Evaluate Vantage

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Asco 2021 – Adaptimmune’s T-cell receptors see a route to market

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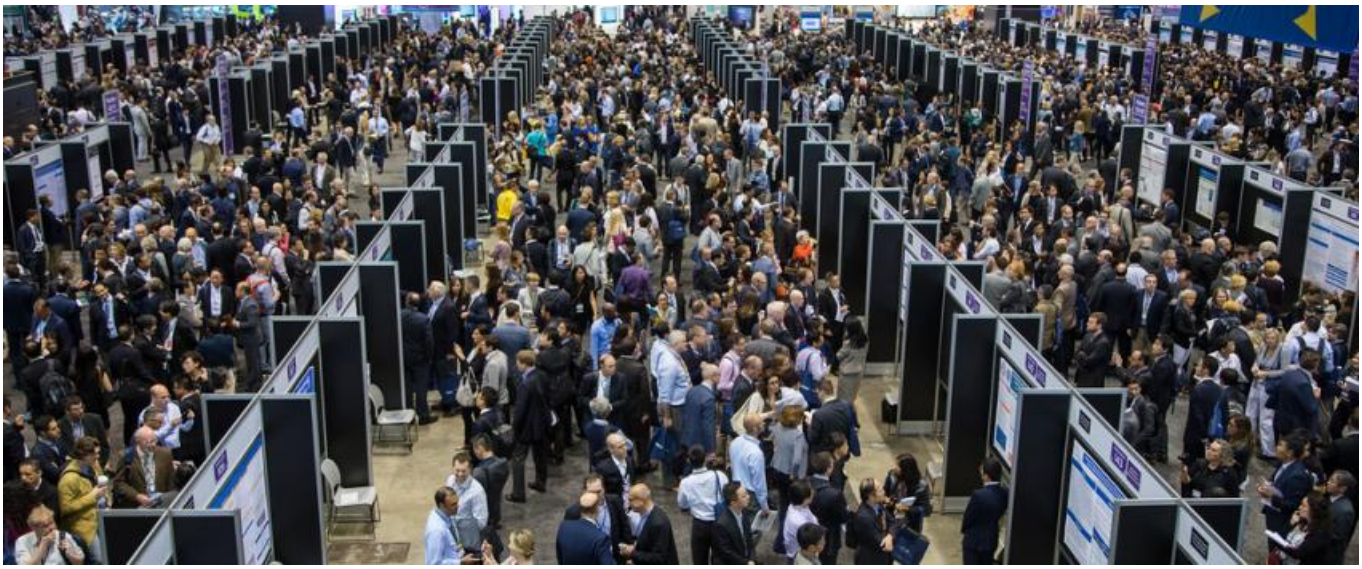


The registrational Spearhead-1 trial of afami-cel backs up the efficacy seen in phase 1, without some of the related toxicities.

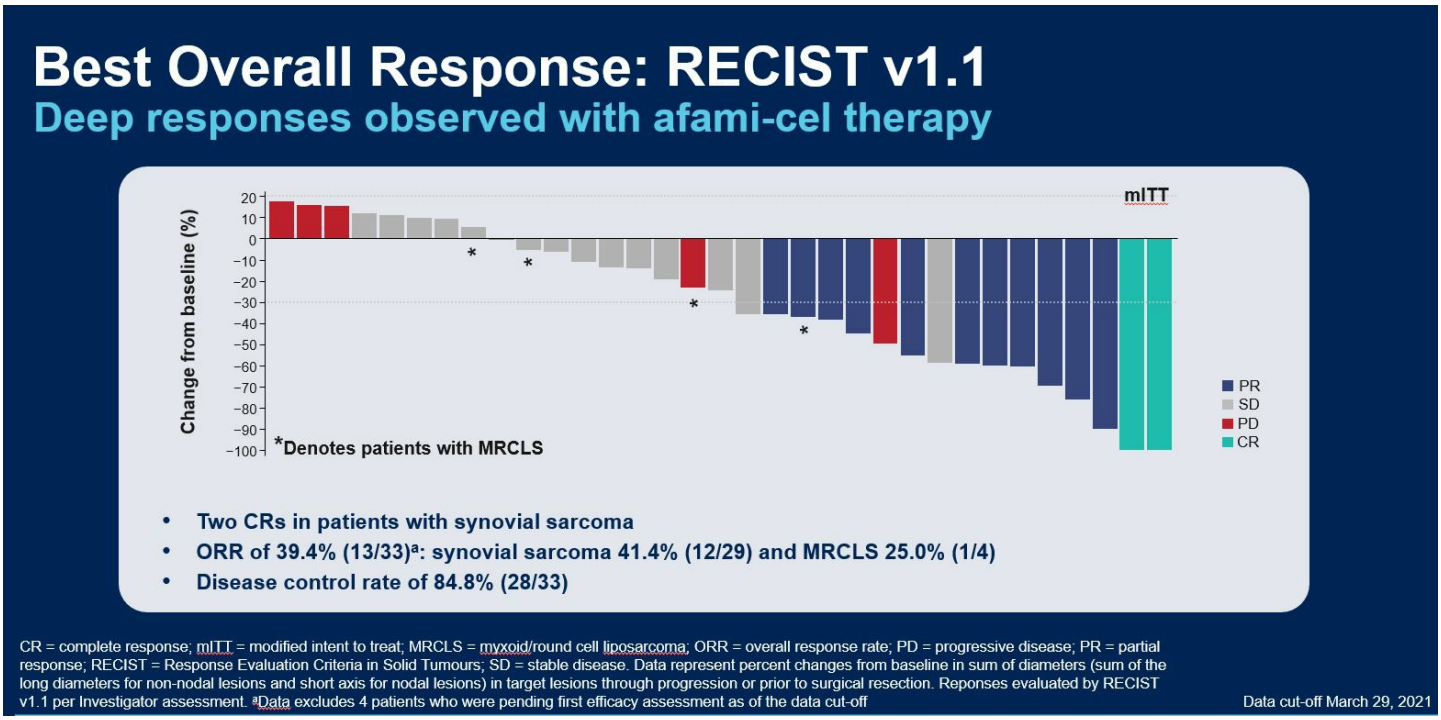
Results of Adaptimmune’s Spearhead-1 study, to be presented at Asco, offer the first glimpse of a dataset the group will take to the US regulator next year. They position afamitresgene autoleucel, a Mage-A4-targeting project, to become the world’s first approved engineered T-cell receptor therapy.

This would be quite the turnaround for an approach that has seriously lagged behind Car-T therapies, and an asset that had been mired in toxicity concerns. Indeed, just as important as the 41% remission just revealed in Spearhead-1 is the absence of treatment-related deaths.

It was in 2019 that toxicity had cast doubts over afami-cel, then known as ADP-A2M4, whose phase 1 study saw a treatment-related death due to pancytopenia/aplastic anaemia (*More deaths raise further questions about Adaptimmune, August 2, 2019*).

No similar concerns have arisen so far in Spearhead-1, a trial in Mage-A4-positive synovial sarcoma and myxoid/round cell liposarcoma. There was a 92% rate of severe treatment-related adverse events, including 16% and 3% respective rates of serious prolonged cytopenia and ALT increases, but none of three deaths was deemed related to T-cell therapy.

Clearly, just like all cell therapies, afami-cel carries significant toxicities, but these now appear more controllable. Speaking to *Evaluate Vantage*, Adrian Rawcliffe, Adaptimmune’s chief executive, put this down partly to the use of a reduced flu/cy lymphodepletion regimen.



Source: Dr Sandra D'Angelo & Asco.

The Asco dataset, to be presented on Friday, June 4, will detail 37 patients who received autologous afami-cel as of March 29, out of 59 enrolled so far. 33 are efficacy evaluable, and among these there have been 13 remissions, including 10 partial and two complete in synovial sarcoma. Phase 1 had shown a 44% ORR in synovial sarcoma.

There will be a further update at November's CTOS meeting from all 45 patients in Spearhead-1's registrational cohort with at least four months' follow-up. A US BLA will then be filed in 2022 for treating synovial sarcoma, a cancer in which some 67% of patients are thought to express Mage-A4.

A next-generation form of afami-cel, ADP-A2M4CD8, additionally causes cell surface presentation of CD8; data from its Surpass study, in Mage-A4-positive lung, oesophageal, head and neck and bladder cancers, are due at Esmo.

The HLA problem

A complication of all engineered TCR therapies is the need to match them to patients' HLA haplotype, a concept somewhat analogous to matching blood groups in blood transfusions. Thus it should be noted that afami-cel is designed to work only in patients with the HLA-A2 type, present in 40% of Caucasians.

Plans are afoot to hit some of the remaining 60% though: the same Mage-A4-targeting TCR is in research in HLA-A24 and HLA-A1 iterations, says Mr Rawcliffe. However, he stresses that targeting additional HLA types is not just a case of making a small tweak to an existing therapy: "It's a new product. But you have removed some element of [antigen] target risk."

Expanding the available population will be particularly necessary for TCRs against liver cancer, for instance, where 80-85% of the burden is outside the US and EU, and in countries where HLA-A2 is not necessarily the most prevalent HLA type.

In a sense these are nice problems to have, given that they become live issues only once compelling clinical data, and a potentially approvable product, are in place. But some will question whether there are just too many complexities in an engineered TCR to fit into broad medical practice.

Mr Rawcliffe is adamant that it comes down to how strong the clinical data are: "I don't think medical practice changes until a physician has a really strong reason to change it. Will doctors want to HLA test or test for Mage-A4? If the value proposition is compelling then absolutely they will."

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