Whether it's Long-Term or One-Off Treatments, Heme Cancer Costs Set to Soar

Daniel Palmer, 9th January 2017

This week will see the annual J.P. Morgan Health Care Investor Conference 2017 take place, providing insights for the year ahead. Intensive talks and spin-off events will allow investors and innovators to discuss the latest pharmaceutical advances, and top of the agenda will be the rapidly evolving oncology landscape. Participating investors and everyone watching will be trying to spot where the next big advancement in cancer treatment will be. With immuno-oncology drugs driving forward with label expansions and new agents entering the market in 2016, what's next for the field? After fever-pitch anticipation and mounds of investment, CAR-T is finally set to launch in 2017, so what should we expect? In this article, we discuss the rising treatment costs in oncology, and what that could mean for new entrants.

The highly promising CAR-T cell therapies should finally arrive this year after Kite Pharma initiated a rolling submission for its anti-CD19, axicabtagene ciloleucel in December after game-changing results in relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL). With full submission expected by early 2017, the CAR-T therapy, which has FDA breakthrough and priority review designations, is expected to have a PDUFA date and an approval decision by the end of 2017. At the conference Kite Pharma will present the latest instalment of results, 6-month durability data from the Phase II portion of the ZUMA-1 study. Unknowns still surround the pioneering cell therapy, including the needs and nature of an advisory committee, and the stakes are high as Kite grasps for the coveted first-to-market advantage. Alongside Kite, the two other front runners in this technology space are Novartis, who plan to file their anti-CD19, tisagenlecleucel-T (CTL 019) in the US in early 2017 for paediatric and young adults with relapsed/refractory ALL. With breakthrough status, Novartis could also reach the market in 2017. A few steps behind, Juno and collaborators Celgene are fighting on with their CAR-T therapy JCAR-015, despite a rollercoaster 2016 with several treatment-related deaths, which set back the companies' development timeline. In addition to US filings, all three companies have the new speedy PRIME designation in the EU. Kite and Novartis have hinted at an EU filing later in 2017 and could be on the European market soon after the US launch. The novel therapies have been heavily touted to be the future cure for many hematological

cancers and as such have already attracted billions in investment to date. Yet, these indications are only the tip of the iceberg, with several CAR-Ts still in clinical development for a wide range of hematology indications.

Whilst great strides are being made to combat the many challenges facing the commercialization of CAR-T cells, including the development of 'off-the-shelf' cell treatments using allogenic donors and the generation of improved treatments to limit the potentially life-threatening side effects, such as cytokine release syndrome and neurotoxicity, the real hurdle will be in the affordability of these potentially curative treatments. Spiraling costs have led the increasingly cost-conscious EU healthcare authorities, and the US and Japanese markets to begin to cautiously evaluate the cost-benefit ratio of incoming oncology drugs. To what extent will the cost of CAR-T therapies be prohibitive in treating patients? If the treatments are widely adopted, what will that mean for drug development in haematology cancers going forward?

If approved, Kite Pharma's first offering will be used to treat stem cell-ineligible refractory DLBCL. DLBCL makes up around half of all NHL cases; around 24,000 cases will be newly diagnosed in the US this year, some of which will be eligible for the therapy. Currently, the average cost of treatment for the most commonly used drug in for DLBCL patients, Roche's Rituxan, is around $50,000 per year. The mega-blockbuster is going to face the launch of biosimilars imminently in the EU, likely lowering the cost of the drug in the future. The CAR-T cells mentioned in this article use patient's own cells, known as autologous cells, which are removed, genetically engineered and re-injected back into the patient. The process of making custom therapies that are tailored to a single patient brings high development costs, in addition to manufacturing and logistical considerations, compared to traditional therapies. However, the hope for these treatments is that a small number of doses, perhaps even a single dose, can cure the patient of their cancer. With such great promise, pricing for these therapies has been estimated to be anywhere up to $750,000 per patient. Should the long-term efficacy hold its promise, and the quality of life for patients be acceptable, moving away from long-term treatments may justify the high up-front costs. Given the investment into this technology, there is certainly a lot at stake. In September 2016, Novartis, whose CAR-T therapy targets a small population in ALL (3,100 diagnosed each year), made a shock decision to integrate its CAR-T division into its cancer research division, leading the pharma community to question the commercial viability of the field. In 2017, the industry will be poised to see Kite become the first to negotiate with reimbursement authorities.

The costs of oncology agents are rising year on year, with the trend exacerbated by the advent of anti-PD-1/PD-L1 immuno-oncology agents. In multiple cancers, these agents can demonstrate dramatic efficacy, improving patients' outcomes and capsizing standard treatment algorithms. Companies have devised broad clinical development programs to grab the most lucrative patient segments, and soon

the agents will be launched as monotherapies in cancers with the highest immunogenicity and biggest unmet needs. However, the treatments command a high cost, the leading PD-1 drug, BMS' Opdivo, can cost $12,500 per month in non-small cell lung cancer.

Whilst these agents have undoubtedly changed the treatment landscape in many cancers, only 20-30% of patients show durable responses. Two strategies are currently being explored to tackle this issue, firstly the improved characterisation of positive responders. The aim is to better stratify patients and inform who should receive such treatment, and to increase understanding of how these agents work. While this is challenging and lengthy, it will help reduce costs in the long-term by treating only patients who are likely to benefit. The second and more advanced approach is to look for agents that can offer synergistic efficacy, simultaneously increasing the number of responders. Combining immune-checkpoint inhibitors with either another immuno-oncology drug or targeted chemotherapy can increase efficacy, and therefore improve treatment duration. Leading companies in this space, including BMS, Merck & Co. and AstraZeneca are continuing to race to find the best combinations for their inhibitors by looking at both their internal portfolios and to external collaborators. BMS have ~150 and Merck & Co. just over 100 ongoing combination trials for Opdivo and Keytruda, respectively. Successful combinations could supersede previous first-to-market advantages and pharma companies will be set apart by the combinations they are able to create through in-house development, partnering, M&A, & in-licensing compounds. Each will have its merits and demerits, though partnering may yield the fastest time to market in this hotly contested race.

Although the progress of checkpoint inhibitors and combination agents has, to date, been more significant in solid tumors, developments are heating up in the haematology oncology space. In a recent announcement BMS revealed it is teaming up with Janssen to trial Opdivo in combination with Darzalex in patients with various cancers including Multiple Myeloma. Genentech is also sponsoring a trial with the Darzalex inhibitor, this time in combination with its anti-PD-L1 Tecentriq and a third immunomodulating agent, either Celgene's Revlimid or Pomalyst. Darzalex, a proteasome inhibitor, is already on course to become a blockbuster drug, with impressive monotherapy and combination data in myeloma patients. Yet Darzalex is an expensive drug, costing $135,550 for the first year in the US, and $76,044 per year thereafter. If the trial read-outs are successful in leading to approval, the launch of two, or possibly even three premium-priced products as a combination therapy is going to be hugely expensive and will drive the average cost per patient considerably. New agents will be approved based on their ability to reduce the risk of disease progression or death and to hopefully extend long term survival. Premium priced agents, in addition to pushing up the monthly cost of treatment incrementally, will increase the average time over which a patient receives a drug, therefore increasing the average cost of treatment per patient considerably. With increasing push-back from EU reimbursement gate-

keepers, the recent unprecedented out-of-cycle re-pricing of Opdivo by Japan's Central Social Insurance Medical Council (Chuikyo), and the mounting drug pricing scrutiny facing the US, a question mark remains over the where the upper limit of oncology pricing lies.

For the first time, the oncology segment is going to garner the highest revenue in pharmaceuticals. Ageing populations and rising incidence of cancer are major market-size drivers in most cancers. The global oncology market is set to grow from $100bn in 2014 to $150bn in 2020 according to IMS health. This growth will be fueled by the projected immuno-oncology mega-blockbusters. Companies are now looking to oncology and more specifically immuno-oncology drugs, that can target large patient populations over multiple cancer types, be used for extended treatment durations, and be combined with the backbone of therapy to create a formidable standard of care hurdle. But how will regulatory agencies and reimbursement authorities handle to growing costs of these agents? Will the upfront costs of a potentially curative therapy be affordable, particularly in times of economic uncertainty and strains on national spending? Will combinations that are increasingly more tolerable and efficacious, transform cancers into chronic conditions? At the conference this week, investors will be busy looking at potential market share for these agents whilst weighing up their efficacy and safety profiles. In the future, their focus may need to shift to the increasingly challenging reimbursement environment.

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