Evaluate Vantage

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Novartis's CAR speeds towards approval with panel nod

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In the end it never seemed in doubt: yesterday's 10-0 panel vote in favour of Novartis's CTL019 has paved the way for it to become the first FDA-approved CAR-T product. Any lingering safety and manufacturing worries were not enough to dampen enthusiasm over CTL019's efficacy – good news for other CAR-T players following in Novartis's wake, including Kite and Juno.

If the adcom lacked drama, this might instead come once CTL019 faces payers. There are still questions over what would be an acceptable price for CAR-T, especially given that the therapy is frequently a bridge to stem cell transplant rather than a cure (*Vantage Point – CAR-T value calculation in the firing line, June 27, 2017*).

But for now Novartis will be celebrating the unanimous vote, which should make a formality of the decision, due by October 3, on approval in children and young adults with relapsed or refractory acute lymphoblastic leukaemia.

The positive tone of the adcom also looks like good news for Kite, whose KTE-C19 has a PDUFA date of November 29 in a different indication, diffuse large B-cell lymphoma.

Also benefitting from the decision was Oxford Biomedica, Novartis's lentivirus manufacturer, which was up as much as 10% this morning.

It works

As expected, the panel did not question the efficacy of CTL019, also known as tisagenlecleucel-T (*The CTL019 adcom mists begin to clear, July 11, 2017*).

Instead, much of the discussion focused on concerns over manufacturing and safety. The former is particularly relevant to CTL019; it has become apparent that in clinical trials the lengthy production process opened up a window in which some patients' disease progressed (*Seven questions CTL019 adcom should consider (and two it won't), July 6, 2017*).

Other CAR-T groups could have an edge here: *EP Vantage* has previously calculated that the "vein-to-vein" time for Novartis's product is 29 days, versus 24 days for Juno's and 17 days for Kite's.

There were also questions over the reproducibility of CTL019, given the fact it is an autologous therapy. This goes back to the unpredictable nature of the starting T-cell subpopulations, which could have a knock-on effect on the safety and efficacy of the end product.

This might play in Juno's favour, as the company has boasted of having a defined cell composition with JCAR017 that could improve uniformity and get around this issue.

But is it safe?

On CTL019's safety, surprisingly the bulk of the discussion centred on two legacy gene therapy issues that have not been seen in CAR-T: insertional mutagenesis and replication-competent retrovirus.

The panellists finally got around to the more relevant adverse events of cytokine release syndrome (CRS) and neurotoxicity in the afternoon, but seemed satisfied with Novartis's CRS management algorithm – although it will be interesting to see how this side-effect will be managed if and when CAR-T becomes more widely used.

Interestingly, the panel debated whether giving Actemra earlier or even prophylactically could reduce this adverse event. Actemra, which is already used to treat CRS, does not seem to hinder cell expansion or efficacy according to Novartis, so earlier use could be feasible.

For now, Novartis plans to restrict CTL019 treatment to 30-35 trained and certified centres as part of its risk mitigation strategy. And the promise to follow patients for 15 years seems to have helped allay any fears over long-term safety.

There was one dissenting voice: during the public hearing, Megan Polanin of the US National Center for Health Research called for at least six months of remission data, saying that the three-month data Novartis has provided makes it impossible to make an accurate decision.

But overall, enthusiasm for CAR-T prevailed, with Tim Cripe of the Nationwide Children's Hospital in Columbus describing it the "most exciting thing I've seen in my lifetime". Meanwhile, Larry Kwak from the City of Hope noted that any manufacturing issues would not be "show-stoppers for the outstanding clinical results that have been obtained to date".

Approval now looks like a given. But CAR-T could cost up to $600,000 per patient, so a bigger battle with payers could await.

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For the full transcript of yesterday's live blog with Jacob Plieth and the Stat journalists Adam Feuerstein and Damian Garde, go to: https://www.statnews.com/2017/07/12/car-t-live-blog/