Evaluate Vantage

December 05, 2015

ASH – US academic studies see Bluebird square off against Kite

Jacob Plieth

The first adoptive cell therapy sessions of the ASH conference have seen two CAR-T studies run by the NCI's Dr James Kochenderfer given top billing. Their relevance to watchers of listed biotechs is that the NCI has separate co-operative R&D agreements in place with Bluebird Bio and Kite Pharma.

At today's media briefing the approaches, one billed an "allogeneic" CD19-directed CAR and the other targeting the BCMA antigen, were respectively described by Dr Kochenderfer as having "significant activity", and being the first case of an anti-BCMA CAR-T eliminating multiple myeloma in humans.

That said, their commercial potential is still some way off, especially as neither industry collaborator formally has a hand in them. The BCMA CAR-T therapy is relevant to Bluebird, which will begin a phase I trial of its own construct next year, and has "nothing whatsoever to do with Kite", said Dr Kochenderfer.

The anti-CD19 CAR-T, meanwhile, uses the same construct that he and Dr Steve Rosenberg had developed at the NCI, and which Kite is using in its multicentre trial. "But Kite does not sponsor this ... small, academic, exploratory study."

Not autologous

Of course, a CD19-directed CAR-T therapy is nothing new – the industry pipeline is full of such projects, largely thanks to the presence of this antigen on all B-cell lineages, making it a particularly popular target for leukaemias affecting this cell type.

As such, the novel aspect of Dr Kochenderfer's first presentation was that the CAR-T cells were not autologous. But they were not off-the-shelf either – that space belongs squarely to Cellectis/Pfizer's Talen nuclease genome-edited assets – instead being derived from the donor of each patient's stem cell transplant.

At first glance the data looked unspectacular. At a time when CD19-targeting CARs are generating response rates as high as 90%, Dr Kochenderfer reported six complete and two partial remissions among 20 patients with a variety of leukaemias and lymphomas.

But he said 90% was the highest response seen in ALL, while 15 of the 20 patients in his trial had "much more difficult-to-treat" diseases, and were more advanced. And the fact that he did not give them any chemotherapy was a key differentiator, he stressed.

Other parallels

There is also a read-across beyond Kite, namely in a different, MD Anderson CAR-T project licensed to Intrexon and Ziopharm (and subsequently picked up by Merck KGaA).

To express the CAR this asset uses not retroviral transfection, but the Sleeping Beauty transposon/transposase DNA plasmid-based system. The lead MD Anderson investigator, Dr Partow Kebriaei, has presented during this and the previous two ASH conferences (*Sleeping Beauty wakes up to $115m deal, January 14, 2015*).

In some cases she has – like the NCI in this instance – used donor-derived T cells. However, the data have underwhelmed, with poor T-cell persistence being one issue, and her stressing the relative safety of MD Anderson's construct could simply be down to post-transplant patients having low disease burden.

On Monday at ASH Dr Kebriaei is presenting an update to a donor-derived CD-19 CAR-T trial that has now enrolled 18 ALL and three NHL patients.

Again, she will highlight safety: patients have not demonstrated any acute or late toxicity to T-cell infusions. Again, efficacy could be questioned: the abstract says that of 19 patients with at least 30 days' follow-up 10 are in complete remission, with a median of 5.2 months.

Cytokine release syndrome

Neither is Dr Kochenderfer's dose-escalation study targeting BCMA – an antigen expressed on plasma cells – plain sailing. Cytokine release syndrome (CRS), a notorious CAR-T-associated side effect, is an issue in both this trial and the anti-CD19 study.

In the BCMA CAR-T trial, in 11 multiple myeloma patients, those on the highest dose of CAR-T cells experienced CRS, as well as muscle pain, and heart and kidney problems. Efficacy on the lowest two doses, meanwhile, was poor: one short partial remission.

The obvious question is whether a therapeutic window even exists with this type of therapy. But Dr Kochenderfer said CRS was manageable and reversible, with two patients being given the anti-IL6 MAb Actemra to treat it.

He highlighted one patient on the highest dose who obtained a stringent complete response, while also experiencing severe toxicity, a common correlation. The important thing was that the CAR-T therapy was able completely to eradicate malignant plasma cells in this patient.

Dr Kochenderfer will be a primary investigator in a phase I trial of Bluebird's anti-BCMA CAR-T, bb2121, under the NCI's CRADA, starting next year (*ASH – Second chances for Bluebird and Novimmune, November 17, 2015*). This will use a different CAR construct, transfected using lentiviral not retroviral technology, and it remains to be seen whether this affects cell persistence or safety.

On Sunday Bluebird will present a poster detailing preclinical findings with bb2121. As its phase I trial gets under way investors will be keeping a close eye on safety, and hoping that Dr Kochenderfer's feat of eliminating malignant plasma cells in very advanced multiple myeloma can be repeated.

Project	Sponsor	Study	Trial ID	ASH abstract
Anti-CD19 CAR-T	NCI (NIH)	20 pts with ALL, CLL, MCL, DLBCL	NCT01087294	99
Anti-CD19 CAR-T	MD Anderson	21 pts with leukaemias & lymphomas	NCT01497184	862
Anti-BCMA CAR-T	NCI (NIH)	12 pts with multiple myeloma	NCT02215967	LBA-1
bb2121	Bluebird Bio	Preclinical trial	–	3094

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