

# Optimizing the Value of CAR T-Cell Therapy: Managed Care Considerations From Recent Clinical Findings

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## HIGHLIGHTS

- › Balancing the CAR T: Perspectives on Efficacy and Safety of CAR T-Cell Therapy in Hematologic Malignancies
- › Improving Outcomes and Mitigating Costs Associated With CAR T-Cell Therapy
- › CE Sample Posttest

# Optimizing the Value of CAR T-Cell Therapy: Managed Care Considerations From Recent Clinical Findings

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## Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in scientific advances of CAR T-cell therapies.

## Activity Overview

Several factors have contributed to the widespread use of chimeric antigen receptor-modified (CAR) T-cell therapy in the treatment of B-cell malignancies. While the cost of CAR T-cell therapy can be more than twice that of standard oncology care, long-term benefits suggest a strong potential for their cost-effectiveness and improved gains in overall survival for patients. These considerations have spurred discussions about earlier initiation of CAR T-cell therapy in treatment algorithms for patients with aggressive B-cell malignancies. With emerging data on indications for therapy and financial regulations for CAR T-cell therapy, managed care professionals will be challenged by the increased volume of patients receiving CAR T-cell therapies and evolving payment and reimbursement schema. To facilitate patient access to these treatments, the multidisciplinary healthcare team must standardize processes for the integration of CAR T-cell therapies into the treatment landscape of patients with B-cell malignancies and determine optimal payment modalities to improve patient outcomes.

## Statement of Educational Need

Chimeric antigen receptor (CAR) T-cell therapy is now integrated in treatment algorithms for acute lymphoblastic leukemia, large B-cell and follicular lymphomas, and multiple myeloma, with research underway in solid tumors as well. In 2017, just 2 CAR T-cell therapies were available, but that number has expanded to 5, including the first CAR T-cell product approved for the treatment of multiple myeloma, and 2 therapies that were approved by the Food and Drug Administration (FDA) in the first 6 months of 2021. As new products gain FDA approval with more manageable toxicity profiles, and as institutions gain experience

with the management of these toxicities, outpatient administration and monitoring should be expected. Managed care professionals need to understand the magnitude of benefit of CAR T-cell therapy relative to other therapies in a given malignancy in addition to the risks for toxicity in order to understand the total cost of care. Payers and healthcare systems will be tasked with tackling the increasingly complex logistics of this powerful but high-cost form of immunotherapy. The cost of CAR T-cell therapy is estimated between \$373,000 and \$475,000 per infusion, not including patient care costs (eg, evaluation, apheresis, chemotherapy, and post-infusion care, including management of complications). Managed care providers should be aware of the barriers to optimal value and access that currently exist, as well as the numerous strategies being developed to tackle them, including improved safety and efficacy of CAR T-cell therapy, the potential for outpatient administration, streamlined manufacturing processes, and new payment and reimbursement mechanisms. Given the number of new products entering the market and significant cost burden of therapies, managed care professionals should understand the clinical trial data, toxicity profile, and place in therapy in lymphoma, myeloma, and acute lymphoblastic leukemia as well as guideline recommendations for adverse effect management associated with CAR T-cell therapies.

## Educational Objectives

Upon completion of this activity, participants will be able to:

- Explore the rationale for CAR T-cell therapy in hematologic malignancies.
- Analyze the evolving landscape of CAR T-cell therapy and the most recent data for new and emerging treatments.
- Investigate strategies being developed to improve outcomes and mitigate costs associated with CAR T-cell therapy.

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## Optimizing the Value of CAR T-Cell Therapy: Managed Care Considerations From Recent Clinical Findings

### OVERVIEW

Through this supplement to *The American Journal of Managed Care*<sup>®</sup>, managed care professionals will increase their knowledge of treatment and management of hematologic malignancies with CAR T-cell therapies.

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# Balancing the CAR T: Perspectives on Efficacy and Safety of CAR T-Cell Therapy in Hematologic Malignancies

Larry W. Buie, PharmD, BCOP, FASHP

## Chimeric Antigen Receptor (CAR) T-Cell Therapy

Innovations in immunotherapy have led to the development of multiple immune-targeted therapies to manage malignancy. Chimeric antigen receptor (CAR) T-cell therapy is designed to enhance the body's immune system to effectively kill malignant cells.<sup>1</sup> CAR T-cell therapy pivotal trials demonstrated unprecedented overall response rates (ORRs) and complete responses (CRs) that led to the FDA approval of 5 CAR T-cell products: tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), lisocabtagene maraleucel (liso-cel), brexucabtagene autoleucel (brexu-cel), and idecabtagene vicleucel (ide-cel). CAR T-cell therapies are limited by the potential to cause life-threatening toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In addition, challenges related to manufacturing a patient-specific product, need for inpatient administration in a tertiary care setting, high costs and inadequate reimbursement have limited access to CAR T-cell therapy.<sup>2,3</sup> Cellular therapy centers, manufacturers, payers, and policy makers will need to work together to address barriers to care as new CAR T-cell products with improved efficacy and tolerability are approved for use in more diverse malignancies.<sup>2</sup>

## Mechanism of Action

CAR T cells are T cells that have been genetically modified through transfection (DNA plasmid inclusion) or transduction (using viral vector) to transmit genes that will produce a new antigen recognition domain on the T-cell surface to facilitate cancer cell detection.<sup>4,5</sup> The CAR molecule consists of 3 parts: (1) an extracellular, antibody-derived, single-chain variable fragment to bind a specific antigen on the tumor cell with a hinge region, (2) a transmembrane domain (part of CD3, CD8, CD28, or FcεRI) and (3) an intracellular domain, consisting of the intracytoplasmic activating domain (CD28, CD27, CD134, CDB7, or CD3ζ) derived from the T-cell receptor with or without a second costimulatory factor (CD28 or 4-1BB) (Figure 1<sup>4</sup>). CAR T cells bind antigens independent of human leukocyte antigens (HLAs), an important feature because HLA downregulation is a key mechanism of cancer cell escape from immune surveillance.<sup>5</sup> Antigen escape

## ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy is an example of how immunotherapy is revolutionizing the treatment of hematologic malignancies with unprecedented response rates in patients with relapsed/refractory lymphoma, multiple myeloma, and acute lymphoblastic leukemia. The process for administering CAR T-cell therapy is complex, with multiple steps including CAR T-cell manufacturing, lymphodepleting chemotherapy, cellular therapy infusion, and management of short-term and long-term toxicities. While effective, broad use of CAR T-cell therapies is limited by potential for life-threatening toxicities, challenges related to manufacturing a patient-specific product, high costs and inadequate reimbursement, and incomplete or unsustained disease response. Pharmacists are intricately involved in the process of providing CAR T-cell therapy both at the organizational level of budgeting and coordinating therapy and in direct patient care roles providing counseling and support for adverse effect management. Research in CAR T-cell therapy is expected to improve tolerability and expand indications to more types of malignancies and earlier phases of disease. Managed care professionals should have an understanding of the clinical trial data and place in therapy in lymphoma, myeloma, and acute lymphoblastic leukemia as well as guideline recommendations for adverse effect management associated with CAR T-cell therapies.

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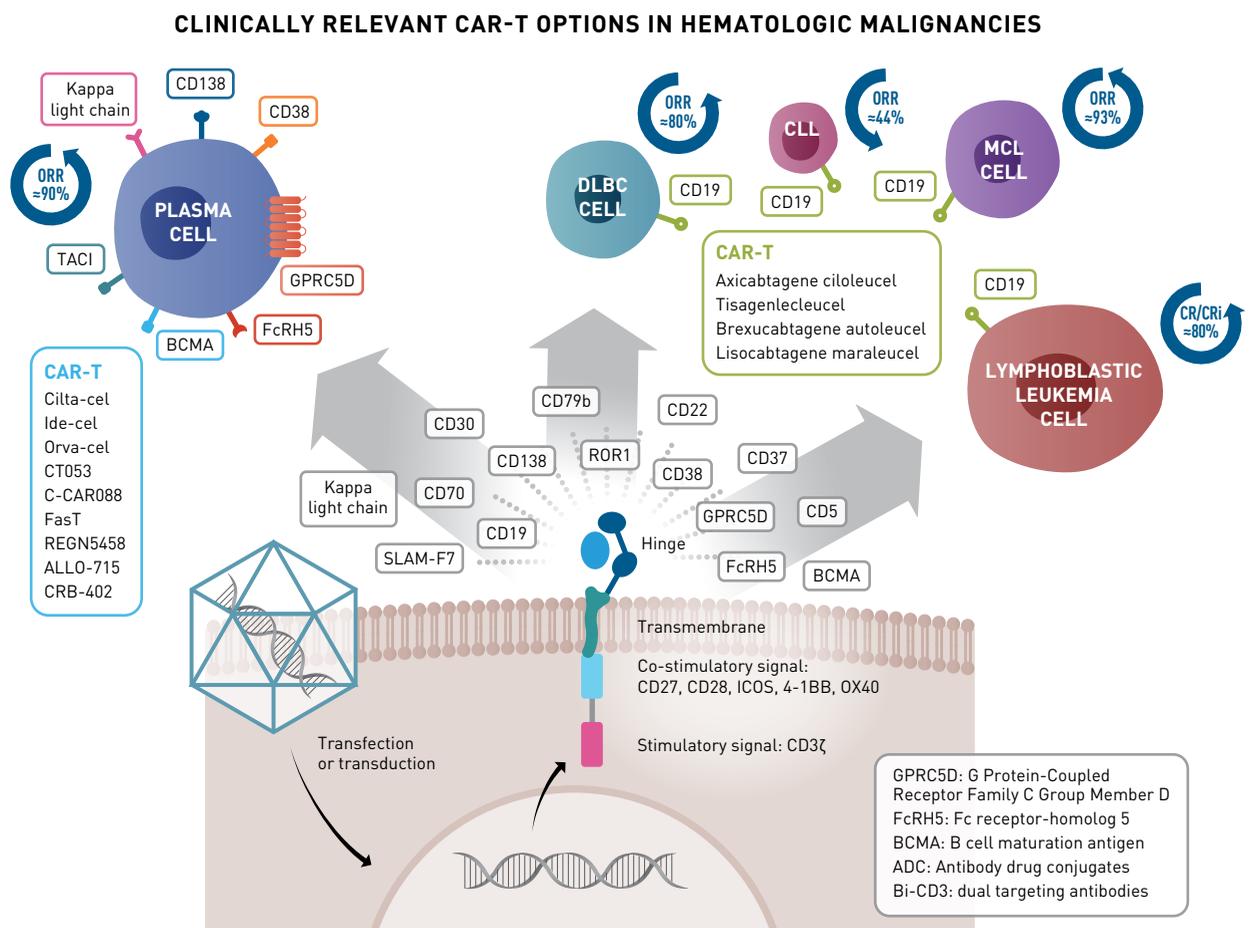
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and lack of CAR T-cell persistence are the most common causes of relapse after CAR T-cell therapy. CAR T-cell products currently approved by the FDA are considered “second generation” because they include an additional costimulatory domain such as 4-1BB or CD28 to improve persistence and potency.<sup>1</sup> To further augment the antitumor activity, a third-generation CAR is being developed with multiple costimulatory domains and a fourth-generation CAR contains a transduction domain to promote production of a T-cell-activating cytokine such as interleukin (IL)-1.<sup>6</sup> Strategies to reduce CAR T-cell-mediated toxicity include modifying the CAR hinge, transmembrane regions, or costimulatory domain; utilizing human/humanized antibody fragments instead of murine-derived CARs; including an “off switch”; and inhibiting macrophage and monocyte-activating cytokines.<sup>7</sup>

### Manufacturing/Administration Process

Currently FDA-approved, CAR T cells are manufactured from autologous T cells, collected from the patient via leukapheresis (Figure 2).<sup>5,6</sup> Manufacturing CAR T cells takes 2 to 4 weeks, during which time the cells undergo gene modification, expansion ex vivo, and freezing for subsequent re-infusion. The patient-specific CAR T-cell product is then transferred back to the hospital and is re-infused into the patient.<sup>6</sup> Patients receive lymphodepleting chemotherapy to enhance CAR T-cell expansion, proliferation, and persistence. Patients typically receive lymphodepleting chemotherapy with fludarabine and cyclophosphamide 2 to 14 days before receiving CAR T-cell infusion.<sup>3,8</sup> After CAR T-cell infusion, the chimeric receptor recognizes an antigen leading to effector cell activation, proliferation, and a milieu of cytokine release including IL-6, soluble IL-6

**FIGURE 1.** CAR T-Cell Use in Hematologic Malignancies<sup>4</sup>



CAR, chimeric antigen receptor; MCL, mantle cell lymphoma; DLBC, diffuse large B-cell.

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receptor, soluble IL-2Ra, interferon gamma (IFN- $\gamma$ ), and granulocyte-macrophage colony-stimulating factor (GM-CSF).<sup>8</sup>

Historically, CAR-T cell patients were observed in hospital after administration to monitor for development of toxicities including CRS.<sup>3</sup> With more experience, a more predictable clinical course, enhanced multidisciplinary care, and desire to minimize overall costs, there is growing interest in and increasing evidence supporting outpatient administration with appropriate thresholds for hospital admission if symptoms, such as fever, occur.<sup>9</sup> Risk Evaluation and Mitigation Strategy (REMS) programs for CAR T-cell therapy require patients to remain within 2 hours of the certified hospital (although some centers elect a smaller radius of 30-60 minutes) and its associated clinics for at least 4 weeks following CAR T-cell infusion. In addition, patients must have a dedicated caregiver present from the start of lymphodepleting chemotherapy through at least 30 days after infusion, and driving is restricted for the first 8 weeks following infusion.<sup>3</sup> Patients who do not reside near the certified hospital will need to arrange for temporary housing.

## FDA-approved CAR T-Cell Therapies in Hematologic Malignancies

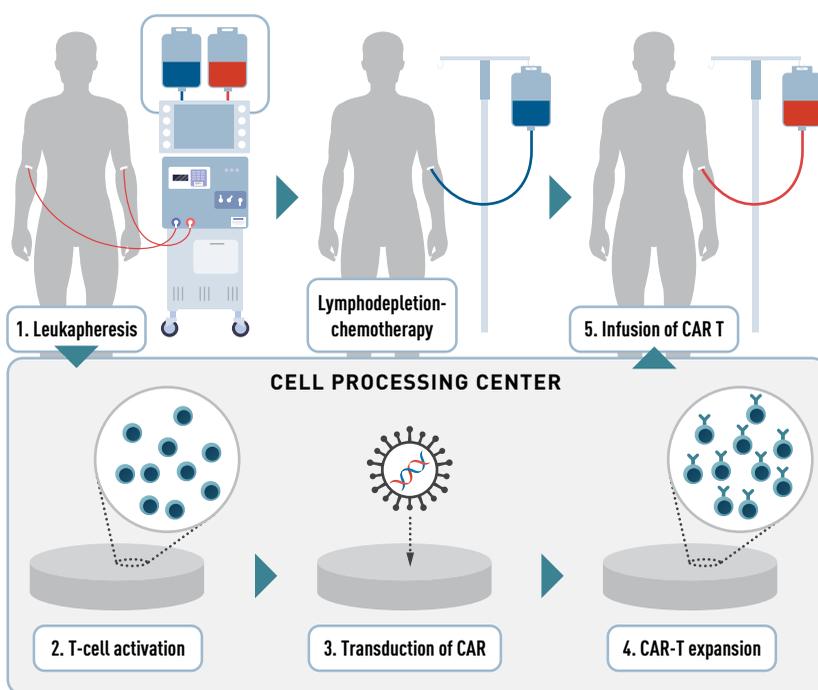
### Non-Hodgkin Lymphoma

#### Large B-cell lymphoma (LBCL)

Approximately 30% of patients with LBCL relapse after initial therapy or after salvage autologous stem cell transplant and may benefit from CAR T-cell therapy in the third-line setting.<sup>10,11</sup> CAR T-cell therapy is considered standard of care for any patient with LBCL (de novo or transformed) in whom at least 2 prior lines of standard therapy have failed.<sup>12</sup> Overall response rates to CAR T-cell therapy in LBCL range from 52% to 82% with CR rates of 40% to 49% and are summarized in [Table 1](#).<sup>13-22</sup> Results of CAR T-cell trials must be interpreted carefully as just 47% of patients screened for CAR-T cell therapy in JULIET actually received therapy; 15% of patients in TRANSCEND-NHL-001 and 9% in ZUMA-1 underwent leukapheresis but did not receive CAR T-cell therapy.<sup>13,17,19</sup> Insurance approvals, prior authorizations, high cost and inadequate reimbursement, travel to tertiary centers, limited apheresis slots, and manufacturing delays/failures are barriers to receipt of CAR T-cell therapy.<sup>2,23,24</sup> In addition, patients in the phase 2 ZUMA-1 study of axi-cel were not allowed to receive bridging therapy; thus, patients with rapidly progressive disease would therefore not have been eligible because they

would not have been able to wait for 3 weeks between apheresis and CAR-T-cell treatment.<sup>13</sup> Both the JULIET and TRANSCEND-NHL-001 studies allowed bridging therapy.<sup>17,19</sup> Of the 3 CAR T-cell studies in LBCL, the TRANSCEND-NHL-001 study is noteworthy for having broad enrollment criteria, allowing patients with low creatinine clearance, poor cardiac function, low absolute lymphocyte count, and high-risk features such as central nervous system involvement to be enrolled.<sup>19</sup> Real-world, postmarketing data of 1000 patients treated with axi-cel showed results similar to those of the clinical trials, with a 70% ORR and a CR of 53%.<sup>25</sup> A recent matching-adjusted indirect comparison of individual patient-level data from JULIET and TRANSCEND-NHL-001 patients found no evidence to suggest differences in overall survival (OS), progression-free survival (PFS), and CR between tisa-cel and liso-cel in relapsed/refractory LBCL.<sup>26</sup> There is also growing evidence to support the use of CAR T-cell therapy in the second-line setting. Early results for ZUMA-7, a randomized phase 3 trial of axi-cel versus second-line standard of care including consolidative autologous stem cell transplantation, show that CAR T-cell therapy improves event-free survival (EFS) in LBCL. Currently, these results are only available through press release and notably the data are immature and there is no overall survival benefit at this time.<sup>27</sup> TRANSFORM (NCT03575351), a randomized,

**FIGURE 2.** CAR T-Cell Process<sup>6</sup>



CAR, chimeric antigen receptor.

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**TABLE 1.** FDA-approved CAR T-Cell Therapies in Non-Hodgkin Lymphoma<sup>13-22</sup>

| Drug                                 | Study             | Disease   | N*  | ORR                       | CR                        | PFS (mo)                        | OS (mo)                                     | FDA indication  |
|--------------------------------------|-------------------|---|-----|---------------------------|---------------------------|---------------------------------|---|---|
| Axicabtagene ciloleucel (Yescarta)   | ZUMA-1            | Large B-cell lymphoma (LBCL)  | 77  | 82%                       | 49%                       | 5.9 (95% CI, 3.3-15.0)          | Not reached (95% CI, 12.8 – not estimable)  | Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including LBCL not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and LBCL arising from FL |
|                                      |                   | Primary mediastinal B-cell lymphoma   | 8   | 83%                       | 71%                       |                                 |   |   |
|                                      |                   | Transformed follicular lymphoma (FL)  | 16  |                           |                           |                                 |   |   |
| Axicabtagene ciloleucel              | ZUMA-5            | Follicular non-Hodgkin lymphoma (NHL)   | 80  | 95%                       | 80%                       | 23.5                            | NR  | Adult patients with relapsed or refractory FL after 2 or more lines of systemic therapy   |
|                                      |                   | Marginal zone NHL   | 14  | 86%                       | 71%                       | 11.8                            |   |   |
| Tisagenlecleucel (Kymriah)           | JULIET            | LBCL  | 88  | 52% (95% CI, 41-62)       | 40%                       | Not reported (≈3 months)        | 12 months (95% CI, 7 months to not reached) | Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including LBCL NOS, high-grade B-cell lymphoma, and LBCL arising from FL   |
|                                      |                   | Transformed follicular lymphoma   | 21  |                           |                           |                                 |   |   |
|                                      |                   | Other   | 2   |                           |                           |                                 |   |   |
| Lisocabtagene maraleucel (Breyanzi)  | TRANSCEND NHL 001 | LBCL  | 131 | 67.9% (95% CI, 59.2-75.8) | 48.9 (95% CI, 40-57.7)    | 6.8 months (95% CI, 3.3 – 14.1) | 21.1 months (95% CI, 13.3 – not reached)    | Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including LBCL NOS (including LBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3B     |
|                                      |                   | Transformed from indolent lymphoma  | 18  | 61.1% (95% CI, 35.7-82.7) | 38.9 (95% CI, 17.3-64.3)  |                                 |   |   |
|                                      |                   | High-grade B-cell lymphoma with gene rearrangements in <i>MYC</i> and either <i>BCL2</i> , <i>BCL6</i> , or both† | 33  | 75.8 (95% CI, 57.7-88.9)  | 60.6% (95% CI, 42.1-77.1) |                                 |   |   |
|                                      |                   | Primary mediastinal B-cell lymphoma   | 14  | 78.6% (95% CI, 49.2-95.3) | 50% (95% CI, 23-77)       |                                 |   |   |
|                                      |                   | Follicular lymphoma   | 57  | 84.2 (95% CI, 72.1-95.5)  | 63.2 (95% CI, 49.3-75.6)  |                                 |   |   |
| Brexucabtagene autoleucel (Tecartus) | ZUMA-2            | Mantle cell lymphoma  | 60  | 93%                       | 67%                       | 12-mo PFS 61%                   | 12-mo OS 83%                                | Adult patients with relapsed or refractory mantle cell lymphoma   |

CI, confidence interval; CR, complete response; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

\*N reported for primary efficacy analysis.

multicenter phase 3 study comparing liso-cel with salvage therapy followed by high-dose chemotherapy and autologous stem cell transplant as second-line treatment in adults with relapsed or refractory LBCL, lists a primary completion date of 2023. In press release only, it was announced that this study met its primary end point of demonstrating a clinically meaningful and highly statistically significant improvement in EFS, as well as secondary end points of complete response rate and PFS compared with salvage. Specific results were not released and data are considered immature until published in a peer-reviewed journal.<sup>28</sup>

### Mantle cell lymphoma

Patients who have disease progression after receipt of Bruton tyrosine kinase inhibitors have poor outcomes with an objective response occurring in 20% to 86% of patients and a median OS of 6 to 24 months.<sup>29-31</sup> Brexu-cel is an anti-CD19 CAR T-cell product that removes circulating CD19-expressing malignant cells during the manufacturing process, allowing it to be used in patients with leukemia or mantle cell lymphoma.<sup>21</sup> In the patients treated with brexu-cel in the ZUMA-2 study, 93% had an objective response and 67% had a CR.<sup>21</sup> At 12 months, the estimated PFS and OS were 61% and 83%, respectively, in the ZUMA-2 study.<sup>21</sup>

### Follicular lymphoma

Most patients with follicular lymphoma have an indolent disease pattern of relapsing and remitting. Nevertheless, approximately 20% of patients will relapse within 2 years of front-line therapy and based on the LymphomaCare study, patients with early relapse have a significantly worse 5-year survival (50%) compared with those who do not (90%).<sup>32</sup> Both axi-cel and liso-cel are approved by the FDA for management of patients with follicular lymphoma based on ORR of 84% to 95% and CR rates of 63% to 80%.<sup>16,19</sup> Tisa-cel has been evaluated in patients with follicular lymphoma as well.<sup>33</sup> Longer follow-up is needed in follicular lymphoma to determine if a subset of these patients are cured; however, some patients receiving CD19 CAR T-cell therapy remain in remission after more than 5 years.<sup>16,34</sup>

### Acute Lymphoblastic Leukemia

Historically, outcomes in adults with relapsed/refractory acute lymphoblastic leukemia (ALL) are poor, with a median OS fewer

than 6 months and attainment of complete remission in only 20% to 40% of adults.<sup>35</sup> Inotuzumab ozogamicin and blinatumomab have significant activity in this population with CR observed in 36% to 81% of patients and median OS of 7 to 8 months.<sup>36-38</sup> The National Comprehensive Cancer Network (NCCN) guideline panel for ALL considers inotuzumab ozogamicin and blinatumomab category 1 recommendations for relapsed/refractory ALL and tisa-cel a category 2A recommendation.<sup>39</sup> Tisa-cel was approved by the FDA for patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.<sup>18</sup> The approval was based on the phase 2 ELIANA study of 75 patients with a median age of 11 years who received tisa-cel after a median of 3 previous therapies.<sup>40</sup> A CR or CR with incomplete hematologic recovery was reported in 81% of patients receiving tisa-cel and all of those patients achieved minimal residual disease-(MRD) negativity (Table 2<sup>18,40</sup>). At 12 months, the EFS was 50% and OS was 76%. A phase 3 trial to compare tisa-cel with blinatumomab or inotuzumab ozogamicin in adult patients with relapsed/refractory B-cell ALL was planned (NCT03628053); however, the study is no longer being pursued because of planned investigation of novel CAR T-cell therapies in this patient population.<sup>41</sup> A phase 2 study (ZUMA-3) of brexu-cel in 55 adult patients with relapsed or refractory ALL reported a CR or CR with incomplete hematologic recovery in 71% of patients, CR in 56%, median relapse-free survival of 11.6 months, and median OS of 18.2 months.<sup>42</sup> MRD-negativity was achieved in 76% of patients receiving brexu-cel.<sup>42</sup> A biologics license application (BLA) has been submitted to the FDA for brexu-cel in adult patients with relapsed or refractory ALL.<sup>43</sup> Similar to studies in lymphoma, not all enrolled patients received therapy, with approximately 18% not receiving tisa-cel and 22.5% not receiving brexu-cel in ELIANA and the ZUMA-3 studies, respectively.<sup>40,42</sup>

### Multiple Myeloma

The treatment landscape of multiple myeloma changes rapidly with multiple new effective therapies approved in the past few years; however, the disease remains incurable.<sup>3</sup> Responses and median PFS vary widely based on multiple factors including transplantation status, number of previous lines of therapy, and the salvage regimen used.<sup>3</sup> Patients who develop resistance to multiple agents including a proteasome inhibitor, an immunomodulatory agent,

**TABLE 2.** FDA-approved CAR T-Cell Therapy in Acute Lymphoblastic Leukemia<sup>18,40</sup>

| Drug             | Study  | Disease                                       | N* | ORR | CR  | EFS (mo)     | OS (mo)      | FDA indication   |
|------------------|--------|---|----|-----|-----|--------------|--------------|--|
| Tisagenlecleucel | ELIANA | Precursor B-cell acute lymphoblastic leukemia | 75 | 81% | 81% | 50% at 12 mo | 76% at 12 mo | Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse |

CR, complete remission; EFS, event-free survival; ORR, overall response rate; OS, overall survival.

\*N reported for primary efficacy analysis.

and an anti-CD38 antibody have a poor prognosis, with survival less than 1 year.<sup>44</sup> The KarMMa study evaluated 128 patients receiving ide-cel for relapsed/refractory myeloma after a median of 6 prior regimens including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody.<sup>45</sup> Nine percent of enrolled patients did not receive therapy. An ORR of 73% was observed with ide-cel; 33% of patients achieved a CR and 26% of patients attained MRD-negativity (Table 3<sup>45-48</sup>). In this heavily pretreated population, the median PFS was 8.8 months and median OS was 19.4 months. Ide-cel is included in the NCCN guidelines as an “other recommended regimen” (category 2A recommendation) for patients who have received at least 4 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody, and is approved by the FDA in this population.<sup>49</sup>

Ciltacabtagene autoleucl is another promising CAR T-cell product for patients with relapsed/refractory multiple myeloma. A phase 1b study of ciltacabtagene autoleucl evaluated 97 patients with relapsed/refractory myeloma after a median of 6 prior regimens including a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody.<sup>47</sup> The ORR was 97% and CR was observed in 67% of patients; 12-month PFS and OS were 77% and 89%, respectively. The FDA has accepted a BLA priority review for ciltacabtagene autoleucl with a Prescription Drug User Fee Act target action date of November 29, 2021.<sup>48</sup> Phase 3 clinical trials are ongoing to compare CAR T-cell therapy versus standard-of-care regimens in patients in earlier stages of multiple myeloma and newly diagnosed patients with high-risk cytogenetic profiles or with residual disease after transplantation.<sup>44</sup>

## Role of Clinical Pharmacists

Clinical pharmacists are involved in multiple aspects of CAR T-cell therapy. Pharmacists should complete a detailed patient profile review and medication reconciliation to evaluate for potential drug-drug interactions before lymphodepletion and CAR T-cell infusion.<sup>3</sup> It is highly recommended that a cellular therapy clinical pharmacist provide patient education on the rationale for and potential

toxicities of lymphodepleting chemotherapy and the cellular therapy product; this service is a way to meet the REMS component of providing patients with a REMS wallet card.<sup>3</sup> The cellular therapy pharmacist typically coordinates with information technology to develop electronic order sets that include lymphodepletion, cellular therapy product, ancillary supportive care, and toxicity management. Pharmacists verify orders of lymphodepleting therapy and may be involved in labeling of the product at some centers.<sup>3</sup> Pharmacists may facilitate documentation in the electronic medical record of the availability of at least 2 doses of tocilizumab that can be administered within 2 hours of cellular infusion for each patient receiving CAR T-cell products, another component of REMS program documentation for commercially available CAR T-cell products.<sup>3</sup> Given the toxicity profile of CAR T-cell therapy, pharmacists are essential in adverse effect management. Lastly, pharmacists in the CAR T-cell therapy process play a valuable role in budgeting and purchasing given the cost of a single dose of CAR T-cell therapy is estimated between \$373,000 and \$475,000 per infusion.<sup>2,3</sup>

## Outpatient management

There are many factors (disease specific, patient specific, cellular therapy specific, and institution specific) that influence the decision for inpatient versus outpatient administration of CAR T-cell therapies.<sup>9</sup> As experience grows and newer constructs are developed that minimize or delay toxicity, they are more likely to be administered in the outpatient setting.<sup>3</sup> The TRANSCEND-NHL-001 study (liso-cel) allowed outpatient administration and approximately 10% of patients received therapy in the outpatient setting.<sup>19</sup> Of those patients, 18 (72%) were subsequently hospitalized for adverse effects including CRS, neurological events, or both. Preliminary results from a phase 2 study, OUTREACH (liso-cel) in the nonuniversity setting indicates similar safety data for inpatients and outpatients, with early (on or before study day 4) and overall hospitalization in outpatients reported in 27% and 63%, respectively.<sup>50</sup> The median time to hospitalization was 5 (range, 2-61) days and median length of stay was 6 (range, 1-28) days. As use of CAR T-cell therapy continues

**TABLE 3.** FDA-approved and Investigational CAR T-Cell Therapies in Multiple Myeloma<sup>45-48</sup>

| Drug                     | Study       | Disease          | N*  | ORR | CR  | PFS (mo)                    | OS (mo)      | FDA indication  |
|--------------------------|-------------|------------------|-----|-----|-----|-----------------------------|--------------|---|
| Idecabtagene vicleucl    | KarMMa      | Multiple myeloma | 128 | 73% | 33% | 8.8                         | 19.4         | Adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody |
| Ciltacabtagene autoleucl | CARTITUDE-1 | Multiple myeloma | 97  | 97% | 67% | Median PFS NR; 77% at 12 mo | 89% at 12 mo | PDUFA date of 11/29/21  |

CR, complete remission; ORR, overall response rate; OS, overall survival; PDUFA, Prescription Drug User Fee Act; PFS, progression-free survival.

\*N reported for primary efficacy analysis.

to expand, changes in payment models, care settings, or both are needed to ensure the sustainability of safe, efficient, and cost-effective treatment.<sup>3</sup>

### CAR T-Cell Toxicity

Overall, the likelihood of CAR T-cell–associated toxicities is high and not all patients can tolerate therapy. The incidence and severity of CRS and ICANS varies with CAR T-cell product and disease (Table 4<sup>3,4,14,16,17,19,21,40,42,45,47</sup>).

While the risk of early death was less than 3% in clinical trials, an analysis based on the FDA adverse event reporting system, including more than 1000 patients treated with tisagenlecleucel or axi-cel, found 7% of patients died due to nonrelapse mortality within 30 days of initial CAR T-cell administration.<sup>51</sup> The most frequent, expected toxicity observed in the week after lymphodepleting

therapy is myelosuppression.<sup>8</sup> Prolonged cytopenias (more than 28 days) have been described in about one-third of patients receiving tisagenlecleucel or axicabtagene ciloleucel.<sup>8,52</sup> Granulocyte colony-stimulating factors should be considered for patients with persistent neutropenia (absolute neutrophil count <500 cells/μL) after day 28 following CAR T-cell infusion, and may be used after day 14 to facilitate neutrophil recovery in the absence of CRS symptoms.<sup>34</sup>

Antiviral prophylaxis with acyclovir or valacyclovir to prevent herpesviruses should be considered starting with lymphodepleting chemotherapy before CAR T-cell infusion and continuing for at least 6 months post CAR T-cell therapy.<sup>34,53</sup> Antimicrobial prophylaxis and antifungal prophylaxis may be considered during periods of severe neutropenia and during periods of persistent neutropenia.<sup>34,54</sup> Mold prophylaxis may be considered in high-risk patients requiring treatment of CRS or ICANS.<sup>53,54</sup> Prophylaxis against *Pneumocystis*

**TABLE 4.** Adverse Effects in Patients Receiving CAR T-Cell Therapy<sup>3,4,14,16,17,19,21,40,42,45,47,a</sup>

| Drug                      | Co-stimulatory    | Study              | Disease   | N   | Cytokine release syndrome |               | Median time to any grade CRS onset, days | Neurotoxicity |               | Median time to any grade neurotoxicity onset, days |
|---------------------------|-------------------|--------------------|---|-----|---------------------------|---------------|--|---------------|---------------|--|
|                           |                   |                    |   |     | All (%)                   | ≥ Grade 3 (%) |  | All (%)       | ≥ Grade 3 (%) |  |
| Axicabtagene ciloleucel   | CD28              | ZUMA-1             | Large B-cell lymphoma   | 101 | 93                        | 13            | 2  | 64            | 28            | 5  |
|                           |                   | ZUMA-5             | Follicular and marginal zone lymphoma   | 94  | NR                        | 11            |  | NR            | 19            |  |
| Brexucabtagene autoleucel | CD28 and CD3-zeta | ZUMA-3             | Acute lymphoblastic leukemia  | 55  | 89                        | 24            | 5  | 60            | 25            | 9  |
|                           |                   | ZUMA-2             | Mantle cell lymphoma  | 68  | 91                        | 15            | 2  | 63            | 31            | 7  |
| Ciltacabtagene autoleucel | 4-1BB             | CARTI-TUDE-1       | Multiple myeloma  | 97  | 95                        | 4             | 7  | 21            | 9             | 8  |
| Idecabtagene vicleucel    | 4-1BB             | KarMMA             | Multiple myeloma  | 100 | 84                        | 5             | 1  | 18            | 3             | 2  |
| Lisocabtagene maraleucel  | 4-1BB             | TRAN-SCEND NHL 001 | Large B-cell lymphoma<br>Primary mediastinal B-cell lymphoma<br>Follicular lymphoma | 269 | 42                        | 2             | 5  | 30            | 10            | 9  |
| Tisagenlecleucel          | 4-1BB             | JULIET             | Diffuse large B-cell lymphoma   | 111 | 58                        | 22            | 3  | 25            | 14            | 6  |
|                           |                   | ELIANA             | Acute lymphoblastic leukemia  | 75  | 77                        | 47            | 3  | 40            | 13            | NR   |

NR, not reported.

<sup>a</sup>Different grading scales were used to define cytokine release syndrome and neurotoxicity.

*jirovecii* pneumonia should be provided through at least 6 months after CAR T-cell infusion.<sup>34,54</sup>

CAR T-cell therapy is also associated with unique acute toxicities that need specialized monitoring and management, including CRS, ICANS, and hemophagocytic lymphohistiocytosis (HLH).<sup>8,55,56</sup> The American Society for Transplantation and Cellular Therapy (ASTCT) published consensus criteria for grading for CRS and ICANS.<sup>57</sup> Management guidelines for patients receiving CAR T-cell therapy do not differ based on the underlying disease, construct, or product used.<sup>8</sup> While there are consensus guidelines for grading CRS and ICANS, evidence-based guidelines for management of these toxicities are not universally endorsed.<sup>52</sup> The NCCN guideline and Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events recommendations for management of CAR T-cell-related toxicities may be used to guide treatment.<sup>34,58</sup> In the absence of randomized trials to support treatment recommendations for CAR T-cell toxicities, institutional management protocols vary at different centers.<sup>1</sup>

### CRS

CRS is observed in the majority of patients receiving CD19- and B-cell maturation antigen (BCMA)-directed CAR T-cell products. Symptoms of CRS include fever, hypotension, and hypoxia, and typically present within 2 to 5 days after CAR T-cell therapy.<sup>19,58</sup> CRS symptoms may last 7 to 9 days and patients may subsequently develop arrhythmias, cardiomyopathy, prolonged QTc, heart block, renal failure, pleural effusions, transaminitis, and coagulopathy.<sup>57,58</sup>

CRS prophylaxis with tocilizumab has been shown to reduce the rate of severe CRS and end-organ dysfunctions without affecting expansion, persistence, and response rates of CAR T cells.<sup>52</sup> Concerns remain over ablation of the cytokine milieu necessary for CAR T-cell proliferation and activity as well as an increased risk of neurotoxicity with prophylactic tocilizumab.<sup>52</sup> Prophylactic use of tocilizumab has not been addressed in current CRS management algorithms and is therefore not recommended.<sup>34,52</sup>

Supportive care with antipyretics, hydration, supplemental oxygen, and vasopressors should be provided as needed for CRS.<sup>52</sup> Two monoclonal antibodies that target the IL-6 receptor, siltuximab and tocilizumab, have been used to manage CRS and tocilizumab is approved by the FDA for treatment of CRS in patients receiving CAR T-cell therapy.<sup>8</sup> Recommendations vary for timing of initiation of tocilizumab with some recommending at grade 2 CRS in adults and others for grade 1 or 2 CRS in patients with persistent fever or hypotension refractory to fluids.<sup>34,58</sup> Tocilizumab is routinely used for patients with grade 3 or 4 CRS.<sup>8,34,58</sup> Corticosteroids have been used to treat severe CRS unresponsive to tocilizumab.<sup>1,34,58</sup> In addition, a study proving early steroid therapy when patients have grade 1 CRS or ICANS was associated with a lower rate of grade 3 or 4 CRS or ICANS in patients receiving axi-cel.<sup>59</sup> Lenzilumab,

anakinra, etanercept, ruxolitinib, itacitinib, ibrutinib, defibrotide, and suicide genes are in clinical trials to determine their role in mitigating CAR T-cell toxicities.<sup>1</sup>

### ICANS

Neurotoxicity, also known as ICANS, is also frequently observed after CAR T-cell therapy. ICANS is defined as a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.<sup>57</sup> ICANS may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and/or cerebral edema.<sup>8,57</sup> Typical time to onset is 4 to 10 days; however, onset may be delayed after CAR T-cell infusion.<sup>8,57,58</sup> Many patients also have headaches, although this alone does not establish ICANS.<sup>57</sup> Symptoms typically last for 14 to 17 days.<sup>58</sup> Baseline characteristics predictive of subsequent ICANS development include younger patient age, B-cell ALL, high marrow disease burden, high CAR T-cell dose, and preexisting neurologic comorbidity.<sup>1</sup> IL-2 and IL-5 at day 3 post-CAR T-cell infusion were also predictors of severe ICANS development.<sup>1</sup>

Treatment with corticosteroids (dexamethasone preferred) with dose intensity relative to the severity of ICANS is recommended for management of grade 2 or higher ICANS.<sup>8,34,58</sup> The SITC guidelines acknowledge a lower risk for complications with 4-1BB CAR T-cell products and indicate steroids may not be required for grade 2 ICANS with those products.<sup>34</sup> Acetazolamide, hyperventilation, and hyperosmolar therapy may be needed to manage elevated intracranial pressure. Electroencephalography is recommended to document seizures, and antiseizure prophylaxis with levetiracetam is commonly used with agents with a higher risk of ICANS.<sup>1,8</sup> Levetiracetam is recommended for management of seizures in patients with ICANS.<sup>34</sup> CRS does not always develop in patients who develop ICANS; however, if both are present, tocilizumab should be administered.<sup>58</sup>

### Hemophagocytic lymphohistiocytosis (HLH)

HLH, also known as macrophage activation syndrome, is caused by proinflammatory cytokine release by cytotoxic T cells and subsequent natural killer cell stimulation of persistent macrophage activation with hemophagocytosis.<sup>8</sup> This results in end-organ tissue damage resulting in kidney injury, liver failure, pancytopenia, and depressed mental status. HLH overlaps with CRS and a consensus on the diagnosis of HLH in CAR T-cell-treated patients has not yet been reached.<sup>8</sup> If HLH does not respond to tocilizumab, an etoposide-based regimen is typically given.<sup>8,58</sup> There may also be a role for other agents such as anakinra in managing HLH.<sup>60</sup>

### B-cell aplasia

B-cell aplasia is a significant off-tumor direct toxicity from effector cells that often leads to hypogammaglobulinemia. B-cell aplasia

can be prolonged, with persistence noted in some patients for at least 4 years. Some clinicians, especially in the pediatric setting, provide replacement therapy with intravenous immunoglobulin infusions, noting that children have fewer established plasma cell clones and might be more susceptible to infections than adults.<sup>8,53</sup> The NCCN guidelines panel recommends intravenous immunoglobulin replacement only in patients with recurrent, serious infections and a serum immunoglobulin G level less than 400 to 600 mg/dL.<sup>58</sup>

## Future Directions

There is significant effort worldwide to develop novel CAR T-cell products that improve response rates, reduce toxicity, facilitate use in more diverse malignancies including solid tumors, reduce production costs, and facilitate allogeneic CAR T-cell products.<sup>61</sup> Forecasts project nearly 900 total registered trials in CAR T-cell therapy between 2020 and 2025.<sup>61</sup> Clinical trials are underway evaluating the use in the first- and second-line settings.<sup>62-64</sup> Autologous CAR T cells must be manufactured for specific patients and failure to manufacture autologous CAR T cells occurs in 1% to 13% of patients.<sup>14,19,21,65</sup> This personalized medicine approach increases the cost and the time required to prepare, deliver, and administer CAR T-cell products, creating significant limitations for large-scale clinical applications. “Off-the-shelf”/ready-to-use therapeutic CAR T cells from an allogeneic donor source offer the potential for large-scale clinical applications and avoidance of patient delays.<sup>61</sup> Natural killer cells engineered to express a CAR have also shown activity in early-phase trials.<sup>66</sup>

## Conclusions

The field of CAR T-cell therapy is evolving rapidly, with 2 new therapies approved by the FDA in the first 6 months of 2021 and a total of 5 products in the past 5 years. While all CAR T-cell products are currently approved in the third- or later-line setting, clinical trials in the first- and second-line setting are underway. Use of CAR T-cell therapy in the second-line setting outside of clinical trials has been observed.<sup>67</sup> All of the studies of CAR T-cell products have been single-arm, phase 1 or 2 studies with no comparison arm; however, markedly improved response rates, PFS, and OS compared with historical data have been observed. The cost of CAR T-cell therapy is estimated between \$373,000 and \$475,000 per infusion, not including patient care costs (eg, evaluation, apheresis, chemotherapy, and post-infusion care, including management of complications).<sup>2</sup> Given the number of new products entering the market and significant cost burden of therapies, managed care professionals should have an understanding of the clinical trial data, toxicity profile, and place in therapy in lymphoma, myeloma, and ALL, as well as guideline recommendations for adverse effect management associated with CAR T-cell therapies. ■

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# Improving Outcomes and Mitigating Costs Associated With CAR T-Cell Therapy

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## Introduction

Chimeric antigen receptor (CAR) T-cell therapies represent a paradigm shift for the treatment of several previously incurable refractory hematologic malignancies. Their use is rapidly expanding as more become approved by the FDA. In 2018, just 2 CAR T-cell therapies were commercially available: axicabtagene ciloleucel for the treatment of relapsed/refractory large B-cell lymphoma (LBCL), and tisagenlecleucel for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and adult patients with relapsed or refractory LBCL.<sup>1,2</sup> Axicabtagene ciloleucel is now also approved for the treatment of patients with relapsed or refractory follicular lymphoma.<sup>3</sup>

In the past 2 years, these CAR T-cell products have been joined by 3 others. In July 2020, brexucabtagene autoleucel became the first approved product for relapsed or refractory mantle cell lymphoma (MCL), while lisocabtagene maraleucel was approved for the treatment of LBCL in February 2021.<sup>3,4</sup> All of the aforementioned CAR T-cell products target the CD19 antigen, but in March 2021, idecabtagene vicleucel made history as the first B-cell maturation antigen (BCMA)-targeting CAR T-cell therapy approved for the treatment of adult patients with relapsed/refractory multiple myeloma.<sup>3</sup> **Table 1**<sup>5-10</sup> summarizes the currently approved CAR T-cell products.

The field continues to rapidly evolve, with the manufacturers of brexucabtagene autoleucel and a second BCMA-targeted CAR T-cell therapy, ciltacabtagene autoleucel, seeking approval of their products for the treatment of relapsed or refractory ALL with a Prescription Drug User Fee Act (PDUFA) date of October 1, 2021 and multiple myeloma with a PDUFA date of November 29, 2021, respectively.<sup>11,12</sup> Many more CAR T-cell therapies are in development, with more than 600 clinical trials underway globally.<sup>13</sup>

Uptake of CAR T-cell therapy has been slow, largely limited to large transplant centers where clinical trials were performed. However, in recent years, it has been rapidly expanding; according to an analysis of the Medicare fee-for-service population, the number of CAR T-cell claims are doubling every 6 months.<sup>14</sup> This is a trend that looks set to continue, with the rush to begin offering CAR T-cell therapy to patients with multiple myeloma, the shift to an

## ABSTRACT

Since the historic approval of tisagenlecleucel for the treatment of B-cell acute lymphoblastic leukemia in 2017, chimeric antigen receptor (CAR) T-cell therapies have altered the treatment paradigm for hematologic malignancies. Five CAR T-cell products are now approved by the US Food and Drug Administration for a growing number of cancer indications and a global market worth billions is anticipated in the next 5 years. While uptake of CAR T-cell therapy is rapidly ramping up, there remain significant barriers to effective implementation and patient access, not least their price tag and substantial ancillary costs of care. CAR T-cell therapies currently have the potential to be cost-effective; however, improved safety and efficacy, outpatient administration, and a streamlined manufacturing process could make them even more so. In the meantime, payers and providers are tasked with facing the logistical complexities of CAR T-cell therapy and developing new payment and reimbursement strategies to ensure value-based care and optimal access today.

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outpatient setting, growing experience in managing the logistics and complexities of CAR T-cell therapy, and improving reimbursement mechanisms. Multiple different market research companies have performed analyses of the current and future trends in the CAR T-cell market. While their predicted growth estimates vary, all anticipate a global market of many billions of dollars within the next 5 years.<sup>15-17</sup> There is an urgent need for payers and healthcare systems to finetune the logistics of CAR T-cell therapy as they gain broader traction.

## Direct Costs

In spite of the growing CAR T-cell market, there are still significant barriers to optimal uptake and effective implementation. The cost of CAR T-cell therapy is one of the biggest challenges, with financial implications for patients, payers, and providers. Drug acquisition is the largest component of the cost of CAR T-cell therapy, with list prices ranging from \$373,000 to \$475,000 depending on the specific drug and indication.<sup>18</sup> However, the costs associated with CAR T-cell therapies are not limited to acquisition costs alone and other ancillary elements of care have a significant impact on healthcare expenditures (Table 2<sup>19</sup>).

CAR T-cell therapies are currently administered at more than 100 medical centers in the United States, primarily in the inpatient setting, although there is an increasing trend toward outpatient

administration.<sup>19-21</sup> Next to drug acquisition, hospital services are the most significant driver of cost for CAR T-cell therapies, particularly for patients who experience toxicities.<sup>19</sup> In 2 separate analyses of the cost outcomes of patients undergoing CAR T-cell therapy identified from hospital administrative data, one in pediatric and young adult patients with ALL, the other in adults with B-cell lymphoma, the majority treated in the inpatient setting, the median total cost of hospitalization for CAR T-cell therapy exceeded \$300,000 and was closer to \$400,000 in pediatric and young adult patients.<sup>22</sup> The primary cause of hospitalization for outpatients or transfer to an intensive care unit (ICU) as an inpatient is cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS). According to a multicenter historical cohort study of 111 patients treated with CAR T-cell therapy at 7 medical centers in the United States who were admitted to the ICU, CRS was the primary cause of admission in 41% of cases, with overlapping CRS and ICANS present in 60% of patients.<sup>23</sup>

Beyond the CAR T-cell therapy itself, there are numerous other associated drug costs that contribute to the total cost of treatment. Among pre-infusion costs are lymphodepleting chemotherapy and potential bridging therapy. With regard to the latter, the average time from apheresis until CAR T-cell infusion varies according to the specific product (the median turnaround times range from 15 days with brexucabtagene autoleucel to 33 days with idecabtagene

**TABLE 1.** FDA-Approved CAR T-Cell Therapies<sup>5-10</sup>

| Therapy and manufacturer   | Construct            | Indications   | WAC  | HCPCS code |
|--|----------------------|---|--|------------|
| Tisagenlecleucel (Kymriah); Novartis                               | Anti-CD19-4-1BB-CD3z | <ul style="list-style-type: none"> <li>Patients aged up to 25 years with B-cell precursor ALL that is refractory or in second or later relapse</li> <li>Adults with R/R LBCL after ≥2 lines of systemic therapy, including LBCL NOS, LBCL arising from follicular lymphoma, high-grade B-cell lymphoma</li> </ul>             | ALL: \$475,000<br>B-cell lymphoma: \$373,000 | Q2042      |
| Axicabtagene ciloleucel (Yescarta); Kite                           | Anti-CD19-CD28-CD3z  | <ul style="list-style-type: none"> <li>Adults with R/R LBCL after ≥2 lines of systemic therapy, including LBCL NOS, LBCL arising from follicular lymphoma, primary mediastinal LBCL, high-grade B-cell lymphoma</li> <li>Adults with relapsed or refractory follicular lymphoma after ≥2 lines of systemic therapy</li> </ul> | \$399,000                                    | Q2041      |
| Lisocabtagene maraleucel (Breyanzi); Bristol Myers Squibb          | Anti-CD19-4-1BB-CD3z | Adults with R/R LBCL after ≥2 lines of systemic therapy, including LBCL NOS (including LBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma grade 3B   | \$410,300                                    | C9399      |
| Brexucabtagene autoleucel (Tecartus); Kite                         | Anti-CD19-CD28-CD3z  | Adults with R/R mantle cell lymphoma  | \$399,000                                    | Q2053      |
| Idecabtagene vicleucel (Abecma); Bristol Myers Squibb/Bluebird Bio | Anti-BCMA-4-1BB-CD3z | Adults with R/R multiple myeloma after ≥4 lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody   | \$419,500                                    | C9399      |

ALL, acute lymphoblastic leukemia; LBCL, large B-cell lymphoma; HCPCS, healthcare common procedure coding system; NOS, not otherwise specified; R/R, relapsed/refractory; WAC, wholesale acquisition cost.

vicleucel) but with administrative delays or manufacturing issues this period may be longer.<sup>8,9</sup> Patients with progressive symptomatic disease may require some kind of treatment to support them during that time, although there are still many outstanding questions about the optimal type of bridging therapy.<sup>24</sup>

During and after CAR T-cell therapy, the majority of other drug-related direct costs are incurred as a result of either prophylaxis or treatment of associated toxicities. CRS and ICANS are the most common adverse effects (AEs) associated with CAR T-cell therapy, and patients are also at increased risk of infection for several reasons. As such, commonly used drugs include seizure prophylaxis (eg, levetiracetam), bacterial, viral, and fungal infection prophylaxis and treatment, growth factors such as filgrastim as standard of care during periods of neutropenia, and the interleukin (IL)-6 receptor antagonists tocilizumab and siltuximab, as well as corticosteroids, for the management of CRS. The FDA Risk Evaluation and Mitigation Strategy (REMS) for CAR T-cell therapy requires that the pharmacy stock a minimum of 2 doses of tocilizumab for each patient.<sup>21</sup> B-cell aplasia and hypogammaglobulinemia can also result from depletion of healthy B cells following CAR T-cell therapy and may be associated with long-term remission and CAR T-cell persistence. B-cell aplasia can be effectively managed with immunoglobulin replacement therapy, but monthly doses of intravenous immunoglobulin can cost as much as \$5000 to 10,000 per infusion.<sup>25</sup>

Several nondrug-related costs are associated with CAR T-cell therapy. Although they are significantly less than drug-related costs, nondrug costs are still substantial, with an estimated range of \$30,000 to \$56,000 from current experience with tisagenlecleucel and axicabtagene ciloleucel.<sup>26</sup> Generation of CAR T-cell therapies begins with the collection of the patient’s blood and isolation of the lymphocytes contained therein via the process of leukapheresis. The Centers for Medicare & Medicaid Services-assigned HCPCS codes for each of the various CAR T-cell products contain the drug name as well as wording stating “including leukapheresis and dose preparation procedures.”<sup>27,28</sup> There have been some objections from provider groups to bundling up the costs of leukapheresis, storage, and handling into the cost of the drug. Many centers are likely to bill for these items separately and commercial payers will be left to determine how they choose to reimburse those items.<sup>29,30</sup> Other nondrug-related costs include laboratory costs, organ procurement, revenue codes, and blood.<sup>22</sup>

**Total Cost of Care**

Beyond the direct costs of CAR T-cell therapy, there is another economic burden that is often overlooked. This includes the numerous out-of-pocket expenses for patients and their caregivers, such as the need for accommodation and transportation. Per the REMS requirements, patients should remain within a 2-hour radius of the medical center for at least 4 weeks after CAR T-cell therapy

and driving within the first 8 weeks post-therapy is restricted. Although the number of centers performing CAR T-cell therapy is expanding, patients and their caregivers may still have to travel long distances if they do not live in proximity to such institutions. There is also a significant potential for loss of earnings during and after treatment for both patient and caregiver.<sup>31</sup>

**TABLE 2.** Model Estimated Direct Costs Associated With CAR T-Cell Therapy for an Average Individual Patient in 2 Healthcare Settings<sup>19</sup>

| Economic input  | Key Healthcare Inputs       |  |
|---|-----------------------------|--|
|   | Academic inpatient hospital | Nonacademic specialty oncology network |
| Drug costs  |                             |  |
| CAR T cell <sup>a</sup>                                   | 373,000                     | 373,000                                |
| Lymphodepletion <sup>b</sup>                              | 1578                        | 1578                                   |
| Tocilizumab <sup>b</sup>                                  | 4368                        | 4368                                   |
| Dexamethasone <sup>b</sup>                                | 2.5                         | 2.5                                    |
| Filgrastim <sup>b</sup>                                   | 315                         | 315                                    |
| Procedure costs (OPPS HCPCS code) <sup>c</sup>            |                             |  |
| Radiography (71045)                                       | 76                          | 22                                     |
| EEG (95812)   | 445                         | 330                                    |
| ECG (833531)  | 656                         | 239                                    |
| Lumbar puncture (62272)                                   | 117                         | 87                                     |
| MRI (70552)   | 441                         | 327                                    |
| 1-h chemotherapy administration (96413)                   | 364                         | 144                                    |
| CAR T-cell administration (38241)                         | 313                         | 176                                    |
| Facility costs <sup>d</sup>                               |                             |  |
| ICU day <sup>e</sup>                                      | 6546                        | 6546                                   |
| Inpatient day <sup>f</sup>                                | 2668                        | 2668                                   |
| Nonacademic specialty oncology network visit <sup>g</sup> | NA                          | 74                                     |

CAR, chimeric antigen receptor; ECG, electrocardiogram; EEG, electroencephalogram; HCPCS, Health Care Common Procedure Coding System; ICU, intensive care unit; MRI, magnetic resonance imaging; NA, not applicable; OPSS, Outpatient Prospective Payment System.

<sup>a</sup>Based on assumption of cost.

<sup>b</sup>Costs were obtained from IBM Micromedex Red Book wholesale acquisition costs: 1 vial of tocilizumab, 80 mg/4 mL, was \$436.81; 1 vial of dexamethasone, 10 mg/mL, was \$2.50; and 1 vial of filgrastim was \$315 (\$3148.33/10 vials of 300 µg each).

<sup>c</sup>Inpatient values were estimated by adjusting the OPSS reimbursement values using methods from Neelapu et al and Meisenberg et al.

<sup>d</sup>Costs were the same regardless of the site of administration. The ICU and inpatient day inputs for nonacademic specialty oncology networks were only relevant when an adverse event occurred.

<sup>e</sup>Costs were based on research performed by Dasta et al.

<sup>f</sup>Costs were based on the National Inpatient Sample from 2015.

<sup>g</sup>Costs were based on the Medicare physician fee schedule for 2018.

There are also hidden costs to the institutions performing CAR T-cell therapy, including the need to hire additional specialized staff and/or train existing staff, gain REMS certification, and educate patients and caregivers. An open question for institutions is whether to treat CAR T-cell therapies as drugs, which determines whether they are processed by the pharmacy or the cellular therapy department. In many cases, institutions are choosing a mixture of both, with the pharmacy involved in billing, registering, verifying, and labeling the product. Indirect costs can present a particular challenge for budgeting and strategizing the introduction of CAR T-cell therapy to an institution.<sup>31</sup>

Gaining a fuller understanding of the total cost of care for CAR T-cell therapy is essential to effective management of this high-cost therapy to reduce the economic burden on payers, providers, and patients. The CAR T-cell therapy field is still in its infancy and available real-world cost data are limited, but several studies have estimated total costs of care to be between \$450,000 and \$480,000, with one study estimating total costs to far exceed \$500,000 in patients with severe CRS (grade  $\geq 3$ ).<sup>19,26</sup> However, there is growing appreciation in the field that the actual total cost of care may be closer to \$1 million or even \$2 million.<sup>32,33</sup> The American Society for Transplantation and Cellular Therapy has advised hospitals administering CAR T-cell therapy to bill 4 to 5 times the price of the drug, or \$2 million to \$2.5 million, to avoid losing money.<sup>33</sup>

## Value and Affordability

Given the staggering cost, determining the value of CAR T-cell therapy and how that compares to alternative therapies has important implications. Several model-based, cost-effectiveness analyses have compared tisagenlecleucel and axicabtagene ciloleucel with standard of care in the US healthcare system. These studies used US-based costs for inpatient CAR T-cell administration and possible

subsequent treatments, as well as the costs of disease monitoring and treatment of AEs over the short and long term, and reported the potential health outcomes gained (commonly quantified as quality-adjusted life-years [QALYs], a function of length and quality of life) per dollar spent.<sup>34</sup>

In pediatric and young adult patients with B-cell ALL, tisagenlecleucel was compared with clofarabine monotherapy, clofarabine combination therapy, or blinatumomab over a patient lifetime horizon. Across these studies, tisagenlecleucel was more costly than standard of care, but was associated with greater health gains. Cost-effectiveness estimates ranged from \$37,000/QALY to \$184,000/QALY, depending on model assumptions relating to cost and long-term survival.<sup>35-37</sup> By comparing the cost and QALYs associated with CAR T-cell and standard-of-care therapies, an incremental cost-effectiveness ratio can be derived; when 40% of patients are presumed to show greater than 5-year progression-free survival, tisagenlecleucel demonstrates an incremental cost-effectiveness ratio of \$168,000/QALY in this setting.<sup>34</sup>

In patients with B-cell lymphoma, the cost-effectiveness of axicabtagene ciloleucel compared with chemotherapy was modeled in 2 different studies. Again, the costs for CAR T-cell therapy were higher, but so were QALYs gained. Cost-effectiveness estimates ranged from \$58,000 to \$289,000/QALY. In a separate study, tisagenlecleucel was shown to have similar cost-effectiveness to axicabtagene ciloleucel in the setting of B-cell lymphoma. A conservative estimate of cost-effectiveness was \$223,000/QALY and an optimistic estimate was \$168,000/QALY for tisagenlecleucel in this cancer type.<sup>38,39</sup>

Costs per QALY can be compared with a predetermined willingness to pay (WTP) threshold to help payers determine the value of funding a therapy (Table 3<sup>34</sup>). The World Health Organization suggests a WTP of 3 times the gross domestic product per capita

**TABLE 3.** Best Case Scenarios for Tisagenlecleucel and Axicabtagene Ciloleucel Modeled Within Peer-Reviewed Cost-Effectiveness Analyses<sup>34</sup>

| CAR T-cell product      | Disease setting | Incremental cost | Incremental QALYs | Cost/QALY gained | Probability of cost-effectiveness at WTP of \$100K/QALY gained |
|-------------------------|-----------------|------------------|-------------------|------------------|--|
| Tisagenlecleucel        | B-ALL           | \$317,000        | 8.47              | \$61,000         | 98.7% <sup>a</sup>   |
|                         |                 | \$329,498        | 7.18              | \$45,871         | Not reported   |
|                         |                 | \$528,200        | 8.18              | \$64,600         | 94.8% <sup>b</sup>   |
| Tisagenlecleucel        | LBCL            | \$360,000        | 3.92              | \$168,000        | 1.8% <sup>c</sup>  |
| Axicabtagene ciloleucel | LBCL            | \$482,000        | 5.50              | \$129,000        | 9.7% <sup>c</sup>  |
|                         |                 | \$380,184        | 6.54              | \$58,146         | >99% <sup>d</sup>  |
|                         |                 | \$403,500        | 4.90              | \$82,400         | Not reported   |

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; QALY, quality-adjusted life-year; WTP, willingness to pay.

<sup>a</sup>Assumes 40% 5-year relapse-free survival.

<sup>b</sup>Assumes 40% 5-year progression-free survival.

<sup>c</sup>Incorporated long-term survival data from Surveillance, Epidemiology, and End Results Database.

<sup>d</sup>Used mixture cure modeling to extrapolate CAR T-cell survival.

per QALY, which would represent \$180,000/QALY in the United States currently, but a range of \$100,000 to \$150,000 is the most universally accepted in the United States. To help inform coverage decisions, the Institute for Clinical and Economic Review (ICER) conducts value assessments of newly approved therapies and most payers will default to this assessment if they formally consider cost-effectiveness in their coverage decisions.<sup>34</sup> ICER panel determined that cost-effectiveness estimates were below or within WTP thresholds in the United States over a lifetime horizon and that tisagenlecleucel for the treatment of ALL was an intermediate long-term value for the money, while axicabtagene ciloleucel for B-cell lymphoma was low-to-intermediate long-term value.<sup>40</sup> At the time of this assessment, tisagenlecleucel was not yet approved for the treatment of B-cell lymphoma. More recently, ICER have released their evidence report of BCMA-targeted CAR T-cell therapy for the treatment of multiple myeloma. The incremental cost-effectiveness ratio for idecabtagene vicleucel compared with current treatment options for heavily refractory multiple myeloma was approximately \$319,000/QALY. ICER suggested that idecabtagene vicleucel would meet a WTP threshold of \$100,000/QALY if its list price were reduced to around \$200,000. The panel concluded that idecabtagene vicleucel was likely to provide small to substantial net health benefits over standard of care.<sup>41</sup>

Overall, cost-effectiveness analyses suggest that CAR T-cell therapies could have significant value at their current price, although it should be noted that the wholesale acquisition cost (WAC) of axicabtagene ciloleucel has increased since these studies were published. However, CAR T-cell therapies must result in a substantial increase in overall survival compared with standard of care to achieve acceptable value.<sup>34</sup> There are a number of limitations to cost-effectiveness analyses; notably, current assessments of cost-effectiveness are based on limited data related to long-term outcomes (with a median follow-up of <28 months), which can significantly impact their accuracy. Other limitations include their reliance on modeling, differing assumptions about the long-term benefits of CAR T-cell therapy and calculations of total costs, static QALY measurements, and ambiguous WTP thresholds. Furthermore, comparing CAR T-cell therapy to the standard of care does not capture real-world treatment patterns, in which patients may already have been treated with standard of care or may go on to receive additional therapies that add to the cost. Nor do they consider the affordability of these therapies and their impact on healthcare budgets, or the different perspectives and priorities of payers and providers in assessing the value of a therapy. The focus of clinicians is typically centered on the individual patient, while institutions and payers are likely more concerned with providing the most benefit to the greatest number of patients. In a real-world scenario, numerous complicating factors can create added financial pressures for payers, which can lessen the long-term value

of a treatment. For example, plan members may change insurers over time or, for small employer groups, expensive therapies could negatively impact the health benefits available to other patients in the group, which can lessen the long-term value of a treatment.<sup>34,42</sup> ICER also performs budget impact assessments that measure affordability and assess how a treatment will affect healthcare budgets. ICER reported that only 38% of adult patients with LBCL could be treated with CAR T-cell therapy in a given year without crossing the budgetary impact threshold at the then list price of \$373,000. Similarly, only 43% of eligible patients with relapsed/refractory multiple myeloma could be treated with CAR T-cell therapy within 5 years before crossing the budgetary impact threshold at the current list price.<sup>40,41</sup>

Comprehension of the total cost of care and value is also important in overcoming the sticker shock of CAR T-cell therapy when compared with the available alternatives. Although CAR T-cell therapy has the most expensive WACs, other therapies may require repeat dosing, increasing the total cost of care, and are less effective, thus having lower long-term value. The approximate cost for 1 cycle of blinatumomab for the treatment of adult and pediatric patients with B-cell ALL is between \$97,000 and \$107,000, but patients may receive up to 9 cycles during a full treatment course, leading to a total cost for drug acquisition of close to \$1 million.<sup>43</sup> Furthermore, blinatumomab and inotuzumab are approved in the maintenance setting and patients have already undergone expensive allogeneic stem cell transplant.

## Managing Costs and Improving Access

As the demand for CAR T-cell therapy increases, there is a growing need to address the financial challenges and improve access, and there are a number of potential solutions being explored. Barriers to use of CAR T-cell therapy include prior authorization, manufacturing waiting time, toxicity, out-of-pocket costs, geographic access, and others.<sup>44</sup> Next-generation CAR T-cell therapies with improved safety and efficacy profiles, manufacturing improvements, and innovative reimbursement strategies may help to improve access (Figure 1<sup>45</sup>).

## Site of Care

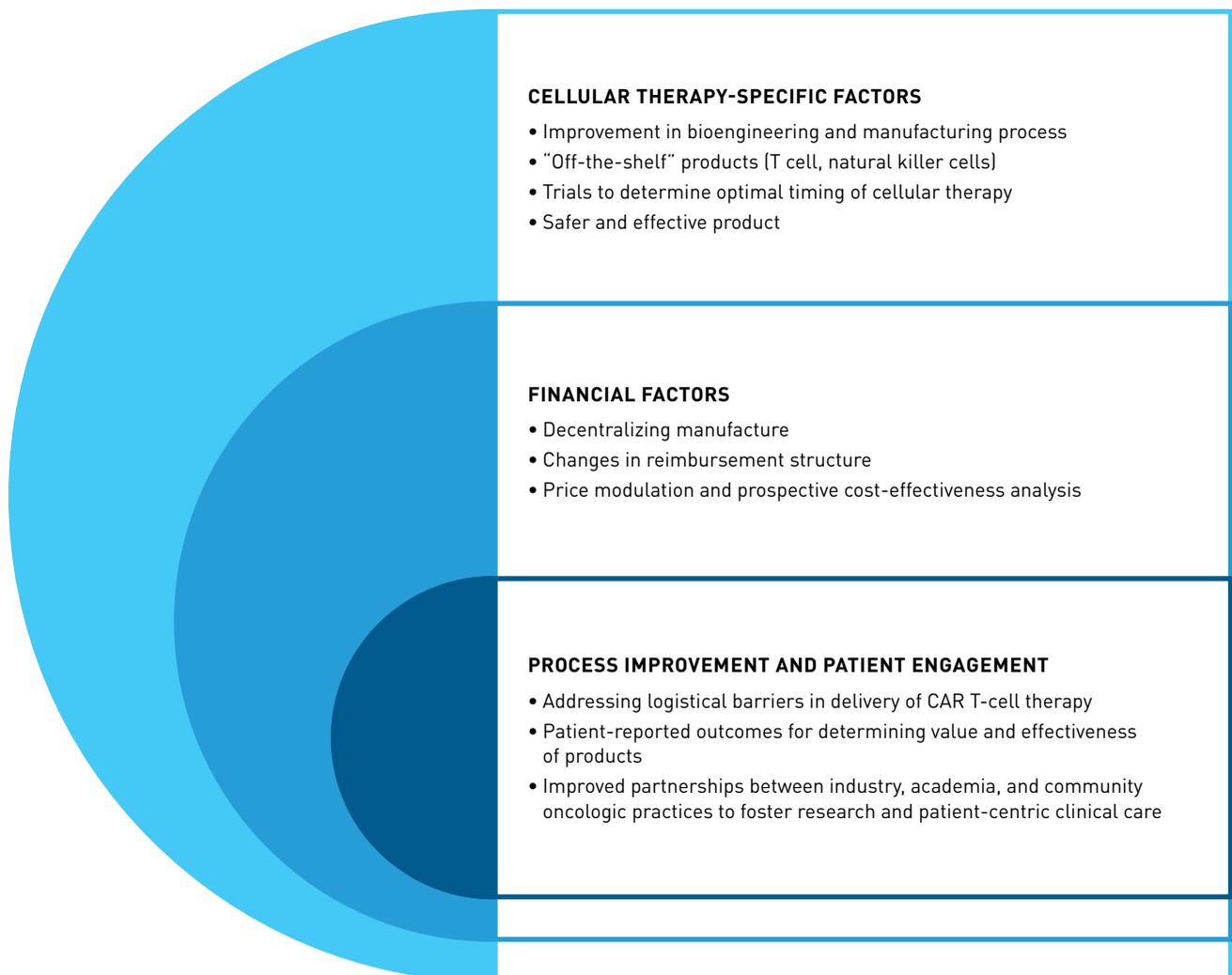
Although CAR T-cell therapy is currently predominantly delivered in the inpatient setting, there is a growing trend toward outpatient administration, particularly as CAR T-cell products with reduced toxicity reach the market and as experience with managing toxicities grows.<sup>19,21</sup> Clinical trials have begun to examine the feasibility of administering CAR T-cell therapy in the outpatient setting. In an analysis of patients with B-cell lymphoma treated with lisocabtagene maraleucel in the outpatient setting in the pivotal TRANSCEND NHL 001 trial and 2 phase 2 trials, 43% of patients remained outpatient. Among patients who required hospitalization, the median time to

hospitalization was 5 days, only 3 patients were admitted within 3 days of infusion, and just 2 patients required ICU-level care.<sup>46</sup> According to a single-center report on hospitalization patterns with tisagenlecleucel, only about one-third of patients receiving outpatient infusion were subsequently admitted to the hospital, with a median time to hospitalization of 5 days.<sup>47</sup>

Although outpatient administration can reduce costs, many patients are still subsequently admitted to the hospital due to toxicity. This is particularly important for the Medicare patient population as, although CAR T-cell therapy is covered under Medicare Part B,

if patients are admitted to the hospital within Medicare's 3-day payment window then the outpatient costs will be bundled with the claim for an inpatient stay and the provider loses the ability to claim Part B benefits. Notably, the site of care influences the cost savings from outpatient administration, with the greatest benefit when CAR T-cell therapy is administered at a nonhospital-affiliated site. Hospital outpatient administration is unlikely to benefit payers because it is the costliest site of service for Part B drugs billed under the medical benefit.<sup>48</sup> According to a recent cost modeling analysis, outpatient administration of CAR T-cell therapy (in the

**Figure 1.** A Proposed Framework to Optimize and Expand Patient Access to CAR T-Cell Therapy<sup>45</sup>



CAR, chimeric antigen receptor.

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setting of a nonacademic specialty oncology network) was associated with a greater than 40% (>\$30,000) reduction in total costs.<sup>19</sup> One limitation of this model is the assumption of equal outcomes to those seen in academic hospital-affiliated clinics. Currently, CAR T-cell therapies are largely restricted to clinics with an established expertise in treating these patients and thus we may not see nonacademic hospital-affiliated clinics caring for these patients in the near future. There are many critical issues that need to be addressed to increase the feasibility of outpatient administration, including the challenge of coordination of care, increasing the availability of resources, ensuring adequate patient and caregiver education, and improving toxicity management.

### Reimbursement Strategies

The current payment model for CAR T-cell therapy in the United States results in a significant reimbursement gap. Medicare fee-for-service beneficiaries present a particular challenge, with the current reimbursement model resulting in substantial losses for providers. CMS first announced national coverage of CAR T-cell therapy in 2019; they allotted CAR T-cell therapy the same Medicare Severity Diagnosis Related Group (MS-DRG) code as autologous bone marrow transplantation but included a New Technology Add-on Payment (NTAP).<sup>49</sup> In 2021, CMS assigned inpatient CAR T-cell therapy its own unique code, MS-DRG 018, but eliminated the NTAP, which likely means limited net financial impact to institutions.<sup>50</sup>

For commercial payers, there is no common payment path. Historically, single-case agreements with the specific payer have been the standard, but this has become unsustainable as the use of CAR T-cell therapy expands.<sup>31</sup> Numerous alternative payment and care delivery models are being explored.<sup>51</sup> These include outcomes-based pricing arrangements, but these present several critical challenges, including determining the optimum outcome to use. Many payers are interested in pursuing a Centers of Excellence model, which concentrates patient care at institutions with specialist providers who have the most experience with CAR T-cell therapy. An advantage of this model is that there is an existing framework from stem cell transplant specialty networks that could be used as a guide.<sup>52</sup> Among other reimbursement strategies are bundled payments—a United Healthcare bundled payment intervention in oncology resulted in more than \$33 million in net savings—credit mechanisms, cost-sharing (eg, HealthCoin), managed entry agreement, and milestone-based contracts, although this intervention did not include CAR T-cell therapies.<sup>51,53,54</sup>

### Honing CAR T-Cell Products

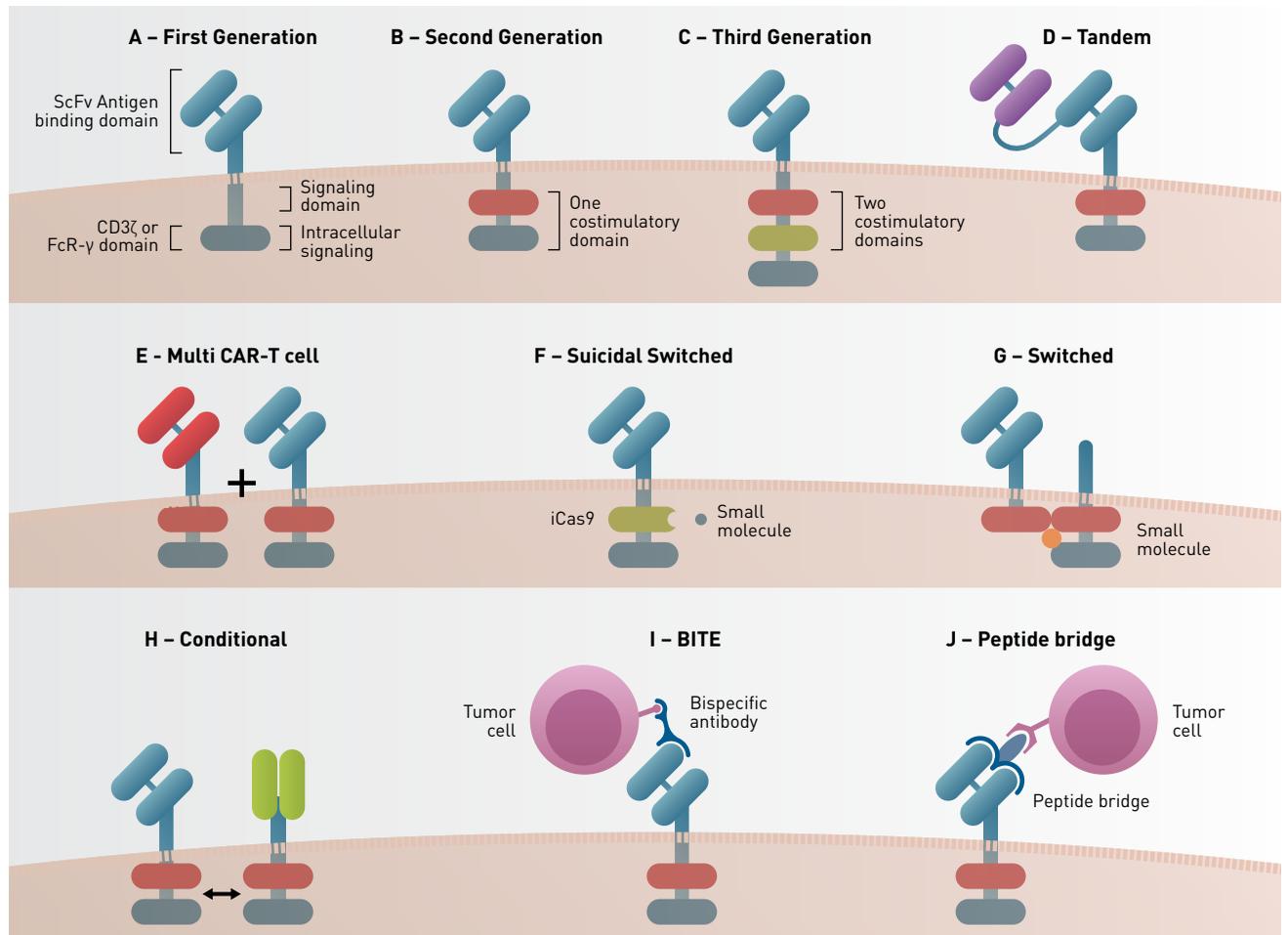
CAR T cells are currently primarily manufactured by pharmaceutical companies using autologous T cells, but academic medical centers are well equipped to take over the manufacturing process with Good Manufacturing Practice-grade facilities. Decentralizing

the CAR T-cell production process could reduce cost and shorten the time from leukapheresis to infusion but is currently limited by the burdensome regulatory pathway for CAR T-cell therapy. Pharmaceutical companies are also searching for ways to improve CAR T-cell manufacturing technology to ensure cheaper and quicker access to CAR T-cell therapies. A major focus is the development of “off-the-shelf” allogeneic CAR T-cell therapies, generated from a donor, but graft-versus-host disease, wherein the transplanted T cells attack healthy tissue causing severe toxicity, presents a significant challenge.<sup>45</sup>

Another central goal is the development of safer and more effective CAR T-cell therapies. A number of strategies for mitigating toxicity are being explored. Disease burden has been shown to be a significant risk factor for severe toxicity and risk-adapted strategies such as debulking therapy to reduce disease burden or reduced CAR T-cell dose in patients with higher disease burden could prove useful. Risk-adapted dosing has been shown to reduce the rates of severe CRS in patients with B-cell ALL and high marrow blast counts.<sup>55,56</sup> Prophylactic treatment of toxicity is also being investigated; prophylactic tocilizumab has been shown to reduce the rates of severe CRS in patients treated with CAR T-cell therapy.<sup>57</sup> A number of next-generation CAR designs are in various stages of clinical development that aim to improve safety or efficacy, such as switchable CARs, armored CARs, tandem CARs, and universal CARs (Figure 2<sup>58</sup>). For now and in the near future, all CAR T-cell products are targeted to treat hematologic malignancies. Work is currently underway to translate this experience into the treatment of solid tumor malignancies. If CAR T-cell therapy expands into the treatment of solid tumors, it will greatly expand the utilization of CAR T-cell therapies based on the much larger number of potential patients.

### Conclusions

CAR T-cell therapy is rapidly expanding, with new FDA-approved indications, an increasing number of centers accredited to administer them, and a global market predicted to be worth many billions of dollars within the next 5 years. The costs associated with CAR T-cell therapy present a major obstacle to effective implementation and patient access. These costs extend well beyond the drug acquisition cost, with total cost of care potentially reaching \$1 million or more, particularly among patients who experience toxicity. Cost-effectiveness analyses suggest CAR T-cell therapies could have significant value at their current price; however, budget impact analyses show that fewer than half of eligible patients could be treated before ICER's budget impact threshold is crossed. A growing trend toward outpatient administration could help to reduce costs and improve value, but only if CAR T-cell therapies become eligible to be administered at nonhospital-affiliated centers and only if Medicare patients can avoid inpatient admission that

**Figure 2.** Alternative CAR T-Cell Designs<sup>58</sup>

**A.** First Generation CAR-T: extracellular ScFv (single-chain fragment variable) domain, transmembrane domain, intracellular signaling domain and CD. or FcR- $\gamma$ . **B.** Second Generation CAR-T began to incorporate costimulatory domains. **C.** Third Generation CAR-T included 2 costimulatory domains. **D.** Tandem CAR-T are composed of 2 ScFv domains in tandem connected by a flexible motif or amino acid sequence. **E.** Multi CAR-T cell are engineered to express multiple ScFv CARs. **F.** Suicidal Switched CAR-T contain an intracellular iCas9 domain which can be activated by the administration of a small molecule leading to CAR-T cell death. **G.** Switched CAR T cells have 1 CAR with an ScFv that transmits the activation signal upon interaction with a small molecule and a second untargeted CAR. **H.** Conditional CAR-Ts involve 2 CARs that interact with each other and are only activated when both are connected to their respective antigens. **I.** BiTE (bispecific t cell engager) CAR-T only ligate to tumoral antigen when a bispecific [CAR-tumor] antibody is administered. **J.** Peptide bridge CAR-Ts are universal CAR-Ts that are activated when a peptide bridge links the CAR-T ScFv domain to a cellular antigen, thus the peptide bridge interacts with the ScFV domain as well as the cellular target.

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triggers the 3-day rule. The current single-case agreement model that predominates in reimbursement is unsustainable and a number of alternative strategies are under investigation. ■

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# Optimizing the Value of CAR T-Cell Therapy: Managed Care Considerations From Recent Clinical Findings

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## Sample of Online Posttest

Choose the best answer for each of the following:

- AD is a 45-year-old man with relapsed/refractory large B-cell lymphoma. He is a candidate for chimeric antigen receptor (CAR) T-cell therapy and the clinical team would like to manage his care as an outpatient. Which treatment is most appropriate for AD given this information?**
  - Axicabtagene ciloleucel
  - Brexucabtagene autoleucel
  - Idecabtagene vicleucel
  - Lisocabtagene maraleucel
- Following receipt of CAR T-cell therapy, AD develops grade 2 cytokine release syndrome (CRS) (fever and new-onset shortness of breath). Which treatment option is the most appropriate for AD at this time?**
  - Tocilizumab
  - Anakinra
  - Methylprednisolone
  - Dexamethasone
- LP is a 54-year-old man with a history of multiple relapses of multiple myeloma. He has had 7 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody and 2 autologous stem cell transplants. He is a candidate for cellular therapy and he wishes to continue aggressive therapy. Which of the following is most appropriate for LP at this time?**
  - Tisagenlecleucel
  - Axicabtagene ciloleucel
  - Brexucabtagene autoleucel
  - Idecabtagene vicleucel
- Which of the following is a barrier to the use of CAR T-cell therapy?**
  - Need to identify a matched donor
  - Inpatient administration in a specialty center
  - Medication adherence
  - Complex medication administration schedule
- What is the current role of CAR T-cell therapy in B-cell lymphomas, including large B-cell, follicular, and mantle cell lymphomas and acute lymphoblastic leukemia?**
  - First line
  - Second line
  - Third line or later
  - No role
- What is the most common reason for hospitalization or escalation of care to an intensive care unit for patients treated with CAR T-cell therapies?**
  - Neutropenic fever
  - Severe tumor lysis syndrome
  - Leukapheresis
  - CRS or immune effector cell-associated neurotoxicity syndrome
- Next to the drug acquisition cost, what is the most significant direct cost associated with CAR T-cell therapy?**
  - Hospital services
  - Patient education
  - Pharmacy costs
  - Lymphodepletion

8. According to the American Society for Transplantation and Cellular Therapy, how much should hospitals consider charging for a single CAR T-cell treatment to avoid losing money?
- A. \$1 million
  - B. \$399,000
  - C. 2 times the price of the drug
  - D. 4-5 times the price of the drug
9. The incremental cost-effectiveness ratio (ICER) for idecabtagene vicleucel compared with other treatment options for refractory multiple myeloma according to a recent ICER report is \$319,500 per quality-adjusted life-year. Limitations to cost-effective analysis for CAR T-cell therapies include:
- A. Limited data related to long-term outcomes
  - B. Direct comparison with real-world treatment patterns
  - C. Clear assumptions of long-term benefits
  - D. Unequivocal willingness-to-pay thresholds
10. Historically, which reimbursement strategy for CAR T-cell therapy has been most widely used by commercial payers?
- A. Outcomes-based pricing
  - B. Single-case agreement
  - C. Bundled payments
  - D. Managed entry agreements



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