

Advancement of Cell Therapy in China – Challenges and Opportunities in 2023

While initial strides in CAR-T therapies were primarily being made in the US markets, the focus is now shifting to China – but can both foreign and domestic players win in China’s CGT market?

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Although chimeric antigen receptor (CAR)-T cell therapy has been booming in recent years, certain shortcomings still exist. Many aspects of the Chinese cell and gene therapy (CGT) ecosystem – such as foreign investment regulation, uncertainty in reimbursement timelines, requirements for technology and intellectual property (IP) localisation, and variance in healthcare provider capabilities – are posing significant challenges in successful commercialisation of CGT products. Both foreign and domestic players looking to win in China’s CGT market will need to address these local nuances with unique commercial models. They will need to formulate their strategy and measure their success by building a matrix of excellence around market entry, regulation, portfolio, IP and commercial viability. They should also consider how to efficiently access the increasingly rich local innovation and develop the know-how to develop these IPs globally through ecosystem partnerships.

The logistics of CAR-T cell delivery are complex, as cell products require timely long-distance transfer between hospitals and industries. Therefore, the delivery of commercial CAR-T cells into clinical cancer treatment requires detailed and careful planning, resource allocation and the utilisation of existing infrastructure.

Several issues should be addressed before and after commercial CAR-T cell delivery, including the following:

1. CAR-T cell research and development *in vitro* and in animal models by hospitals or companies or both
2. Hospital ethics approval by the committee and registration on www.chictr.org.cn or www.clinicaltrials.gov
3. Patient recruitment and enrolment
4. CAR-T cell manufacture in a Good Manufacturing Practice (GMP) facility according to standard operating procedures supervised by hospitals and companies
5. Bridging between hospitals and companies on peripheral blood collection and CAR-T cell delivery
6. Management of CAR-T cell infusion and post-infusion care
7. Financial and clinical data implications.

Introduction

In August 2017, Novartis’ Kymriah (tisagenlecleucel) broke ground by becoming the first CAR-T cell therapy in the world to secure an approval to treat acute lymphoblastic leukaemia (ALL), followed closely by Gilead Sciences’ Yescarta (axicabtagene ciloleucel), indicated for certain types of non-Hodgkin lymphoma (NHL). After the initial US regulatory authorisations, both therapies were approved in Europe the next year.

That the initial approvals happened in the US was illustrative of how CAR-T development was centred primarily in the West, and more specifically, the US, in the mid-2010s. Between 2010 and 2014, over half of newly identified CAR-T therapies were being developed or



co-developed by a US-based company. In 2021, however, that figure had fallen to less than one-third of new drugs. The reason for this is not a drop-off in US focus on CAR-T therapies, but instead, a sharp increase in new CAR-Ts being developed by Chinese companies.

The development of CAR-T therapies in China now appears to markedly outpace research happening in the West, as per an analysis by *Pharmaceutical Technology*. CAR-T drugs now account for over 10% of new drugs developed by Chinese companies, compared to only 2% of drugs developed by US companies. Moreover, the number of CAR-T therapies currently being investigated by Chinese companies is ~50% higher than what is being developed by US companies.¹

A Thriving Environment

There are several unique factors driving this surge in CAR-T developments in China: the need and demand for such therapies, government support, capital flow and Chinese scientist-driven local research, including the establishment of Investigator Initiated Trials (IITs).

CAR-Ts are a complex type of cell therapy, where immune T cells are engineered to express the chimeric antigen

receptor that binds to certain proteins on the tumour cells. Compared to other types of drugs, CAR-Ts require even stricter manufacturing and administration adherence, which makes their development resource-intensive and expensive. As such, development in different parts of the world was hindered by the need to make large upfront investments in R&D, manufacturing and scientific expertise to build a CAR-T-friendly ecosystem.

Currently, CAR-T therapies are mainly indicated for lymphoma. However, compared to Western countries, the incidence of solid tumours remains high in China, creating significant unmet medical needs. Innovative treatment is therefore being greatly encouraged by all levels of government, with increased funding to scientists in support of research related to cell therapy. Several years ago, the Chinese government made a conscious effort to develop CAR-T locally and invested significant funding and resources in setting up hospitals and infrastructure that are critical for this kind of research.

Once the initial foundation was laid, data indicates that China raced ahead to employ this therapeutic approach. Between 2010 and 2014, GlobalData identified around 90 CAR-Ts in development, and in 2021, that number increased to over 300.^{2,3}

Although the number of studies has increased significantly, the majority of clinical trials registered in China are early-stage, small-scale studies with limited patient numbers. Nevertheless, the targets investigated in China are in line with other countries. Chinese scientists have made great efforts in engineering dual-target, or multi-target, CAR-Ts. This is an innovative approach, while further investigation at a clinical stage is required.

Historically, CAR-T therapy has not been covered by the national reimbursed drug list/provincial reimbursement drug list (NRDL/PRDL), which is the main obstacle for patient access, ultimately limiting the market value of CAR-T therapies in China. More recently, ‘HuiminBao insurance’ has been introduced, which is jointly supported by both government and insurance companies. It not only covers expensive CAR-T, but enables access by the general population and enhances the commercial market for cell therapy, making this a promising proposition from a venture capital and investment perspective.^{4,5}

With government support and funding to promote collaboration with research scientists, Chinese physicians are carrying out early-stage clinical research with cell therapies in IITs. These physicians are also able to share experience with peers from other countries at international conferences, enhancing the enthusiasm and motivation of the clinicians developing these complex therapies under stringent conditions. This collaborative research landscape, encouraging innovation and investment often spearheaded by Chinese scientists who have returned to the country after training abroad, is another contributing factor to the growth of specialised cell therapy research.

Manufacturing Chain will be the Key

Unless one has a big funding source, it is not straightforward to manufacture a homegrown CAR-T. Even if a US academic centre makes a CAR-T, which can cost over \$100,000 in associated manufacturing expenses, not all have GMP facilities to then produce them on a wider scale.

Delivery of CAR-Ts also requires a highly personalised and sophisticated approach. CAR-T trials must be well

orchestrated and large, first-tier hospitals have their own experienced teams with investigators and nurses who are eager to initiate and participate in such studies, leading to accelerated research. In China, these hospitals are self-sufficient and govern themselves, and CAR-T development in this kind of environment is deemed ideal.

Cell therapy research studies are primarily carried out in private hospitals rather than public hospitals in China. The local trend is for university research institutions to cooperate with biotech firms and conduct research with the support of the latter’s capital. Although some hospital research laboratories have manufacturing facilities, their capabilities are limited. Cellular production is a relatively standardised process, but the ability to scale will need more attention in terms of infrastructure and cost.

At present, national supervision in China is becoming more and more stringent, and GMP certification of the National Health Commission is also becoming more standardised.

After the pandemic, a new round of GMP certification inspection by the government is about to begin, and there are stricter regulations on the manufacturing environment and associated production conditions to ensure even higher levels of quality.

While the development of most CAR-Ts is led by commercial companies in both the US and China, both have universities and hospitals that have been regularly involved in CAR-T development. In China, for example, these include the General Hospital of the People’s Liberation Army, Peking University Cancer Hospital and Institute, and the First Affiliated Hospital of Zhejiang University.²

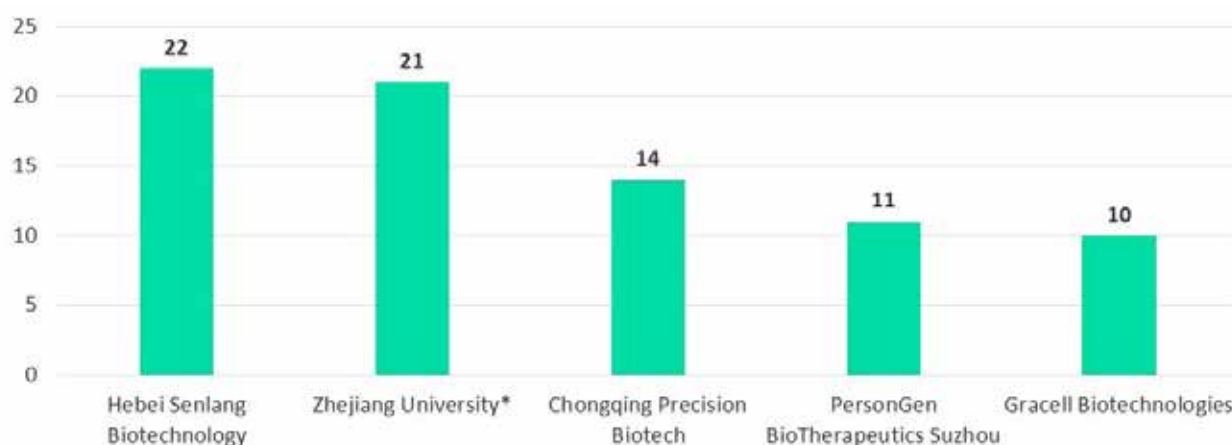
In Beijing, CAR-T research includes universities, clinical researchers or small start-up companies, which have no ability to build their own manufacturing capacity. In response to this challenge, the Beijing government has established a unified production line in the metropolitan science and technology park, providing manufacturing space that can be rented for researchers and start-ups to reduce research and development costs. In addition, Zhejiang University, relying on the professional capabilities of its affiliated hospital and capital support from the government, invests in hospitals, wards, production lines and specialised services as part of a differentiated operational model.

The entire Chinese ecosystem thus fosters the participation of hospitals in clinical research. National policies encourage the establishment of ‘research hospitals’ and support funding. Hospital policies encourage departments to compete to establish Good Clinical Practice (GCP) bases and cultivate clinical research backbones. Clinicians obtain data, publish articles and gain professional growth



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*In collaboration with multiple Chinese Pharma collaborators - Shanghai Yake Biotechnology (17), Gracell Biotechnology (1), CARsgen Therapeutics (1), HRAIN Biotechnology (1), Nanjing Bioheng Biotech (1)

Source: GlobalData Pharma Intelligence Center



Figure 1: Top five Chinese companies sponsoring CAR-T clinical trials in China (17 Aug 2021)

by participating in clinical research. This ensures an overall focus on clinical stage research instead of mere commercial utility.

China's race for a significant presence in this field means that of the ten companies involved in the development of the most CAR-T drugs since 2010, six are based in China. While initial global approvals of CAR-T therapies were gained by large pharmaceutical companies such as Novartis and Bristol Myers Squibb, in China, on the other hand, CAR-T research is undertaken by specialist biotechs. For the ten biggest developers of CAR-T therapies in China, over 80% of their developed drugs since 2010 are CAR-T therapies.⁶

Last year, Legend Biotech, one of the first Chinese companies to make an impact with CAR-T research, secured US Food and Drug Administration approval for Carvykti (cilta-cabtagene autoleucel), which it co-developed with Janssen Biotech in multiple myeloma. Carvykti has a Breakthrough Therapy Designation in China. The initial impressive efficacy data with Carvykti from China has been instructive for ongoing studies in the US that are now exploring it in earlier lines of treatment.

Leveraging Clinical Experience from Local Teams for Global Programme Participation

Even though China has more CAR-Ts in the pipeline, so far, the country's regulatory agency, the National Medical Products Administration (NMPA), has approved only two CAR-T therapies: Gilead's Yescarta, which was co-developed with FosunKite for the China market, and JW Therapeutics' relmacabtagene autoleucel injection or relma-cel, which became the second approved therapy in September 2021.

Several factors have impacted the pace of CAR-Ts coming to market in China, emphasising the need for some degree of global harmonisation. In accordance with Investigational New Drug research standards, the ethics committee process is very standardised, whether for a multinational corporation (MNC) or a start-up in R&D mode. Particularly for small domestic start-ups, the lack of early clinical experience data can be especially limiting as it relates to participation in global studies. Moreover, confidence in considering China as a contributing country to participate in an MNC-sponsored study is based upon previous experience and data generation.⁷

Management of CAR-T cell infusions and post-infusion care needs is important and affects study quality and patient outcomes. Firstly, the selection of endpoints should be strict, and the experienced centres should be carefully chosen. The management of the treatment process should also be strict and standardised, otherwise, it may result in an increase in adverse events and poor data.

It is recommended that the sponsor communicates with the research centre in advance to uniformly implement a clinical process and the appropriate oversight of the study.

It is also necessary to actively share experience among various centres at any time to unify standards, ensure the quality of research and maximise the benefit for patients.

The whole process management principles of CAR-T cell therapy for lymphoma were published by Peking University Cancer Hospital in 2021.⁸ The aim was to share experience on patient screening, peripheral blood mononuclear cell collection, bridging treatment, lymphocyte depletion chemotherapy, CAR-T cell infusion, monitoring and treatment of adverse events after infusion and long-term

follow-up after infusion, in order to guide clinicians to better use CAR-Ts with their patients.

Interestingly, patient recruitment is not a challenge in China. In view of the price of the two CAR-T drugs that have been approved, clinical research of the new CAR-Ts is particularly attractive to eligible patients (who can obtain access to expensive therapies without having to pay from their own pockets), and there is a strong willingness to enrol in a cell therapy trial. Moreover, in terms of clinical benefit, about 40% of patients can achieve disease-free survival after treatment; thus, the patient's motivation is very high due to the innovative therapy.

Despite the disruptive impact of COVID-19 on trials worldwide, studies in general have continued in China, and this is the case with CAR-T therapies, as well. Now that COVID-19 has been somewhat localised and controlled in specific regions, the outpatient volume has basically returned to the level of three years ago.

Types and Targets of CAR-T Research

Current research trends validate the research interests and wins in the CAR-T field in the last ten years. While early CAR-T therapies were personalised, autologous therapies directed toward the CD19 antigen in relatively rare blood cancers, subsequent development has branched out to allogeneic or off-the-shelf therapies in several cancer types. In line with the initial approvals in both the US and China, the most common indication for which CAR-T drugs have been developed is a blood cancer. In fact, 60% of CAR-T drugs developed by Chinese companies and 55% of US CAR-T drugs have blood cancer as a listed indication.²

CAR-T therapies need a target antigen that is ubiquitously (and ideally exclusively) expressed in a tumour, which is the case with haematological cancers. As such, developing this modality in solid tumours continues to be challenging. Still, since the initial successes in ALL and B cell lymphomas, the focus on CAR-T therapies in the US is slowly shifting, with 21% of the current CAR-T therapies being designed against solid tumours. In China, however, this does not appear to be the case yet, with only 9% of all CAR-Ts being developed in solid tumours.³

One potential reason for the worldwide drop in CAR-T research is the rise of effective bispecific antibodies. These offer an off-the-shelf alternative that can compete with CAR-Ts and potentially even leapfrog them. So far, efficacy signals have been encouraging, and these antibodies could also be used more easily in smaller community hospitals.

Local vs Multinational Studies and Patient Access

Even though the two NMPA-approved CAR-T therapies are not yet covered by major insurance in China, several

hundred patients already have received these drugs through private funding or outcome-based reimbursement schemes with the individual company. Relma-cel is a nationally produced CAR-T and is likely to be included in the next NRDL update since national therapies have been favoured over drugs from international companies.

The Chinese government supports local scientific research but does not influence hospitals and policies. At present, many projects are funded by three parties: large companies, national or local municipal governments and hospitals directly. Each hospital mainly cooperates with companies/sponsors to carry out clinical research.

For overseas sponsors conducting research in China, the biggest international challenge comes from the cross-border cell production process. The average MNC does not have a production site in China, so cells are exported and then imported. This involves very complex document preparation, Human Genetic Resources Administration approval and detailed customs procedures. Hospital managers at all levels have to document and sign off, which creates significant administrative burdens.

This international process usually takes seven to eight weeks during which patients have to wait, which may impact overall study outcomes. However, if cells are manufactured in China, the turnaround time can be reduced to within four weeks. Consideration needs to be given to the management of entry and exit procedures, and it is recommended that overseas sponsors identify qualified and compliant production and service providers in advance for use in conducting international cell therapy trials in China. This reduces waiting periods and improves study outcomes.

In addition, considering the cost of transportation, domestic sponsors currently do not propose conducting research in remote provinces. Patients can only travel to hospitals in first-tier cities to participate in studies or receive treatment. Sharing of experiences across research-naïve sites and implementing supportive infrastructure may help to broaden access for patients in this capacity.

Conclusion

From a total of 868 assessed clinical trials, China is currently the country with the majority of ongoing clinical trials on CAR-T cells. (China also has its own clinical trial repository, so the numbers are possibly underestimated.) It is noteworthy that a significant number of clinical trials in China are funded by the industry and federal government, which could explain the great diversity of studies in this region when compared to low- and middle-low-income countries or regions.

CAR-T therapies currently are administered at a limited number of cancer centres and are primarily delivered in the inpatient setting. In addition, pharmaceutical company and biotech start-up CAR-T cell products make up the majority being investigated in clinical trials, although academic CAR-T cell products are gaining traction and are expected to compete with the commercial products. Indeed, 'in-house' production of CAR-T cells can reduce the cost of centralised production due to technological improvements in production automation, and it does not require shipping and handling of the leukapheresis product, saving both time and money.

Combining CAR-T administration with other drugs may also improve therapy efficiency, and drugs that are regularly used in clinical settings, such as immune checkpoint inhibitors, BTKi, lenalidomide and oncolytic viruses, are being employed for that purpose. With the recent findings that CAR-T treatment might be as efficient as the standard of care used to treat relapsed/refractory patients, CAR-T cell administration as first-line therapy does not seem so far from reality anymore. This could represent a paradigm shift in cancer patient care, and it is expected that studies involving CAR-T therapy will increase exponentially in the next few years, especially with the approval of new products by the regulatory agency. Moreover, CAR-T may hold promise as a therapeutic platform not only to treat malignant diseases, but infectious and hereditary diseases alike.

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