Go-to-market Challenges of CAR-T Therapies

CAR-T therapies are set to revolutionise cancer treatment. With first curative therapies gaining market access across the globe, CAR-T therapies are subject to numerous commercial and non-commercial challenges. Despite positive clinical responses, the ability to overcome these challenges will determine the future of CAR-T therapies and show whether pharmaceutical companies can make true on the promise of initiating a new era of cancer care.

Setting the Scene

In 2019, the commercial pharmaceutical industry recorded global sales of ~1300bn USD, and is expected to grow at a CAGR of 6.8% until 2024. Even though the majority of sales is still generated with traditional single-compound medicines, biologics are the major growth driver of the pharmaceutical industry. Development of simple compound medicines has reached its limits and research in this area is almost at peak. Today, biologics are the most promising technology which, combined with increased knowledge of medicinal chemistry and new methods of production, enable companies to develop completely new drugs and treatments.[1] In 2019, biologics accounted for ~21% of global drug sales[2] and represented 21 of 69 Drug License Application Approvals granted by the FDA.[3,4]

Within the field of biologics, advanced therapies have emerged as the innovative spearhead focusing on novel curative treatments. They comprise cell and gene therapies, as well as tissue engineering, as shown in Figure 1.[5] Curative cell therapies today are mostly oncology-focused treatments where genetically modified T-cells are transferred into a patient to target a specific protein and destroy the malignant cells. Gene therapies are treatments that focus on delivering therapeutic DNA into a patient´s cells to cure the underlying disease. Current methods comprise the editing of genetic material, the addition of genetic material and the targeted silencing of genes. Tissue engineering is the umbrella term for therapies which restore, maintain and/or improve damaged tissue or organs by combining scaffolds, cells and biologically active molecules.[6]

As illustrated in Figure 1, there are currently ~1000 registered clinical trials for advanced therapies, accounting for ~15% of all clinical trials conducted globally. The trial landscape is coined by gene therapies focussing on rare diseases across numerous indications and curative cell therapies focussing on oncology. The majority of the ~625 cell therapy trials is investigating the potential of CAR-T treatments, which are regarded to be a revolution in cancer therapy.[7]

CAR-T Therapies at a Glance

CAR-T therapy refers to chimeric antigen receptor (CAR)-T-cell therapy, an innovative and individualised cancer treatment method that combines the capabilities of cell, immune and gene therapy into one therapy concept. T-cells are ex-vivo genetically modified to express a chimeric antigen receptor on their surface that recognises and binds to a specific antigen on the surface of malignant cells. Once the receptor binds to an antigen, the T-cell is stimulated to attack and destroy the malignant cell. Due to the fact that CARs have the ability to combine both antigen-binding and T-cell-activating functions into a single receptor, they are defined as chimeric.[8,9]

T-cells leveraged for the manufacturing of CAR-T therapies may originate from the patient (autologous) or an external donor (allogeneic). As all currently approved CAR-T therapies are autologous, the drug manufacturing process is integrated into the patient treatment journey. Figure 2 illustrates the manufacturing process of a CAR-T therapy.[9]

Prerequisite to initiating the CAR-T manufacturing process is the referral of an identified patient to a specialised CAR-T centre. Only after passing a CAR-T treatment eligibility assessment is the patient approved to undergo leukapheresis.

Non-Exhaustive

Advanced therapy types		Methods	# ongoing clinical trials	# approved curative drugs	Focus
Curative advanced therapies	Cell Therapy	▪ CAR-T Cell Therapy ▪ CAR-NKT Cell Therapy	**~ 625** active clinical trials (Phase I – 211, Phase II – 386, Phase III – 49)	**2**	**Oncology**
	Gene Therapy	▪ Gene adding (Viral vectors, etc.) ▪ Gene editing (CRIPRS-Cas 9, etc.) ▪ Gene silencing (Antisense, etc.)	**~ 362** active clinical trials *(Phase I – 120, Phase II – 210, Phase III – 32)*	**4**	**Rare diseases**
	Tissue Engineering	▪ Nanofiber self-assembly ▪ Textile technologies ▪ ...	**~ 31** active clinical trials (Phase I – 10, Phase II – 20, Phase III – 11)	**2**	**Skin / cartilage replacement**

Figure 1 – Overview of curative advanced therapies[5,6,7]

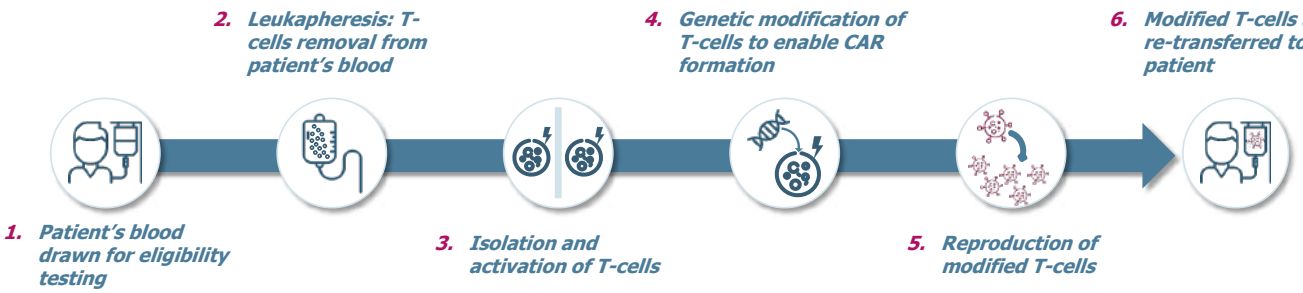

Figure 2 – CAR-T manufacturing process[8,9]

Leukapheresis is the separation and collection of the patient's white blood cells and resembles the first step of CAR-T manufacturing.[8]

The obtained sample of white blood cells is frozen and transported to a specialised manufacturing laboratory, where T-cells are isolated from the sample. Following the isolation is the activation of the cells using monoclonal antibodies. Once the T-cells are activated, they are genetically modified to express a specific CAR on their surface. This is achieved by utilising modified viral vectors to deliver a strand of therapeutic DNA into the cell. Modified CAR-T-cells are then duplicated to achieve a clinically significant number of cells and prepared as an infusion for the patient. The CAR-T therapy is transported back to the CAR-T center and administered to the patient.[10]

Today, there are two CAR-T therapies that have received market approval. Both, KYMRIAH® (Novartis) and YESCARTA® (Gilead Sciences) are curative CAR-T therapies which target liquid tumours with the surface antigen CD19.[11] As targeting these specific surface proteins has proven to be successful in the treatment of haematologic cancer, the majority of clinical trials (~95%) within the field of CAR-T therapies is focussed on liquid tumours for late-stage relapse and refractory patients.[7] So far, translating the mode of action of CAR-T therapies has not proven to be successful.

Even though big pharma has been the first mover with regard to CAR-T market approval, innovation in this field is driven by small biotech firms.[12]

Despite the curative potential and promising clinical responses, CAR-T therapies face numerous go-to-market challenges. These challenges can be divided into non-commercial and commercial challenges, and need to be overcome for CAR-T therapies to gain market traction and make true on the promise to revolutionise cancer treatment. In the following section, the main challenges of CAR-T therapies will be highlighted, and potential solutions on how to tackle these challenges carved out.

Non-commercial Go-to-market Challenges of CAR-T Therapies Manufacturing

An essential part of manufacturing CAR-T therapies is the *ex vivo* genetic modification of autologous T-cells. The process incorporates the manufacturing process of gene therapies into the manufacturing of cell therapies. Following the isolation, enrichment and activation of the T-cells, viral vectors are leveraged to insert therapeutic DNA into the T-cells to trigger the expression of the CAR on the cell surface. This complex multi-level process is not only cost-extensive and time-consuming, but also subject to a high failure rate and thus a low production efficiency (8).

The low efficiency of CAR-T manufacturing is amplified by the fact that autologous T-cells gained through leukapheresis are often not usable as they express lasting damage from previous chemotherapies. This again leads to a decreased efficiency in the expansion of the modified CAR-T-cells and thus the production of the therapy.[14]

Furthermore, the complex process entails manufacturing of CAR-T therapies in highly specified laboratories. Availability of these laboratories is limited, leading to capacity shortage in production.[10] This contrasts with the conventional industrial manufacturing of pharmaceutical products, which allows for high-output production and follows clear Good Manufacturing Practice (GMP) guidelines. As CAR-T therapies are manufactured on a patient-individual basis in a laboratory, it is challenging to implement dedicated quality assessments that ensure a continuous quality control along the manufacturing process.[10,13]

In order to overcome the manufacturing challenges, pharmaceutical companies should consider whether to:

- Leverage innovation in gene therapy to improve viral vector efficiency and consider potential alternatives for genetic modification (i.e. CRISPR-Cas9)
- Foster early storage of "healthier" T-cells in hospitals for patients likely to receive CAR-T therapy to increase manufacturing efficiency and time
- Cooperate with academic institutions to leverage their laboratories and increase manufacturing facilities
- Define standard operation procedures (SOPs) for CAR-T manufacturing to allow for dedicated quality assessment along the manufacturing process steps.

Supply Chain

The limitation to produce CAR-T therapies in highly specified laboratories entails a high degree of centralisation of the available manufacturing facilities.[13] Due to the centralisation and the fact that all currently approved CAR-T therapies are autologous, a patient's blood sample is required for every batch of CAR-T therapy produced.[16] Transporting the blood sample from the CAR-T centre to the specified laboratory, and the genetically modified CAR-T therapy back to the hospital,

requires a complex and sophisticated delivery system with a flawless cooling chain. The stakeholder within this delivery system – specified CAR-T centres, dedicated courier services and the manufacturing laboratories – need to be able to meet the requirements with regard to storage, packaging, shipping and sample tracking. All steps in the delivery system must be coordinated in a way that the time-to-treatment for the patient is optimised. This process is often referred to as patient scheduling.[5]

Sample tracking is the essential part of the delivery system. The tracking system is bi-directional and requires an error-free tracking of the patients' blood sample and the respective individualised CAR-T therapy. As current therapies are autologous, errors in the adequate tracking of a sample lead to the disposal of the therapy and a prolongation of the manufacturing process.[13]

Another challenge related to the supply chain of CAR-T therapies is the availability and production of viral vectors. In addition to CAR-T therapies, gene therapies are also applying the same viral vectors. As there are only a few companies specialising in manufacturing viral vectors, they are not able to meet the continuously increasing global demand. This limited availability entails waiting times during CAR-T development and manufacturing.[16] Furthermore, viral vector production is very cost-extensive and time-consuming, as it is coined by low yields per viral batch (approximately one clinically useful viral particle out of 100,000 produced) due to a low transfection efficiency.[18]

In order to overcome the supply chain challenges, pharmaceutical companies should consider whether to:

- Invest in laboratories/cooperate with academic laboratories to decentralise manufacturing facilities and decrease transportation time and effort
- Cooperate with digital companies / courier services specialising in tracking software and leverage cloud-computing for real-time tracking of patient samples
- Provide end-to-end software to improve overall patient scheduling and supply chain processes by leveraging digital health solutions
- Set-up in-house production facilities for viral vectors or enter exclusivity contracts with manufacturers to avoid supply bottlenecks and decrease costs
- Foster innovation towards allogenic CAR-T therapies to develop patient-independent "off-the-shelf" treatments with simplified supply chain.

Commercial Go-to-market Challenges of CAR-T Therapies
Administration
The administration of a CAR-T therapy entails complex infrastructural, personnel and regulatory requirements. Since the patient is incorporated into the supply and manufacturing process, hospitals and physicians are also integrated. They need to be able to conduct leukapheresis, handle cryopreserved patient blood samples, collaborate with couriers and integrate the sample tracking into their pharmacy supply systems. Furthermore, physicians need to have CAR-T medical expertise and the hospital needs to have specific SOPs in place that allow for a CAR-T dedicated reporting and documentation of side-effects and patient responses. The hospital must be able to cooperate with the manufacturing team at the laboratory with regard to patient information about treatment history, therapy responses and current health status during conditioning therapy. This complexity results in the need for multi-stakeholder cooperation at a scale that the majority of hospitals is not able to deliver. Therefore, administration of CAR-T therapies is allocated to a limited number of dedicated CAR-T centres that can meet these requirements.[17]

Like the manufacturing facilities, specialised CAR-T centres are also coined by a high degree of centralisation. This results in the fact that fragile late-stage cancer patients have to travel to these centres for their diagnosis, treatment preparation, treatment and follow-up monitoring, resulting in a high health risk for the patient. In addition, CAR-T centres face the challenge of patient referral by treating physicians in other hospitals.[17] Thus, the greatest challenge for pharmaceutical companies with regard to administration is transferring the eligible patients to the CAR-T centres and understanding the roles and responsibilities of the stakeholders involved in the patient referral process.

In order to overcome the administration challenges, pharmaceutical companies should consider whether to:

- Support clinics with dedicated services and support knowledge and capability building to increase amount and capacity of approved CAR-T centres
- Develop a sophisticated patient-monitoring programme that can be conducted in non-CAR-T centres and the outpatient sector to decrease pressure on CAR-T centres
- Establish an international CAR-T patient register to improve identification of potential CAR-T therapy candidates
- Invest in laboratories/cooperate with academic laboratories to decrease transportation time and simplify communication with CAR-T centres.

Costs & Reimbursement
Currently, CAR-T therapies entail high costs for the healthcare system. Due to the complex manufacturing, elaborate supply chain and the cost- and time-extensive R&D process, CAR-T therapies come along with a high price tag of >350,000 USD per therapy.[22] This high price, based on the curative nature of the therapy and in contrast to conventional treatments, is concentrated into a single upfront payment. High one-time payments challenge the current budget planning of payers and hospitals, which is set up to spread therapy costs over a defined treatment period.[23] Furthermore, there is a lack of adequate data with regard to long-term efficiency, safety profile and the need for additional patient care of curative CAR-T therapies[10]. This results in the payer having the burden of carrying the financial risk of a therapy upfront, without assurance that the therapy will work efficiently in the long run.

Currently, the pressure on the healthcare system exerted from the high-priced CAR-T therapies is manageable, as only small patient populations receive the treatment. With additional CAR-T therapies coming to market, the price

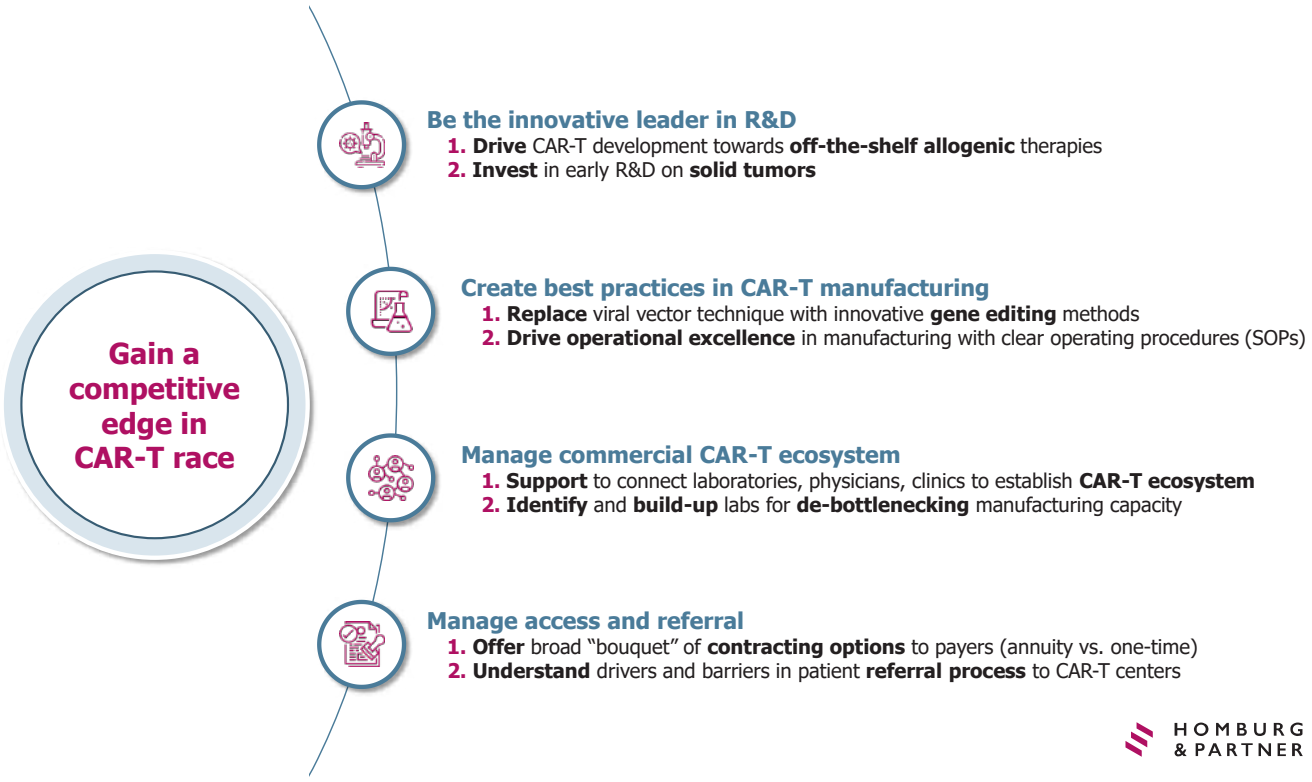

Figure 3 – Key recommendations for pharmaceutical companies

pressure is set to increase, suggesting significant market-access challenges across countries in the future.[22]

In order to overcome the cost and reimbursement challenges, pharmaceutical companies should consider whether to:

- Lead price negotiations with long-term cost-benefit assessments and innovative contracting solutions (i.e. annuity-based contracts, outcomes-based contracts)
- Understand the patient referral process to foster transfer of patients to CAR-T centres to increase market uptake and patient access of CAR-T therapies
- Choose a targeted patient population to be assigned to the right comparative therapy and avoid price cuts (in case of non-superior benefit assessment).

Strategic Recommendations

Set to disrupt and revolutionise conventional cancer therapy, CAR-T therapies – and in turn the developing pharmaceutical companies – are facing numerous challenges, as broadly illustrated. At the same time, defining the right strategy and choosing the most relevant measurements for a successful go-to-market is a challenge itself. Figure 3 outlines four key recommendations for pharmaceutical companies to gain a competitive edge over their industry peers and to overcome go-to-market challenges of CAR-T therapies.

Success with CAR-T therapies will be defined by companies willing to take risks, strive for innovative leadership and set industry standards. This, combined with a strategy focussing on building networks and establishing clearly defined innovative contracting options to secure therapy access and reimbursement, will be the foundation to become an industry leader in CAR-T cancer treatment, despite the present challenges.

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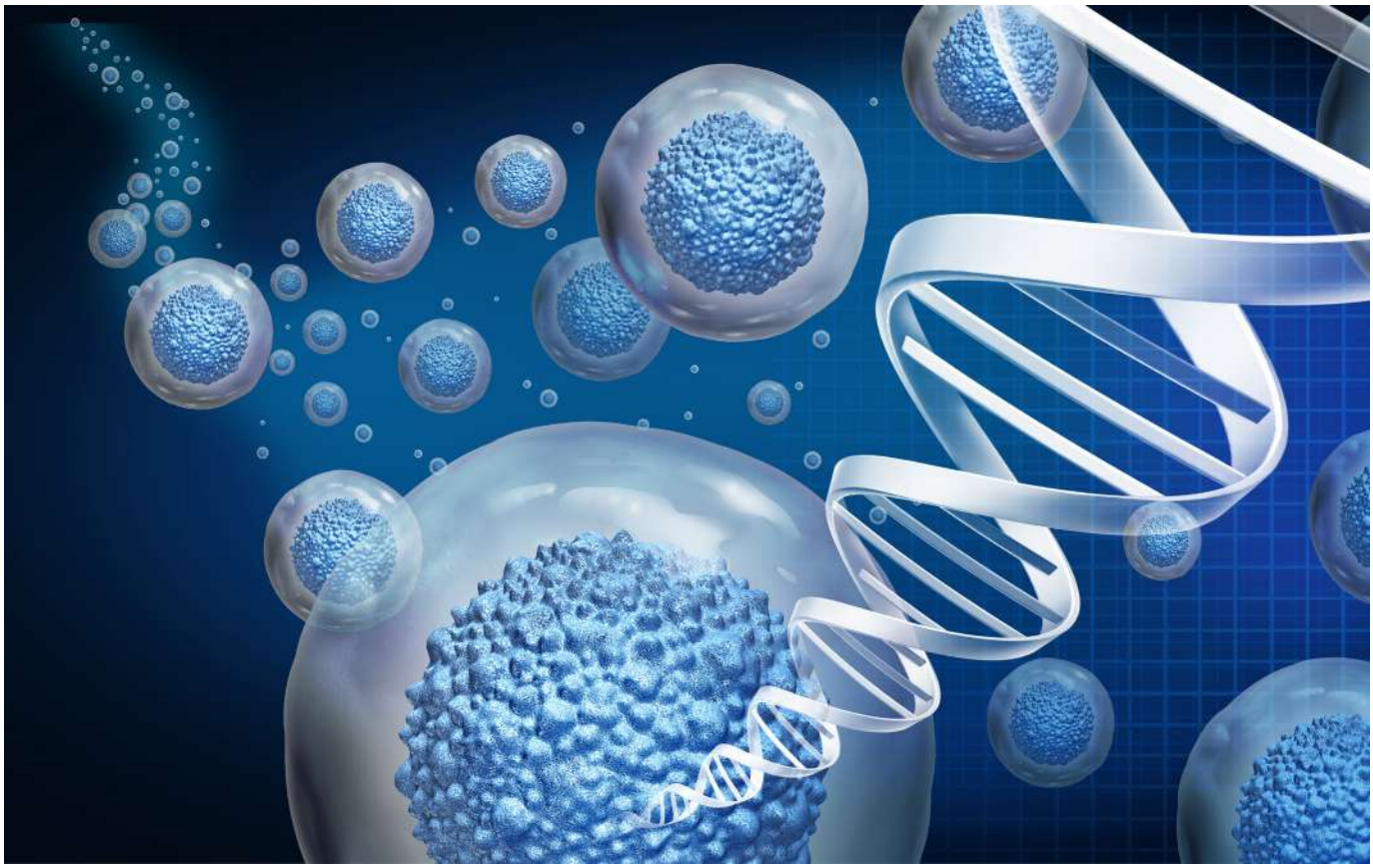

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