NEWS IN BRIEF

IDO takes a blow

Incyte's epacadostat and Merck & Co's pembrolizumab failed in a phase III combination study in unresectable and metastatic melanoma, the companies reported in April, dealing a major blow to hopes for the would-be first-in-class IDO inhibitor.

Whereas most of the immuno-oncology research to date has been on immune checkpoint proteins including CTLA4 and PD1, many patients still do not respond to treatment. In an attempt to improve response rates of checkpoint inhibitors, Incyte is leading a charge against the potentially complementary immuno-metabolism target IDO, which is produced by cancer cells and suppresses T cell activity in the tumour microenvironment (*Nat. Rev. Drug Discov.* **14**, 603–622; 2015).

Incyte and Merck have now halted the first phase III test of a combination of a checkpoint inhibitor plus an IDO inhibitor, after an interim analysis of the ECHO-301/KEYNOTE-252 study in metastatic melanoma showed that the drugs would not improve progression-free survival compared with pembrolizumab monotherapy.

Analysts had forecast blockbuster peak sales for Incyte's drug, and the company had hoped to submit for FDA approval later this year. All eyes are now instead on next clinical readouts from Incyte, Merck and others who have invested heavily in IDO drug development. Incyte and Merck have ongoing phase III trials in non-small-cell lung cancer, renal cell cancer, bladder cancer and head and neck cancer. Bristol-Myers Squibb is combining its IDO inhibitor BMS-986205 with nivolumab in a pivotal trial in melanoma, with another pivotal trial set to start soon in non-small-cell lung cancer. Executives will have their fingers crossed that these trials fare better, be it because of the unique immunogenic signatures of the different cancer types, the differentiated binding characteristics of the IDO inhibitors or for other reasons.

Last year, NewLink's IDO indoximod in combination with taxane chemotherapy disappointed in a phase II study in metastatic breast cancer, prompting Genentech to pull out of a partnership to collaborate on the development of the follow-on IDO inhibitor navoximod.

Asher Mullard

Novartis grows its gene therapy ambitions

Novartis is buying gene therapy company AveXis for US$8.7 billion, expanding its gene therapy capabilities.

AveXis's lead candidate is AVXS-101, a recombinant AAV9-based gene therapy for the treatment of spinal muscular atrophy (SMA). SMA is a neuromuscular disease that is caused by genetic defects in the *SMN1* gene, which leads to loss of motor neurons. AVXS-101 introduces a fully functioning *SMN1* into the nucleus of patient cells to supplement cellular production of the protein.

In a phase I trial of the gene therapy, all 15 patients with SMA type 1 who received a single dose of AVXS-101 were alive and event-free at 20 months, the company reported last year in *The New England Journal of Medicine*. This is up from an 8% historical survival rate.

Novartis expects to file for FDA approval of the breakthrough-designated therapy in the United States in the second half of 2018. If approved, it will compete with Biogen and Ionis Pharmaceuticals' nusinersen, an antisense drug that modulates the splicing of SMN2 to boost production of the compensatory protein. The FDA approved nusinersen in 2016. Whereas nusinersen has to be dosed every 4 months, AVXS-101 is being developed as a single-dose drug. Novartis's small-molecule RNA-splicing enhancer LMI070 is also in phase III development for SMA.

Novartis CEO Vas Narasimhan noted that the deal would bolster Novartis's neuroscience and gene therapy capabilities. AveXis is also developing gene therapies for Rett syndrome and amyotrophic lateral sclerosis. Earlier this year, Novartis also licensed the rights to develop and commercialize Spark Therapeutics' gene therapy voretigene neparvovec outside the United States. The FDA approved Spark's voretigene neparvovec last year for an inherited form of blindness, making it the first FDA-approved gene therapy.

GlaxoSmithKline is moving in the opposite direction, and sold a portfolio of approved and investigational rare disease gene therapies to Orchard Therapeutics in April. This portfolio included Strimvelis, a gene therapy for children with adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID), which in 2016 became the second European Medicines Agency-approved gene therapy.

Asher Mullard

Cashing in with off-the-shelf CAR Ts

Allogene Therapeutics is taking over rights to Pfizer's off-the-shelf chimeric antigen receptor (CAR) T cell pipeline, backed by US$300 million from one of the largest series A funding rounds in the history of biotech.

Last year the FDA approved the first ever CAR Ts, a new type of cellular therapy in which T cells are genetically modified ex vivo to express cancer cell-seeking receptors, and then infused into patients. Despite compelling efficacy for these products in a few blood cancers, the approved and most of the investigational CAR Ts are autologous products that have to be manufactured from a cancer patient's cells, presenting considerable manufacturing challenges (*Nat. Rev. Drug Discov.* **16**, 301–304; 2017).

Allogene — via its portfolio of Pfizer products, which the large pharmaceutical company in turn licensed from Cellectis and Servier — hopes to broaden the reach of this emerging modality by advancing off-the-shelf CAR Ts. Rather than collecting T cells from each cancer patient, their lead product, UCART19, is made by collecting T cells from healthy donors and then engineering these cells with transcription activator-like effector nucleases (TALENs) to inactivate native T cell receptors and thereby prevent activity against healthy tissue.

UCART19, a CD19-targeted CAR T, is in phase I development for acute lymphoblastic leukaemia (ALL) and is set to enter phase II next year. If approved, it would compete with Novartis's tisagenlecleucel and Gilead Sciences' axicabtagene ciloleucel — approved but autologous CD19-targeted CAR Ts.

Allogene has also acquired a portfolio of 16 preclinical off-the-shelf CAR Ts.

Allogene's management team includes former executives of CAR T pioneer Kite Pharma. Gilead acquired Kite last year for $11.9 billion for rights to axicabtagene ciloleucel and other experimental CAR T candidates.

Asher Mullard