Evaluate Vantage

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Remarkably, interest in BCMA continues

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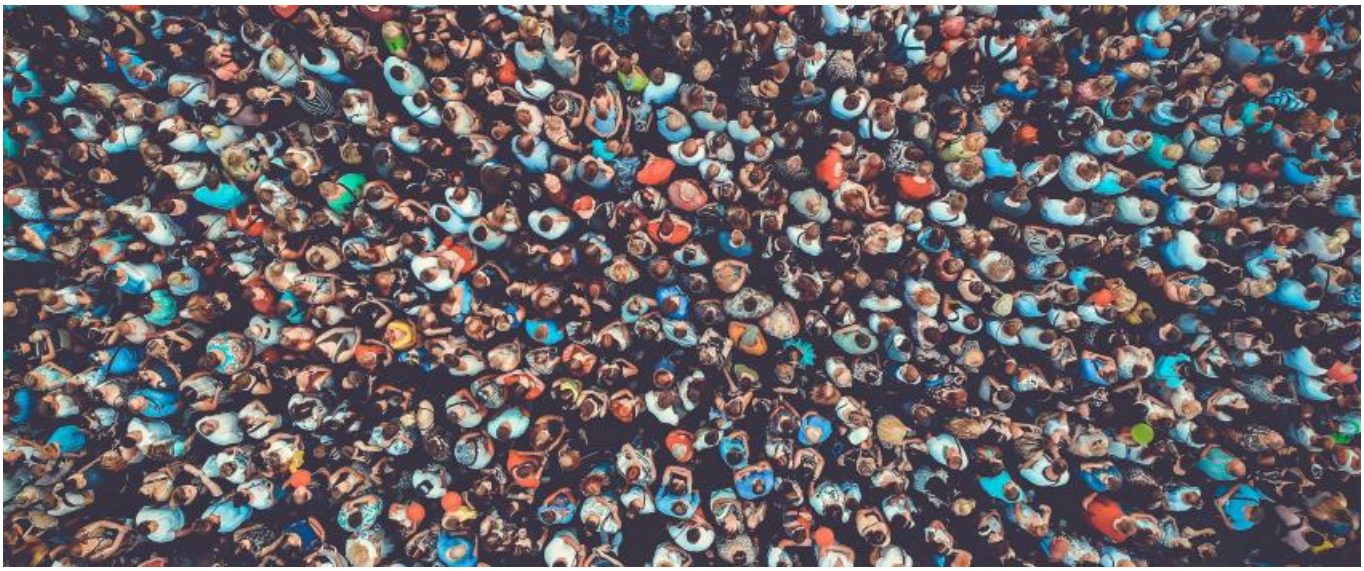

But, as Celyad bows out, how do you compete in a field as crowded as this?

Last week the recently listed Immix Biopharma licensed a BCMA-targeting Car-T project from Hadassah Medical, showing again that interest in this multiple myeloma antigen remains undimmed. But does Immix have any chance of matching its myriad clinical-stage competitors, and can anyone put up a fight against Johnson & Johnson's Carvykti?

The recent Ash conference provided a good reference point, with data on BCMA targeting including four antibody approaches and four cell therapies, in addition to the Arcellx project that secured a licensing deal with Gilead. On a cross-trial basis it looks like Immix has its work cut out, and Celyad bowing out of BCMA today might give pause.

That said, Celyad is in something of a crisis, so its decision to focus on finding partners for its patent estate, and discontinue the allogeneic, shRNA-based anti-BCMA cell therapy CYAD-211, might not be too surprising.

But it comes amid growing realisation that the field is full of some very efficacious assets. Only those with top-level profiles have a chance; Arcellx's CART-ddBCMA, with its 100% overall response rate, is one of these, a fact to which Gilead's $325m up-front payment attests.

High bar

The bar for cell therapy is the 98% ORR and 78% complete response rate put up by J&J/Legend's Carvykti, while for bispecific MAbs J&J's Tecvayli has corresponding numbers of 62% and 31%. Somewhere in between lies Bristol Myers Squibb's Car-T therapy Abecma, and all three carry boxed warnings about cytokine release syndrome (CRS) and neurotoxicity.

Last week the micro-cap biotech Immix gained rights to NXC-201, an academic anti-BCMA Car-T project formerly known as HB10101, on the strength of a paper in Haematologica citing a 75% ORR and 50% complete response rate. ORR was better in patients naive to GSK's now-withdrawn Blenrep (91%) than in those who had progressed on it (55%), and there was no severe CRS, and no neurotoxicity of any grade.

The big caveat is that this is a small academic trial in 20 patients, and excludes two subjects who were not given HB10101 (and one of whom was somehow in complete response). On a simple cross-trial basis, and with the caveat that each patient population is different, the data barely match Abecma.

Ash was notable for seeing further disappointments from allogeneic cell therapies, and the efficacy of Allogene's Car-T ALLO-715 and Fate's Car-NK FT576 caused those companies' share prices to fall. On the other

hand, Bristol unveiled BMS-986354, a Car asset based on the now discontinued orva-cel that looked highly competitive.

Gracell's GC012F also had data at Ash, but as these concerned a curious front-line maintenance setting they are not comparable. And in a small cohort Carvykti was shown to be capable of rescuing patients who had relapsed on prior BCMA-directed therapy.

Selected anti-BCMA Cars at Ash 2022				
Project	FT576	ALLO-715	Carvykti	CC-98633/BMS-986354
Company	Fate	Allogene	J&J/Legend	Bristol Myers Squibb
Mechanism	Car-NK	Allo Car-T	Car-T	Fh Car-T
Study	NCT05182073	Universal	Cartitude-2	NCT04394650
Detail	Dose escalation	Part A (dose level 3 expansion cohort)	Cohort C (post BCMA)	Based on orva-cel, with 5-day manufacturing
ORR	22% (2/9)	65% (15/23)	60% (12/20)	95% (58/61)
CR rate	0%	22%	10%	39%
Safety	No CRS, Icans or GvHD	3 deaths from infection	15% severe Icans, 3 deaths from infection, 1 death from haemorrhage	2% severe CRS & Icans
Note: Fh=hully human; Icans=immune effector cell-associated neurotoxicity. Source: Ash.				

The underperformance of allogeneic cell therapies, especially in terms of durability, is important given that these are not competing against autologous Car-T, arguing for improved convenience, but against antibody approaches, which by definition are off the shelf.

This is where Tecvayli and rival T-cell engaging bispecific antibodies come in. The latter group, featuring candidates from Pfizer, Regeneron and Bristol, were shown at Ash to be capable of generating efficacy broadly in line with the recently approved J&J drug.

Tecvayli also raised the bar in terms of its SC dosing, and while Pfizer and Bristol are likewise able to dose elranatamab and alnuctamab SC, Regeneron's linvoseltamab formulation is still IV. Notably Bristol dosed alnuctamab up to 30mg SC, after toxicity limited the IV formulation to 10mg.

However, lack of safety still looms large, and with steps taken to mitigate CRS it is instead the risk of infections that is gaining prominence. For instance, the ALLO-715 trial saw three die from infections, while linvoseltamab's reported 10 deaths among 252 subjects – six from bacterial infection and four from Covid – though none was deemed treatment related.

Against this background the Ash weekend saw an unlikely winner, with the micro-cap player Harpoon at one point enjoying a 100% intra-day rise on data with the highest doses of HPN217, its trispecific MAb. Harpoon – like Immix – is worth under $30m. From such a low base investors might think that there is little to lose.

Selected anti-BCMA antibodies at Ash 2022				
Project	Elranatamab	Linvoseltamab	Alnuctamab	HPN217
Company	Pfizer	Regeneron	Bristol Myers Squibb	Harpoon
Mechanism	TCE	TCE	2+1 TCE	Trispecific
Study	MagnetisMM-3	NCT03761108	NCT03486067	NCT04184050
Detail	Cohort A (SC, no prior BCMA)	At recommended dose	SC cohort (IV presented previously)	At highest dose levels
ORR	61% (75/123)	64% (37/58)	65% (17/26)	77% (10/13)
CR rate	28%	24%	19%	23%
Safety	2 treatment-related deaths	6% rate of deaths due to infection	1 cerebral haemorrhage death	No Icans, no severe CRS

Note: TCE=T-cell engager; Icans=immune effector cell-associated neurotoxicity. Source: Ash.