Evaluate Vantage

April 15, 2016

AACR – Mage-A3 double-whammy hits Kite

Jacob Plieth

Given its relevance to Kite Pharma, the NCI's data on an engineered T-cell receptor against Mage-A3 was a keenly awaited AACR presentation, but when it went live on Sunday researchers could boast of no new responses versus what had been presented last November.

And even this disappointment was overshadowed by a troubling development at the NCI: new patient recruitment into the institute's cell therapy trials, including the Mage-A3 study, has been voluntarily halted after an ongoing internal review of manufacturing facilities.

Though this halt occurred on April 12 it was not until yesterday – a Saturday – that Kite made its announcement. The company's statement was made with minimal consultation with the NCI, *EP Vantage* understands.

Kite said studies of projects on which it had exercised a full licence, such as KTE-C19, would not be affected. But trials of assets on which it has an NCI co-operative R&D agreement – but not a full licence – are being paused, except for a fully human CD19 CAR-T project.

Kite says it still intends to file a US IND for the Mage-A3 project by the end of the year, which is why the NCI's own data with it are important.

These detailed the first 14 of 16 patients with Mage-A3-expressing metastatic cancers to be enrolled, and at the AACR showed partial responses in three patients; these had cervical, oesophageal or urothelial cancers. However, this was no different from data presented at last year's SITC meeting, at which there had been a hint that a fourth patient might respond.

Like with CAR-T therapy toxicities are important: most patients experienced high fever and high levels of cytokine release. But the NCI's Dr Yong-Chen William Lu insisted that these were manageable, and said the treatment was "much safer than a CD19 CAR-T".

He also highlighted the attractiveness of Mage-A3; while the function of this antigen is unclear, he claimed that it was not expressed in normal tissues, which could minimise the risk of side effects.

Defining cells

Scientifically the anti-Mage-A3 asset is intriguing because, as stressed at AACR, it involves the isolation of CD4+, or helper, T cells for transfection and reinfusion into the patients. The clinical study is the first, the NCI says, of an immunotherapy using gene-engineered CD4+ T cells against metastatic cancer.

Specific selection of the T-cell population is a growing theme in adoptive cell transfer, and while there are several schools of thought the data to back them up are extremely early. For example, Juno has been discussing a "defined-composition" CAR-T project that, according to the latest thinking, will comprise a 50/50 mixture of CD4+ and CD8+ (cytotoxic) T cells.

As far as engineered T-cell receptor (TCR) projects go, Juno's WT-1-targeted JTCR016 uses only CD8+ cells, while Catapult Therapy TCR's related project is a mixture of cytotoxic and helper T cells (*Interview – UK cell therapy minnow squares up to Juno, April 14, 2016*).

The logic of isolating a specific population or subpopulation of cells is to enhance their expansion and persistence, but its therapeutic value is basically unknown. Dr Lu suggested that CD4+ T cells could sometimes "sit in the driver's seat" and perform killing rather than merely having a helper function.

The rationale for isolating a cell population was that a response from a mixture of CD4+ and CD8+ cells would be harder to define to the FDA, he suggested.

Haplotype complexity

Unlike CAR-T constructs, which target cell-surface proteins, TCRs require an intracellular antigen to be presented on a cell's major histocompatibility complex (MHC). In humans many different haplotypes of this

complex exist, and each TCR product has to be matched.

With the Mage-A3 project the NCI transfected patients with an MHC class II-restricted TCR matched with the HLA-DP0401 haplotype, which is present in 60% of the Caucasian population. All other TCR projects have so far used MHC class I-restricted TCRs, and have focused on the HLA-A2 type – the most common for this class.

Another reason for defining the cell composition is that a previous study targeting Mage-A3 with isolated CD8+ T cells, transfected with an MHC class I-restricted TCR, had failed, Dr Lu told *EP Vantage*.

Thus the growing complexity is clear, and will have an important cost consequence – even before considering the expense of extra manufacturing steps. For instance, the NCI has to perform an additional Clinimacs cell-sorting procedure to isolate the CD4+ T cells.

Dr Alexey Bersenev, director of a cell therapy laboratory at Yale University, told *EP Vantage*: “Depending on type of cell isolation, the estimated Clinimacs cost is $4,000-7,000 for each procedure.”

Meanwhile, uncertainty about the NCI's manufacturing continues. Dr Lu said not just cell therapy but other NCI facilities were undergoing manufacturing process improvement. "We cannot enrol new patients. We hope the situation will resolve very soon."

As with CAR-T constructs, there is still a long way to go before engineered TCRs can be seen as a viable commercial proposition.

Study detail	Trial ID	AACR abstract
16 HLA-DP0401+ve pts with various cancers	NCT02111850	CT003