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PLACING YOUR CAR-T BETS

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A REVOLUTIONARY NEW TYPE OF cancer treatment that uses the body's immune system to fight the disease—chimeric antigen receptor T-cell, or CAR-T—is poised to become the most disruptive therapy in biopharma since biologics, in the late 1990s. Many clinical trials are underway around the world, and two CAR-T products, Kymriah and Yescarta, have received FDA approval. These treatments have already helped extremely ill patients beat diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL) where other therapies have failed; up to 90% of advanced relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) patients in clinical studies saw complete remission.[1] If this approach is as effective in treating solid tumors, such as cancers of the breast, prostate, and lung, it will transform the field of oncology.

But there are many obstacles to overcome. CAR-T therapies on the market, as well as the majority in clinical trials, are autologous (that is, created using a patient's own immune cells), which results in complex and costly manufacturing and supply chains. In addition, the CAR-T therapies on the market have proved beneficial only for a limited range of blood cancers so far, which makes for a small patient population.

Companies active in this field need to place their bets wisely. CAR-T therapies are a game-changing approach, blurring the lines between manufacturing and treatment and between academic and commercial organizations. To build a strategy for seizing the opportunities in CAR-T as this therapy evolves, executives must develop a thorough understanding of the scientific, clinical, and supply chain implications. Success will come to companies that leverage cutting-edge innovation in all aspects of design, production, and treatment.

The Transformative Potential of CAR-T

CAR-T has begun to transform oncology, but how much further will it go? The answer depends on two factors: the potential for

CAR-T therapies to reach more patients and industry's ability to simplify the manufacturing and supply chain. The race is on for biopharma companies and academic centers to develop new CAR-T therapies to treat a broader set of cancers—and there's a growing interest in the development of off-the-shelf products that would radically simplify manufacturing and the supply chain.

Expanding the Indications for CAR-T. CAR-T therapies have proved highly effective for certain hematologic cancers, primarily those with B-cell markers. In the liquid tumor microenvironment, T cells can easily access cancerous cells, and the body is able to tolerate B-cell ablation and recovery. But for most types of cancer—non-B-cell hematologic cancers and solid tumors—it's more difficult for CAR-T cells to generate the desired immune response because of challenges related to antigen identification and the solid tumor microenvironment. (See Exhibit 1.)

Since solid tumors account for approximately 90% of cancer cases in the US, researchers are working to develop CAR-T therapies that can treat a much wider range of malignancies. In particular, they are looking to increase the effectiveness of CAR-T by combining the therapy with checkpoint inhibitors and refining the CAR biology.

Developing Off-the-Shelf Products. CAR-T products on the market today are autologous. A patient's T cells are collected and sent to a lab for genetic engineering. Millions, or even billions, of these genetically engineered cells are then returned to the patient's body, where they attach to and kill the cancer cells. Researchers are now working to develop "universal" allogeneic products in which T cells are manipulated so that they can be infused into any patient. With the development of an off-the-shelf treatment, companies could manufacture CAR-T therapies in batches instead of on demand, creating economies of scale and reducing supply chain complexity.

The primary challenge in developing allogeneic products is patient compatibility, which manifests itself in two ways. First, the body may clear allogeneic T cells before they are able to attack cancerous cells. Second, "foreign" T cells can trigger a broad and counterproductive immune response. Scientists are developing approaches to hide allogeneic cells by deleting the native T-cell receptor in them and by engineering rheostatic and "safety switch" technologies, in which cells can be silenced or destroyed by a secondary drug.

Since allogeneic cellular therapies are still relatively immature, they are being devel-

EXHIBIT 1 | Challenges—and Emerging Solutions—in CAR-T Therapies

	CHALLENGES	SOLUTIONS
Antigen identification	• Cancer cells are heterogeneous and do not necessarily display unique or abundant cellular markers; only a minority of tumor-associated antigens are expressed at the cell surface. • Tumors can evolve to downregulate target antigens.	• Design receptors to engage multiple targets through tumor-specific antigen combinations when no unique single target is available. Approaches include bispecific CAR, dual CAR, and tandem CAR constructs. • Identify intracellular antigens and/or rare personalized neoantigens to generate improved CAR and/or TCR constructs.
Performance with solid tumors	• Therapeutic cells are poorly concentrated at solid tumor sites and do not infiltrate tumor tissue, in part because of the immune-suppressive tumor microenvironment. • T-cell exhaustion limits immune activity against cancerous cells.	• Engineer T cells to secrete key immune-activating cytokines (armored CAR constructs) and/or leverage cell types better able to infiltrate tumor tissue. • Leverage checkpoint silencing through genetic silencing in combination with checkpoint inhibitors.

Source: BCG analysis.

oped primarily to treat already proven and effective CAR targets. Autologous technologies will continue to be preferred where new cell types, new receptor designs, or new antigen targets are being tested.

Over the long term, if researchers can resolve the compatibility issues and establish an allogeneic platform, allogeneic technologies could become the format of choice for cellular immunotherapies.

Navigating a Complex Manufacturing Environment

Each autologous CAR-T treatment requires a dedicated production run and personalized raw materials (the patient's own T cells); economies of scale in manufacturing, therefore, are limited. Production facilities resemble labs more than traditional factories, and their operating expenses are driven primarily by consumables and labor, so the cost of manufacturing on a per-lot basis remains largely flat even as production scales up. (See Exhibit 2.)

Given the personalized nature of the raw materials and final product, the associated supply chain issues can be complex. Tracking must be done on a per-patient and per-lot basis, from vein to vein, and a two-way cold chain is required (inbound for the patient's own T cells and outbound for the patient's engineered T cells).

To further complicate matters, a fast turnaround—within days of diagnosis—is desired, if not required. Unfortunately, many relapsed and refractory patients are so severely diseased that the lengthy production timelines may mean treatment arrives too late.

Despite these hurdles, a great deal of innovative work is being done to reduce costs and complexity, and improve processes in CAR-T manufacturing.

Innovations to Decrease Costs. To reduce costs, many cell therapy manufacturers are looking to closed systems, a form of manufacturing that minimizes the risk of contamination from the surrounding environment. Currently, these systems are not well-suited to experimentation with new processes or technologies, and they have limited capacity for cell expansion. But in later clinical stages and in commercial settings, they could provide a standardized

EXHIBIT 2 | Operating Expenses in CAR-T Manufacturing Are Driven by Consumables and Labor

Source: BCG analysis.
Note: Costs reflect facility with throughput of ~430 cell lots per year.
[1]Vector cost estimated at $400,000 and does not include any licensure fee for IP; each vector batch to supply ~100 lots.
[2]Labor includes per-lot costs for the following roles: manufacturing, product development, quality assurance and quality control, support, and management.
[3]Overhead includes per-lot utilities, maintenance, and depreciation costs.

process that may reduce costs. Closed systems offer several advantages:

- They require less hands-on time, which translates into lower labor costs.
- They reduce the environmental GMP (good manufacturing practice) burden, since they are considered "GMP in a box."
- They allow multiple lots to be processed in parallel within a manufacturing suite and with little cross-contamination.
- They enable more consistent cell expansion and throughput, improving robustness and reliability during the manufacturing process.

As noted earlier, if allogeneic therapies become a reality in CAR-T, it will have a more transformational impact on manufacturing—costs will decrease considerably and efficiency will increase. With continued process improvements, allogeneic production could resemble large-scale cell growth in bioreactors. Large-scale production could be achieved with an immortalized T-cell line, or with cells from a pool of human donors and using gene editing to eliminate the graft-versus-host response.

Allogeneic production will allow for the manufacture and release of more than one lot in a given run, reducing manufacturing, quality assurance and quality control, and supply chain costs. The ability to scale up per run (to produce lots of 20 or even 200) will determine the magnitude of the cost reduction. Allogeneic production will also reduce supply chain complexity by eliminating the need for the patient's own T cells. Further development is required, since the process for culturing human immune cells is much more complex than standard bioreactor processes.

Innovations to Increase Control and Safety

CAR-T therapies on the market today use a viral vector to deliver genetic material into a patient's T cells. Advancements in gene-editing technologies paired with new delivery technologies could replace viral vectors. For example, the gene-editing tool CRISPR-Cas9, paired with a cellular insertion technology, such as electroporation, is advancing quickly and may eventually replace viral vectors. This approach allows the CAR genomic construct to be introduced into the genome at specific locations, which is preferable to the random integration seen with viral vectors. By enabling site-specific engineering, CRISPR-Cas9 increases the level of biological control in T-cell manipulation, which improves reproducibility and robustness in manufacturing and enhances safety by reducing the likelihood of insertional mutagenesis.

New technologies such as cell squeezing can deliver the CAR into the cell more safely and efficiently than viral vectors. That said, advancements in GMP and scalable methods of delivery are both required in order to replace viral vectors in next-generation CAR-T therapies.

The Promise of Point-of-Care Manufacturing. In the US, CAR-T therapies are currently offered at a limited number of hospitals. If biopharma companies were to establish a point-of-care manufacturing model, they could produce T cells at or near those hospitals. This manufacturing model would offer two advantages: physicians would gain more control over scheduling and production, and patients would receive treatment in a more timely manner.

Point-of-care manufacturing also has some drawbacks. It may be more difficult to procure key reagents and consumables at all sites, and patient demand fluctuates enough that there is the risk of underutilized capacity. In addition, significant CMC regulatory concerns can arise when oversight of quality control becomes more fragmented. Companies interested in a point-of-care model should wait until the patient population expands enough to keep facilities fully utilized. This will likely be achieved once more therapies enter the market with a broader set of indications and a larger number of institutions participate in CAR-T treatment.

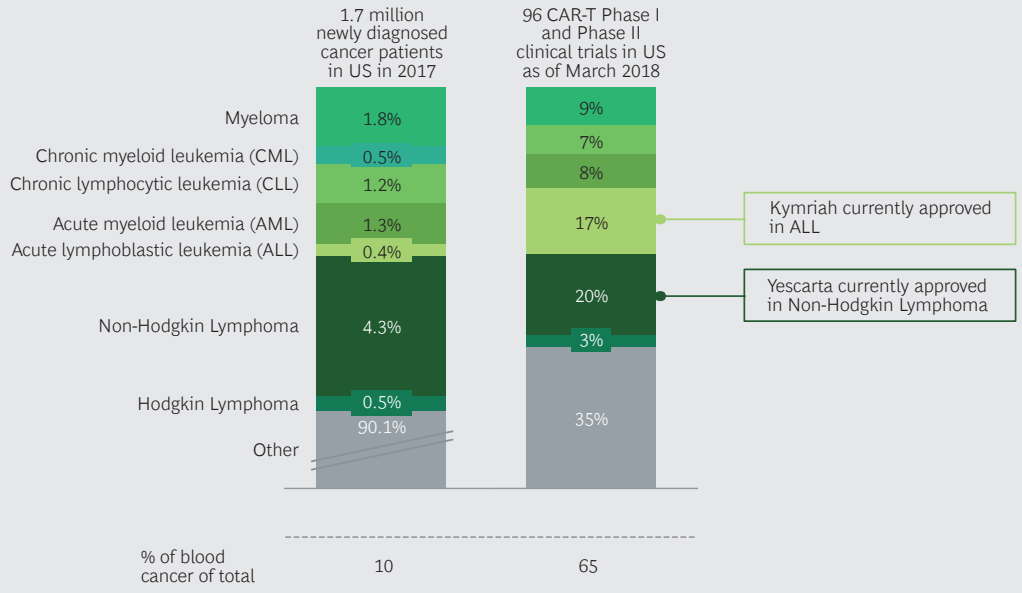
The Patient Population Is Small—but Poised to Grow

Three factors have created a temporary shortage in patients for CAR-T therapies. First, there's currently a narrow population eligible to receive CAR-T treatment. Commercially available therapies treat blood cancers that affect less than 10% of all cancer patients—and these therapies are currently approved for last-line relapsed or refractory cases. Moreover, most clinical trials in CAR-T focus on the same two cancers: ALL and Non-Hodgkin lymphoma. So an already small patient population is being aggressively served by clinical trials. (See Exhibit 3.)

Second, reimbursement is uncertain. On the provider side, the financial burden on physicians may limit patient access. For example, in the US, physicians are currently being under-reimbursed for the cost of the drugs Kymriah and Yescarta when treating Medicare patients. It may take an additional one to two years before the Centers for Medicare and Medicaid Services (CMS) creates the billing procedures to facilitate reimbursement. On the payer side, it is unclear how reimbursement will evolve. Payers are currently reimbursing through existing schemes or agreements on a case-by-case basis, and at least one commercial payer is expressing interest in classifying as a service. In addition, payers have shown an interest in outcomes-based contracts, a risk-sharing arrangement in which rebates are tied to the performance of the therapy in the target population. For example, the price to treat an ALL patient with Kymriah is currently $475,000, but CMS will fully reimburse the manufacturer, Novartis, only if patients demonstrate blast response after one month of treatment. To avoid reimbursement issues for Kymriah and Yescarta, some academic clinicians have expressed a preference to treat in their own clinical trials, thus ensuring that their patients get access to cutting-edge, last-line therapies.

All of these factors may contribute to a patient shortage in the near term, but as CAR-T treatment expands to new indications and gains approval for use in earlier lines of therapy, the patient population will eventually overwhelm academia's demand for trial patients. Similarly, as academics move into new indications (such as solid

EXHIBIT 3 | Hematologic Malignancies Account for 10% of Cancers but 65% of CAR-T Clinical Trials



Sources: National Cancer Institute, seer.cancer.gov; Evaluate Pharma.
Note: Main categories of hematologic cancers shown here. Others were not listed on the seer.cancer.gov website; they probably account for a very small number annually. Clinical trials for the indication category "general blood malignancies" were excluded from the analysis. "Others" includes nonblood cancers and solid tumors. Because of rounding, percentages may not add up to the total shown.

tumors), enrollment opportunities for clinical trials will decline in hematologic cancers and demand for marketed therapies will increase.

Where to Invest Now

Biopharma companies are already making big bets in this space. The first CAR-T therapy to receive FDA approval was Kymriah, in 2017. This Novartis product was approved for use in young people (up to age 25) with ALL who don't respond to standard treatment—and the label has since been expanded to include adults with relapsed or refractory diffuse large B-cell lymphoma. Also in 2017, Gilead Sciences spent $11 billion to purchase Kite Pharma, which quickly received approval for Yescarta, a CAR-T therapy for adults with certain types of Non-Hodgkin lymphoma who have failed at least two other kinds of treatment. Meanwhile, in early 2018, Celgene announced that it would spend approximately $9 billion to acquire Juno Therapeutics, which specializes in CAR-T therapies. All three companies have also made numerous smaller investments to acquire technologies and platforms for cellular therapies.

This rapidly developing field presents enormous opportunities, but also many questions: Which diseases have the potential to be treated with CAR-T? Where is the science leading us? How will manufacturing evolve? These questions, in turn, raise foundational business questions: Where should we deploy our resources? Should we make one or two big bets or several smaller ones?

Where to Invest in Emerging Science. The CAR-T market is hot, with strong M&A activity, as companies look to gain a first-mover advantage with this pivotal therapy. However, it's unlikely that any single approach to CAR-T will become the gold standard. The technology is fast-moving—and a winning strategy in one indication may not apply to others. If you're looking to put a stake in the ground, focus on partnership models that allow you to pursue multiple technologies in parallel. For example, you can develop a core set of in-house platforms, such as cell lines or receptors, and forge external partnerships to access complementary best-in-class technologies that enable these platforms, such as access to antigens or mechanisms to alter the tumor microenvironment. Alternatively, you can seek specific cell therapy assets, partnering with academics to commercialize prospective technologies. Finally, companies should ensure that they build or partner to access core methodologies likely to unlock substantial opportunities across cell therapy design and production, such as process technologies leveraging CRISPR-Cas9.

Where to Invest in Manufacturing. CAR-T therapy is still new and doesn't yet scale well, so there's a shortage of manufacturing facilities. In the near term, plan to build your own. Unlike biologics, which require huge facilities stocked with large, customized equipment (such as bioreactors), autologous cell therapy manufacturing requires fairly straightforward lab instruments and a flexible GMP space. Installation is relatively easy, and CAR-T facilities can be easily repurposed if needs change. It's important to note that Kymriah and Yescarta gained approval without Phase III trials. With products getting to market quickly, it will be important to have facilities ready for production, since there may not be time to work with a CMO on technology transfer.

Over the long term, it makes sense to contract with CMOs or other partners to access CAR-T facilities. As the number of CAR-T therapies in clinical trials has increased, CMOs have ramped up their manufacturing capacity, which suggests that cell therapy manufacturing may mature quickly. By partnering with a CMO, biopharma companies can launch products without committing to centralized manufacturing.

Supply chain issues are still relatively complex when it comes to manufacturing CAR-T therapies. Gaining a competitive advantage will call for innovative approaches, such as building software infrastructure that integrates all aspects of the supply

chain to meet patients' needs quickly and reliably. With CAR-T therapies, superior service can become a matter of life and death. There will be a clear advantage for companies that can provide rapid turnaround and seamless vein-to-vein services.

How to Access Patient Populations. Biopharma companies will need comprehensive networks and infrastructure to identify, engage with, and deliver products to eligible patients. Think about which institutions best serve your patient populations and figure out how to build manufacturing capacity that will support those locations. Proximity may be important, but sound logistics and supply chain management will be critical.

CAR-T represents the new frontier in the war on cancer. With high prices and narrow labels, these therapies have so far been limited in application. But advances in science and manufacturing are coming fast and furious—and CAR-T is poised to be highly disruptive. The time to act is now.

Note

1. See Z. Wang, Z. Wu, Y. Liu, and W. Han, "New development in CAR-T cell therapy," *Journal of Hematology and Oncology,* February 2017.

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