Evaluate Vantage

November 30, 2016

Triple meeting – Bluebird upstages its Ash rivals

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Bluebird Bio investors had little to look forward to from the Ash conference, so it is just as well that organisers of the Triple meeting in Munich agreed to a late-breaking presentation of the first clinical data with its anti-BCMA CAR-T project bb2121.

The data are early but striking: seven of nine late-line, post-transplant, multiple myeloma patients have gone into remission, with no serious toxicities. The result upstages other anti-BCMA CARs in the clinic, including one linked to Novartis, and sets a new benchmark for Kite, Juno and Cellectis's preclinical projects. Bluebird shares opened 20% higher on the news.

Until now the standard for CARs against BCMA, an antigen present on plasma cells, had been set by the NCI's Dr James Kochenderfer, who at the Clinical Applications of CAR-T Cells meeting in March detailed a 33% remission rate in 12 patients.

Dr Kochenderfer is also an investigator in Bluebird's bb2121 trial, and has a co-operative R&D agreement with Bluebird covering BCMA. However, bb2121 is wholly owned by Bluebird and Celgene, which in February opted into development.

Smart move

This looks to have been a smart move, judging by the data being presented today in the late-breaker at the Triple meeting (the EORTC-NCI-AACR Molecular Targets and Cancer Therapies symposium).

Perhaps most encouraging is that, while remission rate in the lowest-dose cohort of 50 million cells is just 33%, at two higher doses up to 450 million cells all six patients have responded, with two complete responses (CRs) and four partial responses (PRs).

Remarkably, there was no neurotoxicity or cytokine storm above grade 2, and no patients had to be given Actemra or steroids – common rescue therapies for CAR-T toxicities. "We have not yet seen dose-limiting toxicity," said David Davidson, Bluebird's chief medical officer, hinting at even better efficacy to come. "We are going to continue our dose escalation."

"We're excited about this data," Bluebird's chief executive, Nick Leschly, told *EP Vantage*. "One of the things we don't exactly know is why [it] is so fundamentally different from the other BCMA constructs."

The NCI study had started patients on a much lower dose and only took this up to nine million cells, before dropping down to three million to counteract side effects. The NCI construct differs in structure and delivery from bb2121, and seems to have a limited therapeutic window.

Work on BCMA at University of Pennsylvania, Novartis's partner, is being presented at Ash, and now also looks unimpressive, with a 33% remission rate and one serious case of neurotoxicity in six patients – plus manufacturing failures in two further patients.

Of course, duration is a major question with CAR-T therapies, and one of the CRs in Dr Kochenderfer's NCI trial relapsed after 17 weeks, though the reason was unclear. The two Bluebird CRs are at four and six months' duration, while the highest-dose cohort is at shorter follow-up.

Mr Davidson said: "This is a really early cut of the data, and [the PR] patients need to continue in their response."

Available clinical data with anti-BCMA CAR-T therapies			
Project	Anti-BCMA CAR	bb2121	CART-BCMA
Group	NCI	Bluebird/Celgene/NCI	Novartis/Penn
Construct signalling	CD3ζ & CD28	CD3ζ & 4-1BB	CD3ζ & 4-1BB
Transfection	Gamma-retroviral	Lentiviral	Lentiviral
Trial ID	NCT02215967	NCT02658929	NCT02546167
Planned enrolment	38	50	27
Highest dose tested	9 x 10e6 cells	45 x 10e7 cells	5 x 10e8 cells
Latest efficacy data	1 CR (relapsed) & 3 PRs in 12 pts	2 CRs & 5 PRs in 9 pts	1 CR & 1 PR in 6 pts
Safety summary	Toxicity substantial but reversible	No CRS or neurotoxicity above grade 2	Severe neurotoxicity in 1 pt

BCMA is fast emerging as a hot target for CAR-T, partly because, like CD19, the loss of normal cells bearing it can be counteracted by giving patients intravenous immunoglobulin. Preclinical work is being presented at Ash on Cellectis/Pfizer's UCART-BCMA, and Kite's KITE-585 and a Juno/Eureka Therapeutics asset have yet to start human trials.

In a recent interview Kite's chief executive, Arie Belldegrun, said he had looked at Dr Kochenderfer's NCI work but decided to develop KITE-585 in house. He said that without the NCI's involvement this was an "unencumbered" asset; unlike bb2121 it uses a fully human binding domain.

Mr Leschly, meanwhile, highlighted the "slew of [anti-BCMA] constructs, adjusting various features", that Bluebird went through, optimising the binding domain to avoid inappropriate signalling, before picking bb2121.

It is not finished yet; a next-generation anti-BCMA CAR, bb21217, will be a "fast follower" into the clinic. This involves culturing the T cells in manufacturing with a PI3k inhibitor to give a better cell phenotype.

Despite the excitement, said Mr Leschly, there is still much to learn about what aspects of CAR design lead to good efficacy without toxicity: "We can point to specific elements [of the CAR], but for us to say 'Aha! This is why!' I think it's too early."

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