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Neurotoxicity only short-term toxic to Juno stock

Jacob Plieth

Most smart CAR-T investors had known that a setback like the US clinical hold imposed on Juno last week would come sooner or later, though it still rocked the sector. The bigger surprise is how quickly the problem has been resolved – a mere five days later.

This should bring great comfort: the FDA is satisfied that the problem can be laid squarely at Juno's fludarabine-containing lymphodepleting regimen, and has been prepared to act in record time to get the show back on the road. Neurotoxicity will continue to dog CAR-T but, like the cytokine release problems that caused Juno's 2014 clinical hold, this seems to have been a storm in a teacup.

This will undoubtedly come as a relief not only to Juno but also to other CAR-T players, though many continue to use fludarabine as part of a standard Cy/Flu chemo conditioning regimen. Juno stock, which had slumped 32% on July 8, opened up 19% this morning, while Kite Pharma was trading up 9% (*Is Juno's hold a CAR crash or just a speed bump?, July 8, 2016*).

Delay

That said, a delay is inevitable while the centres running Juno's pivotal Rocket trial of JCAR015 reopen enrolment. Leerink analysts today wrote that the FDA's response was surprisingly quick, but said the programme could still be delayed by up to three months.

This would put JCAR015 further behind Kite Pharma's KTE-C19 and Novartis's CTL019 as the first CAR-T product to be commercialised – barring further delays to the rivals, of course. Before the clinical hold Juno was to have filed in late 2017.

At least the FDA has accepted Juno's explanation that a recent switch to a high Cy/Flu regimen in the Rocket trial was responsible for the three patient deaths due to neurotoxicity – a known side effect of CAR-T therapy. Under a revised protocol Juno will precondition patients using only cyclophosphamide.

While this shows a clear path forward it could create other problems, such as lack of efficacy or persistence. The point of chemo preconditioning is to destroy a patient's lymphocytes to enhance engraftment of the CAR-T cells.

Indeed, in a separate trial of an anti-CD19 CAR project at the Fred Hutchinson Cancer Center, complete remission in patients given Cy/Flu was 50%, versus just 8% for those given non-Cy/Flu preconditioning. Meanwhile, rates of severe cytokine release and neurotoxicity were 20% and 35% respectively with Cy/Flu, versus 0% and 17% without.

This breakdown was presented by Dr Stanley Riddell an this year's AACR meeting, though it has to be stressed that this concerned a different CAR construct in a different indication – lymphoma, rather than adult ALL in the case of the Rocket trial.

On a webinar hosted by Slingshot Insights on Monday the University of Pennsylvania's Dr Stephan Grupp, a paediatric leukaemia doctor involved with Novartis's CTL019, said lymphodepletion with fludarabine was standard, but its importance had probably been overstated by the CAR-T sector.

Moreover, it is impossible at this stage to pinpoint Cy/Flu as the culprit, and at present all that can be speculated is that the problem is its use, at high doses, specifically with the JCAR015 construct.

Switching priorities?

It is interesting to consider whether this could prompt a switch of focus for Juno from JCAR015, a project derived from the Memorial Sloan Kettering Cancer Center (MSKCC), to JCAR017, based on work at Seattle Children's Hospital.

Even before the clinical hold Juno had been playing up the data it has seen with JCAR017, a defined-composition CAR-T product. Leerink says JCAR015 could be succeeded by JCAR017, which has generated stellar efficacy with better tolerability, but a radical move would be not even to bother with JCAR015.

If the JCAR015 asset is tainted this will spell bad news for MSKCC, several of whose scientists are pioneers dating back to the early years of CAR-T work. Juno's other clinical hold, due to two deaths from severe cytokine release, also related to JCAR015 in an MSKCC-sponsored trial.

That hold, in 2014, seems to have lasted for about a month. However, if one thing is certain it is that the CAR-T space has advanced apace since then, with the experience of many more patients, and new strategies developed to deal with toxicities. The FDA's readiness to act quickly underscores this progress.

The CAR-T race for first to market

Project	Construct	Company	Study	Indication	Timeline	Trial ID
KTE-C19	CD28/γ-retrovirus	Kite	Zuma-1	NHL	Interim data H2 2016; US filing 2016	NCT02348216
CTL019	4-1BB/lentivirus	Novartis	Eliana	Paediatric ALL	US filing 2017	NCT02435849
JCAR015	CD28/γ-retrovirus	Juno	Rocket	Adult ALL	US filing early 2018?	NCT02535364
JCAR017	4-1BB/lentivitus/EGFRt/defined composition	Juno	–	NHL	US filing 2018	NCT02631044

EP Vantage has published a broad overview of the current opportunities and risks in the CAR-T space. A free copy of the report is available by download.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobPlieth on Twitter

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