Evaluate Vantage

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Ash 2022 preview – a new multiple myeloma mechanism makes a splash

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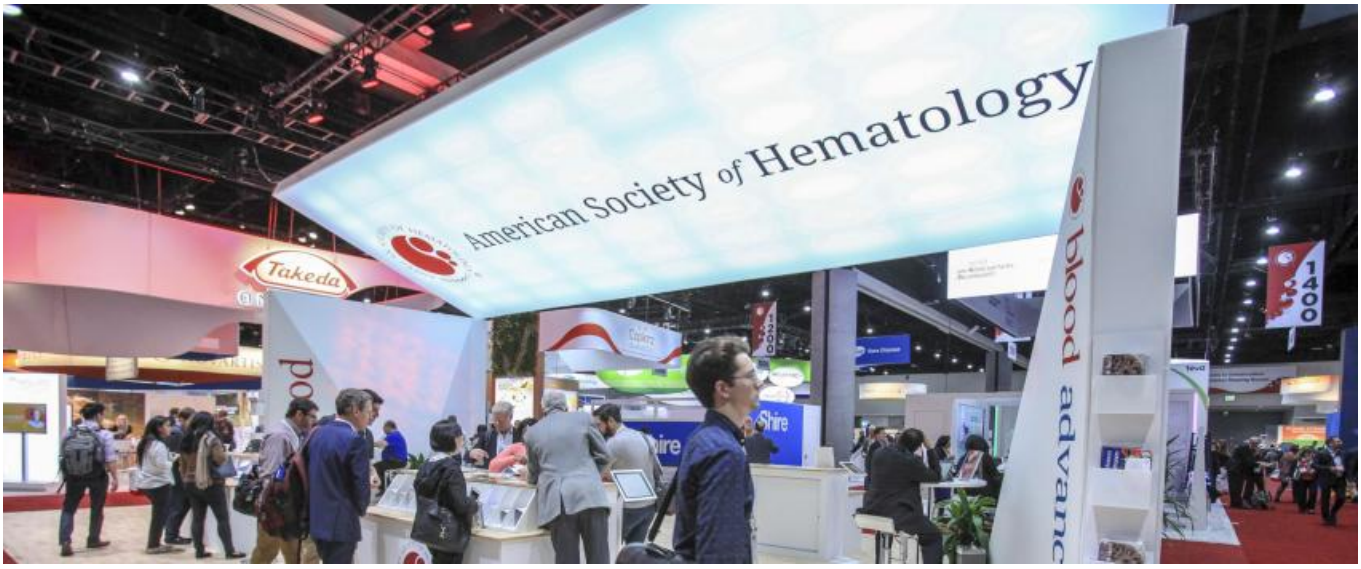

Talquetamab gets top billing in Ash's press programme, but the data raise important issues about the role of targeting GPRC5D.

The appearance of Johnson & Johnson's talquetamab in this year's Ash press programme will highlight GPRC5D blockade as an important new mechanism in treating multiple myeloma.

Hitting GPRC5D made its first splash as part of a preclinical Juno/Celgene Car-T therapy back at Ash 2018, and though it took a long time for this asset to enter the clinic it too appears at this year's Ash. The meeting, most of whose abstracts went live yesterday, also features the usual crowd of BCMA therapies, but the large talquetamab dataset will no doubt raise numerous questions when presented in full.

The headline number is that 73% of the 143 patients given talquetamab at its phase 2 dose in the MonumenTAL-1 trial went into remission, according to the May data cutoff cited in the Ash abstract.

However, close analysis of the swimmers plot reveals that 53 of the 104 responders relapsed, most well within 12 months. Only six remissions appear to be ongoing at over a year.

Relapses

When talquetamab data were presented at Ash two years ago targeting GPRC5D was highlighted as a way of rescuing patients who had relapsed on anti-BCMA therapy. However, while the phase 1 stage of MonumenTAL-1 included these patients, the pooled data being presented at Ash comprise only patients with no prior exposure to "T-cell redirecting therapies".

A separate trial, MonumenTAL-5, does include – and stratify for – patients who have, as well as those who have not, received BCMA therapies. But the MonumenTAL-1 Ash dataset's relatively early setting means that it needs to be held up against BCMA therapies, including Blenrep, Carvykti, Abecma and, as of last month J&J's own Tecvayli – a tough comparison.

Other GPRC5D-directed therapies at Ash include Bristol Myers Squibb's Car-T BMS-986393, which is likely related to the MCARH109 project unveiled at Ash 2018, at which point it was linked to the Bristol legacy company Celgene. And Fate's FT555, which has a preclinical Ash poster, has been revealed as an anti-GPRC5D Car-NK therapy.

Ash 2022: selected multiple myeloma presentations					
Project	**Mechanism**	**Company**	**Abstract**	**Cutoff**	**Data**
ALLO-715	Allo BCMA Car-T	Allogene	2019	22 Jun	Focus on dose level: ORR 15/21
CART-ddBCMA	BCMA Car-T (synthetic ScFv)	Arcellx	3313	3 May	Same data as Asco 2022
GC012F	BCMA/CD19 dual Car-T (2-day manufacturing)	Gracell	366	25 Jul	1st-line: 100% ORR, 9/13 CR
FT576	BCMA Car-NK	Fate	2004	18 Jul	No efficacy data
Elranatamab	BCMA T-cell engager	Pfizer	159	?	Potentially pivotal MagnetisMM-3 trial: 61% ORR
Linvoseltamab (REGN5458)	BCMA T-cell engager	Regeneron	4555	28 Jan	75% ORR at high doses
HPN217	BCMA trispecific	Harpoon/Abbvie	3240	27 Jun	Efficacy & durability to be presented at Ash
Talquetamab	GPRC5D T-cell engager	J&J	157	16 May	73% ORR @0.4 mg/kg QW; 51% relapse rate; no post-BCMA patients
RG6234 (RO7425781)	GPRC5D T-cell engager	Roche	161	8 Jun	IV: 71% ORR; SC: 60% ORR
BMS-986393 (CC-95266)	GPRC5D Car-T	Bristol Myers Squibb	364	24 May	86% ORR, 44% patients post-BCMA
Source: Ash.					

All Ash abstracts except the late-breakers are now live, though the early data cutoffs in most mean that investors must wait until the meeting itself to see up-to-date results.

Thus a presentation of Fate's anti-BCMA Car-NK project FT576 for now reveals no efficacy findings, and neither do abstracts on Fate's FT596 (anti-CD19 Car-NK) and FT538 (CD38-knockout Car-NK cells for multiple myeloma).

Those looking at the burgeoning BCMA space will take interest in data on Pfizer's elranatamab and Regeneron's linvoseltamab – like Tecvayli these are bispecific T-cell engagers.

And investors appear to have already picked an early winner: Gracell closed up 11% after its fast-manufactured, dual anti-BCMA/CD19 Car GC012F was claimed to have yielded a 100% remission rate, though the swimmers plot contains ambiguity about the patients' pre-infusion status. Arcellx rose 4%, though its abstract on CART-ddBCMA, with a May cutoff, offers no advance on data presented at Asco.

On the debit side, Allogene fell 6%. The company has an unusually low-key presence at Ash, the highlight of which is an abstract claiming a 71% ORR in patients given a high dose of its allogeneic anti-BCMA Car ALLO-715. Perhaps to make up for missing the Ash submission deadline, Allogene is instead directing investors to an "R&D showcase" event on November 29.

The Ash conference is due to take on December 10-13 in New Orleans, Louisiana.

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