NEWS IN BRIEF

CAR–T cell companies cash in

With promising chimeric antigen receptor T-cell (CAR–T cell) therapies from Novartis, Juno Therapeutics and Kite Pharma barrelling through the clinic, pharmaceutical companies are eyeing up access to alternative anticancer T-cell-reprogramming technologies. Merck Serono was the latest to back a contender, partnering with Intrexon in March. It follows Amgen, who partnered with Kite Pharma in January. Last year, Pfizer partnered with Cellectis, and GlaxoSmithKline (GSK) partnered with AdaptImmune (*Nature Rev. Drug Discov.* **13**, 568–569; 2014). Intrexon, Cellectis and AdaptImmune have not yet advanced a CAR–T cell therapy into the clinic.

Under the terms of the Merck Serono–Intrexon tie up, Merck Serono gets to nominate two anticancer targets and Intrexon will then develop CAR–T cell treatments for investigational new drug (IND) application filings. Merck Serono will pay US$115 million upfront and up to $826 million in milestones for these products. Intrexon can explore other targets independently, but will grant Merck Serono opt-in rights during clinical development.

In the Amgen–Kite deal, Amgen contributed targets and agreed to pay $60 million upfront to fund the research and development of CAR–T cell therapies through to IND application. Each company will then be responsible for the clinical development of their respective CAR–T cell programmes, and each will be eligible for up to $525 million in milestone payments from the partner. Kite has two CAR–T cell therapies — targeting variant III epidermal growth factor (EGFRvIII) and CD19 — that are in Phase I/II trials.

Pfizer has also partnered with Cellectis to work together on the preclinical development of CAR–T cell treatments. It paid $80 million upfront, and committed milestones of up to $185 million for each of 15 projects. GSK has partnered with AdaptImmune to preclinically co-develop a related approach, modifying T cells with enhanced T cell receptors (TCRs) to home in on the cancer-testis antigen NY-ESO-1 and other targets. GSK could pay up to $350 million over 7 years through this deal.

Separately, Juno and Novartis settled a patent litigation case that had been ongoing since 2012. The patent dispute started between St Jude Children's Research Hospital in Memphis, Tennessee, and the University of Pennsylvania, but broadened to include Juno when the company partnered with St Jude, and to involve Novartis when Novartis partnered with the University of Pennsylvania. Under the agreement, Novartis will pay Juno $12.25 million upfront, plus future milestones and royalties for products related to the disputed patent. Juno's and Novartis' lead CAR–T cell treatments both target CD19, and are in Phase I/II and Phase II development, respectively, for haematologic cancers.

Asher Mullard

DPP4 inhibitors dodge cardiovascular bullet

A US Food and Drug Administration (FDA) independent advisory committee voted in April that a cardiovascular safety signal for two antidiabetes dipeptidyl peptidase 4 (DPP4) inhibitors — AstraZeneca's saxagliptin and Takeda's alogliptin — could be handled by updating the drugs' labels.

The panel was convened to discuss the results of two post-approval cardiovascular outcome studies. In the 16,492-patient SAVOR trial, saxagliptin was associated with a 27% increase in risk of hospitalization for heart failure (*New Engl. J. Med.* **369**, 1317–1326; 2013). In the 5,380-patient EXAMINE trial, alogliptin was associated with a numerical increase in hospitalization for heart failure, but the effect was not as marked as with saxagliptin (*New Engl. J. Med* **369**, 1327–1335; 2013). An FDA sensitivity analysis of the saxagliptin data also suggested "significant or near-significant increases in all-cause mortality," according to a regulatory briefing released before the meeting.

Panellists were concerned by the increased risk of hospitalization for heart failure in particular, but voted 13 to 1 that saxagliptin had an acceptable cardiovascular risk profile (with 1 abstention). 14 panellists voted to update the labelling and 1 voted to withdraw the drug from the market. The voting was more favourable for alogliptin, with 13 experts voting to update the label and 3 voting that no changes were needed.

The FDA often follows the recommendations of its panellists, but it doesn't have to.

The jury is still out, however, on whether the adverse cardiovascular effects are class effects. Merck & Co. will present cardiovascular outcome data from a post-marketing study of its market-leading sitagliptin at the American Diabetes Association meeting in June. If there is a class effect that has an impact on sales, Merck is likely to take the biggest hit. Merck earned around US$4 billion from sitagliptin in 2014. In the same year, AstraZeneca earned over $800 million from saxagliptin, and Takeda earned over $400 million from alogliptin.

Asher Mullard

Phase II antisense sets Crohn disease precedents

In Crohn disease, elevated levels of SMAD7 lead to decreased levels of the immunosuppressive transforming growth factor-β1 (TGFβ1). Celgene's mongersen, a 21-base single-strand oligonucleotide that binds *SMAD7* mRNA to reduce its translation, may be able to normalize these levels, with impressive clinical effect, suggest new Phase II data. In the 166-patient trial, 65% of the patients who received the highest dose of mongersen achieved remission after 15 days of treatment, compared with 10% of the patients in the placebo group (*New Engl. J. Med.* **372**, 1104–1113; 2015).

These results are "unprecedented" compared with the anti-inflammatory standards of care — including infliximab, adalimumab and vedolizumab — for moderate-to-severe active Crohn disease, comments Séverine Vermeire, a gastroenterologist at the University Hospitals Leuven in Belgium, in an editorial (*New Engl. J. Med.* **372**, 1166–1167; 2015). The trial data also suggest that whereas symptoms usually recur rapidly after withdrawal of traditional anti-inflammatory drugs, the effects of mongersen seemed durable. But narrow inclusion criteria and a lack of congruence between clinical remission and biological remission (as measured by C-reactive protein) cloud interpretation of the results, Vermeire adds. "The impressive clinical effects of mongersen beg for follow-up studies to confirm that we have indeed entered a new phase of Crohn's disease treatment," she concludes.

Celgene plans to initiate Phase III studies of the drug in Crohn disease in the second half of 2015. It is also set to start testing mongersen in a Phase II trial in ulcerative colitis. Around 30 other drugs for Crohn disease are also in clinical development, but none of these targets SMAD7.

Asher Mullard