Evaluate Vantage

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AACR – Solid tumour CAR-T foray lives up to its low-key billing

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For some time now solid tumours has been seen as the next big battleground for CAR-T therapy, but based on the underwhelming early data released yesterday at the AACR meeting the best that can be said is that the jury is still out.

A very early trial of Novartis and the University of Pennsylvania's CART-meso failed to generate any responses and, more worryingly, reported poor persistence of the CAR-T cells. Not that this has curbed sellside enthusiasm – some analysts see encouraging signs of early potential here – but the data justify the Swiss firm's low-key stance on this project.

The phase I trial in question aims to recruit 24 patients, though yesterday's late-breaking presentation detailed the first six enrolled. These had either epithelial mesothelioma, ovarian cancer or pancreatic cancer, and had been heavily pretreated, said Dr Janos Tanyi, an assistant professor at Penn.

Four stable diseases

The primary outcome concerns the number of adverse events, but it was hints of efficacy that some analysts had hoped to see. In the event, while four patients reported stable disease after 28 days, there were no remissions.

The potential had been spelled out by Mizuho analysts, who wrote last week that CART-meso (earlier called MesoCART) was among the first to be used in solid tumours, and should provide early indications of CAR-T therapy in this much bigger market. US solid cancer incidence outnumbers by 10 to one that of haematological malignancies, where CAR-T competition is intense.

CART-meso is an autologous project in which patient's T cells are engineered to express a CAR directed against mesothelin, a protein present on normal mesothelial cells and overexpressed in mesothelioma and ovarian and pancreatic adenocarcinoma.

It might be that mesothelin is simply a poor target. But a bigger problem is that the scientists said peak blood levels of CART-meso were only half that seen with CTL019, the lead leukaemia project. Moreover, the CAR-T cells seemed to wane after 28 days – a major barrier to efficacy, which in T-cell therapy relies on long-term cell persistence.

In light of the poor efficacy and persistence it might come as little surprise that CART-meso tolerability was good. Cytokine release syndrome and neurotoxicity are closely watched side effects of CAR-T therapy, but tend to be associated with efficacy; the Penn researchers reported no acute adverse events and no off-tumour toxicities despite cell trafficking to off-tumour, on-target sites.

Intractable

CART-meso is one of several approaches targeting mesothelioma, a relatively intractable cancer in which patients after first-line chemo have no approved therapies (*Therapy focus – Potential for progress in mesothelioma is on the horizon, April 8, 2015*).

Specifically in mesothelioma there was better news at the AACR with presentation of data from the 320-patient phase I Keynote-028 trial of Merck & Co's anti-PD1 antibody Keytruda. A subset of 25 second-line mesothelioma patients was featured in an AACR late-breaker, showing seven partial responses and 12 stable diseases, with one case of liver enzyme elevation and one thrombocytopenia.

Merck highlighted the resulting 76% disease-control rate, and the key fact that all of the remitting patients were still responding at the time of the data cutoff. Interestingly it had recruited only PD-L1-positive patients into this portion of the trial, finding 45% of those evaluable to have this biomarker, according to its criteria.

Meanwhile, Novartis and Penn's underwhelming CART-meso results did not stop Mizuho and Leerink analysts from touting them as being supportive of solid tumour potential. The NCI is separately studying a mesothelin-

directed CAR-T, as is Memorial Sloan Kettering, a hospital associated with Juno Therapeutics, though the latter does not feature in Juno's pipeline.

Novartis is separately working on a CAR-T against EGFRvIII, though it has not made any more noise about this than about CART-meso, while other solid tumour targets include L1CAM and ROR1 at Juno, 5T4 at Cellectis and PCSA at Bellicum.

CAR-T stocks traded down this morning, Juno falling 7% and Kite off 5%. It might not exactly be a case of going back to the drawing board in solid tumours, but it will take better data to warrant some analysts' excitement.

Project	Study	Detail	Trial ID
CART-meso	–	24 pts with mesothelin-expressing cancers	NCT02159716
Keytruda	Keynote-028	Subset of 25 second-line mesothelioma pts	NCT02054806