WHITE PAPER

LOOKING FORWARD: CATALYSTS FOR CHANGE IN CAR-T

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OVERVIEW OF CAR-T

CAR-T cell therapy is currently one of the most exciting areas of clinical research. To create these living therapies, human T cells are genetically modified to express a CAR (chimeric antigen receptor) that has been programmed to target specific antigens found on the surface of cancer cells.

The CAR-T treatment paradigm of today involves use of autologous T cells, meaning the cells originate from the patient. In the production of autologous CAR-T therapy, a patient's T cells are apheresed (extracted from blood), activated, genetically modified, expanded to larger volumes, and then re-infused for therapeutic effect [*Fig. 1*].

CAR-T therapies are currently being investigated for leukemias and lymphomas, as well as liver, lung, pancreatic, breast, brain, and colorectal cancers.

The degree of complete remission seen in clinical trials from these therapies is striking. Novartis published results from a pediatric ALL trial, showing 83% combined CR/CRi in patients, and Kite Pharma has released results from the ZUMA-1 trial in NHL and DLBCL showing an ORR of 82%.

Industry has taken notice of the exciting clinical success of CAR-Ts and has ramped up development. This has led to a rapid increase in clinical trials involving autologous CAR-T therapies [*Fig. 2*].

In addition to ramping up investments in clinical trials, pharma companies are also bolstering partnerships with smaller biotech companies and academia in several ways, including licensing and acquisitions. Within the past 12 months, pharma has inked many key deals, the most notable of them being Gilead's acquisition of Kite Pharma for $12B in August 2017.

Figure 1: CAR-T Cell Therapy Workflow[1]

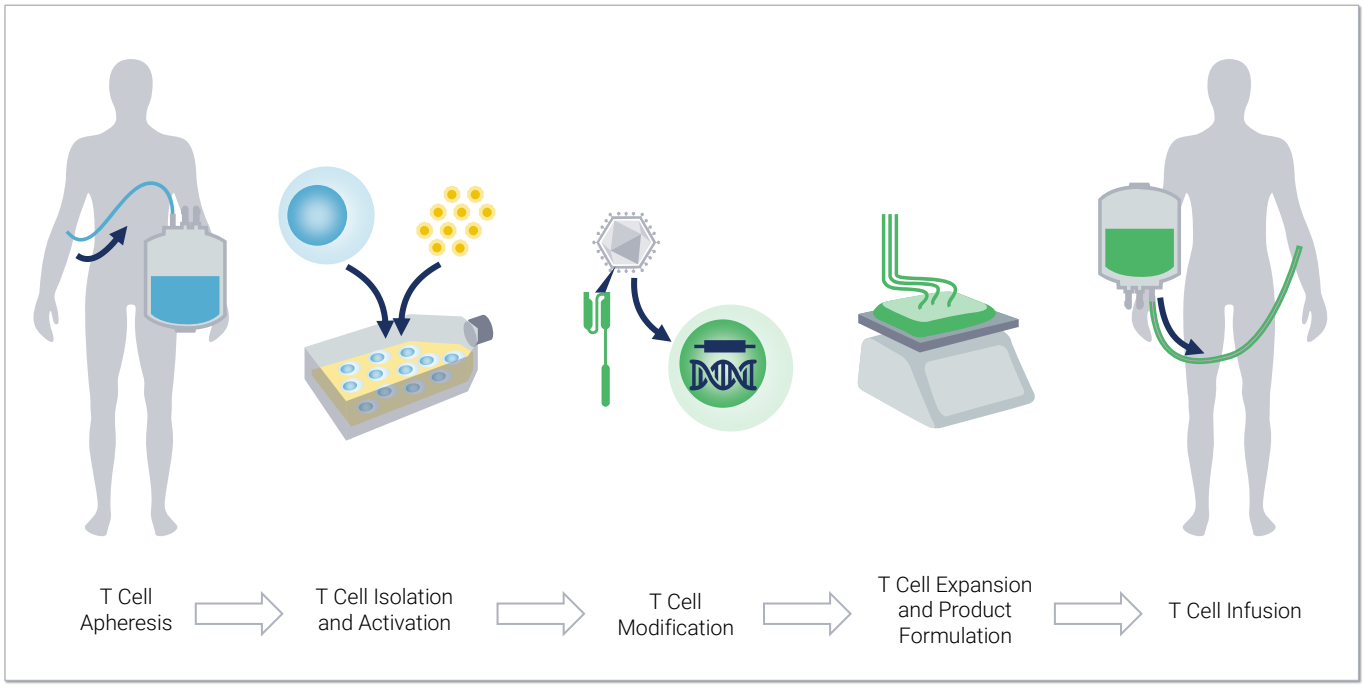
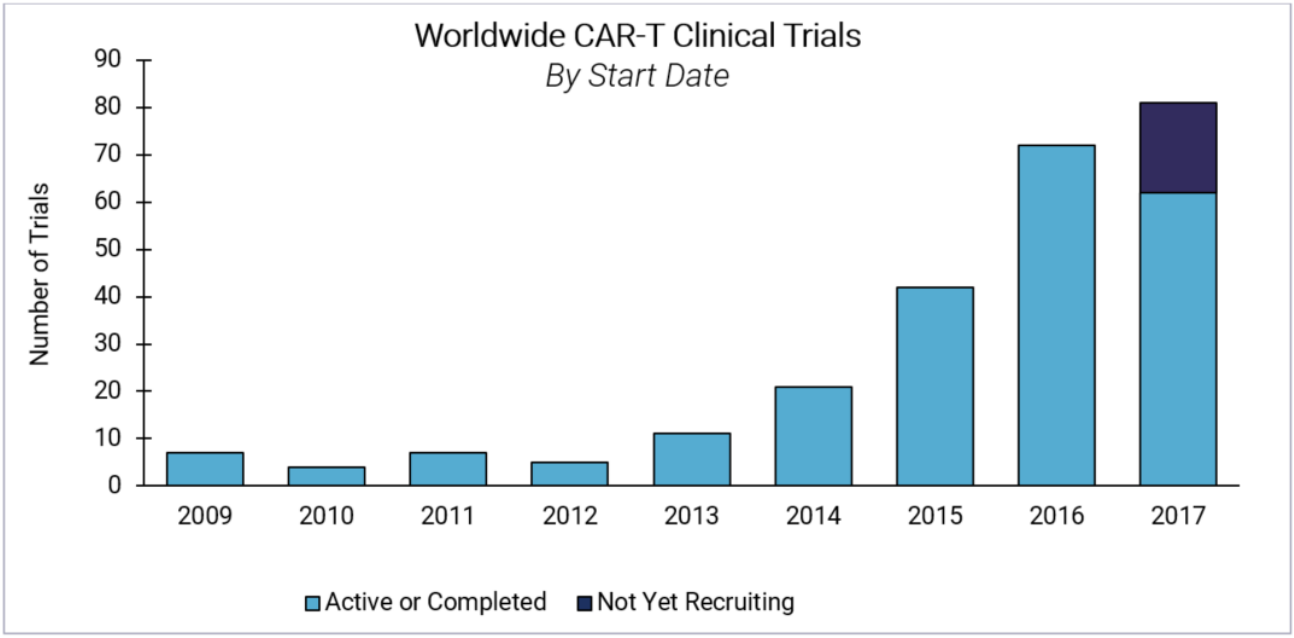


Figure 2. Annual Worldwide CAR-T Clinical Trials[2]



Novartis continues its commitment to CAR-T and licensed nonexclusive rights to Celyad's patents on production of allogeneic CAR-T cells. Bluebird Bio Inc. raised $235M through the public offering of shares to support development of its CAR-T candidate. These are just a few examples of the bevy of activity in CAR-Ts.

Despite the growing buzz and enthusiasm, the highly personalized nature of current autologous CAR-T therapies creates a unique set of challenges in product development and commercialization. Given the nascent state of the industry, and the many open questions that could dramatically alter the future landscape for CAR-T, the field is replete with technical and commercial risk.

Will success in CAR-T remain limited to liquid tumors? Will autologous CAR-T remain the standard for therapy, or will donor-derived CAR-T win-out? If CAR-Ts are developed for larger indications, how will manufacturers meet demand? What future role will regulatory bodies hold in the approval process? If a large number of CAR-Ts gain approval, how will payers and health systems approach reimbursement?

Given the current high-risk high-reward state of CAR-T therapies, the industry is seeking a better understanding of potential commercial trends. Below, we outline four potential scenarios that could dramatically alter the CAR-T landscape.

Scenario 1: CAR-T continues success in liquid tumors but fails to make the jump into solid tumors

Although the buzz continues to increase for CAR-T, nearly all clinical success of CAR-T therapies to date has been limited to liquid tumors, which only constitute ~10% of all new cancer diagnoses in the US. The vast majority of unmet need in cancer treatment resides in the remaining 90% of cancers composed of solid tumors such as breast, lung, and colon cancers.

However, despite being obvious targets for drug developers due to their large population sizes, CAR-T therapies have not yet been able to address solid tumors with repeatable clinical success. Molecular and cellular complexities present the greatest barriers to the development and testing of CAR-T therapies for solid tumors. These complexities present themselves in two major ways: the tumor microenvironment and specificity of biomarkers.

First, the tumor microenvironment of solid tumors is characterized by oxidative stress, nutrient depletion, acidic pH, hypoxia, and T-cell-intrinsic negative regulatory mechanisms[3], and these variables can differ among solid tumor types. These variables can limit the penetration of T cells in the tumor and further limit the activity of cells that do reach the tumor. These barriers are absent in hematological malignancies, but must be overcome for modified CAR-T cells to reach and destroy solid tumors.

Second, identifying specific targets is a much bigger challenge in solid tumors than liquid tumors. Most patients with hematological malignancies express a specific biomarker (e.g., CD19 on B cells in ALL patients), which allows the targeted CAR-T therapy to be effective in the vast majority of patients. However, in solid tumors, few patients carry somatic mutations specific to the tumor, and as a result, the therapy does not carry the same level of specificity across a broad group of patients.

The molecular complexities of solid tumors listed above also pose challenges in clinical trials. Owing to the quick onset, severity of disease, and relative ease of monitoring treatment response in hematological malignancies, investigators can obtain data readouts for liquid tumor trials faster than in solid tumor trials. Contrary to liquid tumors, assessing endpoints such as overall survival in solid tumors can often take many years. Altogether, these complex molecular challenges will likely lead to longer development timelines and ramps[4].

Ultimately, failure to penetrate the solid tumor market would be a major setback for the CAR-T modality, since continued drug development for new indications may be severely limited. If this scenario plays out, developers would have to think critically about clinical development timelines, bringing CAR-Ts to earlier lines of therapy, and expanding to other hematologic cancers.

Scenario 2: Allogeneic CAR-T thrives

The current CAR-T paradigm focuses heavily on autologous CAR-T therapies that target hematological malignancies such as ALL, CLL, and DLBCL. The first two FDA-approved CAR-Ts, Kymriah (Novartis, approved August 2017) and Yescarta (Kite Pharma/Gilead, approved October 2017), are both autologous CAR-T therapies. Of the over 200 CAR-T clinical trials worldwide, over 90% are using autologous therapies. Autologous therapies are a popular choice for drug developers because of the lower risk of immunogenic response, either from rejection or from graft vs host disease (GvHD). While autologous therapies lend themselves to rapid clinical development, they create a large number of production and logistic problems that could dampen commercial prospects.

At the crux of these issues lies the challenges in large-scale production and the logistics of delivering the CAR-T drug. Traditional molecular therapies, such as small molecules and biologics, are manufactured and tested in batches, where multiple drug doses are created in each production run. Autologous CAR-T therapies, however, can only be produced as one patient-dose per batch, which drastically reduces the economies of scale in manufacturing and production. Many firms, including Invetech, Cellectis, Hitachi, and GE, are working feverishly to industrialize and automate the autologous CAR-T production process, but even if production is fully optimized, bottlenecks including transportation time, transformation, cell expansion, and batch testing will always remain and serve as barriers to decreasing lead-time.

The most significant scientific development that has the near-term potential to address these challenges is the development of viable allogeneic CAR-T therapies. In allogeneic therapy, T cells are collected from a healthy donor and modified in a similar process as autologous cells. An additional step is carried out to inactivate the endogenous TCRα gene, thereby reducing the risk of GvHD. Since the donor patient's cells can be collected and modified in advance, allogeneic CAR-T therapies can be manufactured and tested in batches and stored in freezers until infusion, at which time they are thawed and administered to the patient.

Before considering the manufacturing benefits that allogeneic therapies provide, clinical equivalency and safety must be demonstrated to win the favor of physicians. Autologous CAR-T therapies possess the clinical upper hand, with high CR/CRi rates relative to the current standard of care, for example, 83% in Kymriah's Phase III trial. While early trials of allogeneic therapy have shown some efficacy validating this approach, the CR rates are not up to par with autologous therapy[5]. Safety, on the other hand, may be where allogeneic therapy could hold an advantage. Although Cellectis' allogeneic UCART123 was placed on clinical hold in September 2017, other early studies[6] have shown favorable tolerance to allogeneic CAR-T. This arena is rapidly developing, and ultimately, larger trials that are in progress will shed more light on the tolerability of allogeneic CAR-T therapy.

From a logistics standpoint, physicians may prefer allogeneic over autologous therapies, assuming clinical equivalence, since they would provide faster turnaround time from prescription to drug delivery.

The use of donor cells in allogeneic therapy is also a critical differentiator, because patients that are candidates for CAR-T often possess low immune cell counts (leukopenia) due to prior chemotherapy, and do not have the raw starting material needed for autologous CAR-T production in the first place. The main advantage of allogeneic therapy is that it creates an "off the shelf" alternative to autologous therapies, thereby reducing some of the challenges in production and fulfillment. As a result, allogeneic therapies lend themselves more favorably to scale-up and meeting demand when compared to autologous therapy.

Overall, allogeneic therapy provides enormous advantages in manufacturing and logistics that have the potential to reduce the overall cost of treatment; however, clinical efficacy and safety of allogeneic CAR-Ts have yet to be proven. These game-changing clinical breakthroughs in allogeneic therapy have the potential to make recent investments in CAR-T manufacturing obsolete unless pharma can either build flexibility into the process or pivot to retrofit manufacturing plants and processes for allogeneic use.

Scenario 3: CAR-T becomes gold standard for cancer therapies, but developers fail to meet demand

If CAR-T continues to show clinical promise in new indications, and succeeds in moving to earlier lines of therapy, it is highly probable that this therapy could become the gold standard for cancer treatment. CAR-Ts have raised the bar in efficacy, giving them more staying power in the market, and they face relatively low risk of genericization because of the complex manufacturing process.

However, one major challenge to achieving success is that the ramp to peak autologous CAR-T production across the industry could take years, if not decades. The sheer magnitude of infrastructure needed to treat millions of cancer patients in the US with autologous CAR-T, and the investment required to see it to fruition, would be monumental. Consider that Kite Pharma's new state of the art 43,500 square foot autologous CAR-T and TCR production facility will have the capacity to create only 5,000 patient therapies every year[7]. To address this barrier, Kite is collaborating with GE offshoot GE Global Research, with the aim of expanding capacity and automating more of its manufacturing system[8].

Underlying these challenges are concerns over product quality and consistency. The entire process for autologous therapies, from collecting patient cells to final drug delivery, is ripe for inconsistencies among care sites and manufacturing plants. Raw materials, protocols, and quality measures are influencing the cellular phenotype and functionality of the final drug product and they must be carefully controlled[9].

The rollout of patient-specific CAR-T factories will require intense sustained investment over long timeframes, and new drug modalities unknown today may cause the current process to become obsolete before production output ever reaches its theoretical peak. Pharma has to think carefully about gaining efficiencies throughout the entire process, including collecting cells, modifying, and administering the final drug product.

Scenario 4: Payers set more stringent limitations on CAR-T use due to large budget impact

Assuming many CAR-T therapies for solid and liquid tumors gain approval in the near future, nearly any pricing model eventually leads to "tragedy of the commons" scenarios. Any individual company greatly benefits from setting price high by benchmarking to other gene therapies or HSCTs, but if too many highly efficacious CAR-T therapies enter the market with ~$500,000 price tags, the total budget impact would far exceed what most payers are currently capable of paying. Even with optimistic health economics and pay-for-performance setups, the reimbursement environment will remain challenging, especially if CAR-T begins to move to first-line treatment.

Payers currently appear willing to absorb the $475,000 price for Kymriah, but this drug is limited to ALL patients who have relapsed from or are refractory to early line treatments. The US incidence of ALL is only 6,500 patients and only 500-1000 R/R patients less than 25 years old are currently eligible for the therapy every year. Even with the small patient population, Novartis collaborated with the Centers for Medicare and Medicaid Services (CMS) to offer a pay-for-performance model upon launch, where CMS is only required to reimburse if the drug shows clinical efficacy in the first month after administration.

It is possible that some health systems, especially in England and France, will attempt to implement capped annuity models, where a fraction of the drug cost is payed over a number of years in order to lessen the upfront budget impact. In fact, NICE UK studied such a reimbursement model, and the study concluded that a discount model combined with a lifetime leasing model could be effective in managing reimbursement of high-priced therapies[10], but there is still uncertainty whether accumulated capped annuities could be sustainable. Such systems are much more difficult to implement in highly privatized health systems like the US.

Overall, continued scientific and clinical success of CAR-T, though welcomed by patients and clinicians, would undoubtedly create financial burden. Payers, providers, and patients could reach a deadlock if innovative pricing models cannot be designed to make these treatments more affordable for the masses. In the event that many competitive CAR-T therapies enter the market, pharma would need to assess the importance of entering alternative and novel pricing models to solidify their position in the market and make these life-changing drugs available to patients in need.

CONCLUSION

CAR-T appears to have a very bright future for numerous clinical reasons, but as with any new therapy, there will be hurdles in managing how the healthcare ecosystem reacts. Entry into solid tumors, expansion to allogeneic-based therapies, difficulty meeting demand, and challenging reimbursement are just a few of the potential affairs that inject uncertainty.

Despite the risk in this new arena of healthcare, there is also a huge opportunity for the industry to capitalize on this high-stakes situation, to arm doctors with new tools in the fight against cancer, and to give new hope for critically ill patients. The industry has a real opportunity to shape the way cancer patients are treated with these life-changing therapies, and this necessitates thoughtful and deep strategic planning to traverse the myriad of challenges in drug development, commercialization, and reimbursement.

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Glossary of Terms

ALL	Acute Lymphoblastic Leukemia
CAR-T	Chimeric Antigen Receptor T Cell
CMS	The Centers for Medicare and Medicaid Services
CR/CRi	Complete Response/With Incomplete Platelet or Blood Count Recovery
DLBCL	Diffuse Large B-Cell Lymphoma
EBV	Epstein-Barr Virus
GvHD	Graft vs. Host Disease
HSCT	Hematopoietic Stem Cell Transfer
NHL	Non-Hodgkin Lymphoma
NICE	The National Institute for Health and Care Excellence
R/R	Relapsed/Refractory
ORR	Overall Response Rate
TCR	T Cell Receptor