NEWS IN BRIEF

FDA approves first BCMA-targeted therapeutic

The FDA has approved GlaxoSmithKline (GSK)'s belantamab mafodotin for relapsed or refractory multiple myeloma. The antibody–drug conjugate (ADC) is the first therapeutic from the crowded BCMA-targeted pipeline to secure approval.

BCMA, a member of the TNF-receptor superfamily, is expressed on normal B lymphocytes as well as on multiple myeloma cells. Despite early efforts to target BCMA with canonical monoclonal antibodies, early candidates did not have sufficient efficacy to move forward. In recent years, however, drug developers have had more success with ADCs, bispecific antibodies and CAR-T cell therapies.

The FDA's accelerated approval of belantamab mafodotin, for patients with multiple myeloma who have had at least four prior therapies, was based on an open-label trial in 97 heavily pre-treated patients. The overall response rate in this trial was 31%, and 73% of responders had a response duration of at least 6 months. Common adverse reactions included corneal epithelium change, and a black box warning on the drug's label notes the associated risk of severe vision loss.

GSK is still developing the ADC for earlier lines of therapy, and in combination with other agents. A benefit of the ADC approach is that it provides an off-the-shelf product.

BCMA-targeted CAR-T therapies that are made to order for each patient are also approaching the market, setting the stage for a modality showdown. Bristol Myers Squibb and Bluebird Bio resubmitted their idecabtagene vicleucel for FDA approval in July, following an earlier submission and refuse-to-file letter. Johnson & Johnson and partner Legend Biotech are expected to file their CAR-T therapy JNJ-4528 for approval by the end of the year.

BCMA is the second most popular defined cancer target in the global cell therapy pipeline, trailing only behind CD19.

Amgen's BCMAxCD3-targeted bispecific T cell engager AMG 420, another off-the-shelf product, is in phase II trials.

Belantamab mafodotin is the tenth ADC to secure FDA approval.

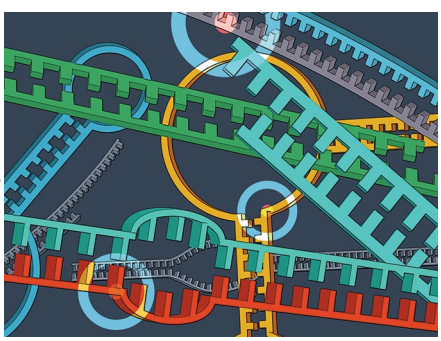
Asher Mullard

FDA approves RNA-targeting small molecule

The FDA has approved Roche and PTC Therapeutics' risdiplam, an RNA splice-modifying small-molecule drug, for spinal muscular atrophy (SMA).

Drugs that can force the alternative splicing of mRNA templates, shifting protein production profiles, have long been on industry's watch list. Pioneering approvals in this space include Sarepta's eteplirsen, for Duchenne muscular dystrophy, and Biogen and Ionis Pharmaceuticals' nusinersen, for SMA. But whereas both these agents are oligonucleotide therapeutics, risdiplam is a small-molecule drug.

Like nusinersen, risdiplam modulates the splicing of the *SMN2* gene to promote exon 7 inclusion. This results in the production of a full-length SMN protein, compensating for loss-of-function mutations in *SMN1* that otherwise cause the muscle wasting disease. The FDA approved risdiplam on the basis of two studies. In an open-label study in 21 patients with infantile-onset SMA, 41% of patients were able to sit independently for more than 5 seconds after 12 months of treatment. Also, 90% of infants were alive without permanent ventilation at 12 months of treatment and reached 15 months of age or older. Natural history studies of untreated infantile-onset SMA suggest that infants would otherwise not be able to sit independently, and only 25% would survive without permanent ventilation beyond 14 months of age. In a placebo-controlled trial in 180 patients with later-onset SMA, treated patients experienced an increase in motor function, as assessed by the MFM32 test, of 1.36 on treatment, compared with a 0.19 decrease on placebo.



Credit: S.Harris/Springer Nature Limited

Whereas nusinersen is dosed intrathecally in the clinic, risdiplam is orally available and can be administered at home.

In addition to competition from nusinersen, risdiplam will also face off against Novartis's gene therapy onasemnogene abeparvovec, which delivers a functional SMN transgene.

Industry's interest in RNA-targeted small-molecule drugs is growing. In April, Roche partnered with Arrakis Therapeutics on RNA-targeted small-molecule drug discovery. Other biotechs that are working preclinically on RNA-targeted small molecules include Expansion Therapeutics, Skyhawk Therapeutics and Ribometrix.

Asher Mullard

FDA approves first GPCR biased agonist

The FDA has approved Trevena's μ-opioid agonist oliceridine for moderate to severe acute pain in adults. Oliceridine was once heralded as an exemplar of the possibilities of biased GPCR agonists, drugs that can preferentially activate only a subset of a receptor's signalling pathways. Even with the approval, however, the purported clinical benefits of these agents remain to be demonstrated.

"I don't think this is going to move the field [of biased agonism] in one direction or another," says Bryan Roth, a pharmacologist at the University of North Carolina who discovered another biased opioid agonist called PZM21. "It is a big win for Trevena," he adds.

Traditional opioid agonists are associated with adverse events including respiratory depression and gastrointestinal complications. Some evidence suggests, however, that the analgesic effects of these GPCR agonists may be a result of associated G-protein signalling whereas the adverse events are a result of associated β-arrestin 2 signalling. With oliceridine, Trevena sought to preferentially stimulate the G-protein signalling, in the hope of developing a next-generation opioid with a cleaner safety profile.

The company first submitted the drug for approval in 2017. An FDA advisory committee voted against approving the drug in 2018, after the agency noted concerns with the drug's safety and benefit–risk profile. Months later, the FDA rejected the drug. Now, even as the agency approved the drug, it noted that the safety profile of the drug "is similar to other opioids".

Earlier this year, three laboratories reported on their efforts to collaboratively evaluate whether the side effects of opioids are due to β-arrestin 2 signalling. Writing in the British Journal of Pharmacology, they concluded that their results "call into question the concept of developing G protein-biased μ-opioid receptor agonists as a strategy for the development of safer opioid analgesic drugs".

Asher Mullard