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CAR T Cells and T-Cell Therapies for Cancer
A Translational Science Review

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IMPORTANCE Chimeric antigen receptor (CAR) T cells are T lymphocytes that are genetically engineered to express a synthetic receptor that recognizes a tumor cell surface antigen and causes the T cell to kill the tumor cell. CAR T treatments improve overall survival for patients with large B-cell lymphoma and progression-free survival for patients with multiple myeloma.

OBSERVATIONS Six CAR T-cell products are approved by the US Food and Drug Administration (FDA) for 6 hematologic malignancies: B-cell acute lymphoblastic leukemia, large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and multiple myeloma. Compared with standard chemotherapy followed by stem cell transplant, CAR T cells improved 4-year overall survival in patients with large B-cell lymphoma (54.6% vs 46.0%). Patients with pediatric acute lymphoblastic leukemia achieved durable remission after CAR T-cell therapy. At 3-year follow-up, 48% of patients were alive and relapse free. In people with multiple myeloma treated previously with 1 to 4 types of non–CAR T-cell therapy, CAR T-cell therapy prolonged treatment-free remissions compared with standard treatments (in 1 trial, CAR T-cell therapy was associated with progression-free survival of 13.3 months compared with 4.4 months with standard therapy). CAR T-cell therapy is associated with reversible acute toxicities, such as cytokine release syndrome in approximately 40% to 95% of patients, and neurologic disorders in approximately 15% to 65%. New CAR T-cell therapies in development aim to increase efficacy, decrease adverse effects, and treat other types of cancer. No CAR T-cell therapies are FDA approved for solid tumors, but recently, 2 other T lymphocyte–based treatments gained approvals: 1 for melanoma and 1 for synovial cell sarcoma. Additional cellular therapies have attained responses for certain solid tumors, including pediatric neuroblastoma, synovial cell sarcoma, melanoma, and human papillomavirus–associated cancers. A common adverse effect occurring with these T lymphocyte–based therapies is capillary leak syndrome, which is characterized by fluid retention, pulmonary edema, and kidney dysfunction.

CONCLUSIONS AND RELEVANCE CAR T-cell therapy is an FDA-approved therapy that has improved progression-free survival for multiple myeloma, improved overall survival for large B-cell lymphoma, and attained high rates of cancer remission for other hematologic malignancies such as acute lymphoblastic leukemia, follicular lymphoma, and mantle cell lymphoma. Recently approved T lymphocyte–based therapies demonstrated the potential for improved outcomes in solid tumor malignancies.

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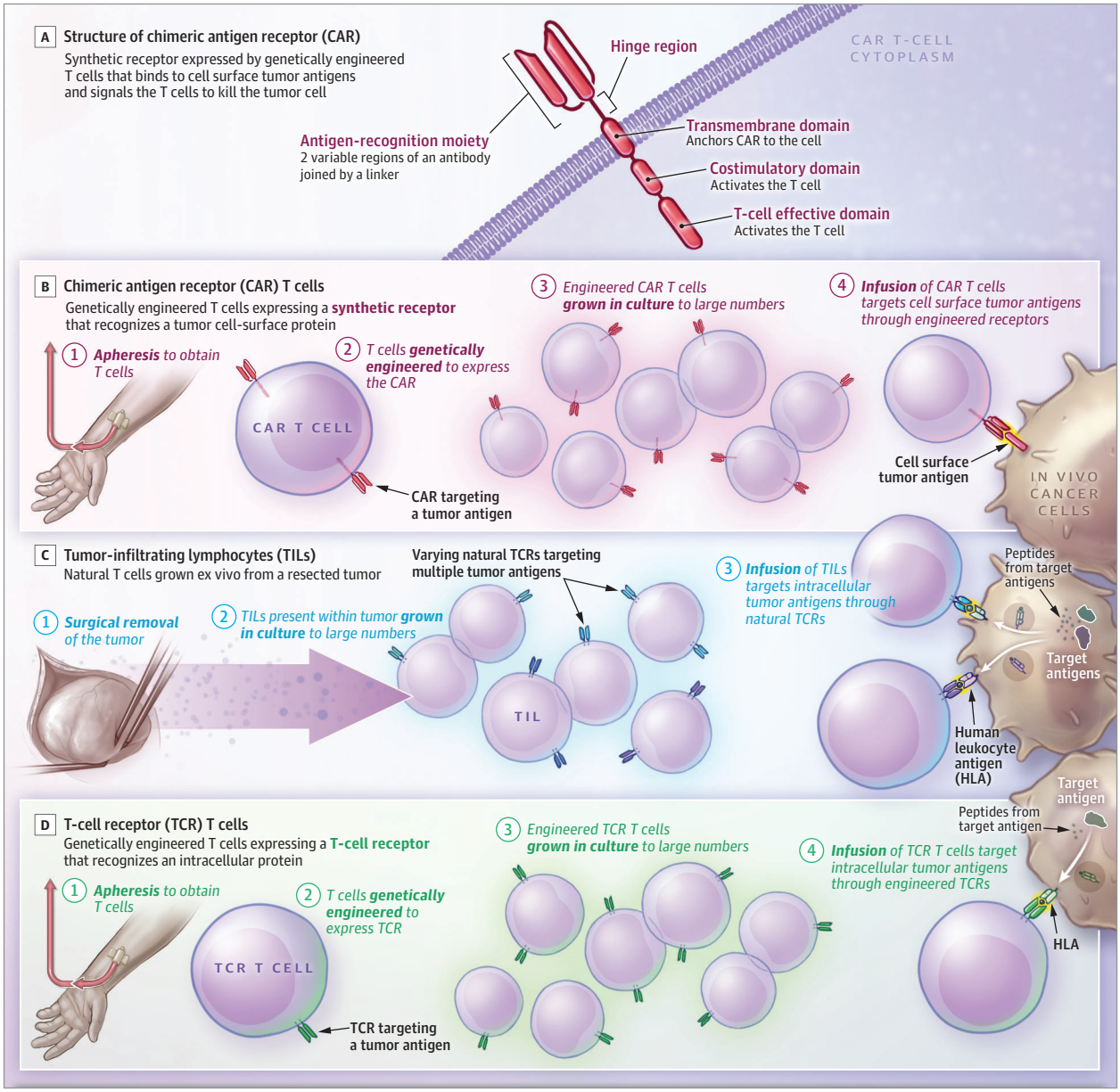
Cellular immunotherapies consist of immune cells that are manipulated to recognize and kill malignant cells and have been referred to as *living drugs*. Chimeric antigen receptor (CAR) T cells consist of T cells that are genetically engineered to express a synthetic receptor that recognizes a tumor cell-surface protein. Tumor-infiltrating lymphocytes (TILs) are natural T cells grown ex vivo from a resected tumor. T-cell receptor (TCR) T cells are genetically engineered T cells expressing a natural TCR that recognizes an intracellular protein (**Figure**, A-D; **Box**). This review summarizes evidence regarding cellular immunotherapies for cancer.

Introduction to Cellular Therapies and Approved CAR T-Cell Therapies

The CAR protein is a synthetic receptor expressed by genetically engineered T cells that binds to an extracellular malignancy-associated antigen on a tumor cell, thereby signaling the T cells to kill the tumor cell (Figure, A). The CAR consists of 2 major components: (1) an extracellular antigen-recognition moiety, generally derived from the variable regions of an antibody, and (2) intracellular T-cell–derived components that activate the T cell, usually a CD3ζ T-cell activation domain, and a costimulatory domain, usually CD28 or 4-1BB (Figure, A). Typically, autologous T cells are permanently genetically modified via a viral vector to express the CAR protein on the surface of the cell (Figure, B). Chemotherapy, such as cyclophosphamide and fludarabine, is typically administered prior to CAR, TCR, and TIL T-cell infusions to deplete other cells, such as T regulatory cells or myeloid-derived suppressor cells, that may suppress or compete with the therapeutic cells, and to increase serum levels of cytokines such as interleukin (IL) 7 and IL-15, which enhance CAR T-cell activity.[1,2] High-dose IL-2 infusions are administered after some TIL and TCR T-cell therapies to enhance the proliferation of T cells in the body. Adverse

Figure. Schematic Diagram of a CAR and Different Types of T-Cell Therapies for Cancer



A, The structure of a CAR generally includes an extracellular antigen-recognition moiety, typically composed of the 2 variable regions (light and heavy chains) of a monoclonal antibody, connected by a linker. Hinge and transmembrane domains connect the antigen recognition moiety and intracellular components. The intracellular costimulatory domain, typically CD28 or 4-1BB, and a T-cell activation domain, typically CD3ζ, activate the T cell. B, CAR T cells are generated using the same type of gene-engineering processes as TCR T cells. Like TCR T cells, they possess defined antigen specificity and most commonly target a single antigen. CARs differ from TCRs in that they are single-chain chimeric proteins with the self-contained capability to bind target antigens and to activate T cells. Because of their antibody-like antigen recognition, CARs target cell surface antigens and generally cannot target intracellular antigens such as most oncoproteins, mutated gene products, and cancer germline antigens. However, CARs have the advantage that, unlike TCRs, their target recognition does not require a specific HLA molecule, which broadens the number of patients who can be treated with a given therapy. C, TILs are autologous T cells grown in a laboratory from a surgically resected fresh tumor specimen. The approach requires surgery to obtain a tumor specimen and generally requires several weeks to grow out cells for treatment. In contrast to CAR and TCR T cells, TILs are not genetically engineered to express an antigen receptor. TIL cell products are highly variable; they may target any number of tumor antigens or may not target any tumor antigens. The T cells in a TIL cell product engage tumor cells through their native TCRs, which bind to peptides complexed with HLA molecules. D, TCR T-cell therapies use T cells genetically engineered to express a TCR targeting a tumor-associated antigen. The T cells for genetic engineering are isolated from peripheral blood mononuclear cells obtained by an apheresis procedure, a method of removing T cells from blood. Genetic engineering may be accomplished using varied technologies, including viral vectors, transposons, or CRISPR-Cas9. TCR gene engineering involves the transfer of TCR α- and β-chains. These chains form a complex with endogenous CD3 molecules (γ, δ, ε, and ζ chains), which provide signaling function. Engineered TCR T cells are like TIL T cells in that they engage a target peptide-HLA complex through a TCR. The HLA molecule in the target complex must be matched to an HLA molecule in the patient's haplotype (eg, if the therapeutic TCR targets a peptide presented by HLA-A*01:01, the patient must have the HLA-A*01:01 allele). TCR T cells are different from TIL T cells in that they possess defined specificity, generally for a single-target antigen.

Box. Commonly Asked Questions About Cellular Therapy for Cancer

What Is CAR T-Cell Therapy?
Chimeric antigen receptor (CAR) T cells are T lymphocytes that are genetically engineered to express a synthetic receptor that recognizes a tumor cell surface antigen and causes the T cell to kill the tumor cell.

What Hematologic Cancers Can be Treated by CAR T-Cell Therapy?
The currently Food and Drug Administration (FDA)–approved indications for CAR T-cell therapy are B-cell acute lymphoblastic leukemia, large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and multiple myeloma.

Is There Cellular Therapy Available for Solid Tumor Cancers?
The tumor infiltrating lymphocyte (TIL) therapy lifileucel is FDA approved for advanced melanoma. The T-cell receptor (TCR) T-cell therapy afamitresgene autoleucel is FDA approved for advanced synovial sarcoma. No other cellular therapies are FDA approved for solid tumor cancers.

What Are Adverse Effects of Cellular Therapies for Cancer?
CAR T-cell therapies can cause cytokine release syndrome, an inflammatory syndrome characterized by fevers, tachycardia, hypotension, and hypoxia, and immune effector cell–associated neurotoxicity syndrome, a neurologic disorder characterized by multiple symptoms, including encephalopathy, dysphasias, and decreased alertness. TIL and TCR T-cell therapies, because they are administered with high-dose interleukin-2, can cause fevers and capillary leak syndrome.

effects of TIL and TCR T-cell therapies include bone marrow suppression from the conditioning regimen, fevers from the cells and the high-dose IL-2, and capillary leak syndrome from IL-2, which manifests primarily as fluid retention, pulmonary edema, and kidney dysfunction.

Currently, 6 CAR T-cell therapies are approved by the US Food and Drug Administration (FDA) and commercially available (**Table 1**).[3-26] A CAR T-cell product is defined by the structure of the CAR protein expressed, the viral vector that mediates gene transfer, and elements of the cell culture process used to grow the number of cells ex vivo before reinfusion into the patient.

Generic CAR T-cell products generally have names with 2 words: the first indicates the gene component and the second describes the cell component.[27] The letters *cabta* in the first word indicate "cell expressed antibody and T cell activation."[27] Autologous CAR T-cell products, derived from the patient requiring treatment, often have 2-word names with the second word starting with *auto*.[27] The ending of the second word, *-cel*, indicates the product is a cellular drug.[27] Tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel are cellular drugs engineered to recognize the B-cell antigen CD19 and treat specific B-cell non-Hodgkin lymphomas, B-cell acute lymphoblastic leukemia, and chronic lymphocytic leukemia. Idecabtagene vicleucel and ciltacabtagene autoleucel target the plasma cell–associated protein B-cell maturation antigen (BCMA) and treat multiple myeloma. Tisagenlecleucel, the first commercially available cellular immunotherapy, was FDA approved in 2017 for children and young adults 25 years and younger with B-cell acute lymphoblastic leukemia. In a phase 2 clinical trial of patients with acute lymphoblastic leukemia, tisagenlecleucel resulted in remission in 82% of patients.[3,4] At 3-year follow-up, tisagenlecleucel attained a relapse-free survival rate of 48%.[4] In a retrospective analysis including 511 patients that compared tisagenlecleucel vs standard of care therapy, tisagenlecleucel significantly improved 2-year overall survival (59.5% vs 36.2%).[28]

In 101 patients with previously treated large B-cell lymphoma, axicabtagene ciloleucel resulted in a complete remission rate of 54% and an estimated 5-year survival rate of 43%[9] compared with an overall survival of 20% at 2 years in a historical control consisting of patients with previously treated large B-cell lymphoma treated with standard therapies.[29] Randomized clinical trial data for axicabtagene ciloleucel and lisocabtagene maraleucel for large B-cell lymphoma in patients who did not have a response to their first standard chemotherapy regimen or progressed within 12 months of initial remission demonstrated superior progression-free survival compared with standard treatment with second-line chemotherapy followed by autologous stem cell transplant.[10,30,31] Axicabtagene ciloleucel had superior overall survival in this context.[31] Anti-CD19 CAR T-cell therapy has the potential to cure patients with these B-cell malignancies who previously were refractory to treatments. Patients with follicular lymphoma and mantle cell lymphoma can also achieve long-lasting remissions after CAR T-cell therapy. The 2-year progression-free survival rates following axicabtagene ciloleucel and tisagenlecleucel treatment for follicular lymphoma were 63% and 57%, respectively.[8,32] The 12-month progression-free survival rates following brexucabtagene autoleucel and lisocabtagene maraleucel for mantle cell lymphoma were 61% and 53%, respectively.[14,22] However, whether CAR T-cell therapy can cure these malignancies remains unclear.

In patients with multiple myeloma with a median of 6 prior cancer treatments, idecabtagene vicleucel was associated with a response rate of 73%, and ciltacabtagene autoleucel had a response rate of 98%, with median progression-free survival rates of 8.8 and more than 27 months without additional treatment, respectively.[23,25] Randomized clinical trials comparing anti-BCMA CAR T-cell therapy with idecabtagene vicleucel in one trial and ciltacabtagene autoleucel in another trial vs standard of care treatments for patients with previously treated multiple myeloma and 1 to 4 prior cancer treatments demonstrated superior progression-free survival with CAR T-cell therapy.[33,34] Idecabtagene vicleucel resulted in a median progression-free survival of 13.3 months compared with 4.4 months with standard treatments.[34] Similarly, among 419 randomized patients with lenalidomide-refractory multiple myeloma, ciltacabtagene autoleucel achieved progression-free survival of 75.9% at 12 months compared with 48.6% in the standard treatment group.[33] Twenty-one percent of clinical trial patients attained progression-free survival of 5 years or more after ciltacabtagene autoleucel.[35] It is currently unknown whether these CAR T-cell therapies can cure multiple myeloma.

Challenges Associated With Cellular Therapies

Hematologic Cancers

Challenges in treating hematologic malignancies with CAR T-cell therapy include acute and long-term adverse effects, limited efficacy and durability, lack of effective salvage treatments, and long wait times for and limited access to CAR T-cell therapy (**Table 2**).[36-40] Each of these challenges is discussed below.

Table 1. Indications, Efficacy, and Toxicities of Commercially Available CAR T-Cell Products[a]

CAR T-cell product	Antigen target	Indications	Malignancy response of complete or partial remission, %	Overall survival estimates	Proportion with adverse effects, %			
					Cytokine release syndrome[b]	Neurologic toxicity[c]	Severe infections[d]	Prolonged cytopenias[e]
Tisagenlecleucel	CD19	Pediatric and young adult B-cell acute lymphoblastic leukemia[3,4]	82	63% Overall survival at 3 y	77	39	24	35
		Large B-cell lymphoma[5,6]	53	Median overall survival, 11.1 mo	57	20	19	34
		Follicular lymphoma[7,8]	86.2	87.7% Estimated overall survival at 24 mo	49	37	9.3	Neutropenia: 15.5%; thrombocytopenia: 16.5%; anemia: 3.1%
Axicabtagene ciloleucel	CD19	Large B-cell lymphoma[9-11]	83	42.6% Estimated overall survival at 5 y	93	64	28	38
		Follicular lymphoma[12,13]	94	76% Estimated overall survival at 36 mo	78	56	15	33
Brexucabtagene autoleucel	CD19	Mantle cell lymphoma[14,15]	91	Median overall survival, 46.6 mo	91	63	32	26% at more than 90 d
		Adult B-cell acute lymphoblastic leukemia[16,17]	71	Median overall survival, 25.4 mo	89	60	25	36
Lisocabtagene maraleucel	CD19	Large B-cell lymphoma[18,19]	73	50.5% Estimated overall survival at 2 y	42	30	12	37
		Chronic lymphocytic leukemia[20]	48	Median overall survival, 43 mo	85	45	17	54
		Follicular lymphoma[21]	97	93% Overall survival at 12 mo	58	15	5	22
		Mantle cell lymphoma[22]	83	Median overall survival, 18.2 mo	61	31	15	40
Idecabtagene vicleucel	BCMA	Multiple myeloma[23,24]	73	Estimated median overall survival, 19.4 mo	84	18	22	Neutropenia: 41%; thrombocytopenia: 48%
Ciltacabtagene autoleucel	BCMA	Multiple myeloma[25,26]	98	70.4% Overall survival at 27 mo	95	22[f]	20	Neutropenia: 30%; thrombocytopenia: 41%

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.

[a] Based on results from the clinical trials leading to commercial approval.

[b] Rates of cytokine release syndrome may not be directly comparable as per different grading scales being used.

[c] Common neurologic adverse effects included confusion, altered speech, changes in level of consciousness, and hand tremors. Possible severe neurologic adverse effects included motor defects, cranial nerve defects, seizures, and cerebral edema.

[d] Infections of grade 3 or higher by Common Terminology Criteria for Adverse Events grading scale.

[e] Cytopenias of grade 3 or higher by Common Terminology Criteria for Adverse Events grading scale lasting more than 28 to 30 days.

[f] Includes patients experiencing delayed movement disorders.

Adverse Effects

Anti-CD19 CAR T cells, when administered for B-cell malignancies, can proliferate in the recipient, often by as much as 1000-fold, elevating levels of multiple cytokines, such as IL-6 and interferon-γ, and other immunologic proteins.[41-44] These elevated circulating proinflammatory substances can cause cytokine release syndrome, which manifests as fever, hypotension, and coagulopathies and can be life-threatening.[41,44] Cytokine release syndrome can be attenuated by administering tocilizumab after symptoms develop, which blocks the IL-6 receptor,[41,44] a finding that led to FDA approval of tocilizumab for CAR T-cell–mediated cytokine release syndrome.[45] Glucocorticoids, such as dexamethasone, 10 mg (prednisone equivalent, 66.7 mg) given every 6 to 12 hours, can be administered as second-line agents to treat cytokine release syndrome[46,47] until toxicity decreases. Cumulative dexamethasone-equivalent doses of more than 1000 mg (prednisone dose >6600 mg) have been used in patients with severe, refractory cytokine release syndrome or neurologic toxicities.[48,49] CAR T cells can cross the blood-brain barrier[41,44] and cause reversible neurologic syndromes, including encephalopathy, dysphasias, decreased alertness, tremors, and, in the more severe forms, focal motor defects, seizures, and cerebral edema.[44,50] This neurologic toxicity has been termed *immune effector cell–associated neurotoxicity syndrome*.[51] Glucocorticoids are first-line treatment for this disorder.[51] A consensus grading scale was devised by an American Society for Transplantation and Cellular Therapy committee,[51] and multiple professional societies have published guidelines for cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome management.[52-54] Movement disorders have also occurred weeks to months after anti-BCMA CAR T-cell therapies and are poorly understood.[26,55,56] Because expertise is required to manage cytokine release syndrome and neurologic toxicities, CAR T-cell therapy is currently administered primarily at experienced tertiary care centers, with only 9% to 24% of patients receiving outpatient CAR T-cell infusions in clinical trials in

Table 2. Common Challenges Associated With CAR T-Cell Therapy

Clinical problem	Ranges and frequency of occurrence	Possible solution	Comments/details
Potential for long period between cell collection and CAR T-cell infusion allows progression of malignancy and may result in deaths	Varies per CAR T-cell product: Range of median reported cell processing times[a] for FDA-approved products: 13-54 d	Allogeneic CAR T cells derived from healthy donors can be manufactured in advance, cryopreserved, stored, and delivered for infusion into patients on demand. This process can decrease the time from the decision to treat to the cell infusion to just a few days (5-9 d).[36,37]	Gene-editing technologies have been necessary to knockdown the T-cell receptor α chain to prevent the CAR T cells from causing graft-vs-host disease. There is a concern that multiple gene-editing steps could hypothetically increase the risk of development of secondary T-cell malignancies.
Change in antigen expression by the cancer can cause cancer progression or relapse	Varies per CAR T-cell product, eg, tisagenlecleucel for pediatric leukemia: 91%, axicabtagene ciloleucel for large B-cell lymphoma: 28%, and idecabtagene vicleucel: 4%	CAR T cells directed at multiple malignancy-associated antigens may be able to target an antigen that continues to be expressed by the malignant cell despite loss of expression of 1 or more other target antigens. Patients with relapsed or refractory malignancy after CAR T cells targeting 1 antigen may be able to receive CAR T cells targeting a different antigen as salvage therapy.	Options include CAR proteins designed to target multiple antigens at once; incorporation of sequences for multiple CAR proteins into 1 vector, resulting in multiple CAR types on the T-cell surface; and coinfusion of multiple CAR T-cell products, each CAR T-cell product targeting a different malignancy-associated antigen
CAR T cells with a more differentiated phenotype with loss of tumor-killing functions lead to low efficacy	Not reported	Modified CAR protein structure and cell-processing techniques to produce more naive, more functional CAR T cells Use of CAR T cells as an earlier line of malignancy therapy, so that patient T cells are less affected by prior chemotherapy treatments	The efficacy of combination therapies, such as BTK inhibitors and immune checkpoint inhibitors, is not established. Experience with immune checkpoint inhibitor combination therapy has not shown clear improvement in efficacy.
Severe[b] cytokine release syndrome and neurologic toxicities	Varies per CAR T-cell product. Severe CRS range: 0%-47% Severe neurologic toxicity range: 2%-32%	Continued prospective evaluation of anticytokine, small-molecule, and low-dose glucocorticoids for prevention and early intervention for these adverse effects	Agents of interest include siltuximab, anakinra, emapalumab, JAK/STAT pathway inhibitors, BTK inhibitors
		Development of less-toxic CAR T-cell therapies	Structural changes to the CAR protein to decrease cytokine release, genetic switches that induce apoptosis, so-called *suicide genes*, CAR T cells engineered to secrete cytokine blockers, and changes to the cell culture process
Risk of second malignancies	Myeloid malignancies: 2%-10%[38,39] T-cell malignancies: 22 cases reported out of >27 000 doses administered[40]	Use of CAR T cells as an earlier line of malignancy therapy may decrease exposure to prior chemotherapies that can lead to secondary myeloid malignancies Long-term monitoring for second malignancies, including T-cell malignancies	Role of next-generation sequencing as screening for mutations that predispose to second malignancies is not established

Abbreviations: BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; FDA, Food and Drug Administration; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

[a] Cell processing times reported as any of the following: time from patient cell collection to completion of manufacturing or delivery of the CAR T-cell product from the central manufacturing center to the health care facility, time from manufacturer's receipt of patient cells to completion of manufacturing of CAR T-cell product, or as time from patient clinical trial enrollment to CAR T-cell infusion.

[b] Grade 3 or higher per varying grading scales, as reported on clinical trials.

which outpatient infusions were permitted.[3,18] While cytokine release syndrome can be managed by tocilizumab, followed by glucocorticoids if needed, and control of immune effector cell–associated neurotoxicity syndrome can be managed with increasing doses of glucocorticoids, large cumulative doses of glucocorticoids may have detrimental effects on CAR T-cell function and were associated with poorer progression-free and overall survival in one retrospective series.[49] However, with earlier use of tocilizumab and glucocorticoids to manage toxicity, overall survival rates have improved and rates of high-grade cytokine release syndrome decreased from approximately 9% to 4% of patients receiving CAR T-cell therapy in one retrospective analysis from the UK that included 726 patients.[57] The treatment-related mortality reported in clinical trials of the commercially available products is approximately 0% to 6%.[48]

Long-term adverse effects of CAR T-cell therapy include prolonged myelosuppression—defined as high-grade neutropenia, anemia, or thrombocytopenia lasting more than 28 to 30 days, which affects approximately 22% to 54% of patients—and immunosuppression, which may have contributed to severe infection in 5% to 32% of patients in clinical trials (Table 1). Cytopenias lasting more than 1 month after CAR T-cell infusion are believed to be mediated by elevated cytokines, although the pathophysiology is not entirely known.[58] Anti-CD19 CAR T cells, such as tisagenlecleucel or axicabtagene ciloleucel, may eliminate normal CD19-expressing B cells, leading to complete B-cell depletion, termed *B-cell aplasia*. B-cell aplasia is termed an *on-target* toxicity because it consists of destroying normal cells expressing the same antigen that the CAR T cells target on malignant cells. B-cell aplasia and resulting hypogammaglobulinemia can be treated with immunoglobulin replacement therapy, although adults may not require these treatments after anti-CD19 CAR T-cell therapy because their mature plasma cells, which do not express CD19, are preserved.[59] Because of possible adverse effects of B-cell aplasia, CD4 lymphopenia, and prolonged cytopenias, patients are at high risk of infection following CAR T-cell therapy, including severe infection due to SARS-CoV-2.[60,61] Bacterial infections most commonly occur during the month following anti-CD19 CAR T-cell infusion. Viral infections, especially respiratory viral infections, may occur more than 1 year after CAR T-cell treatment.[62] Invasive fungal infections occur in approximately 8% of patients. Candidal infections most commonly occur in the first month after treatment. *Aspergillus* and other mold infections most commonly occur in the first 90 days after treatment.[62]

Secondary myeloid malignancies, such as acute myeloid leukemia and myelodysplastic syndrome, affect approximately 2% to 10% of patients within 5 years after CAR T-cell infusion.[38,39,63,64] Patients are already at risk for these secondary myeloid malignancies due to mutagenic properties of their prior chemotherapy, including potentially chemotherapy received immediately prior to CAR T-cell infusion. In December 2023, the FDA approved an updated box warning for the package insert for ciltacabtagene autoleucel stating that secondary hematologic malignancies, including acute myeloid leukemia and myelodysplastic syndrome, had been reported in patients treated with this CAR T-cell product, with a total of 10% (10/97) of patients in a clinical trial later developing these secondary malignancies.[39] However, these patients had received many other treatments, including treatments after the CAR T-cell infusion,[39] and whether CAR T-cell treatment causes secondary myeloid malignancies remains unclear.[63,64]

The role of CAR T cells in causing T-cell malignancies is under investigation, with at least 22 cases reported out of more than 27 000 treatments administered, including 3 T-cell malignancies expressing the CAR protein.[40] This raises concern that the genetic engineering process may cause malignant transformation of the CAR T cells because viral insertion of the CAR gene proximal to genetic regions controlling the T cell's growth could cause malignancies via a process termed *insertional mutagenesis*. However, thousands of patients have received CAR T-cell therapy for life-threatening hematologic malignancies and these events are rare, with the benefit of CAR T-cell therapy outweighing the risk.[65]

Efficacy

Even with potentially curable malignancies, such as large B-cell lymphoma and B-cell acute lymphoblastic leukemia, many patients do not achieve durable remission with CAR T-cell therapy. Following axicabtagene ciloleucel for large B-cell lymphoma, 63% of patients who achieved partial or complete remission experienced relapse, refractory malignancy, or death, and following tisagenlecleucel for B-cell acute lymphoblastic leukemia, 36% of patients who achieved remission experienced relapse.[4,9] One mechanism of relapse is evolution of the malignancy so that it either no longer expresses the antigen targeted by the CAR T cell, expresses the antigen less strongly, or expresses the antigen in an altered form that is not recognized by CAR T cells. This phenomenon, termed *antigen escape*, affects approximately 91% of patients with relapse after initial remission following tisagenlecleucel therapy for B-cell acute lymphoblastic leukemia,[4] 28% following axicabtagene ciloleucel for large B-cell lymphoma[66] and 4% after idecabtagene vicleucel for multiple myeloma (Table 2).[23] Another mechanism of low efficacy of CAR T-cell therapy is poor quality of the autologous T cells collected by leukapheresis, which can cause poorer-quality manufactured CAR T cells. Higher treatment response rates and more durable responses were associated with more immature T cells with greater retained ability to proliferate in the patient after administration.[24,67,68] The reasons for poorer-quality or less-functional T cells at the time of T-cell collection are incompletely understood. Patients receiving more prior cancer treatment regimens may be at higher risk for less-functional T cells, and these patients were less likely to achieve remissions in retrospective series.[68,69] Resistance to CAR T-cell therapy is associated with poorer outcomes. Patients with large B-cell lymphoma without response or who relapsed after anti-CD19 CAR T-cell therapies had a median overall survival of only 5.2 months in a French registry analysis that included 550 patients.[70]

Challenges in Treatment Delivery

Length of wait time between leukapheresis of patients' cells and infusion of CAR T cells, termed *vein-to-vein times*, was approximately 13 to 54 days for the FDA-approved CAR T-cell products (Table 2). In clinical trials and during commercial use of approved CAR T-cell therapies, 0% to 31% of patients did not receive CAR T-cell infusions due to either cell manufacturing failures or, more commonly, malignancy progression associated with deteriorating clinical status during wait times.[3,5,7,11,23,71] CAR T-cell therapies cost hundreds of thousands of dollars, which can be a barrier to treatment.[72] In the US, Medicare covers the cost of CAR T-cell therapy,[73] but Medicaid coverage varies by state, with some states having more restrictive policies regarding which patients are eligible.[74] Patients without health insurance have limited access to CAR T-cell therapy, and less than 1% of CAR T-cell recipients have not had insurance or another payer.[75] Some US centers have waitlists to receive CAR T-cell therapy for multiple myeloma. The waitlist model of "first come, first served" may disadvantage patients of lower socioeconomic status and worsen health care disparities.[76]

Solid Tumor Cancers

Efficacy of CAR T-cell treatments for solid tumors has been limited, although tumor responses have been observed in certain cancers, and other types of T lymphocyte–based treatments have gained FDA approval.[77-83] Laboratory research in which mice were implanted with tumors to model cancer treatment identified T-cell–related factors that influence treatment efficacy, such as the ability of the CAR T cells to migrate to the tumor, proliferate, and remain viable in the patient; overcome inhibitory factors such as transforming growth factor-β that permeate the tumor microenvironment; and sustain their antitumor functions. It remains unclear which, if any, of these mechanisms limit treatment efficacy in humans. Major limitations for cell therapy and other immunotherapies may be due to tumor-cell–intrinsic factors such as target antigen expression, antigen presentation, and sensitivity to T-cell effector molecules.[78,84,85] The identification and targeting of "clean" targets, specific molecular structures in cancer cells that can be targeted without severe toxicity from injury to healthy cells, remains a major challenge.[48,86]

Improving CAR T-Cell Therapy for Hematologic Cancers

CAR T-cell therapy could be improved by decreasing toxicity, improving efficacy, and expanding the patient population eligible to receive CAR T-cell therapy. Pharmacologic treatment to reduce acute CAR T-cell toxicities is evolving. Benefits of anticytokine therapies, such as siltuximab, anakinra, or emapalumab, and small molecules, such as ibrutinib, dasatinib, or itacitinib, for treating CAR T-cell toxicity are not established. Few excellent animal models of CAR T-cell toxicity exist.[51] Mouse models of cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome have suggested that IL-1 blockade may prevent or reduce

adverse effects.[87,88] Small prospective trials have suggested that prophylactic use or early intervention with tocilizumab, the IL-1 receptor antagonist anakinra, or low doses of glucocorticoids may prevent severe cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome toxicities.[89-93] Anticytokine therapies, such as the IL-6 antagonist siltuximab, anakinra, and the interferon-γ blocker emapalumab, have been used off-label as glucocorticoid-sparing agents and to treat toxicities unresponsive to glucocorticoids[94-96]; however, algorithms recommending administration of these therapies in a specific order have not been tested in randomized clinical trials (Table 2).

Modifying the structure of the CAR can change the toxicity profile of CAR T cells, often by decreasing cytokines and other immunologic proteins secreted by CAR T cells and by other immune cells in the patient's blood without decreasing CAR T-cell efficacy.[97] Cytokine release syndrome and/or immune effector cell–associated neurotoxicity syndrome adverse effects have been decreased in clinical trials by changing the strength of binding of the antigen-recognition moiety (Figure, A) to the cancer-associated antigen.[98] These toxicities may also be decreased by changing the sequence of the hinge and transmembrane domains (Figure, A), which connect the extracellular antigen recognition moiety to the intracellular components that activate the T cell (Figure, A),[97] and by changing the structure of the CD3ζ T-cell activation domain (Figure, A).[99] Evaluating CAR T cells with modified CAR structures in clinical trials and developing less-toxic CAR T-cell therapies may facilitate more widespread use of CAR T-cell therapy (Table 2).

Increasing Efficacy and Durability of CAR T-Cell Therapy

In early clinical trials, patients with the greatest proliferation of their CAR T cells, termed *cell expansion*, had the best antitumor responses.[11,100] This finding has been confirmed in multiple malignancies and with multiple CAR T-cell products, including those targeting BCMA in multiple myeloma.[23] Potential strategies to improve the efficacy and increase expansion of CAR T cells and their efficacy in vivo include modifying the cell culture process to select for less-differentiated phenotype T cells, which may improve antimalignancy efficacy.[101] Combination therapy with Bruton tyrosine kinase inhibitors, such as ibrutinib, may improve CAR T-cell expansion and promote a more efficacious CAR T-cell phenotype,[102] although evidence has been inconsistent.[103] Combining CAR T-cell therapy with immune checkpoint inhibitors or administering immune checkpoint inhibitors as salvage for CAR T-cell therapy failure or relapse could ameliorate CAR T-cell functional deterioration in vivo, but clinical trials have shown low efficacy.[104-106]

CAR T cells are under development to treat malignancy relapse that occurs when tumor cells stop expressing the antigen that the first-line CAR T-cell therapy was designed to recognize, so-called *antigen escape*. Examples include CAR T cells directed against the B-cell antigen CD22 to treat B-cell acute lymphoblastic leukemia that no longer expresses CD19 after anti-CD19 CAR T-cell therapy. Anti-CD22 CAR T-cell therapy has shown preliminary efficacy in clinical trials.[107] In a phase 1 dose-escalation study of 17 patients with multiple myeloma with a median of 6 prior treatments, CAR T cells directed against the antigen G-protein–coupled receptor, class C, group 5, member D demonstrated early evidence of efficacy for patients with multiple myeloma who had relapsed after anti-BCMA CAR T-cell therapy.[108] Alternative antigen targets for CAR T-cell therapy for lymphoma currently undergoing testing in early-phase clinical trials include CD79b and CD37.[109-111] Targeting multiple antigens simultaneously to prevent antigen escape, such as with CAR T cells directed against both CD19 and CD20 for B-cell lymphoma, is undergoing investigation.[112]

Commercially available CAR T-cell therapies are approved as second-line or later therapies for hematologic malignancies (Table 1). Clinical trials are evaluating CAR T-cell therapy as first-line therapy or administered earlier in the course of treatment than previously approved. In the ZUMA-12 clinical trial of axicabtagene ciloleucel for patients with high-risk large B-cell lymphoma, 40 patients were treated with CAR T cells after they did not achieve remission with 2 cycles of standard chemotherapy as the first treatment.[113] In these patients, a higher proportion of less-differentiated, more-proliferative T cells were identified in the preinfusion CAR T cells compared with the ZUMA-1 trial that evaluated axicabtagene ciloleucel as third-line or later treatment. CAR T-cell therapy earlier in the treatment course may lead to more functional CAR T cells, possibly because the T cells have been exposed to fewer prior cell-damaging chemotherapies.[113]

Currently, FDA-approved CAR T-cell products, and those in late-stage trials, consist of autologous T cells. However, CAR T cells manufactured from cells collected from normal, healthy donors and stored until use, termed *off-the-shelf CAR T cells*, have been investigated in early-phase trials.[36,37] Typically, gene-editing technologies, such as transcription activator-like effector nucleases or clustered regularly interspaced short palindromic repeats, are used to remove the T-cell receptor to prevent graft vs host disease. Because allogeneic cells could be rejected by the host immune system, higher doses of chemotherapy and in some cases infusion of monoclonal antibodies against CD52 to prolong T-cell depletion may facilitate the expansion of donor-derived cells. Gene-editing technologies may delete a T-cell marker, such as CD52, such that T-cell–depleting conditioning therapies do not kill the donor-derived CAR T cells. These CAR T-cell products can be used without human leukocyte antigen matching between donor and recipient. Early evidence of efficacy with both anti-CD19 and anti-BCMA off-the-shelf CAR T cells is available, with shorter times between cell collection and reinfusion of CAR T cells compared with commercially available CAR T cells.[36,37] However, T-cell–depleting conditioning therapies increase rates of long-term immunosuppression from T-cell depletion and increase rates of opportunistic viral infections, such as cytomegalovirus.[36,48]

Cellular Therapy for Solid Tumors

TIL Therapy

Cellular therapy for solid tumors has primarily been with TILs, natural T cells grown ex vivo from a resected tumor (Figure, C; **Table 3**).[121-125] The TIL therapy lifileucel received accelerated FDA approval to treat unresectable or metastatic melanoma in patients previously treated with at least 1 systemic therapy. FDA approval was based on an overall response rate of 31.5% (95% CI, 21.1%-43.4%) and median duration of response that was not reached (95% CI, 4.1 months-not reached).[126] Tumor responses were reported with TIL therapy for human papillomavirus (HPV)–associated cancers with responses in 5 of 18 patients (28%)

Table 3. Example Phase 1/2 Clinical Trials of Engineered Antigen Receptor Therapy in Solid Tumors Directed Against Selected Target Antigens[a]

Source	Target	Cancer	Antigen receptor	Trial phase	Patients with responses/sample size, No. (%)[b]
Ishihara et al,[114] 2022	NY-ESO-1	Mixed types such as synovial sarcoma, myxoid liposarcoma, and malignant salivary tumor	TCR	1	3/7 (43)
D'Angelo et al,[115] 2018	NY-ESO-1	Synovial sarcoma	TCR	1/2	6/12 (50)
Robbins et al,[116] 2015	NY-ESO-1	Synovial sarcoma and melanoma	TCR	2	11/18 (synovial sarcoma; 61) 11/20 (melanoma; 55)
Lu et al,[117] 2017	MAGE-A3	Mixed types such as melanoma, cervical cancer, breast cancer, and urothelial carcinoma	TCR	1/2	4/17 (24)
Hong et al,[82] 2023	MAGE-A4	Synovial sarcoma and mixed types	TCR	1	7/16 (synovial sarcoma; 44) 2/22 (mixed; 9)
D'Angelo et al,[118] 2024	MAGE-A4	Synovial sarcoma and myxoid round cell liposarcoma	TCR	2	17/44 (synovial sarcoma, 39) 2/8 (myxoid round cell liposarcoma, 25)
Doran et al, [119] 2019	HPV E6	HPV-positive cancers such as cervical, anal, and head and neck cancers	TCR	1/2	2/12 (17)
Nagarsheth et al,[120] 2021	HPV E7	HPV-positive cancers such as cervical, anal, and head and neck cancers	TCR	1	6/12 (50)
Qi et al,[81] 2024	Claudin18.2	Gastrointestinal cancers	CAR T	1	38/98 (39)
Del Bufalo et al,[79] 2023	GD2	Neuroblastoma	CAR T	1/2	17/27 (63)

Abbreviations: CAR, chimeric antigen receptor; HPV, human papillomavirus; MAGE, melanoma-associated antigen; NY-ESO-1; New York esophageal squamous cell carcinoma 1; TCR, T-cell receptor.

[a] Trials of systemic therapy targeting the indicated tumor antigen that resulted in at least 2 objective responses in a solid tumor type are included. Combination therapies and trials terminated due to severe toxicity are not included.

[b] Response data are by RECIST criteria with the exception of the GD2 CAR T study in neuroblastoma, which used Revised International Neuroblastoma Response Criteria with International Society of Paediatric Oncology Europe Neuroblastoma Group scoring.

with cervical cancer and 2 of 11 patients (18%) with other HPV-associated cancers such as oropharyngeal cancer.[121-123] Two patients with cervical cancer had complete responses for more than 5 years after a single infusion of TIL cells. The FDA has granted Breakthrough Therapy Designation, a status for a treatment that may offer substantial improvement that provides expedited FDA review, for a TIL cervical cancer treatment.

TCR T-Cell Therapy

TCR T-cell therapies consist of administration of T cells that are genetically engineered ex vivo to express a TCR that targets a tumor-associated antigen. They differ from TILs because they are genetically engineered to have a characterized TCR that targets a known, characterized tumor-associated antigen, whereas TILs are not genetically engineered and have uncharacterized, natural TCRs that target unknown antigens (Figure, C and D). The TCR T-cell therapy afamitresgene autoleucel has received FDA approval for treating synovial cell sarcoma after prior chemotherapy.[83] It targets the antigen melanoma-associated antigen A4 (MAGE-A4), a molecule from the cancer germline antigen class that is expressed by certain cancers, and during embryonic development and by germ cells, but not by healthy cells. Approval was based on an overall response rate of 39% with median duration of response of 11.6 months in a single-group study.[83,118] Other TCR T-cell therapies have antitumor effects exhibited by tumor responses in early-phase clinical trials for synovial cell sarcoma, melanoma, and HPV-associated cancers (Table 3). Melanoma and synovial cell sarcoma treatments have been directed against cancer germline antigens such as MAGE family members and New York esophageal squamous cell carcinoma 1 with demonstrated response rates ranging from 39% to 61%.[82,114-117] Treatments for HPV-associated cancers have been directed to the HPV oncoproteins, cancer-causing viral proteins termed *E6* and *E7*, which are constitutively expressed by cancers and not expressed by healthy tissues.[119,120] TCR T cells directed against E7 demonstrated tumor responses in 6 of 12 patients including 4 of 8 patients with programmed cell death protein 1–refractory tumors.[120] Treatment resistance was primarily due to tumor-intrinsic defects in antigen presentation. Loss of genes involved in interferon response and antigen presentation may serve as predictive biomarkers.[119,120,124,125,127-131]

CAR T-Cell Therapy

CAR T-cell therapy has been difficult to adapt to treatment of solid tumors, partially because of limited antigens that can be targeted by CARs, which typically only recognize cell surface antigens (Figure, B). Several CAR T-cell therapies for solid tumors have been limited by adverse effects because they are directed at antigens with shared expression by tumors and healthy tissues. However, some encouraging results have been reported.[78] For example, CAR T cells directed against disialoganglioside GD2 achieved responses according to revised International Neuroblastoma Response Criteria in 17 of 27 patients (63%) with pediatric neuroblastoma.[79] A treatment directed at prostate-specific membrane antigen in prostate cancers showed reduced prostate-specific antigen, although 1 patient died of sepsis and multiorgan dysfunction following severe cytokine release syndrome.[132] A treatment directed at Claudin18.2 in gastrointestinal cancers showed partial or complete responses in 38 of 98 patients (39%), although responses were generally short and potentially related to the antimalignancy activity of the chemotherapy given prior to the CAR T-cell infusion.[81,133] To diminish CAR T-cell toxicity, researchers are testing locoregional therapies in which cells are given directly

into or around the tumor, especially in central nervous system cancers.[80,134,135]

Limitations

This review has several limitations. First, the quality of included evidence was not formally reviewed. Second, some relevant articles may have been missed. Third, topics such as cancer therapy using immune cells other than T cells, such as NK cells, and CAR T- cell therapy for diseases other than cancer, such as autoimmune or degenerative diseases, were not covered.

Conclusions

CAR T-cell therapy is an FDA-approved therapy that has improved progression-free survival for multiple myeloma, improved overall survival for large B-cell lymphoma, and attained high rates of cancer remission for other hematologic malignancies such as acute lymphoblastic leukemia, follicular lymphoma, and mantle cell lymphoma. Recent approvals of lifileucel and afamitresgene autoleucel demonstrate the potential of T lymphocyte–based therapies to improve outcomes in solid tumor malignancies.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Brudno reported being an unpaid scientific advisory board member for and receiving travel expenses from Kyverna Therapeutics Inc. Dr Maus reported being an inventor on patents related to adoptive cell therapies held by Massachusetts General Hospital (some licensed to Promab) and University of Pennsylvania (some licensed to Novartis); receiving grant/research support from Kite Pharma and Moderna; serving as a consultant for multiple companies involved in cell therapies; holding equity in 2Seventy Bio, Century Therapeutics, Neximmune, Oncternal Therapeutics, and TCR2 Therapeutics; and serving on the board of directors for 2Seventy Bio. Dr Hinrichs reported receiving grants from the National Cancer Institute during the conduct of the study and personal fees from Neogene Therapeutics, Capstan Therapeutics, GlaxoSmithKline, Vir Biotechnology, and PACT Pharma, equity from Scarlet TCR (company officer), and sponsored research agreements from T-Cure Biosciences and Neogene Therapeutics outside the submitted work. In addition, Dr Hinrichs had a patent for tumor-infiltrating lymphocytes from human papillomavirus (HPV)–positive tumors for the treatment of cancer with royalties paid from Iovance Biotherapeutics; a patent for T-cell receptor targeting an HLA-A2 restricted epitope of human papillomavirus-16 E6 with royalties paid from SQZ Biotechnologies; a patent for T-cell receptor targeting an HLA-A2–restricted epitope of human papillomavirus-16 E7 with royalties paid from Precision BioSciences, Rubius Therapeutics, SQZ Biotechnologies, and Scarlet TCR; a patent for tethered interleukin-15 (IL-15)/IL-21 to enhance T cells for cellular therapy with royalties paid from Iovance Biotherapeutics; a patent for T-cell receptor targeting the cancer/testis antigen KK-LC-1 with royalties paid from Zelluna Immunotherapy and T-Cure Bioscience; a patent for combination PDL1 and TGF β blockade in patients with HPV+ malignancies issued; a patent for discovery of TCR against HLA-A*02:01-restricted CD20 epitope pending; a patent for enhanced tumor reactivity of T cells expressing T-cell antigen receptors containing a mutant nonsignaling CD3zeta chain pending; a patent for discovery of T-cell receptors (TCR) against HLA-A*02:01-restricted CD22 epitope pending; a patent for single domain antibodies targeting HPV E6/E7 oncogenic peptide/MHC complexes pending; a patent for tiered screening of therapeutic TCRs for identification of autoimmune cross-reactivity pending; a patent for method for manufacturing TCR T-cell therapy products targeting tumor antigen(s) from patients with HIV and cancer pending; and a patent for anti-HPV 16 E7 TCR with HLA-B*40:01 restriction pending.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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