New Technology Commercialization Opportunities and Challenges – CAR-Ts

by groupH

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WHAT IS IT?

- Chimeric antigen receptor (CAR) T-cell therapy is a revolutionary treatment approach that uses a patient's own T-cells
- For **autologous CAR-Ts**, a patient's T-cells are harvested via leukapheresis, transported to a manufacturing facility, enriched, transformed (genetically modified) to express CARs targeted against a specific tumor antigen (e.g. CD19), expanded, shipped back to the treatment center, and then re-infused back into the patient
- In contrast, **allogeneic CAR-T cells** are derived from a healthy donor ahead of time, processed and stored until needed

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COMMERCIALIZATION OPPORTUNITIES

General

- CAR-T cell therapy has brought unprecedented response rates to late-line heme-onc patients (approximately 40% to 54% in DLBCL and 81% in ALL) providing meaningful benefits to patients with poor prognosis
- Multiple autologous CAR-T products are now launched (Kymriah, Yescarta, Breyanzi, Abecma, Tecartus), increasing confidence in the platform and awareness among patients and community HCPs (necessary for referrals to certified tertiary care centers)
- Provider HCP experience at tertiary care centers continues to accumulate and side-effect mitigation strategies continue to improve, meaning better outcomes for patients and an increase in the number of patients considered appropriate for treatment
- CAR-Ts in development are exploring heme-onc targets that have been validated by other modalities, meaning that CAR-Ts could expand into additional heme-onc indications

Autologous

- The durability of autologous CAR-T cells enables a 'one-and-done' treatment approach (albeit a complex treatment process)

- Numerous opportunities exist to reduce some of the barriers associated with autologous CAR-T therapy:
    - Current manufacturers are improving their production timelines and next-gen CAR-T manufacturing technologies are expected to improve production timelines further. These effects will reduce turn-around-time (TAT) for patients and reduce the need for bridging therapy
    - Furthermore, as CAR-Ts move into earlier lines of therapy where (1) turn-around-time is less of a concern and (2) patients have fitter T-cells, barriers to CAR-T therapy will reduce
    - Next-gen CAR-T construct technologies (such as dual targets, logic gates, etc) are expected to reduce antigen escape and on-target, off-tumor toxicities. This should expand the pool of eligible patients, improve outcomes for patients, reduce the burden on providers managing side effects, and expand the number of treatment centers able to offer therapy

Allogeneic

- Allogeneic CAR-Ts are in early clinical development and bring the promise of an 'off-the-shelf' option, that could greatly simplify treatment logistics and the time to start treatment, thereby improving patient access
- There is a theoretical scalability from manufacturing multiple doses in a single production batch that may enable higher manufacturing capacity and economies of scale (although some manufacturing challenges remain); furthermore, batch production is expect to generate a more standardized product than autologous CAR-Ts
- This combination of 'off-the-shelf' use and scalable manufacturing gives developers hope of bringing allogeneic CAR-Ts into wider regional hospitals / the outpatient setting, further improving patient access
- It is anticipated that allogeneic CAR-T therapies could be manufactured more cheaply than autologous, bringing cost savings to manufacturers

COMMERCIALIZATION CHALLENGES

Autologous

- CAR-Ts have a poor safety profile due to cytokine release syndrome (CRS) and neurologic toxicity, which limits their applicability to life-threatening conditions and restricts use to treatment centers with ICU availability and trained staff for post-treatment care
- Considerable investment is required by manufacturers to build and staff facilities to process patient T-cells and guarantee supply chain fidelity, meaning that a clear business case is necessary for new entrants
- Furthermore, given the personalized nature of autologous cell processing, manufacturing economies of scale are hard to come by
- When first launched, centers providing CAR-T therapy made a financial loss on each inpatient Medicare patient they treated, due to high product acquisition costs and uncertain reimbursement levels. There was little incentive for non-academic hospitals to take on this financial burden and risk (see our Mar 2019 post on CAR-T Reimbursement in the US). Reimbursement progress, such as the recent creation of an MS-DRG for CAR-T therapy and changes to the NTAP pathway (described in our Aug 2019 post Our Take on CMS's Latest Memo on CAR-T Reimbursement) are easing these concerns, but can remain a challenge
- Payers are sensitive to large upfront treatment costs meaning that new pricing and reimbursement models have been needed. Risk-sharing and capped annuity approaches have been considered, but come with implementation challenges in many markets (see our paper on The Payers' Perspective on Gene Therapies)
- Patients who live far from certified CAR-T centers are burdened by the need to travel long distances with their caregiver(s) for therapy
- High barriers exist for new entrants because treatment centers are incentivized to stick with a single CAR-T ecosystem due to logistical challenges and certification requirements

Allogeneic

- Despite their promise, allogeneic CAR-Ts are in early development and have yet to show compelling/competitive efficacy

- GvHD is a potential issue when using donor cells – mitigation strategies are being developed to reduce this, but need to balance the need to retain high levels of immune activity of the effector cells
- Due to shorter cell persistence, allogeneic CAR-Ts will likely involve a less convenient dosing schedule than autologous CAR-Ts, with patients requiring multiple doses, much like a cycle of chemotherapy or a targeted mAb. The patient/caregiver convenience could be further eroded if allogeneic products cannot expand into wider regional hospitals / the outpatient setting, meaning that patients could need to travel regularly to tertiary care centers
- While allogeneic CAR-Ts have theoretical manufacturing and distribution advantages over autologous, these have yet to be proven at commercial scale; some challenges remain e.g. feasibility of batch culture

Expanding beyond heme-onc

- Scientific barriers to expanding CAR-T therapies to solid tumors remain (e.g. tumor antigen heterogeneity, trafficking and infiltration into tumor tissue, and the immunosuppressive tumor microenvironment[1], greatly limiting CAR-T commercial potential; these barriers need to be overcome and solutions tested in clinical trials
- Expanding CAR-T use into other disease areas, such as autoimmune diseases, will require approaches that greatly improve the side-effect profile to treat non-life-threatening conditions
- Building manufacturing and supply chain capacity for the significantly higher number of patients in 'non-rare' diseases will require considerable investment
- As CAR-T therapies move from rare indications to larger indications and therapeutic areas with more diverse competition, they will likely face increased scrutiny from payers who may be strained by increased budget impact. 2019 analysis found that the high reimbursement for cell and gene therapies means that the total costs could exceed what the healthcare system can manage[3]

Impact of COVID-19

- CAR-T treatment strategies have encountered complications and challenges amid the COVID-19 pandemic, such as staff and resource shortages (e.g. reduced availability of hospital beds and ICU beds), as well as potential delays in shipment of cellular therapy products
- Guidelines have been developed that impact most aspects of care; examples include COVID-19 testing patients within 48-72 hours of lymphodepleting chemotherapy and within 7 days of CAR-T cell infusion, limiting in-person visits and substituting with telemedicine visits, and delaying T-cell apheresis, lymphodepleting chemotherapy, and/or CAR T cell infusion if a patient tests positive[2]

WHAT TO GET RIGHT

- A small number of academic hospitals and research centers are taking a particularly large role in developing new CAR-T technologies, leading clinical development, and selecting which patients will be enrolled in which studies – manufacturers need to form very close and productive partnerships with these groups
- Increasing community oncologist willingness to refer patients to tertiary care centers where the current generation of CAR-Ts are delivered is key to increasing use
- Reducing patient barriers to accessing CAR-Ts is also important; some manufacturers are providing travel assistance programs to reduce the travel burden on patients and caregivers
- As the CAR-T platforms mature, reducing side-effects to eliminate the need to give CAR-T therapy at certified facilities with ICU availability will be key in moving CAR-T therapy into wider regional hospitals / outpatient setting
- We believe that allogeneic CAR-Ts are caught in the middle between autologous CAR-Ts and emerging 'full-sized' bispecifics. They lack the dosing convenience and efficacy of autologous CAR-Ts, and also lack the expected community reach of bispecifics. Approaches to improving efficacy, tolerability, and persistence of allogeneic CAR-Ts will be necessary to develop a unique and compelling value proposition in this market dynamic
- Manufacturers may need to embrace novel reimbursement models and gather the necessary supporting data through clinical development

WHAT CAN GROUPH OFFER?

groupH has conducted…

- Projects mapping the CAR-T landscape across several oncology indications
- Numerous competitor strategy and positioning projects involving CAR-T therapies

- Technology deep-dives into current CAR-Ts and next-generation technologies, working with cross-functional teams to identify drivers for adoption, and technical barriers to be overcome
- In-depth market access research, looking at payer needs, funding pathways and provider economics of CAR-T therapies

groupH can conduct…

- Technology scans of next-gen CAR-T technologies (dual CAR-T, in vivo, adaptors, etc)
- Early TPP testing and development to optimize product positioning in the treatment landscape, refine value proposition, identify any commercial challenges or barriers to prescribing, and inform clinical strategy
- Robust opportunity assessments and forecasts incorporating physicians', patients' and payers' views
- CAR-T therapy pricing and reimbursement research to understand the payer landscape, characterize the value proposition, understand the payer value elements in the TPP, assess the evidence generation against payers' needs and understand the implications of any gaps, understand the price potential and rationale and any potential access restrictions for given price points, and identify any potential market access hurdles and develop potential approaches to overcome these hurdles

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