NEWS IN BRIEF

The FDA approves a first farnesyltransferase inhibitor

The FDA has approved Eiger BioPharmaceuticals's lonafarnib for Hutchinson-Gilford progeria syndrome, a rare and fatal premature aging disease. This is the first approval for a farnesyltransferase inhibitor, a class of drugs that was once thought to hold promise in oncology — and that still might.

Hutchinson-Gilford progeria syndrome is caused by mutations in *LMNA* that result in the production of progerin, a mutant form of the lamin A protein. Progerin is permanently tagged with a farnesyl group, a post-translational modification that is thought to contribute to the altered nuclear membrane morphology associated with the disease. Farnesyltransferase inhibitors aim to reduce the farnesylation of progerin.

The approval of lonafarnib is based on two single-armed trials of the drug, in a total of 62 patients. These were compared with outcomes from untreated patients in a separate natural history study. The drug increased the average lifespan by 3 months through the first 3 years of treatment, and by an average of 2.5 years though the maximum follow-up of 11 years.

The first of these studies started recruiting patients in 2007, backed by then sponsor Schering-Plough. Merck & Co. merged with Schering-Plough in 2009, and licensed the drug to Eiger in 2010. Eiger is also developing the drug for hepatitis D.

Industry's initial interest in farnesyltransferase inhibitors stemmed from their potential applications in cancer, however. Many large pharmaceutical firms once pursued this drug class, drawn in by evidence that farnesyltransferase activity might be crucial for the oncogenic function of RAS proteins. Multiple farnesyltransferase inhibitors have failed in cancer trials, but these hopes live on.

Most notably, Kura Oncology is developing tipifarnib — a drug it licensed from Johnson & Johnson — for cancers including HRAS-mutant squamous head and neck cancer. Kura's rationale is that previous trials did not test the right patient populations. Whereas a redundant pathway may enable the oncogenic activity of KRAS and NRAS even when farnesyltransferase activity is inhibited, HRAS activity seems to be exclusively reliant on farnesyltransferase processing.

Asher Mullard

Parsing exceptional responders

Even when a clinical trial fails to meet its efficacy end point, some patients experience outsized benefits from treatment. In an attempt to tease translational opportunities out of these anecdotes, the National Cancer Institute (NCI) has systematically studied the characteristics of a subset of these 'exceptional responders' in oncology trials. The efforts provide "a wealth of testable hypotheses", it now reports in *Cancer Cell*.

The NCI first put out a call in 2014 for examples of exceptional responders, defined as patients for whom a complete or partial response was expected in less than 10% of similarly treated patients or whose duration of response lasted three times the published median or longer. It has now published an analysis of tumour specimens from 111 such patients, looking at mutations, aberrant methylation, the cellular makeup of the tumour microenvironment and other factors that might impact drug sensitivity. It found plausible mechanistic explanations for 26 (23%) of the exceptional responders.

The mechanisms discovered fell into several broad categories, including differences in the tumour's ability to repair DNA damage and differences in the immune system's response to the tumours. In many cases, multiple mechanisms were likely in play. "These analyses revealed synthetic lethal relationships that may be exploited therapeutically and rare genetic lesions that favor therapeutic success," the authors wrote.

But 85 cases could not be explained, "leaving ample room to investigate these [exceptional responder] tumors by alternative analytical methods in the future".

Asher Mullard

COVID-19 vaccines buoy hope

Barely a year since the emergence of the SARS-CoV-2 virus, multiple vaccine developers are poised to secure emergency authorization in the USA and the EU.

Pfizer and BioNTech's BNT162b2 — an mRNA-based vaccine — was the first of the candidates to reach a final, event-driven efficacy analysis. The company reported on 18 November that a 43,000-patient phase III trial had reached 170 confirmed cases of COVID-19, with only 8 of these in the treatment arm. These findings equate to an efficacy rate of 95%. The company observed ten severe cases of COVID-19 in the trial, with only one of these in the treatment arm.

Severe adverse events included fatigue and headache following the second vaccine dose.

Moderna's mRNA-vaccine mRNA-1273 offered 94% efficacy, showed a final analysis of their 30,000-patient phase III trial. Moderna's trial accrued 196 cases of COVID-19, with just 11 of these in the treatment arm. The company observed 30 cases of severe COVID-19, none of which were in the treatment arm.

Common adverse reactions included injection site pain, fatigue and myalgia.

AstraZeneca has reported promising interim results for AZD1222, an adenovirus-based vaccine developed in partnership with Oxford University. As of 23 November, the company had observed 131 confirmed cases of COVID-19 in a pivotal trial of the vaccine. The average overall efficacy estimate is 70%. For subjects who accidentally received a half-dose of the vaccine at a first visit, followed by a full dose at a second, the estimated vaccine efficacy is 90%.

AstraZeneca's results raised optimism that its vaccine supply could be stretched further, but also questions about why a lower dose may have worked better and concerns about how this dosing mistake was made.

The Russian Gamaleya Center's Sputnik V vaccine, another adenovirus-based vaccine, offers an efficacy of 91%, showed an interim analysis. This estimate is based on 39 confirmed cases of SARS-CoV-2 infection.

As *Nature Reviews Drug Discovery* went to press, none of these findings had been published in peer-reviewed papers. Outstanding questions include the duration of the effect and the long-term safety of these vaccines. An FDA advisory panel will discuss the Emergency Use Authorization of Pfizer's vaccine on 10 December, and of Moderna's vaccine on 17 December.

The UK's MHRA has authorized Pfizer's vaccine for emergency use.

Other candidates in phase III trials include more traditional protein subunit vaccines and inactivated virus vaccines.

This pipeline is set to defy historic vaccine development timelines and success rates. The average time for a vaccine to move from phase II to licensure is 4.4 years, found a recent analysis of the development trajectories of 220 vaccines for viral diseases that were developed in 2005–2020. The average probability of progressing from phase II to licensure within 10 years was 10%.

Asher Mullard