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Novartis and Gilead’s multiple myeloma CARs diverge

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As Gilead bows out of BCMA, Novartis pins its hopes on a BCMA/CD19 combo.

Competition in the BCMA-targeting space has been hotting up for some time. But Gilead’s exit from the field earlier this week – apparently after the company realised that its anti-BCMA CAR-T project would not be best in class – still took some by surprise.

And Novartis appears to have admitted that it might also struggle to gain a foothold, shifting its focus to a combination of BCMA and CD19-targeting CARs. Pascal Touchon, head of the company's cell and gene therapy division, justified this decision by saying that results with projects targeting BCMA alone had fallen short of expectations.

Not transformative

“Preliminary clinical results with first-generation BCMA CAR-Ts are not as transformative in multiple myeloma as [CD19-targeting CAR-Ts] were in DLBCL, especially in terms of durability of response,” he told *Vantage*.

The most advanced anti-BMCA CAR-T candidate is Celgene/Bluebird Bio’s bb2121, which will soon see the involvement of Bristol-Myers Squibb through that company’s buyout of Celgene. But Glaxosmithkline reckons it could have the first BCMA-targeting project on the market in the form of its antibody-drug conjugate GSK2857916. The group today said it would file this year on the pivotal Dreamm-2 trial in fourth-line disease, which is due to report in the second half.

Glaxo said a smaller study called Dreamm-1, in heavily pretreated patients, would be published shortly; this will show median PFS of 12 months, an improvement on the 7.9 months reported previously. In comparison, bb2121 has shown median PFS of 11.8 months in patients who have failed seven prior therapies.

With competition so fierce, perhaps it is no wonder that Gilead and Novartis have had a rethink. In this week’s earnings report Gilead revealed that it had canned its BCMA-targeting asset KITE-585, derived from the company’s $11.9bn takeover of Kite Pharma, adding the remarkable fact that this had prompted an $820m write-off.

This was a shock to some investors, but had been foreshadowed by comments during a breakout session at last month’s JP Morgan conference, when executives said the group would only develop a best-in-class asset. The latest decision implies, therefore, that KITE-585 was not such an asset.

Though the non-cash charge is little more than an accounting curiosity, it shows the lengths to which credibility was being stretched to apportion the value of the Kite business being acquired: $820m approximates to the carrying value of KITE-585 – then a preclinical asset – on Gilead's balance sheet.

Mono or combo?

As for Novartis, Mr Touchon would not confirm whether the company's new combo approach meant that it had abandoned hopes for its BCMA-targeting CAR-T agent, MTV273, as monotherapy. The group does not appear to have started any trials looking solely at the project, but a monotherapy study sponsored by the University of Pennsylvania, from which Novartis licensed the project, is ongoing.

Mr Touchon noted that the trial of the BCMA/CD19 combination did include a BCMA-only arm. "We need to prove the difference, so that's part of the study," he said.

Of course, Novartis is not the only company taking the combo route in CAR-T therapy for multiple myeloma. Autolus's Auto2 is said to hit both BCMA and Taci through its use of the April ligand, while Johnson & Johnson/Nanjing Legend's JNJ-4528 targets two separate epitopes on the BCMA antigen.

Pairing BCMA with CD19 antagonism might seem strange, as the vast majority of plasma cells, the malignant type in multiple myeloma, do not express the latter antigen. But a 2015 *NEJM* paper reported a complete remission in a multiple myeloma subject given Kymriah, suggesting that very dim CD19 expression could nevertheless be enough.

This rationale likely lies behind Novartis's choice of combo. It should also be noted that the Swiss group is pairing MTV273 not with Kymriah but with a separate CD19-targeting Penn CAR-T asset, CTL119, which uses a humanised binding domain to reduce risk of graft rejection (*Novartis hopes Kymriah acceleration can save its CAR, January 30, 2019*).

Opting in?

It is unclear whether Novartis has formally licensed CTL119 or other Penn assets to which it has opt-in rights under a 2012 deal that saw it pick up Kymriah and MTV273.

"Penn in that collaboration is conducting first-in-human trials and, depending on clinical results, we may decide to pursue the development of such," said Mr Touchon when asked about the status of CTL119 and other Penn-originated projects, including CAR-T candidates against CD22, CD123 and EGFRv3.

Curiously, Novartis highlighted several of these assets when discussing its next-generation of CAR-T therapies during a press event in Basel last week.

The company seemed keen to distance itself from rumours that its interest in cell therapies was waning after a disappointing commercial performance from Kymriah so far.

Mr Touchon dismissed doubts about the group's commitment here, noting that the cell and gene unit now employed 1,000 people – although he would not say how many of these were in R&D.

He also revealed to *Vantage* that, as well as the Penn-originated candidates, Novartis was developing several of its own CAR-T projects at its Institute for Biomedical Research (NIBR). "In 2019 we will see the first of these new CAR-Ts reaching the clinic," Mr Touchon said, declining to say, for example, whether these targeted different antigens from the Penn-originated assets.

He stressed that Novartis was not disappointed with current Kymriah sales, saying: "We're building the foundations of a blockbuster. This is the beginning of a long journey."

But the latest twists in the road suggest that the most optimistic CAR-T watchers might still need to adjust their expectations.