

# First CAR T-cell therapy approvals bolster booming immunotherapy market

There were a number of landmark approvals by the US Food and Drug Administration (FDA) in 2017 for cancer therapies, among them, the approval of the first two chimeric antigen receptor (CAR) T-cell therapies for cancer: tisagenlecleucel (in August) and axicabtagene cilolucecl (in October).<sup>1</sup> CAR T-cells are a type of adoptive cell therapy or immunotherapy, in which the patient's own immune cells are genetically engineered to target a tumor-associated antigen, in this case CD19. In tisagenlecleucel, CD19 proteins on B cells are targeted in the treatment of B-cell precursor acute lymphoblastic leukemia. Axicabtagene cilolucecl, the second anti-CD19 CAR T-cell therapy, was approved for the treatment of refractory, aggressive B-cell non-Hodgkin lymphoma.

## Tisagenlecleucel

Tisagenlecleucel was approved for the treatment of pediatric patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) whose disease is refractory to treatment or who have relapsed after second-line therapy or beyond.<sup>2</sup> Approval was based on the pivotal ELIANA trial, a single-arm, global phase 2 trial conducted at 25 centers worldwide during April 2015 through April 2017. Patients were eligible for enrollment if they had relapsed or refractory B-cell ALL and were at least 3 years of age at screening and no older than 21 years of age at diagnosis, had at least 5% lymphoblasts in the bone marrow at screening, had tumor expression of CD19, had adequate organ function, and a Karnofsky (adult) or Lansky (child) Performance Status of  $\geq 50$  (with the worst allowable score, 50, indicating a patient who requires considerable assistance and frequent medical care [Karnofsky] and lying around much of the day, but gets dressed; no active playing but participates in all quiet play and activities [Lansky]). Exclusion criteria included previous receipt of anti-CD19 therapy, concomitant genetic syndromes associated with bone marrow failure, previous malignancy, and/or active or latent hepatitis B or C virus (HBV/HCV) infection.

The overall remission rate (ORR) was evaluated in 75 patients who were given a single dose of tisagenlecleucel (a median weight-adjusted dose of  $3.1 \times 10^6$  transduced viable T cells per kg of body weight) within 14 days of completing a lymphodepleting chemotherapy regimen. The confirmed ORR after at least 3 months of follow-up, as assessed by

## What's new, what's important

The approval of tisagenlecleucel for the treatment of pediatric patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia was based on findings from the ELIANA trial in which 75 patients were given a single dose of tisagenlecleucel after completing a lymphodepleting chemotherapy regimen. The most common adverse events (AEs) associated with tisagenlecleucel treatment included cytokine release syndrome, hypogammaglobulinemia, infection, pyrexia, decreased appetite, among others. AEs were of grade 3/4 severity in 84% of patients. To combat serious safety issues, the FDA approved tisagenlecleucel with an REMS that requires health care providers who administer the drug to be trained in their management. Common toxicities include hypersensitivity reactions, serious infections, prolonged cytopenias, and hypogammaglobulinemia. Patients should be monitored for signs and symptoms of infection. Viral reactivation can occur after tisagenlecleucel treatment, so patients should be screened for HBV, HCV, and HIV before collection of cells. The administration of myeloid growth factors is not recommended during the first 3 weeks after infusion or until CRS has resolved. Patients should also be monitored for life for secondary malignancies.

Axicabtagene cilolucecl was approved for the treatment of adult patients with certain types of relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for the treatment of patients with primary central nervous system lymphoma. Approval was based on the ZUMA-1 trial. The most common grade 3 or higher AEs included febrile neutropenia, fever, and CRS, among others. Serious AEs occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias, and serious infections. Grade 3 or higher CRS or neurologic toxicities occurred in 13% and 28% of patients, respectively. Three patients died during treatment. Axicabtagene cilolucecl is also approved with an REMS. Patients should be monitored for serious infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies, and potential neurologic events affecting the ability to drive and operate dangerous machinery.

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## Mechanism of action: tisagenlecleucel and axicabtagene ciloleucel

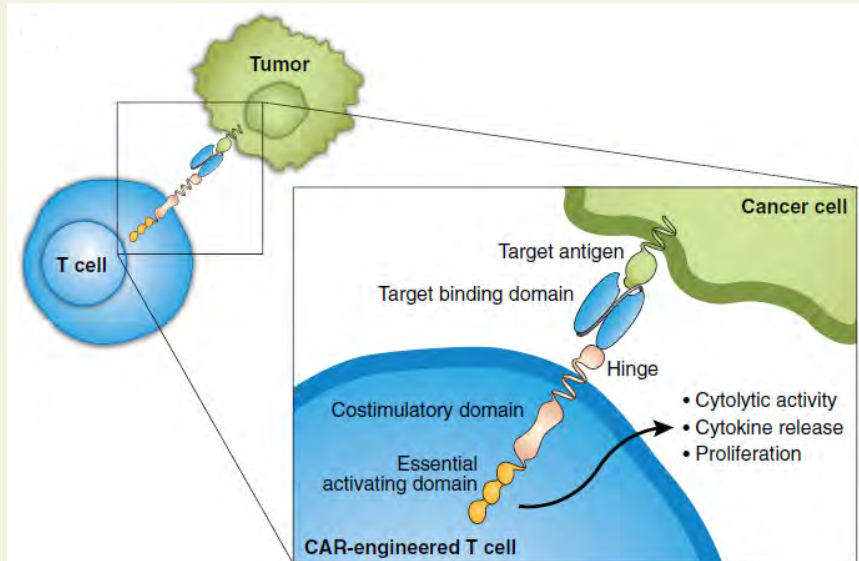
Reprogramming the immune system's killers. It has long been understood that there is a dynamic and complex relationship between a tumor and the host immune system. Unique antigens displayed on a cancer cell can distinguish it from a healthy cell and drive an anti-tumor immune response. However, tumors have also evolved a multitude of mechanisms to subvert that immune response.

In recent years, a new brand of cancer therapy has sought to exploit the anti-tumor immune response by redirecting its cytotoxic activity against the tumor. CAR T-cell therapy is a particularly promising form of cell-based immunotherapy, in which the patient's own immune cells are genetically engineered to endow them with tumor cell specificity.

The T cells are the main effectors of the cell-based adaptive immune response and patrol the body seeking out foreign invaders and damaged host cells that are marked by unique antigens.

On encountering one of these antigens displayed on the surface of antigen-presenting cells (such as macrophages) and bound to major histocompatibility complex (MHC) molecules, the T cell is activated by engagement of the T-cell receptor (TCR) on its surface, triggering the downstream receptor signaling pathways that the TCR orchestrates.

CAR T-cells are engineered to express a different activating receptor, known as a chimeric antigen receptor (hence, CAR). The CAR is a synthetic receptor composed of the single-chain variable fragment (scFv) of an antibody that binds to a particular tumor-associated antigen – in the case of tisagenlecleucel and axicabtagene ciloleucel, the target antigen is CD19. The scFv is fused to a part of the TCR protein that is responsible for initiating downstream signaling pathways on TCR activation – the CD3 zeta chain – and a costimulatory domain that provides a secondary signal to fully activate the T cell.



**FIGURE** CAR T-cell mechanism of action. CAR T-cells are derived from a patient's own T cells that have been genetically modified to express a synthetic immune receptor on their surface. This receptor couples the specificity of an antibody for a specific tumor-associated antigen with the T cell activating machinery and allows T cells to kill tumor cells in an MHC-independent fashion. Reproduced under a Creative Commons license: Roberts ZJ, et al. Axicabtagene ciloleucel, a first-in-class CAR T-cell therapy for aggressive NHL. *Leuk Lymphoma* 2017. doi: 10.1080/10428194.2017.1387905.

The CAR is designed to couple the tumor cell specificity of an antibody with the T-cell activation machinery, allowing direct activation of the T cell that expresses the CAR by a tumor-associated antigen, without the need for that antigen to be presented to the cell in a complex with MHC. Once a CAR T cell has been activated by the target antigen, it acts similarly to a normal T cell, rapidly proliferating and releasing cell-killing products, as well as cytokines that attract other immune cells to the site of the tumor.

For CAR T-cell therapy, the patient's T cells are collected via a procedure known as leukapheresis, and the CAR is introduced into the T-cell membrane through the use of a virus. The CAR-positive T cells are then infused back into the patient after a regimen of chemotherapy that is designed to deplete the patient's normal T cells, to give the CAR T-cells the best chance of success.

independent central review, was 81%, which included 60% of patients in complete remission (CR) and 21% in complete remission with incomplete hematologic recovery, all of whom were negative for minimal residual disease.

The most common adverse events (AEs) associated with tisagenlecleucel treatment were cytokine release syndrome (CRS), hypogammaglobulinemia, infection, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting,

viral infectious disorders, hypoxia, fatigue, acute kidney injury, and delirium. AEs were of grade 3/4 severity in 84% of patients.<sup>3</sup>

To combat serious safety issues, including CRS and neurologic toxicities, the FDA approved tisagenlecleucel with a Risk Evaluation and Mitigation Strategy (REMS) that, in part, requires health care providers who administer the drug to be trained in their management. It also requires the facility where treatment is administered to have immediate,

onsite access to the drug tocilizumab, which was approved in conjunction with tisagenlecleucel for the treatment of patients who experience CRS.

In addition to information about the REMS, the prescribing information details warnings and precautions relating to several other common toxicities. These include hypersensitivity reactions, serious infections, prolonged cytopenias, and hypogammaglobulinemia.

Patients should be monitored for signs and symptoms of infection and treated appropriately. Viral reactivation can occur after tisagenlecleucel treatment, so patients should be screened for HBV, HCV, and human immunodeficiency virus before collection of cells.

The administration of myeloid growth factors is not recommended during the first 3 weeks after infusion or until CRS has resolved. Immunoglobulin levels should be monitored after treatment and hypogammaglobulinemia managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement according to standard guidelines.

Patients treated with tisagenlecleucel should also be monitored for life for secondary malignancies, should not be treated with live vaccines from 2 weeks before the start of lymphodepleting chemotherapy until immune recovery after tisagenlecleucel infusion, and should be aware of the potential for neurological events to impact their ability to drive and use dangerous machinery.<sup>4</sup>

Tisagenlecleucel is marketed as Kymriah by Novartis Pharmaceuticals. The recommended dose is 1 infusion of  $0.2\text{-}5 \times 10^6$  CAR-positive viable T cells per kilogram of body weight intravenously (for patients  $\leq 50\text{kg}$ ) and  $0.1\text{-}2.5 \times 10^8$  cells/kg (for patients  $>50\text{kg}$ ), administered 2-14 days after lymphodepleting chemotherapy.

## Axicabtagene ciloleucel

Axicabtagene ciloleucel was approved for the treatment of adult patients with certain types of relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.<sup>5</sup> It is not indicated for the treatment of patients with primary central nervous system lymphoma.

Approval followed positive results from the phase 2 single-arm, multicenter ZUMA-1 trial.<sup>6</sup> Patients were included if they were aged 18 years of age and older, had histologically confirmed aggressive B-cell non-Hodgkin lymphoma that was chemotherapy refractory, had received adequate previous therapy, had at least 1 measurable lesion, had completed radiation or systemic therapy at least 2 weeks before, had resolved toxicities related to previous therapy, and had an Eastern Cooperative Oncology Group Performance

Status of 0 (asymptomatic) or 1 (symptomatic), an absolute neutrophil count of  $\geq 1000/\mu\text{L}$ , a platelet count of  $\geq 50,000/\mu\text{L}$ , and adequate hepatic, renal and cardiac function. They were treated with a single infusion of axicabtagene ciloleucel after lymphodepleting chemotherapy.

Patients who had received previous CD19-targeted therapy, who had concomitant genetic syndromes associated with bone marrow failure, who had previous malignancy, and who had active or latent HBV/HCV infection were among those excluded from the study.

Patients were enrolled in 2 cohorts; those with DLBCL ( $n = 77$ ) and those with PMBCL or transformed follicular lymphoma ( $n = 24$ ). The primary endpoint was objective response rate, and after a primary analysis at a minimum of 6 months follow-up, the objective response rate was 82%, with a CR rate of 52%. Among patients who achieved CR, the median duration of response was not reached after a median follow-up of 7.9 months.

A subsequent updated analysis was performed when 108 patients had been followed for a minimum of 1 year. The objective response rate was 82%, and the CR rate was 58%, with some patients having CR in the absence of additional therapies as late as 15 months after treatment. At this updated analysis, 42% of patients continued to have a response, 40% of whom remained in CR.

The most common grade 3 or higher AEs included febrile neutropenia, fever, CRS, encephalopathy, infections, hypotension, and hypoxia. Serious AEs occurred in 52% of patients and included CRS, neurologic toxicity, prolonged cytopenias, and serious infections. Grade 3 or higher CRS or neurologic toxicities occurred in 13% and 28% of patients, respectively. Three patients died during treatment.

To mitigate the risk of CRS and neurologic toxicity, axicabtagene ciloleucel is approved with an REMS that requires appropriate certification and training before hospitals are cleared to administer the therapy.

Other warnings and precautions in the prescribing information relate to serious infections (monitor for signs and symptoms and treat appropriately), prolonged cytopenias (monitor blood counts), hypogammaglobulinemia (monitor immunoglobulin levels and manage appropriately), secondary malignancies (life-long monitoring), and the potential effects of neurologic events on a patient's ability to drive and operate dangerous machinery (avoid for at least 8 weeks after infusion).<sup>7</sup>

Axicabtagene ciloleucel is marketed as Yescarta by Kite Pharma Inc. The recommended dose is a single intravenous infusion with a target of  $2 \times 10^6$  CAR-positive viable T cells per kilogram of body weight, preceded by fludarabine and cyclophosphamide lymphodepleting chemotherapy.

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