The emerging individualized and living-cell-based genetic engineering chimeric antigen receptor T (CAR-T) therapy demonstrates great curative effects in some hematological tumor treatments, thus it is turning out to be a star immunotherapy method of the world.

Recently, the China National Medical Products Administration (NMPA) approved launching applications of two CAR-T cell cancer products, Axicabtagene Ciloleucel (FKC876) and Relmacabtagene Autoleucel (Carteyva), which marked the beginning of the CAR-T cell therapy era in China (Figure 1). Axicabtagene Ciloleucel (FKC876) from Fosun Kite Biotech is the first product of its kind and is approved for the treatment of adult patients with relapsed or refractory large B cell lymphoma (r/r LBCL) after two or more lines of systemic therapy, including diffuse LBCL (DLBCL) not otherwise specified, primary mediastinal LBCL (PMBCL), high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma. Relmacabtagene Autoleucel from JW Therapeutics is the second anti-CD19 autologous CAR-T cell therapy product approved by NMPA for treating adult patients with r/r LBCL after two or more lines of systemic therapy.

It is worth noting that both of the approved CAR-T products are based on highly efficient international joint ventures’ Hi-Tech cooperation. Axicabtagene ciloleucel (FKC876), the CD19-targeting autologous CAR-T cell therapy product, was introduced from Kite Pharma’s core product Yescarta in 2017, while Relmacabtagene Autoleucel (JWCAR029) was developed as a new therapy product based on Juno Therapeutics's Lisocabtagene Maraleucel (Liso-cel; JCAR017) research platform in 2016. After several years of localized research and development (R&D) and clinical trials, both CAR-T cell therapy products have been approved and supplied new options and hopes to r/r LBCL patients that had previously exhausted all viable treatment options in China.

As one of the world’s leading CAR-T products, Yescarta has been shown to have good efficacy in a series of clinical studies. For example, the 2-year follow-up result of the ZUMA-1 study showed that in B cell lymphoma, the objective response rate (ORR) reached 83%, the complete response rate was 58%, and 39% of patients were in continuous remission. According to the Chinese bridging trial results, 79.2% of patients achieved a response after a single infusion of Axicabtagene Ciloleucel (FKC876), which demonstrated a similar efficacy and safety profile between FKC876 and Yescarta in the treatment of adult patients with r/r LBCL.

The approval of Relmacabtagene Autoleucel is based on the results of a single-arm, multi-center, pivotal study. The corresponding RELIANCE study enrolled 59 patients with r/r LBCL who failed to respond to at least two lines of therapy. As of the June 17, 2020, data cut-off, the best overall response rate was 75.9%, with a best complete response rate of 51.7% in 58 evaluable patients and a 12-month overall survival (OS) rate of 76.8%. Accordingly, Relmacabtagene Autoleucel was the first CAR-T product approved as a category 1 biological product of China and the sixth approved CAR-T product globally. It is worth noting that the US Food and Drug Administration (FDA) also approved Lisocabtagene maraleucel for r/r LBCL in February of 2021, according to the clinical trial results of adult r/r LBCL.
LBCL patients after at least two lines of therapy. Of the 192 patients evaluable for a response, the overall response rate (ORR) per an independent review committee assessment was 73%, with a complete response (CR) rate of 54%.

Over the last 4 years, FDA has approved five CAR-T products, including Kymriah from Novartis, Yescarta and Tecartus from Gilead, and Breyanzı and Abecma from Bristol Myers Squibb (Figure 1). The first four products are genetically CD19-targeting modified autologous T cell immunotherapies, while the last one is a B cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy. These CAR-T cell therapies have been shown to be effective in treating different late-stage hematological tumors. Generally, based on a single administration, the genetically modified CAR-T cells recognize and kill tumor cells in a major histocompatibility complex (MHC)-independent fashion. CAR-T therapy significantly prolongs the survival time of patients and even cures some patients. Based on the great potential in hematological tumor treatments, there are abundant fierce CAR-T programs in R&D and clinical trials for cancer therapy that have been designed with unique advantages (e.g., dual-target, fully human CAR fragments, etc.). However, the mainstream use of CAR-T therapy is still in the second generation of CAR with 4-1BB as a costimulatory molecule, which enhances T cell proliferation and cytotoxicity through a costimulatory domain.5

Recently, CAR-T therapy has also shown some breakthroughs in solid tumors other than blood tumors. At present, more than 14 solid tumor targets are in the clinical trials, including vascular endothelial growth factor (VEGF), prostate-specific membrane antigen (PSMA), epithelial cellular adhesion molecule (EpCAM), GPC3, and CLDN18.2. By selecting specific targets that are highly expressed in tumor tissues and optimizing the structure of CARs, a series of recent studies have shown the prospect of using CAR-T therapy in solid tumors, including melanoma, cervical cancer, lung cancer, mesothelioma, and esophageal cancer. More ongoing clinical trial information for CAR-T immunotherapy can be obtained through the following websites: US Clinical Trial (https://clinicaltrials.gov/) and Chinese Clinical Trial Register (ChiCTR; http://www.chictr.org.cn/en/index.aspx).

However, autologous CAR-T cell therapy needs individualized production and release, which lead to a long production cycle and extremely high costs. In order to reduce the long production cycle, scientists work in two ways: one is the development of the FastCAR platform for shortening the CAR-T cell product preparation cycle, and the other is the allogeneic CAT technology, by which scientists try to generate off-the-shelf, universal CAR-T products using cells from allogeneic health donors through gene editing. To eliminate graft-versus-host disease (GVHD), TCR genes and HLA-I genes of T cells can be destroyed by gene-editing tools such as ZFN, TALEN, and CRISPR-Cas9.5 Another problem related to the therapy is the possible adverse reactions, which may include lymphodepleting chemotherapy, adverse cardiovascular and pulmonary events, cytokine release syndrome, and neurotoxicity.5 However, at this point, it is still too early to be able to recognize such adverse reactions for clinics.

As a rising star immunotherapy therapeutic approach, CAR-T therapy has been receiving increasing attention. Accompanied by accelerated new technology and multi-disciplinary cooperation, the shortcomings will be gradually solved. Development of new CAR-T therapies will increase treatment options for patients with hematological or solid tumors.

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DECLARATION OF INTERESTS
The authors declare no competing interests.