NEWS IN BRIEF

FDA approves first immunotherapy combo

US regulators approved Bristol-Myers Squibb's combination of nivolumab and ipilimumab for the treatment of metastatic melanoma, marking the first approval for an immunotherapy combination.

Both drugs are checkpoint inhibitors that remove the brakes from T cells. Ipilimumab, first approved in 2011 for the treatment of melanoma, blocks cytotoxic T lymphocyte antigen 4 (CTLA4) to enable activation of T cells in lymph nodes. Nivolumab, first approved in 2014, ties up the programmed cell death protein 1 (PD1) to prevent T cell inactivation by PD1 ligands, which are overexpressed in some types of cancers. Although both drugs provide compelling efficacy when used as monotherapies, oncologists have been awaiting immunotherapy combinations since the original approval of ipilimumab.

The new approval was supported by a 142-patient study in previously untreated patients with unresectable or metastatic melanoma. 61% of patients treated with the combination achieved the primary end point of an objective response rate, compared with 11% treated with ipilimumab alone (*N. Engl. J. Med.* **372**, 2006–2017; 2015). 22% of combination-treated patients achieved a complete response, compared with no patients in the ipilimumab monotherapy arm. The trial has not yet reached a median progression-free survival for the combination arm, with a minimum of 11 months of follow up. Patients who received the combination therapy did report almost twofold as many grade 3 or 4 adverse events as did the patients who received ipilimumab monotherapy.

Despite excitement over this efficacy, oncologists have been raising concerns over the cost of immunotherapy drugs, especially as the field moves towards multidrug regimens. In the case of this first combination, in the United States, patients will receive four doses of ipilimumab plus nivolumab at a cost of around US$140,000, followed by nivolumab alone at a cost of over $12,000 per month, until the disease progresses.

With dozens of drugs in development against other immunotherapy targets, researchers are exploring lots of other combination options (*Nat. Rev. Drug. Discov.* **14**, 561–584; 2015).

Asher Mullard

Roche hits multiple sclerosis landmarks

Roche presented promising pivotal data for its ocrelizumab, including first Phase III evidence of efficacy for the treatment of primary progressive multiple sclerosis (PPMS). 10% of MS patients suffer from PPMS, a form of disease that is characterized by steady worsening of neurological function. There are currently no approved drugs for PPMS. The data, presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting in October, could pave the way for regulatory filings of the CD20-targeting antibody in the first quarter of 2016.

B cells are thought to have a key role in MS pathogenesis, because they produce self-reactive antibodies and because they present antigens and secrete cytokines that can lead to abnormal activation of T cells and macrophages. CD20-targeting antibodies, which deplete levels of CD20-expressing B cells, have therefore been considered as possible MS agents for years. Roche's first-in-class CD20-binding rituximab yielded promising signs of efficacy in MS, but development in this indication was discontinued for undisclosed reasons. Ocrelizumab, a fully humanized successor to the chimeric rituximab antibody, now picks up the chase.

In two Phase III trials in relapsing MS, ocrelizumab beat interferon beta-1a, reducing the annualized relapse rate by nearly 50% compared with the interferon beta-1a comparator.

The antibody also outperformed placebo in PPMS. In a 730-patient trial, ocrelizumab reduced the risk of progression of clinical disability sustained for at least 12 weeks by 24% compared with placebo.

BioMedTracker analysts forecast global peak sales of ocrelizumab of over US$2 billion in 2024. The antibody was also in development for rheumatoid arthritis, lupus and ulcerative colitis, but has been suspended in all these indications.

Asher Mullard

CETP set-back, again

Eli Lilly halted a Phase III trial of its evacetrapib after an interim analysis found that the lipid-modulating drug had a low probability of being effective. Lilly is now the third big pharma company to scrap a Phase III cholesteryl ester transfer protein (CETP) inhibitor for the treatment of atherosclerosis, reducing the odds for the few remaining companies, including Merck & Co., that are still invested in the space.

The first high-profile failure of a CETP inhibitor came in 2006, when Pfizer was forced to discontinue development of torcetrapib after the drug increased the risk of death and heart problems. Drug developers including Roche, Lilly and Merck eventually concluded that torcetrapib's failure was not likely to be a class effect, and cautiously advanced their programmes. In 2012, however, Roche pulled the plug on its dalcetrapib in Phase III after an interim analysis suggested that the trial was unlikely to meet its end points.

The results bode poorly for Merck's anacetrapib, which is in Phase III development. An interim efficacy analysis of a key pivotal trial is expected by the end of this year, and the trial is due to complete in 2017. Amgen, too, could be affected. In September, Amgen said it will gain rights to the Phase III CETP inhibitor DEZ-001 through the US$300-million acquisition of the biotech company Dezima Pharma.

One remaining glimmer of hope for the class is the possibility that a set of genetic polymorphisms can predict which patients will benefit from CETP inhibition (*Circ. Cardiovasc. Genet.* **8**, 372–382; 2015). Earlier this year the biotech DalCor acquired rights to dalcetrapib on the basis of these findings, and the company plans to launch a Phase III trial of that drug this year that will only enrol patients with appropriate genetic profiles.

Asher Mullard