NEWS IN BRIEF

FDA approves landmark tissue-agnostic cancer drug

The FDA granted accelerated approval to Loxo Oncology and Bayer's larotrectinib for patients with solid tumours that have neurotrophic receptor tyrosine kinase (NTRK) gene fusions. Larotrectinib is the first drug to be developed entirely for a tissue-agnostic cancer indication that doesn't depend on where the cancer originated.

Last year the FDA granted a supplementary approval to Merck & Co's PD1 blocker pembrolizumab for microsatellite instability-high (MSI-H) tumours, but this immunotherapeutic antibody is also used widely on a tissue-dependent basis.

The FDA's approval of larotrectinib was based on data from three open-label, single-arm trials of the drug. The first 55 patients with NTRK fusion-positive cancers enrolled into the trial had an overall response rate of 75%. The median duration of the response had not been reached at the time of data lock, but 73% of patients reached at least 6 months, and 39% of patients reached at least 12 months.

NTRK fusions, which result in persistent oncogenic signalling, are thought to be present in <1% of all solid tumours. Analysts have forecast annual sales of US$500 million to $1 billion for the drug, but have noted that Loxo and Bayer may have difficulties identifying potentially responsive patients and overcoming tissue-based thinking among oncologists.

Some oncologists suspect that opportunities for tissue-agnostic drugs may be few and far between, but a number of other such candidates are in development (*Nature Reviews Drug Discovery* **17**, 227–229; 2018). Ignyta and Roche's entrectinib is in phase II development for NTRK fusion-positive solid cancers, as a potential competitor to larotrectinib. Loxo as well as Ignyta and their partner Roche are also working on earlier-stage clinical candidates for RET-mutant solid tumours. And Plexxikon is exploring tissue-agnostic potential in KIT-mutant and BRAF-mutant solid tumours.

Asher Mullard

Peanut allergy potential

Aimmune Therapeutics' AR101 helped peanut allergy sufferers to tolerate peanuts, showed pivotal trial data published in the *New England Journal of Medicine* and presented at the American College of Allergy, Asthma & Immunology meeting in Seattle.

In the 551-patient phase III desensitization trial, Aimmune randomized patients to daily treatment with either AR101, which is an orally administered defatted peanut flour, or to placebo. At the start of this trial, patients were able to tolerate on average less than half a peanut. After 1 year in the trial, 67% of treated patients could tolerate the equivalent of four peanuts. Only 4% of the patients in the placebo arm could tolerate this much peanut protein at the end of the trial.

AR101 does not cure peanut allergy, but instead enables patients to build up a tolerance to accidental exposure. Allergy sufferers probably need to keep taking the drug in order to see sustained desensitization.

In an accompanying editorial, Michael Perkin, an allergist at St George's, University of London, noted that the market for a peanut allergen immunotherapy could be in the billions. But "desensitization was not easy on the patients," he wrote. Nearly 12% of the treated participants withdrew from the study because of severe adverse events, compared with 2% in the placebo group. 14% of the treated patients needed epinephrine during the course of the trial, versus 7% in the placebo group. "This is not something to start at home," he wrote.

Some research groups have previously desensitized patients by giving them controlled doses of "peanut flour costing peanuts", he added. An approval for AR101 "may result in the peanut being deemed an unlicensed medicinal product."

Aimmune is expected to file the drug for approval by the end 2018. The company is partnered with Regeneron and Sanofi to explore whether combination use of AR101 and the IL-4 receptor antibody dupilumab can improve outcomes.

DBV Technologies is also developing a peanut allergen immunotherapy, using a patch to deliver peanut protein through the skin. The company filed for regulatory approval for their drug Viaskin Peanut in 2018, after narrowly missing their primary end point in a pivotal trial.

Approvals for these products could pave the way for the development of products to desensitize patients with other food allergies (see *Nature Reviews Drug Discovery* **15**, 149–150; 2016).

Asher Mullard

Low-cost non-profit drug repurposing

The EMA recommended approval for Drugs for Neglected Diseases initiative (DNDi) and Sanofi's fexinidazole for sleeping sickness. DNDi, a non-profit drug developer, celebrated the European approval as a first all-oral treatment for the parasitic tropical disease and the first new chemical entity that they have developed through to approval.

Fexinidazole is a 5-nitroimidazole derivative that was discovered in the 1980s by Hoechst (now Sanofi) and then abandoned for strategic reasons. DNDi and its collaborators rediscovered the drug while screening for anti-parasitic activity in 2005, and DNDi partnered with Sanofi to develop, manufacture and distribute the drug in 2009. DNDi says it executed this repurposing work for US$55 million, with funding from seven European countries, the Bill & Melinda Gates Foundation, Médecins Sans Frontières and others. DNDi hopes to apply this low-cost repurposing model more broadly.

Regulators approved at least two other repurposed or reprioritized drugs for neglected and tropical diseases in 2018. In June, the FDA approved Medicines Development for Global Health's (MDGH's) moxidectin for river blindness. Moxidectin is a macrocyclic lactone with a history as a veterinary anthelmintic drug. In July, the FDA approved the Medicines for Malaria Venture (MMV) and GlaxoSmithKline's tafenoquine for Plasmodium vivax malaria. Tafenoquine was discovered in 1978 as a potential anti-malarial, but languished in development lingo until the 2000s.

Both of these US approvals came with priority review vouchers (PRVs). MDGH plans to sell its PRV to enable its future non-profit drug development work. In a recent Viewpoint in *PLoS Neglected Tropical Diseases*, scientists from the WHO and MDGH caution that oversupply of PRVs, market values of less than $100 million for PRVs and other factors could undermine the ability of PRVs to support drug development costs.

MDGH estimates that the total cost to bring moxidectin to market probably exceeded $50 million. SIGA sold a PRV, gained for its approval of a smallpox drug, for $80 million in November.

Asher Mullard