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Focusing on CAR-T cell therapy for solid tumours

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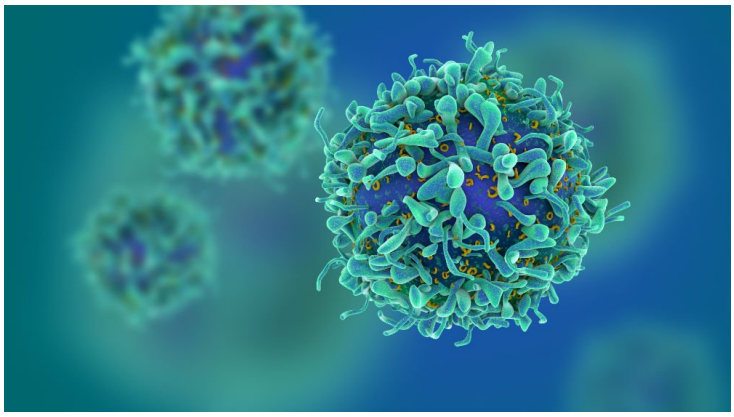
The USFDA (The U.S. Food and Drug Administration) approved the first ever CAR-T (A chimeric antigen receptor-therapy) of Novartis' Kymriah in 2017. Since then, the CAR-T landscape has expanded rapidly, offering hope for life-changing benefits that the treatment provides for cancer patients. BioSpectrum brings the latest and crucial trends pertaining to this crucial therapy.



Chimeric antigen receptor therapy (CAR-T) is developing at a significant pace and is all set to revolutionise oncology with the potential to treat autoimmune diseases, apart from a range of other conditions. There are currently 542 active clinical trials globally.

''Since the initial approvals of Kymriah (Novartis) and Yescarta (Kite/Gilead) in 2017, CAR-T therapies have begun to transform the treatment landscape for patients with cancer, in many cases offering a chance at long-term disease control, and in some cases a chance at a cure. Currently, the six commercially available CAR-T therapies in the U.S. are approved for refractory forms of blood cancer, including leukemia, lymphoma, and myeloma. However, much work is underway to move this modality into earlier forms of cancer and to expand its reach into solid tumors. The field has grown increasingly competitive with dozens of new biopharmaceutical companies advancing hundreds of developmental-stage CAR-T candidates through clinical trials. Given the high degree of investment and fast pace of innovation, it is almost inevitable that multiple breakthroughs will follow," said Dr Eric Schmidt, Chief Financial Officer, Allogene Therapeutics, USA.

Allogene is pioneering this field of"off-the-shelf" CAR-T cell therapy candidates with the goal of delivering readily available cell therapy faster, more reliably, and at greater scale to more patients.

Current landscape

The earliest approvals, Novartis' Kymriah and Gilead's Yescarta, have been commercially available since 2017 and 2018, respectively. In July 2020, the US FDA approved a third CAR-T cell therapy, Kite Pharma's Tecartus. In February 2021, Breyanzi (Juno Therapeutics, Inc., a Bristol-Myers Squibb Company) became the fourth to get approval for CAR-T. In March 2021, the U.S. FDA approved Abecma (Celgene, a BMS company) for the treatment of relapsed or refractory multiple myeloma after four or more prior lines of therapy. Additionally, JW Therapeutics announced the NMPA (National Medical Products Administration) approval of Relmacabtagene Autoleucel Injection within China in September 2021. This is the first CAR-T product independently developed in China and approved as a Category 1 biologics product.

In February 2022, US FDA approved CARVYKTI (ciltacabtagene autoleucel), Janssen's First Cell Therapy, a BCMA-Directed CAR-T Immunotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma.

All these therapies are approved for several hematological malignancies. CAR-T cells in B-cell non-Hodgkin lymphoma, acute lymphocytic leukemia, and multiple myeloma, have been lucrative, with combined sales of over $1.7 billion globally, a figure that is projected to reach $28 billion by 2027, according to GlobalData estimates.

''This commercial success has led to a highly competitive early-stage R&D race, with the number of Phase I/Phase II cell therapy products, including CAR-T, surpassing any other immuno-oncology modality. B-cell lymphomas remain the key focus of clinical development, and most CAR-T cells in the clinic target the de-risked CD19 and BCMA antigens, raising questions about the sustainability of very similar approaches in a market that is getting more crowded by the year,'' said Dr Sakis Paliouras, Senior Oncology Analyst at GlobalData, UK.

It's worth noting that most of the approved therapies and also the ones in late stage trials currently are autologous therapies. That's changing slowly. There is a shift away from autologous CAR-T therapies towards allogeneic CAR-T therapies. Initially, the researchers focused on using gene editing tools to enable cells to be used in allogeneic settings. Gene editing increases the complexity and manufacturing cost. Hence currently, there is a shift to looking for new types of immune cells that can be used in an allogeneic without the need for gene editing.

''We truly believe that the future of CAR-T is allogeneic, and we are seeing the R&D landscape continue to trend towards an off-the-shelf approach. Despite the approval of autologous CAR-T cell therapies, the industry has been developing allogeneic cell therapies to solve many of the issues associated with the autologous approach, including the difficulty of providing a way to treat a large population of patients, including those with solid tumors, in a timely manner. We are seeing the industry not only push to find solutions for the treatment of solid tumors but also develop new technologies and strategies to further expand the reach of an allogeneic approach," said Filippo Petti, Chief Executive Officer, Celyad Oncology, Belgium.

Celyad Oncology is using a single vector approach to generate CAR-T cells and its proprietary non-gene edited technologies helps expedite and expand patient access to these novel treatment options with a quicker turnaround time from cancer treatment decision to infusion.

Key trends

Let's look at the key trends expected to influence CAR-T therapy research in 2022 and the near future:

Targeting solid tumours/ multi-target CARs: CAR-T therapy has shown good results with haematological malignancies, but has yet to demonstrate the same efficacy in solid tumours.

"Furthermore, we are starting to see patient relapsing, with cancer shedding the CAR targets. Therefore the key trend is to develop CAR-T cell therapy for solid tumours, and also CARs that are able to recognise multiple targets at a go,'' said Dr Tan Wee Kiat, Chief Operating Officer, Cytomed, Singapore.

Incorporated in 2018, CytoMed Therapeutics is a spin-off from Singapore's Agency for Science, Technology and Research (A*Star) and focuses on translating its patented technologies into gamma delta (??) T cell- and natural killer (NK) cell-based "off-the-shelf" immunotherapeutics for a wide range of cancers.

Majority of the research in this space is currently in the discovery and preclinical stage.

Off-the-shelf CAR-T cells : A trend that has been identified as the most eagerly-awaited approach by physicians is the development of allogeneic, off-the-shelf CAR-T cells. All currently approved CAR-T therapies are “autologous” in nature. This means that manufacturing starts with the collection of T cells from an individual cancer patient. T cells are engineered to recognise a target on the surface of cancer cells and subsequently re-infused into the patient from which they were collected.

‘’While autologous CAR-T therapies have been associated with unprecedented efficacy, the delivery of an individualised therapy is complex, time consuming, and expensive. In fact, logistical considerations often limit the number of patients who can reap benefits from CAR-T therapies. Despite unprecedented efficacy, modern CAR-T will need to address resistance which is very common in many haematological diseases, and move this modality into solid tumours where progress has been lagging. The ability to genetically engineer allogeneic (“off-the-shelf”) CAR-T products will make this the modalities of the future as they can be engineered a priori to be administered on demand,” Dr Schmidt.

Allogenics drugs would eliminate the current manufacturing requirement for CAR-T cells which take weeks before they can be administered to a patient.

‘’While such molecules remain unproven in a large-scale clinical trial, if successful, they would address the major hurdle of 1st generation CAR-T cells, which is logistics and manufacturing,’’ said Dr Paliouras.

CAR-T as first line therapy: All the approved CAR-T are indicated as a second line treatment.

‘’Another trend is the clinical investigation of moving current products into earlier lines of therapy, with the goal to ultimately use CAR-T cells for newly diagnosed patients or as a replacement for stem cell transplant in certain blood cancers,’’ said Dr Paliouras.

To that effect, in April 2022, Gilead won the USFDA approval for Yescarta as a first in line treatment for Relapsed or Refractory Large B-cell Lymphoma (LBCL)- a momentous milestone for the sector.

All the approved CAR-T therapies are being investigated from only as last line therapy to earlier (2nd or 1st) line treatment.

Multiple Dosing: The aspect of multiple dosing has also started to come into the forefront when developing these therapies.

‘’Specifically, we predict multiple dosing around allogeneic CAR-T will become a more prominent industry conversation as companies are starting later-stage trials and thinking about the opportunity to maximise the treatment benefit and how that may impact commercialisation of these cell therapies. These discussions will likely influence the development of CAR-T because we will be seeing more company refinement of clinical trial designs, including the impact on preconditioning in advance of these treatments, which will hopefully help to expedite candidates to commercialisation and to the patients who will need these therapies the most. Given where the industry currently stands, we expect to see this dynamic continue to unfold over the next few years as additional understanding of the true potential of allogeneic CAR-T therapeutics emerges,’’ said Filippo.

China’s dominance: With Chinese companies undertaking the highest number of CAR-T cell therapy trials, GlobalData anticipates the country is likely to dominate the treatment landscape in coming years. According to the GlobalData Pharma Intelligence Center, there are nearly 60 CAR-T therapies in the overall clinical pipeline in China which are being developed by domestic pharma companies. Of which, there are 25 CAR-T therapies in Phase II pipeline.

CAR-T therapy is pharma’s most advanced and expensive treatment and is set to transform cancer care. As the research evolves and regulations mature, we finally may have the elusive cancer cure.

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