Novel CAR-T cell therapies: it can't be ALL about price

LONDON, UK----8th May 2017----ExpertREACT. Novartis' new CAR-T therapy, CTL019 could be a blockbuster – but it needs more indications, more age groups and forward thinking stakeholders to reward innovation. Success would create a market platform for next generation allogeneic approaches, but safety concerns still haunt the field.

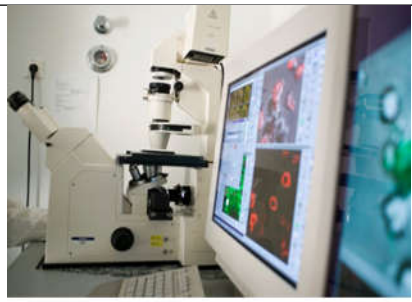
Swiss Pharmaceutical giant, Novartis made ground breaking news back in late March of this year in the field of chimeric antigen receptor T-cell (CAR-T) therapy. The company announced that the US FDA had accepted it's BLA filing for **CTL019 (tisagenlecleucel-T, CD19-specific CD3ζ/ CD137 2nd CAR-T)** and granted priority review for relapsed and refractory (r/r) pediatric and young adults with B-cell acute lymphoblastic leukemia (ALL) **(1).** CTL019 is likely to the first CAR-T therapy to be approved but many obstacles (and competitors) still lay ahead. Will CAR-T cell therapies become a high value market segment for immune-oncology? **iOnco Analytics** discusses latest developments in this **ExpertREACT** article.

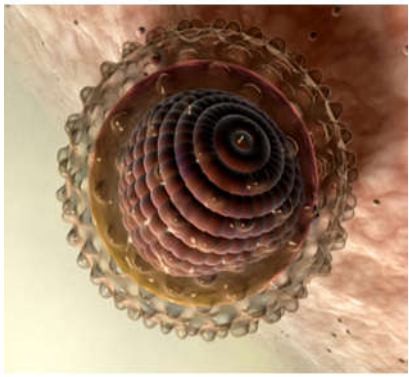
CAR-T therapy is a specialised autologous technology whereby a patient's own T-cells are transfected with an engineered chimeric antigen receptor and then re-introduced to the body to fight cancer. The technology, first described in 1989, enables a CAR-T lymphocyte to have antigen specificity to a variety of targets e.g. including proteins, carbohydrates and glycolipids but also incorporates a T-cell signaling mechanism to allow for T-cell activation and a cytotoxic response. In the clinic, polyclonal CAR-T cells expressing CD19 with either CD28 ζ or 41BB.ζ signaling domains showed some impressive early results (reviewed in 2013) **(2).** Antitumor activity was dependent on significant T-cell expansion in vivo, but was associated in several patients with a life-threatening cytokine storm.

Despite controversy regarding safety (Juno's JCAR015, KTEC19) and skepticism around commercial viability, the field of CAR-T research and development is still burgeoning. By our calculations around 190 CAR-T trials were identified to be ongoing (March 2017) with a steady yearly increase in number since 2009 **(3)**. CAR-T trials are mostly being conducted by non-industry academic sponsors, but importantly there is enough large company interest (Pfizer, GSK, Amgen and Novartis) to ensure momentum. Most CAR-T studies are still at early clinical stages i.e. Phase I/II clinical development, with a clear majority for haematological cancers such as leukaemia, lymphomas, or myeloma (CD19 based targets).

Novartis' priority review designation and BLA submission for CTL019 was based on the Novartis-sponsored **Phase II ELIANA** study (NCT02435849). In the study, 82% (41 of 50) of patients infused with CAR-T cells achieved complete remission or complete remission with incomplete blood count recovery at three months' post CTL019 infusion. There were no deaths due to cytokine release syndrome (CRS). The data were presented at the American Society of Hematology meeting in December 2016 **(4).** Novartis is also soon to release data from a study named: **JULIET** which is focused on diffuse large B-cell lymphoma (DLBCL). Novartis could file for this second, larger indication as early as the fourth quarter 2017. A recent **iOnco Analytics** forecast suggested CTL019 B-ALL revenues could reach ~$500m in 2023 (scenario dependent) **(5)** but CTL019 needs a high price and more than pediatric r/r B-ALL to be a blockbuster.

Another key competitor in the CAR-T field is **Kite Pharma**. Kite's, KTE-C19, (axicabtagene ciloleucel, CD28/CD3ζ) is close behind CTL019 but for the indication of refractory aggressive Non-Hodgkin Lymphoma (ineligible for autologous stem cell transplant). KTE-C19 achieved FDA Breakthrough Therapy Designation status in 2015 and has since completed rolling submission with the US FDA based on the pivotal results from its ZUMA-1 study **(6).** If approved, Kite plans to commercially launch axicabtagene ciloleucel in US 2017 with also regulatory submission to the European Medicines Agency (EMA). Like Juno's JCAR015, Kite has experienced a patient death but remains confident the program will continue. In other studies, ZUMA-3 (NCT02614066) and ZUMA-4 (NCT02625480) Kite Pharma is pursuing relapsed/refractory B-precursor Acute Lymphoblastic Leukaemia (r/r ALL) in both paediatric, adolescent and adult subjects which directly challenge Novartis' CTL019.





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Aside from concerns about safety, one of the biggest discussions around novel CAR-T therapies is their potential price. A backdrop of new expensive "checkpoint inhibitors" such as Ipilimumab, Yervoy®, Nivolumab, Opdivo® and Pembrolizumab, Keytruda®, although bringing new hope to patients have pushed the upper boundaries of yearly treatment costs to over $100,000 per patient **(7)**. But these are monoclonal antibodies which have a very different (and more straightforward) production process than CAR-T cell therapies. CAR-T therapies are currently made by a cumbersome, bespoke process involving many complex steps under controlled GMP compliant conditions with no potential economies of scale. Costs are likely to be ~$25-35,000 per patient even before additional costs associated with administration, follow-up and monitoring **(8).**

Some might argue, surely the price per patient of **PROVENGE** (Sipuleucel-T) at ~$93K is a more appropriate case study for novel CAR-T therapies? This is also an autologous cellular immunotherapy with similarities in its manufacturing process. However, CAR-T cell therapies might bring a more profound level of clinical efficacy than Sipuleucel-T, based on data so far. Indeed, the UK National Institute of Clinical Excellence (NICE), well known for its rigorous approach to cost-effectiveness analyses, has assumed a CAR-T acquisition price (based on an appraisal threshold of £50,000 per QALY) to be **£356,100** to **£528,600** for a *bridge to HSCT* (7.46 QALYs) and *curative intent* (10.07 QALYs) target product profile (s) respectively. These acquisition prices, which may not necessarily reflect product price, are high but become more appealing if payment is made only for patients which achieve remission as substantial benefits would be realized. In any case, the NICE appraisal committee noted that "innovative payment methodologies" need to be developed to share risk with manufacturers which may involve methods such as monthly leasing **(9).**

Innovation should be rewarded. Regulators and payors should realise that the CAR-T field requires products to be on the market delivering real gains to manufacturers who have borne the risk. First-generation products (if approved) such as **tisagenlecleucel-T** and **axicabtagene ciloleucel** can always be improved upon if the financial motivation is there. For example, **Pfizer** is collaborating with **Cellectis/Servier** on an allogeneic "off the shelf" technology (UCART19) which may overcome the complex manufacturing/supply challenges associated with autologous approaches **(3).** "Kill switches" may improve safety. Novartis also recently invested in a **Celyad** non-exclusive license for allogeneic TCR-deficient CAR-T cells patents which could cost the Swiss company up to $96m and single digit royalties **(10)**. If CAR-T cell therapies deliver their promised efficacy on a large scale and are safe, they will be transformative. Healthcare payment systems should consider a re-invention so that this ground-breaking field can be furthered.

Sources: Corporate press releases and the below

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