Evaluate Vantage

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Fate delivers, up to a point

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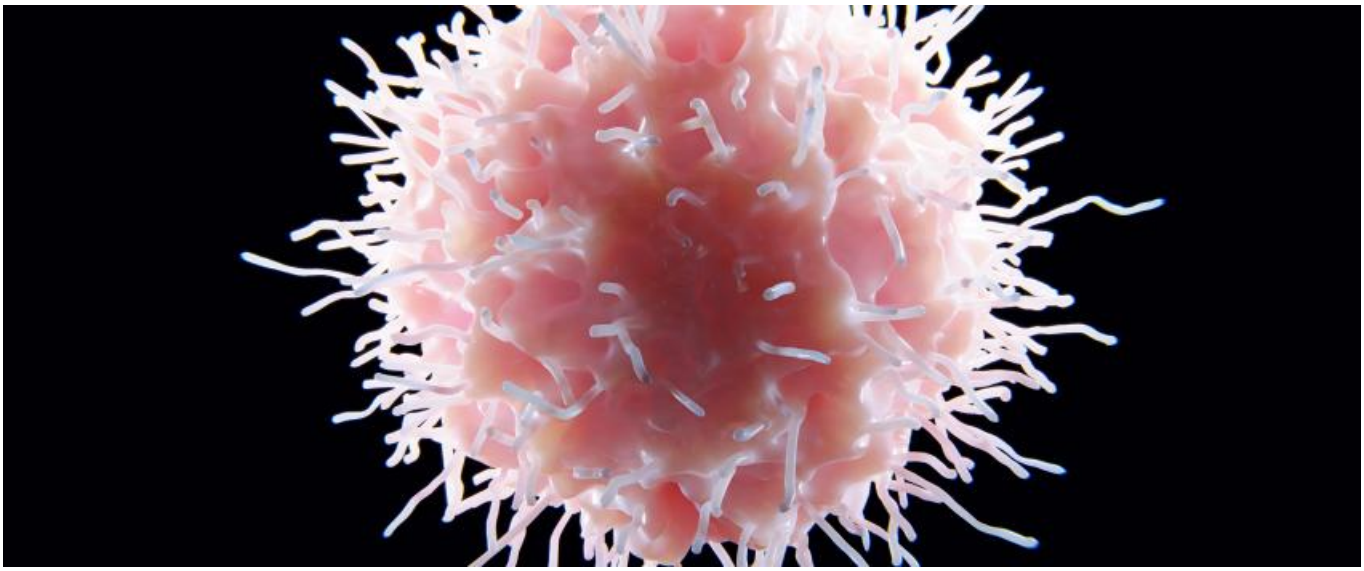

The first human data from the Car-NK project FT596 are impressive – but not impressive enough for a company worth $9bn.

It's not that the first human data Fate revealed at long last yesterday for its lead Car-NK asset, FT596, were bad – far from it. But the company fell 18% this morning, showing just how overblown market expectations had been.

The problem is that exuberant investors had driven up the group's valuation to a remarkable $9bn with no clinical validation, and in the absence of knockout data the only way Fate could trade was down. But FT596 does appear to have efficacy on a par with Car-T therapy, and a remarkably clean safety profile, albeit with important doubts over durability.

FT596 comprises allogeneic NK cells modified to express an anti-CD19 Car construct plus high-affinity CD16 and the cytokine complex IL15RF. Its first-in-human lymphoma study tests two cohorts, monotherapy and a Rituxan combo, and first results from both were presented to analysts yesterday evening – 17 months after the trial started.

FT596 at two highest single doses (90m and 300m cells)				
	ORR*		CR*	
	Monotherapy	Rituxan combo	Monotherapy	Rituxan combo
Car-T naive patients	6/6	2/4	3	2
Car-T relapsed/refractory	0/1	2/3	0	2
Total	10/14 (71%)		7/14 (50%)	
*Note: *29-day remission rates. Source: Fate.*				

The headline numbers looked good. Efficacy was effectively non-existent at the lowest dose, but materialised at higher doses of 90 and 300 million cells, enabling Fate to argue that it was seeing a dose-response relationship.

And, zeroing on these two highest doses, overall remission rate was 86% in seven monotherapy subjects, and

71% in the Rituxan combo. Analysts' baseline expectations had been for Car-T-like efficacy, meaning ORRs of 50-73% for autologous or 75% for allogeneic therapy.

Moreover, safety was impressive. There was no cytokine release syndrome or neurotoxicity of any grade with monotherapy, and infections were said to be unrelated to FT596. In the combo cohort there was a 20% rate of CRS, all below grade 3.

So far so good. However, only 60% of subjects had what was termed "aggressive" lymphoma. Four subjects had failed Car-T therapy, but the only two to respond were in the Rituxan combo cohort.

But perhaps worst of all for bulls was that remission data concerned only day 29, with no indication of long-term durability. And many took a separate update from Fate's non-Car-modified NK cell project FT516 as a bad omen: here three of eight initially responding lymphoma subjects had relapsed by six months.

Still, relapses are a known problem with allogeneic Car-T therapy, as Allogene most recently showed. And, like allogeneic Car-T, Car-NK cells can easily be given repeatedly, something that with higher dosing now becomes a big hope for Fate; the group says the FDA has allowed a second FT596 dose to be given in the lymphoma trial without further agency consent.

Next stop Ash

The company played up FT596 as a Car-T-like modality with potential for outpatient treatment, whose safety profile differentiates it from T cell-mediated therapies like Car-T and bispecifics. However, durability will remain a major question until Fate presents longer-term data, likely at Ash in December.

Mizuho analysts said the initial Fate investor reaction was a mismatch to the data presented, and said there was a significant opportunity for FT596 even if it was limited to Car-T refractory or ineligible patients rather than as a full-on Car-T replacement.

And Salim Sayed, who covers Fate's rival Nkarta, said the FT596 data represented clinical validation of the Car-NK approach, including potentially of Nkarta's NKX019. While until yesterday Fate was valued at some $9bn, Nkarta's market cap is just over $1bn.

Clearly Fate's investors had priced in a home run. FT596 works, this much is clear, but it is still well short of a home run.