Evaluate Vantage

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# Juno throws down the multiple myeloma gauntlet to Bluebird

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Sharp-eyed CAR-T watchers will have immediately realised the significance of Juno's tie-up with Eureka Therapeutics and Memorial Sloan Kettering last week, for a CAR-T project targeting BCMA to treat multiple myeloma. The move directly challenges Bluebird Bio, whose own CAR-T hopes initially rest on the same approach.

Not only is Juno muscling in on Bluebird's territory it is doing so with what should be a better construct, using a fully human binding domain while Bluebird's is murine. The development could also threaten Bluebird's CAR-T partnership with Celgene, which ironically paid Juno $1bn in a major, 10-year alliance last year.

That deal related to CAR-T projects against the CD19 antigen, and saw Celgene scale back its earlier tie-up with Bluebird. Juno's Eureka/Memorial alliance could in time see Celgene back further away from Bluebird, since if it gives rise to a better anti-BCMA CAR it might tempt Celgene to try and gain rights to this asset instead.

**Fully human**

Under the new deal, announced after market close on Thursday, Juno gained rights to a BCMA CAR with a fully human binder that could enter the clinic early next year, along with two undisclosed multiple myeloma targets.

Memorial is a long-standing Juno partner, serving as the source of its lead anti-CD19 CAR, JCAR015, while an earlier deal with Eureka, a private biotech, gave Juno rights to a fully human binder for the anti-MUC16 CAR-T project JCAR020. The new BCMA project will use a 4-1BB co-stimulatory domain and, eventually, a defined-cell manufacturing system, Juno said.

BCMA is a member of the TNF receptor superfamily that is expressed by plasma cells and some mature B cells, and represents the biggest hope for treating multiple myeloma with CAR-T. Clinical data are limited to those reported from an NCI trial run by Dr James Kochenderfer, who is also the primary investigator in Bluebird's study of bb2121, which uses a slightly different construct.

The NCI trial has treated 12 multiple myeloma patients so far, yielding three partial responses and one stringent complete response, though the responding patient relapsed after 17 weeks. Understanding whether relapse was due to waning cell persistence or loss of the antigen could be crucial to the potential of BCMA.

Novartis has revealed little about its University of Pennsylvania-partnered anti-BCMA CAR, while Cellectis has on occasion said that one of its preclinical allogeneic projects targets this antigen. Separately, GlaxoSmithKline is developing a BCMA-targeting antibody-drug conjugate, GSK2857916.

| BCMA-targeting CAR-T projects against multiple myeloma | | | | | |
|---|---|---|---|---|---|
| **Project** | **Company/centre** | **Co-stim/transfection** | **Trial ID** | **Enrolment** | **Notes** |
| bb2121 | Bluebird Bio & Celgene | 4-1BB/lentiviral | NCT02658929 | 50 | Celgene option exercised 17 Feb 2015 |
| – | NCI | CD28/gamma-retroviral | NCT02215967 | 38 | Earlier suspended for a vector production issue |
| CART-BCMA | Novartis | 4-1BB/lentiviral | NCT02546167 | 30 | Novartis calls this a potential future prospect |
| – | Juno & Eureka | 4-1BB/? | Preclinical | – | Fully human binder |
| UCART-BCMA | Cellectis | ? | Preclinical | – | Allogeneic; TCRα knockout |
| *Source: EP Vantage, Clinicaltrials.gov.* | | | | | |

The latest Juno tie-up underlines the increasing importance of fully human CAR constructs; a growing body of evidence suggests that the use, common until recently, of murine binding regions has been responsible for rejection of the cells by the host, leading to lack of persistence.

True, the initial wave of CAR-T projects is still expected to feature murine binders, and Juno last week confirmed the delay to its lead, JCAR015, which it does not expect to be approved until 2018 (*Neurotoxicity only short-term toxic to Juno stock, July 13, 2016*). Its follow-up defined-cell product, JCAR017, also uses a murine binder.

However, a keenly watched study of Novartis's CTL019 has started testing CTL119, a humanised anti-CD19 CAR, while Kite last month took out a full licence to Dr Kochenderfer's own fully human CD19-targeting CAR-T construct, which is in phase I. Any companies announcing adoptive cell therapy deals that still involve murine constructs now risk looking rather foolish.

*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.*

*This story was amended to correct the ownership status of GSK2857916.*

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