Evaluate Vantage

December 07, 2015

ASH – CAR-T struggles to travel beyond leukaemia

Jacob Plieth

If ASH was another scientific meeting where interest in CAR-T therapies mounted, an obvious theme was just how much more work still needs to be done to get beyond the relatively accessible low-hanging fruit of acute lymphoblastic leukaemia (ALL).

And that goes for all the big players – Novartis, Juno and Kite Pharma – whose leading CD19-directed projects featured in several presentations over the conference. While remission rates of 90% are common in ALL, in lymphomas they are closer to 50%; moreover, some fundamental problems continue to plague CAR-T therapies.

One is safety: cytokine release syndrome and neurotoxicity remain problematic, though the NCI said it was now using an adverse event treatment grading flowchart to minimise toxicity while maximising response. Another is durability: even in ALL studies hitting 90% initial remission, most of these relapse within a year.

Then there is manufacturing. A particularly worrying revelation by the University of Pennsylvania's Dr Stephen Schuster came from a study of the most advanced CAR-T player, Novartis's CTL019, in a study in patients with relapsed/refractory B-cell lymphomas.

Of 43 patients enrolled, 13 could not be infused – six owing to production failure. Followers of a project that apparently is to be filed for regulatory approval next year could find this alarming.

Bigger trials

A recent Leerink survey of key opinion leaders suggested that CAR-T therapy was "almost certain" to become a future standard in relapsed/refractory ALL, with lymphomas providing the next target.

But lymphomas need bigger trials as well further treatment optimisation to improve remission rates. Kite recently started Zuma-2, a regulatory study in mantle cell lymphoma, in addition to pivotal trials for childhood and adult ALL.

Lymphomas are also harder to treat with CAR-T, possibly owing to their nodal nature and an immune-suppressive tumour microenvironment that renders T cells less active. Across the ASH presentations the theme of low remission rates relative to ALL was obvious.

Selected lymphoma studies of CAR-T presented at ASH

Project	Sponsor	Indication	Data	Trial ID	ASH abstract
CTL019	Novartis	r/r CD19+ lymphomas	30 pts; 14 CRs, 2 PRs	NCT02030834	183
JCAR014	Juno	B-cell NHL cohort	30 pts; 10 CRs, 9 PRs	NCT01865617	184
CD30.CAR	Baylor College*	CD30+ lymphomas	9 pts; 2 CRs, 1 PR	NCT01316146	185
KTE-C19	Kite	r/r NHL	7 pts; 4 CRs, 1 PR	NCT02348216**	3991

*NB: *former Celgene involvement; **Zuma-1 study.*

There were other points of note, too. Grade 3 or 4 cytokine release syndrome was seen in four patients in the CTL019 trial, and in four patients in a separate study of Juno's JCART014, including two deaths; 25% of the JCAR014 patients had grade 3-4 neurotoxicity, and one died.

The Fred Hutchinson Cancer Research Center's Dr Cameron Turtle, presenting the JCAR014 data, suggested that toxicity might be related to the lymphodepleting regimen patients received before CAR-T cell infusion. Severe cytokine release and nerotoxicity was more common in patients depleted using cyclophosphamide/fludarabine than non-Cy/Flu regimens.

On the other hand, Cy/Flu lymphodepletion was associated with higher remission rates. Lymphodepletion – the destruction of a person's immune system – is necessary to boost efficacy of adoptive cell therapy, as demonstrated by Baylor College's Dr Carlos Ramos, who blamed poor remission rates in a study of a CD30-directed CAR-T therapy on the fact that patients had not been lymphodepleted.

Another possible worry is duration of response. In the CTL019 study two partial remissions turned to progressive disease in six to 12 months, while in Kite's seven-patient Zuma-1 trial of KTE-C19 one complete remission relapsed in three months, there was a grade 4 cytokine storm and a death unrelated to treatment.

Leukaemia more impressive

That ALL is an easier indication than lymphomas was also borne out by Dr James Kochenderfer's NCI study earlier in the meeting (*ASH – US academic studies see Bluebird square off against Kite, December 5, 2015*).

Various sponsors' leukaemia trials continue to post far more impressive remission rates – though not without relapses and toxicity: in a CTL019 trial 88% of patients had cytokine release of all grades, while in a chronic lymphoblastic leukaemia cohort of the JCAR014 study there was a cytokine release-related death and three neurotoxicities.

JCAR014 is a retrovirus-transfected construct that Juno said was being de-emphasised at the time of its IPO a year ago. The company has two other CD19-directed CAR-T assets – JCAR017, also with Fred Hutchinson, and JCAR015, a lentivirus-transfected project derived from Memorial Sloan Kettering Cancer Center.

The hospital's Dr Jae Park presented a JCAR015 update in which 24% patients had severe cytokine release, 28% had severe neurotoxicity, and there were two deaths.

More positive news came from the NCI's study of a an anti-CD19 CAR-T in which a 60% complete remission rate was accompanied by just 15% severe cytokine release, thanks to the use of Dr Daniel Lee's grading assessment/treatment flowchart.

Selected leukaemia studies of CAR-T presented at ASH

Project	Sponsor	Indication	Data	Trial ID	ASH abstract
CTL019	Novartis	Childhood r/r ALL	59 pts; 55 CRs at 1mth; 55% ORR at 1yr	NCT02228096	681
JCAR015	Juno	Adult r/r ALL	45 pts; 37 CRs	NCT01044069	682
JCAR014	Juno	CLL cohort	9 pts; 4CRs, 4PRs	NCT01865617	184
CD19 CAR	NCI*	ALL	45 pts; 27 CRs	NCT01593696	684
UCART19	UCL/GOSH**	Child with CD19+ ALL	CR	Case report	2046

*NB: *has CRADA with Kite; **used Cellectis CAR-T project.*

In ALL studies there was also better news on production failures, with Dr Park saying the failure rate was under 5% in his trial. In the paediatric ALL study of CTL019, patients under three years old have had the highest manufacturing failure rate, and are being excluded from Novartis's multicentre trial.

The Swiss firm claims that this is the largest clinical study of a CAR-T therapy, and has been expanded beyond the US to the EU and Asia. The group already has a manufacturing plant bought from Dendreon, while Juno and Kite are constructing facilities, the latter's for strategic reasons adjacent to Los Angeles airport.

To embark on building manufacturing capacity well before approval is bullish – especially considering how far there is still to go before adoptive cell therapy can make the leap from a niche procedure into a product with broad commercial potential.

This story has been modified to correct the one-year remission rate for CTL019.

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

@JacobPlieth on Twitter