 15 years of follow-up, subsequent visits may be spaced out as clinically indicated.
  - CAR T-cell persistence: for CD19 CAR T cells, a reliable surrogate for CAR T-cell persistence is the absence of circulating CD19 cells. As such, flow cytometric measurement of circulating CD19 lymphocytes should be performed at each follow-up visit. More specific testing for circulating CAR T cells is not readily available clinically, but is often incorporated into clinical trial testing.
  - Disease surveillance: although recommendations in this area are malignancy-dependent, in general for commercially treated R/R Philadelphia chromosome (Ph)–negative ALL and R/R DLBCL, response assessments via imaging and other necessary measures should be performed at day 28 and month 3. Assuming CR, surveillance should be considered every 6 months for 2 years, and subsequently as needed. If a patient is not in CR, clinical judgement is warranted. For Ph-positive ALL, molecular monitoring of peripheral blood may ease follow-up, and can be performed every 3 months if the patient is in complete molecular response 3 months post–CAR T-cell therapy.
  - Additional follow-up measures should include IgG and B-cell/T-cell recovery monitoring, with considerations for antimicrobial and intravenous immunoglobulin prophylaxis until recovery occurs, and revaccination similar to guidelines for autologous transplantation.[139]

Operational Considerations

Program Initiation and Institutional Organization

The process of launching FDA-approved CAR T-cell products at cancer centers or institutions involves several important components driven by the institutions and manufacturers, including site audits by the manufacturers, implementing required Risk Evaluation and Mitigation Strategies (REMS) for approved products, developing trade agreements/contracts, pharmacy coordination, setting patient selection criteria, social work screening, prior authorization, payor contracts or single-case agreements, establishing product ordering and institution review processes, developing training and educational processes, and systems for data management and event reporting. The process of securing prior authorization at institutions varies and can take anywhere from a few days to several weeks. Adverse events need to be reported to the FDA or the pharmaceutical sponsor as part of the REMS program, although there is variability regarding what grade event is reported, and some institutions only report events that are grade ≥3.

In addition, although policies and protocols may vary across institutions, dedicated and trained key personnel in each of the clinical and administrative departments that manage work associated with CAR T-cell therapy and agreed-upon workflow processes are essential to help facilitate cross-departmental communication and cross-functional collaboration. Some of these departments include regulatory and quality assurance, finance/legal contracting, apheresis, cell therapy laboratory, outpatient oncology clinic, and inpatient oncology unit. Furthermore, education, training, and collaboration are required across multiple departments, including intensive care unit (ICU)/critical care, emergency medicine, infectious disease, cardiology, and neurology. As clinical operations continue to develop, ideally a balance between standard of care and research programs will continue to evolve and improve these processes. Patient-selection protocols between research and standard of care will also continue to be important.

Program and Infrastructure Development

Each organization that endeavors to deliver CAR T-cell therapy will have a unique challenge, depending on where they are starting. Given the variety of services involved in CAR T-cell therapy, including patient intake/selection, financial clearance, cell collection and processing, treatment, and monitoring in ambulatory and inpatient settings, organizational assessment and program planning are warranted. In such an assessment, a key decision point will be whether current facilities have the capacity to scale to predicted volume levels or whether additional and/or separate units are needed. Prior to establishing a program, it will be critical to conduct service utilization analysis, metrics, and data development, which will help the institution better understand the service impact and provide a foundation for demand forecasting. Key factors to consider for program development include the desired medical practice and patient care model, clinical and administrative resource needs and reporting structure, teaming concepts, and space planning. Additionally, workflow and process design for work within and across departments and the development of daily management systems can provide a foundation for optimal patient flows and continuous improvement.

Dedicated cellular immunotherapy programs can be developed, with integration across administrative departments, ambulatory clinics, bone marrow transplantation, and inpatient and outpatient services. When developing a model of care, having well-defined care pathways to provide the patient with uninterrupted access to required services in a continuous flow is crucial to minimize treatment delays. The size and scale of a program may also determine how quickly a service can be created. Patients may also need to transition to an inpatient setting to manage toxicities or other acute care needs. Some of the benefits of dedicated integrated programs include having specialized teams for infusion or triage, enhanced communication through proximity, quick turnaround times for laboratory results or reduced wait times, and overall increased standardization of processes. If departments and services are not integrated, potential challenges can arise before and after CAR T-cell infusion when transitioning patients to other departments (ie, ensuring that there are appropriate staff to manage the patients) and ensuring a continuity of care.

Given the potential toxicities that occur with CAR T-cell therapy, short- and long-term continual cross-care is likely needed between departments to ensure that optimal care is delivered. In addition, given the many variables involved in implementation and conduct of clinical trials, it may be diffi-

cult to forecast patient volumes, and this will require continual refinement.

Psychosocial Support

As a critical part of the clinical team, oncology social workers provide psychosocial assessments to gather information from patients and their families regarding their strengths and resources, and to identify barriers that may affect treatment. They also offer education and support in terms of advance directives and provide referral to mental health resources when appropriate. Some barriers to treatment include stressors outside of the diagnosis (eg, other life responsibilities, such as career/family) and financial constraints, considering that most patients have likely undergone several rounds of prior therapy, and may find it difficult to also cover costs associated with transportation and local housing, if needed. Some patients may also struggle to access required financial documentation, including insurance documents and most recent tax return. In these cases, oncology social workers can help patients secure appropriate lodging during the treatment. In an effort to mitigate costs to patients, some manufacturers, in concert with institutions, have started support programs to provide travel and copay assistance and facilitate treatment access.

Implementing Institutional Protocols

Multidepartmental infrastructure management is critical for CAR T-cell therapy. In original data from the ELIANA trial, 59% of patients were admitted to the ICU, with a median stay of 8 days.[140] Similarly, grade ≥3 adverse events seen in the ZUMA-1 trial[141] suggest that intensive management is required to safely administer CAR T-cell therapy. Therefore, comprehensive training of inpatient and outpatient clinic staff (eg, physicians, certified physician assistants, advanced registered nurse practitioners, and pharmacists) who manage patients undergoing CAR T and other gene-modified cellular therapy is required. To develop a consistent approach for managing CAR T-cell–associated toxicities, the CAR-T-cell-therapy-associated TOXicity (CARTOX) Working Group was formed, with representatives from multiple institutions and medical disciplines.[63] The CARTOX committee also proposed algorithms for managing CAR T-cell–associated toxicities[63,65] that can be incorporated into data management systems. Of note, the American Society for Blood and Marrow Transplantation recently held a meeting to discuss the development of a new singular consensus scale for grading toxicities based on 2 current algorithms—one of which is the CARTOX algorithm—and this scale will be published in the coming months.

Based on experience from the CARTOX program at The University of Texas MD Anderson Cancer Center, all new TCR T cell, natural killer cell, and CAR T-cell clinical programs are presented to the CARTOX group before patients are enrolled. Weekly meetings are held to discuss CAR T-cell or TCR T-cell inpatients, with a focus on ICU patients, and algorithms for diagnosis and management toxicities are developed and revised as needed. Toxicity and efficacy outcomes data for each protocol are presented by the principal investigator of the study annually. Other institutions also have initial reviews conducted by similar working groups, and subsequently, the NCI requires that these protocols are also reviewed by the institutional review board and protocol review and monitoring committees. In addition, as previously mentioned, FACT has published standards for IEC therapy, which were used in the development of the CARTOX program. As more programs emerge, securing FACT accreditation for common standards in IEC therapies in addition to HSCT will be an essential component for institutions delivering CAR T-cell therapies.

Cost and Coverage Considerations

With limited therapeutic options, the FDA approval of CAR T-cell therapies represents a major advancement in the management of R/R ALL and DLBCL. A recent report from the Institute for Clinical and Economic Review concluded that the cost of approved CAR T-cell products aligns with clinical benefit.[142] However, steep costs and limited authorized centers are major barriers to patient access. Presently, authorized centers administer tisagenlecleucel at price points of $475,000 for R/R ALL and $373,000 for R/R DLBCL, and axicabtagene ciloleucel at a price point of $373,000 for R/R DLBCL. Most commercially insured patients have coverage for at least one of the approved products, but some specific plans or employer-sponsored groups may have limitations on patient clinical eligibility.

To fully estimate the costs associated with CAR T-cell therapy, all aspects of therapy must be considered, including the costs of the product, apheresis, bridging chemotherapy, lymphodepletion, CAR T-cell infusion, inpatient stay (the average length of stay for CAR T-cell treatment is approximately 2–3 weeks), ICU, ambulatory clinical care, laboratory services, and mechanisms for FDA-mandated disease surveillance, including PET scans. It is important to incorporate these estimated costs into agreements with manufacturers to begin to build a framework for standardization in the protocols for insurance coverage. Additionally, controversy exists about whether the product should be "marked up" (ie, billed at a multiple of the purchase price) on par with other drugs due to its very high list price. Without billing through the markup mechanism, institutions have very little opportunity to recoup the significant processing and quality assurance costs associated with shipping, handling, and receiving of the cells when the manufacturer does not reimburse for them. As CAR T-cell treatment becomes more established and expands to other disease sites, the main financial onus is on treatment centers. Many academic medical centers have taken an early-adopter, mission-related risk, understanding that there will be significant financial losses for the first several years as government payers determine their reimbursement strategies.

Based on current institutional experience, manufacturers and payers will likely be looking for centers that have demonstrated clinical trial expertise with CAR T-cell therapy and are compliant with FACT accreditation. Government payers will vary in their coverage and reimbursement policies. Few pediatric Medicaid programs publicly post their coverage policies, but several (Massachusetts, California, and New York) have publicly posted that they will begin coverage of CAR T-cell therapy. The Centers for Medicare & Medicaid Services (CMS) uses codes based on the International Classification of Diseases (ICD) to process reimbursement for inpatient care, and there is an ICD-10 code assigned to the procedure of infusing CAR T-cell products; in fiscal year 2019, this code will be used to assign inpatient CAR T-cell administration to a specific Medicare Severity Diagnosis Related Group (MS-DRG 016 "Autologous Bone Marrow Transplant with CC/MCC or T-cell Immunotherapy").[143] As the field expands, additional codes will be needed to more specifically identify individual products and the differing level of severity of cases based on toxicities.

In the Medicare outpatient setting, CMS has issued drug payment codes specific to each product that correspond to payment at the standard drug rate of average sales price (ASP) + 6%. Use of the outpatient payment rate is complicated by the fact that payment defaults to the inpatient rate if a patient is admitted to the hospital within a set period after outpatient infusion; due to this discrepancy, provider societies are seeking a mechanism for site-neutral and equitable reimbursement for provision of CAR T-cell therapy. Separate from the reimbursement mechanism, CMS recently began a national coverage analysis for CAR T-cell therapy that will be in process until May 2019.

Considering the demography of patients with cancer and that patients on Medicare can represent a significant portion of the patient population, a reimbursement solution that covers the issues outlined is paramount. Medicare finalized the Inpatient Prospective Payment System guidelines in early August 2018, but they included limited relief for CAR T-cell therapies. The 2 CAR T-cell products will receive new technology add-on payment (NTAP) status and CAR T-cell therapy was assigned to a specific MS-DRG for payment purposes. However, the NTAP payment is limited to a maximum of half the product cost ($186,500) and the base MS-DRG rate is approximately $39,000, which leaves hospitals still substantially short of full reimbursement for incurred costs. If the Medicare reimbursement shortfall continues, increasing pressure will be placed on manufacturers to lower the cost of the product. In the long term, if these issues remain unresolved, this may limit the ability of institutions to keep in step with developments in future CAR T-cell therapy products.

Conclusions and NCCN CAR T-Cell Therapy Task Force Recommendations

- Initiating programs for CAR T-cell products at institutions requires significant specialized expertise, resources, investment, and organization.
- Psychosocial support is an integral part of CAR T-cell–associated patient care.
- Accreditation via FACT is crucial when securing and implementing CAR T-cell therapy–related institutional protocols.

- CAR T-cell therapy is being performed in an outpatient setting in some centers. The task force recommends close monitoring and rapid transition to an inpatient setting at the first sign or symptom of toxicity to manage acute toxicities and minimize the possibility of a serious adverse event.
- Improved standardized reimbursement structures are needed to enhance the use of CAR T-cell therapy in cancer management.

Conclusions

CAR T-cell therapy represent a significant shift in the landscape of anticancer therapy. This class of therapeutics was recognized as the advancement of the year in the 2018 ASCO annual report.[144] Tremendous advancements have been made in durable remissions in aggressive B-cell leukemias and lymphomas, and emerging studies suggest potential in other disease sites. The NCCN CAR T-Cell Therapy Task Force discussed these data and identified areas that need to be developed to enhance clinical uptake of this new technology. Based on discussion, considerable interest exists in developing CAR T-cell–specific guidelines. Although ideal, the task force recognizes that it will be challenging to establish uniform approaches for all CAR T-cell therapies at this juncture because of heterogeneous product design, disease application, and clinical study design. However, as the data develop and mature, such guidelines will help stratify commonalities and differences in terms of product-specific management.

References

1. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med 2018;379:64–73.
2. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A 1989;86:10024–10028.
3. Eshhar Z, Waks T, Bendavid A, Schindler DG. Functional expression of chimeric receptor genes in human T cells. J Immunol Methods 2001;248:67–76.
4. Firor AE, Jares A, Ma Y. From humble beginnings to success in the clinic: chimeric antigen receptor-modified T-cells and implications for immunotherapy. Exp Biol Med (Maywood) 2015;240:1087–1098.
5. Kawalekar OU, O'Connor RS, Fraietta JA, et al. Distinct signaling of coreceptors regulates specific metabolism pathways and impacts memory development in CAR T cells. Immunity 2016;44:380–390.
6. Long AH, Haso WM, Shern JF, et al. 4-1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. Nat Med 2015;21:581–590.
7. van der Stegen SJ, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. Nat Rev Drug Discov 2015;14:499–509.
8. Almasbak H, Aarvak T, Vemuri MC. CAR T cell therapy: a game changer in cancer treatment. J Immunol Res 2016;2016:5474602.
9. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. Mol Ther 2009;17:1453–1464.
10. Hay KA, Turtle CJ. Chimeric antigen receptor (CAR) T cells: lessons learned from targeting of CD19 in B-cell malignancies. Drugs 2017;77:237–245.
11. Fedorov VD, Themeli M, Sadelain M. PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses. Sci Transl Med 2013;5:215ra172.
12. Kershaw MH, Westwood JA, Darcy PK. Gene-engineered T cells for cancer therapy. Nat Rev Cancer 2013;13:525–541.
13. Crotta A, Zhang J, Keir C. Survival after stem-cell transplant in pediatric and young-adult patients with relapsed and refractory B-cell acute lymphoblastic leukemia. Curr Med Res Opin 2018;34:435–440.
14. Kantarjian HM, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. Cancer 2010;116:5568–5574.
15. O'Brien S, Thomas D, Ravandi F, et al. Outcome of adults with acute lymphocytic leukemia after second salvage therapy. Cancer 2008;113:3186–3191.
16. Ruella M, Maus MV. Catch me if you can: leukemia escape after CD19-directed T cell immunotherapies. Comput Struct Biotechnol J 2016;14:357–362.
17. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6:224ra25.
18. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129:3322–3331.
19. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385:517–528.
20. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507–1517.
21. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 2018;378:449–459.
22. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126:2123–2138.
23. Maude SL, Teachey DT, Rheingold SR, et al. Sustained remissions with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children with relapsed/refractory ALL [abstract]. J Clin Oncol 2016;34(Suppl 15):Abstract 3011.
24. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439–448.
25. Shah BD, Stock W, Wierda WG, et al. Phase 1 results of ZUMA-3: KTE-C19, an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in adult patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) [abstract]. Blood 2017;130(Suppl 1):Abstract 888.
26. Shah BD, Wierda WG, Schiller GJ, et al. Updated results from ZUMA-3, a phase 1/2 study of KTE-C19 chimeric antigen receptor (CAR) T cell therapy, in adults with high-burden relapsed/refractory acute lymphoblastic leukemia (R/R ALL) [abstract]. J Clin Oncol 2017;35(Suppl 15):Abstract 3024.
27. Braig F, Brandt A, Goebeler M, et al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. Blood 2017;129:100–104.
28. Fischer J, Paret C, El Malki K, et al. CD19 isoforms enabling resistance to CART-19 immunotherapy are expressed in B-ALL patients at initial diagnosis. J Immunother 2017;40:187–195.
29. Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. Nat Med 2018;24:20–28.

30. Gardner R, Wu D, Cherian S, et al. Acquisition of a CD19-negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T-cell therapy. Blood 2016;127:2406–2410.
31. Jacoby E, Nguyen SM, Fountaine TJ, et al. CD19 CAR immune pressure induces B-precursor acute lymphoblastic leukaemia lineage switch exposing inherent leukaemic plasticity. Nat Commun 2016;7:12320.
32. Rayes A, McMasters RL, O'Brien MM. Lineage switch in MLL-rearranged infant leukemia following CD19-directed therapy. Pediatr Blood Cancer 2016;63:1113–1115.
33. Shalabi H, Kraft IL, Wang HW, et al. Sequential loss of tumor surface antigens following chimeric antigen receptor T-cell therapies in diffuse large B-cell lymphoma. Haematologica 2018;103:e215–218.
34. Sotillo E, Barrett DM, Black KL, et al. Convergence of acquired mutations and alternative splicing of CD19 enables resistance to CART-19 immunotherapy. Cancer Discov 2015;5:1282–1295.
35. Maude SL, Pulsipher MA, Boyer MW, et al. Efficacy and safety of CTL019 in the first US phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: results of an interim analysis [abstract]. Blood 2016;128:Abstract 2801.
36. Maude SL, Shpall EJ, Grupp SA. Chimeric antigen receptor T-cell therapy for ALL. Hematology Am Soc Hematol Educ Program 2014;2014:559–564.
37. Riddell SR, Sommermeyer D, Berger C, et al. Adoptive therapy with chimeric antigen receptor-modified T cells of defined subset composition. Cancer J 2014;20:141–144.
38. Qin H, Haso W, Nguyen SM, Fry TJ. Preclinical development of bispecific chimeric antigen receptor targeting both CD19 and CD22 [abstract]. Blood 2015;126:Abstract 4427.
39. Qin H, Nguyen SM, Ramakrishna S, et al. Novel CD19/CD22 bicistronic chimeric antigen receptors outperform single or bivalent cars in eradicating CD19+CD22+, CD19-, and CD22- pre-B leukemia [abstract]. Blood 2017;130(Suppl 1):Abstract 810.
40. Shah NN, Stevenson MS, Yuan CM, et al. Characterization of CD22 expression in acute lymphoblastic leukemia. Pediatr Blood Cancer 2015;62:964–969.
41. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800–1808.
42. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. Hematology Am Soc Hematol Educ Program 2011;2011:498–505.
43. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant 2016;51:51–57.
44. Abramson JS, Palomba ML, Gordon LI, et al. High durable CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort [abstract]. Blood 2017;130(Suppl 1):Abstract 581.
45. Neelapu SS, Locke FL, Bartlett NL, et al. Long-term follow-up ZUMA-1: a pivotal trial of axicabtagene ciloleucel (Axi-Cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL) [abstract]. Blood 2017;130(Suppl 1):Abstract 578.
46. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531–2544.
47. Schuster SJ, Bishop MR, Tam CS, et al. Primary analysis of Juliet: a global, pivotal, phase 2 trial of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma [abstract]. Blood 2017;130(Suppl 1):Abstract 577.
48. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med 2017;377:2545–2554.
49. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Mol Ther 2017;25:285–295.
50. Locke FL, Ghobadi A, Jacobson CA, et al. Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma [abstract]. J Clin Oncol 2018;36(Suppl):Abstract 3003.
51. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood 2016;128:1688–1700.
52. Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. J Clin Oncol 2018;36:2267–2280.
53. Kim MY, Yu KR, Kenderian SS, et al. Genetic inactivation of CD33 in hematopoietic stem cells to enable CAR T cell immunotherapy for acute myeloid leukemia. Cell 2018;173:1439–1453.e19.
54. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 2015;7:303ra139.
55. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med 2011;365:725–733.
56. Ramos CA, Ballard B, Zhang H, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-redirected lymphocytes. J Clin Invest 2017;127:3462–3471.
57. Turtle CJ, Hay KA, Hanafi LA, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol 2017;35:3010–3020.
58. Wang CM, Wu ZQ, Wang Y, et al. Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial. Clin Cancer Res 2017;23:1156–1166.
59. Berdeja JG, Lin Y, Raje NS, et al. First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: updated results [abstract]. J Clin Oncol 2017;35(Suppl):Abstract 3010.
60. Fan F, Zhao W, Liu J, et al. Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma [abstract]. J Clin Oncol 2017;35(Suppl):Abstract LBA3001.
61. Raje NS, Berdeja JG, Lin Y, et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: updated results from a multicenter phase I study [abstract]. J Clin Oncol 2018;36(Suppl):Abstract 8007.
62. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321–3330.
63. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47–62.
64. Halton E, Llerandi D, Diamonte C, et al. Developing infrastructure: managing patients with cancer undergoing CAR T-cell therapy. Clin J Oncol Nurs 2017;21:35–40.
65. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188–195.
66. Porter D, Frey N, Wood PA, et al. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel [published correction appears in J Hematol Oncol 2018;11:81]. J Hematol Oncol 2018;11:35.
67. Locke FL, Neelapu SS, Bartlett NL, et al. Preliminary results of prophylactic tocilizumab after axicabtageneciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-Hodgkin lymphoma (NHL) [abstract]. Blood 2017;130(Suppl 1):Abstract 1547.
68. Chen F, Teachey DT, Pequignot E, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J Immunol Methods 2016;434:1–8.
69. Giavridis T, van der Stegen SJ, Eyquem J, et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 2018;24:731–738.
70. Kenderian SS, Ruella M, Shestova O, et al. Ruxolitinib prevents cytokine release syndrome after CART cell therapy without impairing the anti-tumor effect in a xenograft model [abstract]. Blood 2016;128:Abstract 652.
71. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med 2018;24:739–748.
72. Shah NN, Shalabi H, Yates B, et al. Beyond cytokine storm: optimizing treatment strategies to target the complex interplay between CAR mediated inflammatory response, disseminated intravascular coagulation and macrophage activation syndrome [abstract]. Blood 2017;130(Suppl 1):Abstract 1277.
73. Hu Y, Sun J, Wu Z, et al. Predominant cerebral cytokine release syndrome in CD19-directed chimeric antigen receptor-modified T cell therapy. J Hematol Oncol 2016;9:70.
74. Lacey SF, Shaw PA, Teachey DT, et al. Biomarker profiling differentiates sepsis from cytokine release syndrome in chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia (ALL) [abstract]. Blood 2016;128:Abstract 2812.

75. Santomasso BD, Park JH, Salloum D, et al. Clinical and biologic correlates of neurotoxicity associated with CAR T cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov 2018;8:958–971.
76. Teachey DT, Lacey SF, Shaw PA, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Cancer Discov 2016;6:664–679.
77. Wang Z, Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. Biomark Res 2018;6:4.
78. Hay KA, Gauthier J, Hirayama AV, et al. Factors impacting disease-free survival in adult B cell B-ALL patients achieving MRD-negative CR after CD19 CAR-T cells [abstract]. J Clin Oncol 2018;36(Suppl):Abstract 7005.
79. Gust J, Hay KA, Hanafi LA, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov 2017;7:1404–1419.
80. Brown CE, Alizadeh D, Starr R, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. N Engl J Med 2016;375:2561–2569.
81. Kueberuwa G, Kalaitsidou M, Cheadle E, et al. CD19 CAR T cells expressing IL-12 eradicate lymphoma in fully lymphoreplete mice through induction of host immunity. Mol Ther Oncolytics 2018;8:41–51.
82. Sampson JH, Choi BD, Sanchez-Perez L, et al. EGFRvIII mCAR-modified T-cell therapy cures mice with established intracerebral glioma and generates host immunity against tumor-antigen loss. Clin Cancer Res 2014;20:972–984.
83. Abken H. Driving CARs on the highway to solid cancer: some considerations on the adoptive therapy with CAR T cells. Hum Gene Ther 2017;28:1047–1060.
84. Castellarin M, Watanabe K, June CH, et al. Driving cars to the clinic for solid tumors. Gene Ther 2018;25:165–175.
85. Abramson JS, McGree B, Noyes S, et al. Anti-CD19 CAR T cells in CNS diffuse large-B-cell lymphoma. N Engl J Med 2017;377:783–784.
86. Brown CE, Aguilar B, Starr R, et al. Optimization of IL13Ralpha2-targeted chimeric antigen receptor T cells for improved anti-tumor efficacy against glioblastoma. Mol Ther 2018;26:31–44.
87. Brown CE, Starr R, Aguilar B, et al. Stem-like tumor-initiating cells isolated from IL13Ralpha2 expressing gliomas are targeted and killed by IL13-zetakine-redirected T Cells. Clin Cancer Res 2012;18:2199–2209.
88. Kahlon KS, Brown C, Cooper LJ, et al. Specific recognition and killing of glioblastoma multiforme by interleukin 13-zetakine redirected cytolytic T cells. Cancer Res 2004;64:9160–9166.
89. Brown CE, Badie B, Barish ME, et al. Bioactivity and safety of IL13Ralpha2-redirected chimeric antigen receptor CD8+ T cells in patients with recurrent glioblastoma. Clin Cancer Res 2015;21:4062–4072.
90. Ahmed N, Brawley V, Hegde M, et al. HER2-specific chimeric antigen receptor-modified virus-specific T cells for progressive glioblastoma: a phase 1 dose-escalation trial. JAMA Oncol 2017;3:1094–1101.
91. O'Rourke DM, Nasrallah MP, Desai A, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med 2017;9:eaaa0984.
92. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–674.
93. Beatty GL, Haas AR, Maus MV, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. Cancer Immunol Res 2014;2:112–120.
94. Hegde M, Mukherjee M, Grada Z, et al. Tandem CAR T cells targeting HER2 and IL13Ralpha2 mitigate tumor antigen escape. J Clin Invest 2016;126:3036–3052.
95. Kloss CC, Condomines M, Cartellieri M, et al. Combinatorial antigen recognition with balanced signaling promotes selective tumor eradication by engineered T cells. Nat Biotechnol 2013;31:71–75.
96. Caruso HG, Hurton LV, Najjar A, et al. Tuning sensitivity of CAR to EGFR density limits recognition of normal tissue while maintaining potent antitumor activity. Cancer Res 2015;75:3505–3518.
97. Liu X, Jiang S, Fang C, et al. Affinity-tuned ErbB2 or EGFR chimeric antigen receptor T cells exhibit an increased therapeutic index against tumors in mice. Cancer Res 2015;75:3596–3607.
98. McGray AJ, Hallett R, Bernard D, et al. Immunotherapy-induced CD8+ T cells instigate immune suppression in the tumor. Mol Ther 2014;22:206–218.
99. Moon EK, Wang LC, Dolfi DV, et al. Multifactorial T-cell hypofunction that is reversible can limit the efficacy of chimeric antigen receptor-transduced human T cells in solid tumors. Clin Cancer Res 2014;20:4262–4273.
100. Cherkassky L, Morello A, Villena-Vargas J, et al. Human CAR T cells with cell-intrinsic PD-1 checkpoint blockade resist tumor-mediated inhibition. J Clin Invest 2016;126:3130–3144.
101. Chmielewski M, Abken H. CAR T cells transform to trucks: chimeric antigen receptor-redirected T cells engineered to deliver inducible IL-12 modulate the tumour stroma to combat cancer. Cancer Immunol Immunother 2012;61:1269–1277.
102. Hanafi LA, Gauchat D, Godin-Ethier J, et al. Fludarabine downregulates indoleamine 2,3-dioxygenase in tumors via a proteasome-mediated degradation mechanism. PLoS One 2014;9:e99211.
103. John LB, Devaud C, Duong CP, et al. Anti-PD-1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells. Clin Cancer Res 2013;19:5636–5646.
104. Koneru M, Purdon TJ, Spriggs D, et al. IL-12 secreting tumor-targeted chimeric antigen receptor T cells eradicate ovarian tumors in vivo. Oncoimmunology 2015;4:e994446.
105. Mohammed S, Sukumaran S, Bajgain P, et al. Improving chimeric antigen receptor-modified T cell function by reversing the immunosuppressive tumor microenvironment of pancreatic cancer. Mol Ther 2017;25:249–258.
106. Ninomiya S, Narala N, Huye L, et al. Tumor indoleamine 2,3-dioxygenase (IDO) inhibits CD19-CAR T cells and is downregulated by lymphodepleting drugs. Blood 2015;125:3905–3916.
107. Prosser ME, Brown CE, Shami AF, et al. Tumor PD-L1 co-stimulates primary human CD8(+) cytotoxic T cells modified to express a PD1:CD28 chimeric receptor. Mol Immunol 2012;51:263–272.
108. Walter S, Weinschenk T, Stenzl A, et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med 2012;18:1254–1261.
109. Adusumilli PS, Cherkassky L, Villena-Vargas J, et al. Regional delivery of mesothelin-targeted CAR T cell therapy generates potent and long-lasting CD4-dependent tumor immunity. Sci Transl Med 2014;6:261ra151.
110. Katz SC, Point GR, Cunetta M, et al. Regional CAR-T cell infusions for peritoneal carcinomatosis are superior to systemic delivery. Cancer Gene Ther 2016;23:142–148.
111. Priceman SJ, Tilakawardane D, Jeang B, et al. Regional delivery of chimeric antigen receptor-engineered T cells effectively targets HER2(+) breast cancer metastasis to the brain. Clin Cancer Res 2018;24:95–105.
112. Katz SC, Burga RA, McCormack E, et al. Phase I hepatic immunotherapy for metastases study of intra-arterial chimeric antigen receptor-modified T-cell therapy for CEA+ liver metastases. Clin Cancer Res 2015;21:3149–3159.
113. You F, Jiang L, Zhang B, et al. Phase 1 clinical trial demonstrated that MUC1 positive metastatic seminal vesicle cancer can be effectively eradicated by modified anti-MUC1 chimeric antigen receptor transduced T cells. Sci China Life Sci 2016;59:386–397.
114. Craddock JA, Lu A, Bear A, et al. Enhanced tumor trafficking of GD2 chimeric antigen receptor T cells by expression of the chemokine receptor CCR2b. J Immunother 2010;33:780–788.
115. Di Stasi A, De Angelis B, Rooney CM, et al. T lymphocytes coexpressing CCR4 and a chimeric antigen receptor targeting CD30 have improved homing and antitumor activity in a Hodgkin tumor model. Blood 2009;113:6392–6402.
116. Moon EK, Carpenito C, Sun J, et al. Expression of a functional CCR2 receptor enhances tumor localization and tumor eradication by retargeted human T cells expressing a mesothelin-specific chimeric antibody receptor. Clin Cancer Res 2011;17:4719–4730.
117. Caruana I, Savoldo B, Hoyos V, et al. Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes. Nat Med 2015;21:524–529.
118. Lo A, Wang LS, Scholler J, et al. Tumor-promoting desmoplasia is disrupted by depleting FAP-expressing stromal cells. Cancer Res 2015;75:2800–2810.
119. Schuberth PC, Hagedorn C, Jensen SM, et al. Treatment of malignant pleural mesothelioma by fibroblast activation protein-specific re-directed T cells. J Transl Med 2013;11:187.
120. Mirzaei HR, Rodriguez A, Shepphird J, et al. Chimeric antigen receptors T cell therapy in solid tumor: challenges and clinical applications. Front Immunol 2017;8:1850.
121. Saudemont A, Jespers L, Clay T. Current status of gene engineering cell therapeutics. Front Immunol 2018;9:153.
122. Barker JN, Doubrovina E, Sauter C, et al. Successful treatment of EBV-associated posttransplantation lymphoma after cord blood transplantation

using third-party EBV-specific cytotoxic T lymphocytes. Blood 2010;116:5045–5049.

123. Comoli P, Basso S, Labirio M, et al. T cell therapy of Epstein-Barr virus and adenovirus infections after hemopoietic stem cell transplant. Blood Cells Mol Dis 2008;40:68–70.

124. Dong L, Gao ZY, Chang LJ, et al. Adoptive transfer of cytomegalovirus/Epstein-Barr virus-specific immune effector cells for therapeutic and preventive/preemptive treatment of pediatric allogeneic cell transplant recipients. J Pediatr Hematol Oncol 2010;32:e31–37.

125. Doubrovina E, Oflaz-Sozmen B, Prockop SE, et al. Adoptive immunotherapy with unselected or EBV-specific T cells for biopsy-proven EBV+ lymphomas after allogeneic hematopoietic cell transplantation. Blood 2012;119:2644–2656.

126. Papadopoulou A, Gerdemann U, Katari UL, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. Sci Transl Med 2014;6:242ra83.

127. O'Reilly RJ, Prockop S, Hasan AN, et al. Virus-specific T-cell banks for 'off the shelf' adoptive therapy of refractory infections. Bone Marrow Transplant 2016;51:1163–1172.

128. Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. Blood 2010;116:4099–4102.

129. Bhoj VG, Arhontoulis D, Wertheim G, et al. Persistence of long-lived plasma cells and humoral immunity in individuals responding to CD19-directed CAR T-cell therapy. Blood 2016;128:360–370.

130. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood 2018;131:121–130.

131. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 2003;302:415–419.

132. Scholler J, Brady TL, Binder-Scholl G, et al. Decade-long safety and function of retroviral-modified chimeric antigen receptor T cells. Sci Transl Med 2012;4:132ra53.

133. Lacey SF, Xu J, Ruella M, et al. Cars in leukemia: relapse with antigen-negative leukemia originating from a single B cell expressing the leukemia-targeting CAR [abstract]. Blood 2016;128:Abstract 281.

134. Cornetta K, Duffy L, Turtle CJ, et al. Absence of replication-competent lentivirus in the clinic: analysis of infused T cell products. Mol Ther 2018;26:280–288.

135. Ariza-Heredia EJ, Granwehr BP, Viola GM, et al. False-positive HIV nucleic acid amplification testing during CAR T-cell therapy. Diagn Microbiol Infect Dis 2017;88:305–307.

136. De Ravin SS, Gray JT, Throm RE, et al. False-positive HIV PCR test following ex vivo lentiviral gene transfer treatment of X-linked severe combined immunodeficiency vector. Mol Ther 2014;22:244–245.

137. Laetsch TW, Maude SL, Milone MC, et al. False-positive results with select HIV-1 NAT methods following lentivirus-based tisagenlecleucel therapy. Blood 2018;131:2596–2598.

138. Maus MV, Nikiforow S. The why, what, and how of the new FACT standards for immune effector cells. J Immunother Cancer 2017;5:36.

139. Palazzo M, Shah GL, Copelan O, et al. Revaccination after autologous hematopoietic stem cell transplantation is safe and effective in patients with multiple myeloma receiving lenalidomide maintenance. Biol Blood Marrow Transplant 2018;24:871–876.

140. Grupp SA, Laetsch TW, Buechner J, et al. Analysis of a global registration trial of the efficacy and safety of CTL019 in pediatric and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL) [abstract]. Blood 2016;128:Abstract 221.

141. Neelapu SS, Locke FL, Bartlett NL, et al. Kte-C19 (anti-CD19 CAR T Cells) induces complete remissions in patients with refractory diffuse large B-cell lymphoma (DLBCL): results from the pivotal phase 2 Zuma-1 [abstract]. Blood 2016;128:Abstract LBA-6.

142. Tice JA, Walsh JM, Otuonye I, et al. Chimeric antigen receptor T-cell therapy for B-cell cancers: effectiveness and value. https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf. Institute for Clinical and Economic Review. Published March 23, 2018. Accessed August 20, 2018.

143. Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2019 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Electronic Health Record (EHR) Incentive Programs (Promoting Interoperability Programs) Requirements for Eligible Hospitals, Critical Access Hospitals, and Eligible Professionals; Medicare Cost Reporting Requirements; and Physician Certification and Recertification of Claims. Final Rule. Federal Register 2018;83:41144–41784. Available at: https://www.federalregister.gov/d/2018-16766. Accessed August 21, 2018.

144. Heymach J, Krilov L, Alberg A, et al. Clinical cancer advances 2018: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 2018;36:1020–1044.