Evaluate Vantage

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Asco 2022 – Carvykti casts a long shadow

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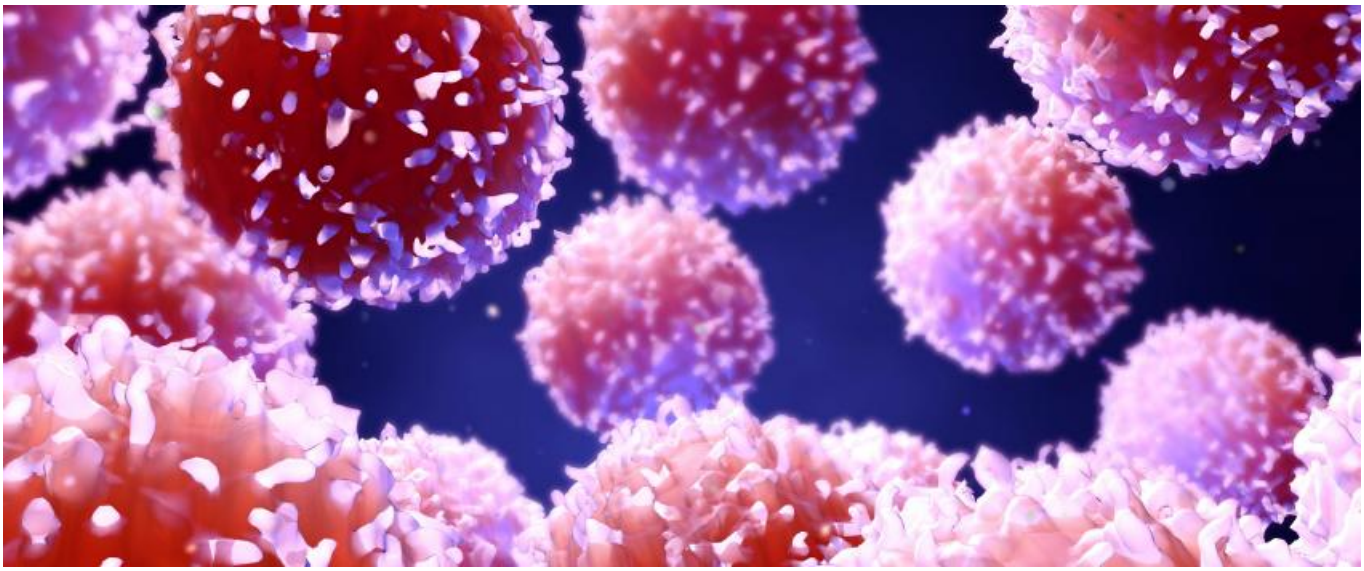


Arcellx, Gracell and Oricell work hard to prove that there is still space for new Car-T therapies in multiple myeloma.

For Arcellx investors, who backed the group's audacious $124m flotation in February, in the middle of a biotech slump, Asco was a key test. Judging by today's data for the group's lead Car-T project the enthusiasm was not entirely misplaced.

Arcellx was not the only company with Car-T data in multiple myeloma at Asco. Today also featured oral presentations on Gracell's fast-manufactured dual-acting project and on a novel follow-on approach from the venture capital-backed Chinese group Oricell. As impressive as many of these data are, however, Johnson & Johnson's Carvykti casts a long shadow.

Indeed, Carvykti's Cartitude-1 trial, on the basis of which this anti-BCMA Car-T therapy was approved in fifth-line multiple myeloma, seems insurmountable on efficacy: response rate was 98%, including a 78% rate of complete responses. On a cross-trial basis this beat the other two approved BCMA-directed products, Bristol Myers Squibb's Abecma and GSK's Blenrep.

And yesterday's Asco update of Cartitude-1 reported PFS and OS rates, at 28 months' follow-up, of 55% and 70% respectively. The big chink in the armour of all three approved therapies is toxicity; Carvykti carries a black box warning of cytokine release, neurotoxicity, macrophage-activation syndrome, Parkinsonism – of which one new case has been seen in Cartitude-1 – and Guillain-Barré syndrome.

Arcellx

Perhaps this is where Arcellx comes in. Dr Matthew Frigault, of Massachusetts General Hospital, reported just one case of grade 3 cytokine release, and two grade 3 neurotoxicities, among 31 multiple myeloma patients given CART-ddBCMA.

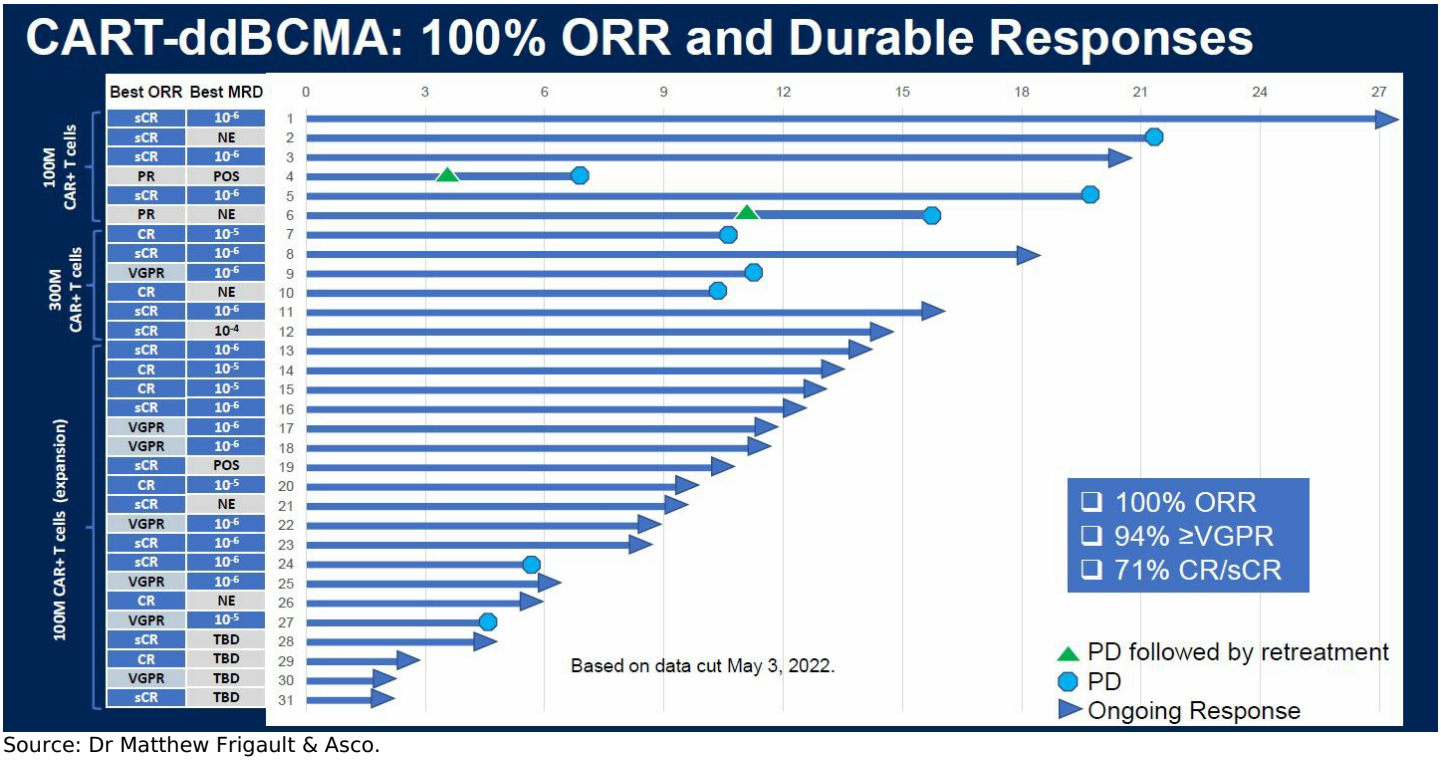
As for efficacy, all 31 patients went into remission, with a 71% complete response rate, though there were nine relapses by the May 3 data cutoff. CART-ddBCMA has "best-in-class potential", Rami Elghandour, Arcellx's chief executive, told *Evaluate Vantage*.

He highlighted CART-ddBCMA's activity in extramedullary disease, a negative prognostic factor, claiming: "We're largely achieving very similar result to [Carvykti], in a much harder to treat patient population, with arguably a very attractive safety profile."

In terms of design, what makes CART-ddBCMA different is its use of a synthetic binding region instead of an

antibody-derived one; this, says Mr Elghandour, results in more transduced cells being Car-positive than with Carvykti, so the cell dose can be lower. And he cites reduced tonic signalling, meaning that the Car-T cells remain relatively fresh.

Interestingly, CART-ddBCMA is being positioned as a product in its own right rather than as a test of this technology, and Arcellx has designed a pivotal study, to start by the year end, in a similar population to Cartitude-1. The BCMA market can support multiple players, Mr Elghandour insists.



Source: Dr Matthew Frigault & Asco.

If so this is good news for Gracell, which is touting a fast-manufactured multiple myeloma Car-T asset that targets CD19 as well as BCMA, in an attempt to counteract BCMA antigen-negative relapse.

This project, GC012F, has generated an 83% ORR among 28 patients, and all 27 patients evaluable for MRD status were negative; 87.5% of eight patients evaluable at 12 months remained MRD-negative. The longest ongoing responses are over 29 months out, Dr Juan Du, of Shanghai Chang Zheng Hospital, told Asco today.

Perhaps in this small population Gracell can make a case for this dual antigen targeting approach. CD19 might seem an unusual second antigen to hit in multiple myeloma, but a 2015 NEJM paper famously described a case report of a multiple myeloma patient who went into sustained complete remission after getting Kymriah, despite lacking CD19 on most malignant cells. It was hypothesised that the remission was brought about because Kymriah targeted rare, CD19-expressing myeloma precursor cells.

Novel antigen

It was Oricell that brought to Asco data on a novel antigen, specifically GPRC5D, which is hit by its Car-T project OriCAR017.

Its study enrols patients with GPRC5D expression on at least 20% of their multiple myeloma cells, 10 of whom appear at an April 30 data cut. All 10 are reported to have gone into remission (six complete responses) across three doses; five of the patients had relapsed on BCMA-targeted Car-T cell therapy.

Still, there is already competition building here, too. Johnson & Johnson's bispecific talquetamab is probably the most advanced GPRC5D-targeting agent, and posted impressive data at Ash 2020. In 50 evaluable subjects given over 20µg/kg the ORR was 66%, and in the 13 who had received 405µg/kg subcutaneously, which has been set as the phase II dose, ORR was 69%.

While Oricell remains a little-known private Chinese group, Arcellx is basking in its status as a newly minted listed biotech. "Good companies, even in difficult times, are able to go public and are able to fund raise," said Mr Elghandour. "I think I'd rather be public than private."

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