Evaluate Vantage

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# Vantage Point – CAR-T value calculation in the firing line

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The upcoming US FDA review of Novartis's leukaemia project CTL019 should have payers taking a close look at how to value the rush of therapies that promise to engineer patients' own immune cells to fight their cancer.

Throwing a serious spanner into the assessment of these CAR-T therapies compared with standard small-molecule drugs or biologicals, however, is the fact that for now they are frequently a bridge to stem cell transplant rather than a cure. Novartis could also point to its complex manufacturing programme and argue that this deserves extra compensation. FDA review will serve as the first big test of precision medicine, a business model that might turn out to be even more perplexing to insurers than it already is to biopharma companies.

Because the agency considers only efficacy and safety, these questions will probably not arise at the US oncologic drugs advisory committee meeting on July 12 or in the staff review leading up to an approval decision in paediatric acute lymphoblastic leukaemia, expected by September 29. Yet they are sentinel events for pharmacy benefit managers like Express Scripts and big insurers like United Health in assessing how much they are willing to pay for CTL019, also known as tisagenlecleucel-T.

"It highlights for me the importance we will have to attach to fast and furious learning," Steven Pearson, president of the Institute for Clinical and Economic Review (ICER), said of the upcoming red-letter dates. ICER, the most prominent US cost-effectiveness evaluator, has not yet scheduled its own review of CTL019, something that the UK's Nice has attempted to do at a theoretical level. Promisingly, Nice determined that in some circumstances a cost of over $600,000 might still be acceptable to payers.

**True blood**

Many cancer treatments have associated institutional costs resulting from hospital stays and ancillary procedures, and this will be true of CTL019 too. However, CAR-T is more complex than standard care.

The procedure requires white blood cells to be extracted from patients' blood, and after a complicated series of steps that in the US will take tissues to and from Novartis's plant in Morris Plains, NJ – purchased from Dendreon – the engineered, tumour-fighting CAR-T cells are re-injected into patients.

This obviously will be more costly than ordinary biological manufacturing, which does not rely on patient-specific tissue to manufacture a treatment-ready product. It also increases the risk of pre-infusion failure, as patients can progress during the manufacturing window or the product can fail to be produced if the patient does not have enough T cells of sufficient quality to begin with (*ICML – Novartis's non-infusion mystery centres on Juliet's design, June 14, 2017*).

Who bears which costs and how they are factored into the price calculation is for now unknown. As Professor Mark Fendrick, director of the University of Michigan Center for Value Based Insurance Design, says, "This never comes up when drugs are expensive but aren't hard to make."

**Past is prologue**

Dendreon provides an example. Its dendritic cell immunotherapy Provenge, originally priced at $31,000 per infusion, imposed a $93,000 cost that delivered a four-month survival benefit in castrate-resistant prostate cancer.

The product's subsequent owner Valeant withdrew its marketing authorisation in Europe citing commercial reasons. It should be noted that the group had difficulty proving a cost-effectiveness case when it came to the big technology assessment agencies, the UK's Nice and Germany's IQWIG – a case that was not helped by comparisons with Zytiga, a newly introduced drug that changed the prostate cancer treatment landscape.

Provenge remains on sale in the US, and last year recorded $303m in revenues, likely down to more generous payer attitudes in the world's biggest drug market. This will be a matter for Sanpower to consider once it completes its acquisition of the Dendreon unit from Valeant.

As for CTL019, until it is approved and Novartis announces a price, a value calculation is difficult to make. The UK's Nice has made a first stab at a cost-effectiveness judgement.

That endeavour was marked by uncertainty surrounding small datasets and, of course, an actual price. One conclusion did stand out: the cost-effectiveness case will be less difficult to prove if CTL019 can show a sustained remission on its own, rather than serving as a bridge to transplant.

In trying to make a cost-effectiveness determination, the UK agency estimated prices of £356,000-£529,000 ($453,000-$674,000), depending on whether the CAR-T treatment was a bridge to transplant or a cure, and excluding the costs of T-cell extraction and conditioning therapy for patients undergoing transplant.

Those prices, of course, were aligned to achieving what the agency estimated would be a cost of no more than £50,000 per quality adjusted life year gained over the standard of care.

**The payer response**

Taking Provenge as an example, it might be assumed that US payers will be just as open to CTL019 – if a four-month benefit was worth $93,000 then a product that potentially offers a cure in some instances might be worth much more.

However, the years since Provenge's 2010 approval have seen a glut of expensive new advanced treatments – when the product was launched the sector was at a near-pause in revenue growth because of major patent expiries – since then payers have become more assertive and sophisticated in their approach to high-price drugs as cost-growth has accelerated.

Value-based pricing has been imposed in some instances. Amgen set a new precedent for the sector when it offered a money-back guarantee for patients who suffer a heart attack or stroke while taking the cholesterol-lowering agent Repatha. Glaxosmithkline's gene therapy Strimvelis for severe immunodeficiency disorders has been subject to efficacy-based pricing agreements.

US payers have found it difficult to restrict access to oncology drugs, however, which has started to stretch their budgets.

**Financial risks**

As Professor Kevin Schulman, director of the Center for Clinical and Genetic Economics at Duke University, says of the bridge-to-transplant approach: "With a life-threatening condition like cancer, people are willing to take [financial] risks to restore a benefit to their health. Health insurance is not set up to finance that."

With the Amgen and Glaxo agreements as a precursor, it is conceivable that payers could take the stance of paying only for patients who achieve remission – for CTL019 in paediatric ALL that number was 83% at three months.

What constitutes a reimbursable "remission" would be left not just to the views of the scientific community but might also be resolved in the negotiations between payers and Novartis's medical affairs team. It should be noted that CAR-T therapy is still plagued by poor persistence, and in the Novartis study remission at six months fell to around 60%.

Professor Schulman is sceptical of reimbursing by remissions, however, suggesting that pharma companies will just raise their prices to meet revenue expectations. "It's a nice little trick but it doesn't work," he says.

Nevertheless, assuming that the adcom and the FDA back CTL019, payers will need to develop or apply strategies in response, which could serve as a model for a future in which more medicine is individually tailored to increase the odds of treatment success. Approval of the Novartis project is the "tip of the iceberg" in terms of the financial pressures of this so-called precision medicine approach, Dr Schulman says.

ICER's Mr Pearson says that, although the biopharma sector and payer community alike appreciate the science leading towards precision medicine, they are less sure about how to make it work within the framework of health insurance as it is practised in the US.

"In general everybody, including payers, understands the promise of personalised treatments," he says. "On the other hand, if treatments are really expensive on a one-by-one basis, how we afford it is an open question."

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