CAR-T Cell Therapy in Cancer Treatment

IQVIA Ark Patent Intelligence — March 2024

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Introduction

Cancer is a multifaceted illness that is expanding rapidly and stands as the second primary cause of death worldwide. It is marked by the uncontrolled proliferation of abnormal cells that may infiltrate or metastasise to other parts of the body. Current cancer treatments encompass pharmaceuticals or chemotherapy, radiation therapy, and surgical procedures. Chimeric antigen receptor (CAR)-T cell therapy is a novel form of treatment that is emerging as a transformative approach in cellular immunotherapy.[1] In 2021, the global market for CAR-T cell therapy was estimated to be 1.5 billion USD and it is forecasted to grow to approximately 7.6 billion USD by 2026, demonstrating a compound annual growth rate (CAGR) of 39.1%. Concurrently, the number of CAR-T clinical trials is on the rise, with continual improvements to the CAR-T constructs aimed at boosting their effectiveness and minimising adverse outcomes.[2] The therapeutic promise has stirred an interest in patent filings protecting CAR technology all over the globe. As per Ark Patent Intelligence data, patent filings have significantly increased in the last few years, starting with a mere 10 key patent filings in 1992 and this figure has now surpassed 500 key patents filed worldwide.

The idea of a chimeric T-cell receptor was initially reported in the 1980s and then, following a series of developments, the first generation of CARs, or genetically engineered T-cells, was created in 1993. Later, a lot of other modifications were made which led to more efficient CARs.[3] August 2017 witnessed a historic approval of the first CAR-T Cell therapy drug- Kymriah® (Tisagenlecleucel) by the US Food and Drug Administration (FDA), with successive approvals

Chimeric antigen receptor (CAR)-T cell therapy is a novel form of treatment that is emerging as a transformative approach in cellular immunotherapy.[1]

in Europe, Canada, and Australia in 2018. Yescarta® (Axicabtagene Ciloleucel), the second CAR-T Cell therapy drug was approved by the FDA in October 2017 and was later approved in Europe, Canada, and Australia between 2018 and 2020. A succession of other CAR-T cell products received approval thereafter. Currently, the approved CAR-T cell therapies are designed to target CD19 or BCMA antigens and are primarily indicated for B-cell lymphomas (BCL), multiple myeloma (MM), or acute lymphoblastic leukaemia (ALL).

Method for preparing CAR-T cells and the treatment process

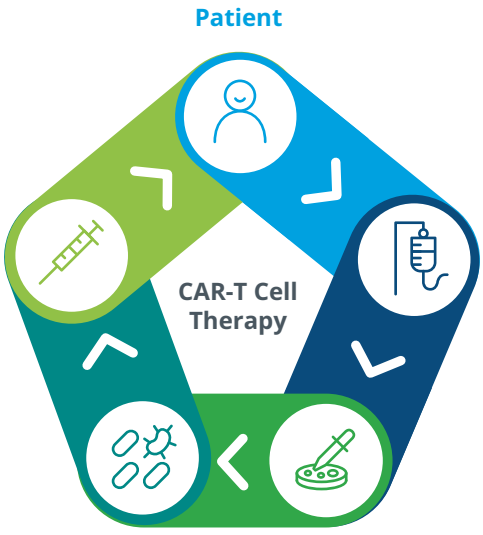
CAR-T cells are made by reprogramming T-cells to express CARs on their surfaces which are specific to cancer cell antigens. These CAR-T cells can recognise and attach to a particular cancer antigen, which allows them to target and destroy cancerous cells. Structurally, a CAR construct consists of four important parts: an extracellular antigen recognition domain that is derived from an antibody, a hinge region, a transmembrane domain, and an intracellular domain for T-cell activation. First-generation CARs include a signalling module derived from CD3ζ, second-generation CARs incorporate an additional costimulatory domain, and third-generation CARs feature two costimulatory domains.[4] The production of CAR-T cells and the entire treatment process encompass several stages, as illustrated in Figure 1.

Benefits of CAR-T Cell treatment and related complexities

CAR-T cell therapy offers numerous advantages, including but not limited to, quick single infusion treatment, a shorter maximum inpatient stay of fifteen days, and reduced recovery time compared to chemotherapy and stem cell transplants. It is a precision treatment that reduces damage to healthy cells and can be designed to target different types of cancer. The therapy is durable and suitable for patients where transplants may not be curative or for those prone to relapse. It remains effective over long periods, allowing it to combat cancer recurrence. The ever-increasing need for personalised therapies and the availability of sophisticated healthcare infrastructure support the promising market prospects of CAR-T cell therapy. Companies like Novartis, Celgene, Takeda, and others are investing in enhancing its efficacy and broadening its application beyond blood cancers.[5]

These major market players are persistently finding ways to expand the reach of CAR-T cell therapy to benefit more patients. However, this innovative therapy has several drawbacks, such as cytokine release syndrome, macrophage activation syndrome (MAS), and potential neurotoxicity. The production of CAR-T cells is complex, time-consuming, and is limited by production capacity and stringent quality controls. This may result in treatment delays and the disease progression may, then, cause patient ineligibility to such treatment options. Additionally, the antigen escape phenomenon where tumour cells stop expressing the targeted antigens can reduce treatment efficacy. The on-target off-tumour effect where target-specific CAR-T cells may also destroy normal cells and tissues because of the expression of the target antigen in normal cells, can sometimes have fatal outcomes. Nevertheless, despite these obstacles, innovative strategies and potential solutions are constantly emerging, paving the way for more efficient and secure therapies in the future.[6]

Figure 1: CAR-T cell therapy — preparation and treatment process



Infusion
The patient receives these cells intravenously while concurrently undergoing chemotherapy. The cancer cells that carry a specific antigen on their cell surface are subsequently recognized by these cells, which further destroy cancerous cells.

Isolation of T lymphocytes
The T-cells are removed from the patient's blood by a non-invasive process called 'aphresis'.

Gene transfer or T-cell engineering
Antibody like proteins CARs, specific to a particular target are genetically engineered on the surface of the T-cells. Ultimately cells start expressing the CAR engineered to recognize a given antigen of the patient's cancer cells and activate the CAR-T cells' expansion and cytotoxic potential upon recognition.

Expansion of the T-cells
The T-cells are multiplied and grown in static and stable conditions in the lab until the count is in millions before infusion.

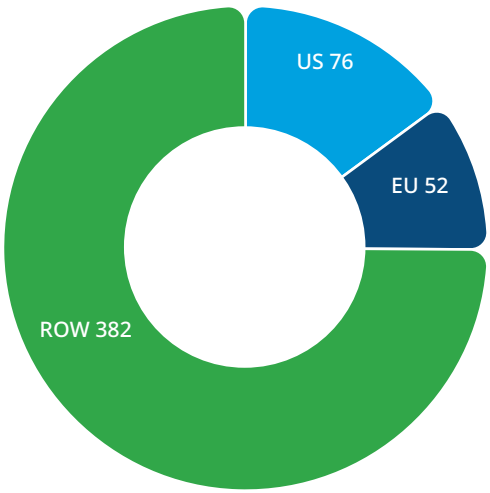
Source: IQVIA white paper[2]

Using Ark Patent Intelligence to identify CAR-T cell therapy

According to the Ark Patent Intelligence database's Key Patents Module, as of March 2024, there are a total of 510 CAR-T cell therapy patents/patent applications (Figure 2).

IQVIA's Ark Patent Intelligence database contains data for 13 CAR-T cell therapies globally. Of these, 11 CAR-T cells are marketed while 2 are in the pre-registration phase. These CAR-T cells can be identified in Ark using the EPHMRA ATC code — L1X5 (Table 1). The Drug Snapshot module offers a holistic summary of all information contained in the other modules of Ark for these therapies, including their tradenames and approved indications.

Figure 2: Number of patents from key patent families per jurisdiction



Source: Ark Patent Intelligence.

Table 1: CAR-T cell therapy details from various modules of Ark Patent Intelligence

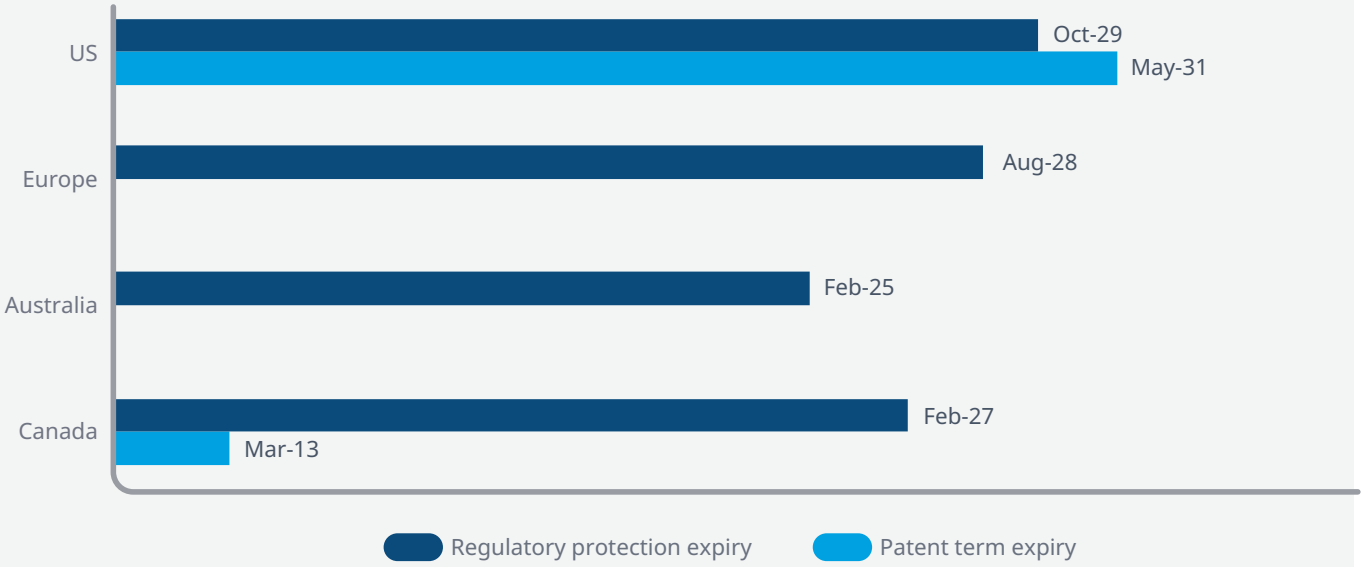
				KEY PATENT FAMILIES	
TRADENAME/ LAB CODE	MOLECULE NAME	APPROVAL STATUS	COMPANY NAME	REPRESENTATIVE FAMILY	FAMILY TYPE
Yescarta®	Axicabtagene Ciloleucel	Marketed	Gilead; Kite	WO9319163	Biotechnology
NexCAR19®	Actalycabtagene Autoleucel	Marketed	Indian Inst Tech	WO2019159193	Molecule
Tecartus®	Brexucabtagene Autoleucel	Marketed	Gilead; Kite	WO2021092290	Method of Use
Carvykti®	Ciltacabtagene Autoleucel	Marketed	Johnson & Johnson	WO2017025038	Molecule
Fucaso®	Equecabtagene Autoleucel	Marketed	Nanjing Iaso; Innovent	WO2019149250	Molecule
Abecma®	Idecabtagene Vicleucel	Marketed	Bristol-Myers Squibb	WO2015164759	Molecule
CNCT 19®	Inaticabtagene Autoleucel	Marketed	Juventas Cell Therapy	WO2021121227	Molecule
Breyanzi®	Lisocabtagene Maraleucel	Marketed	Bristol-Myers Squibb	WO2014031687	Molecule
Carteyva®	Relmacabtagene Autoleucel	Marketed	Juno Therapeutics	WO2021163391	Method of Use
Kymriah®	Tisagenlecleucel	Marketed	Novartis	WO2012079000	Molecule
ARI-0001	Varnimcabtagene Autoleucel	Marketed	Hospital Clinic De Barcelona	WO2022234158	Method of Use
OBE-CEL	Obecabtagene Autoleucel	Pre-registration	UCL Business PLC	US10457730	Molecule
ZEVOR-CEL	Zevorcabtagene Autoleucel	Pre-registration	Carsgen Therapeutics	WO2020057666	Molecule

Source: Ark Patent Intelligence.

Case study: Yescarta

Yescarta (Axicabtagene Ciloleucel) has received approval in the US (October 2017), EU (August 2018), Australia (February 2020), and Canada (February 2019) for the treatment of B-cell lymphoma and follicular lymphoma. As per the Ark Patent Intelligence database, Yescarta has received New Chemical Entity (NCE) exclusivity in Europe, Canada, and Australia, including an additional 2 years of Market protection (MP) in Europe and Canada. In the US, it has received Biosimilar Application Submission Exclusivity (BASE) and Biosimilar Application Approval Exclusivity (BAAE) protection. The US patent US7741465 had its expiry date extended to May 2031 due to the General Agreement on Tariffs and Trade (GATT) reset and patent term extension (PTE). The Canadian equivalent patent CA2132349 expired in March 2013. Patents expiring within these four jurisdictions showcase dynamically different timelines where it will be interesting to monitor markets like Europe and Australia, where the patent equivalents, EP0638119 and AU668156 have already lapsed, but the market remains restricted by innovators through existing granted exclusivities (Figure 3).

Figure 3: Yescarta patent and regulatory protection expiry case study



Source: Ark Patent Intelligence.

Conclusion

CAR-T cell therapy, a form of precision immunotherapy, has revolutionised treatment options, offering personalised solutions that may reduce treatment time. However, it poses risks like cytokine release syndrome, MAS, and neurotoxicity. The transition from lab research to clinical use requires significant expertise, infrastructure, and time. Despite its promise, CAR-T therapy is expensive in terms of research, development, and treatment. Approved therapies target certain lymphomas, myelomas, and leukaemia such as BCL, MM and ALL, with research ongoing for other diseases such as solid tumours, autoimmune diseases, amyloidosis, and more. The complexity of developing, approving, and patenting CAR-T therapies is notable, as is the anticipation of new treatments entering the market and the dynamic patent landscape.

References

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