NEWS IN BRIEF

What should go into a booster shot for COVID-19?

With COVID-19 vaccines providing waning levels of protection against the evolving SARS-CoV-2 virus, the FDA convened its panel of independent experts to discuss the path forward for booster shots. "We have to give serious consideration to a booster campaign this fall to help protect us from another COVID-19 surge," said the FDA's Peter Marks at the start of the one-day VRBPAC meeting in late June. On the agenda: should boosters include the spike protein from the Omicron variant of the virus? If so, which sub-lineage of the variant is optimal? And, is a monovalent or bivalent booster best?

Three vaccine developers presented data. Pfizer and its partner BioNTech made the case for a monovalent mRNA booster that expresses the spike from the Omicron BA.1 variant, and for a bivalent mRNA candidate that expresses spikes from the ancestral form of the virus and from Omicron BA.1. Moderna showcased its bivalent mRNA vaccine candidate, also encoding the spikes of the ancestral and the Omicron BA.1 variant. Novavax's NVX-CoV2373 is a recombinant protein subunit vaccine that is based on the spike of the original strain. As boosters, all of these candidates increased levels of neutralizing antibodies against the now-dominant Omicron BA.4 and BA.5 sub-lineages, compared to first-generation vaccines. Sponsors have yet to present clinical efficacy data from any of these.

Credit: Andriy Onufriyenko/Moment/Getty

Panellists debated whether to push vaccine developers to update their candidates to carry the BA.4/BA.5 spike protein — and highlighted the need for better insights into the correlation of vaccine efficacy with antibody levels and T cell activity. They voted 19 to 2 in favour of incorporating an Omicron spike into a booster vaccine, with varied opinions on sub-lineage prioritization.

"Bottom line, it seems like a BA.4/BA.5 bivalent was the sense of the committee," summarized the FDA's Peter Marks at the end of the meeting. The WHO favours a booster with an Omicron BA.1 composition, leading some panellists to call for a globally aligned booster development plan.

This is "science at its hardest," said Marks. By the time irrefutable evidence is available for the best path forward, a new variant of the virus may have emerged.

Days before the meeting, Sanofi and GSK press released the first efficacy results from their bivalent recombinant protein subunit vaccine — using spike proteins from the ancestral and Beta variants. In a phase III trial in 13,000 adult volunteers, it had an efficacy of 65% against symptomatic COVID-19, and 75% efficacy in patients previously infected with COVID-19. The efficacy against Omicron-confirmed symptomatic disease was 72%.

Sanofi and GSK are hoping for a possible authorization later this year.

Asher Mullard

BRAF plus MEK inhibitor combo secures tumour-agnostic FDA approval

Novartis's combination of dabrafenib and trametinib has secured accelerated approval from the FDA for metastatic solid tumours with *BRAF*^{V600E} mutations — the latest cancer approval to prioritize mutational status over tissue of origin.

The green light was granted on the basis of the phase II ROAR trial and the NCI-MATCH trial — 'basket' trials that recruited patients with multiple different cancer types on to treatment. These trials recruited 131 patients with *BRAF*^{V600E}-mutant cancers. The combination resulted in overall response rates of up to 80%, says Novartis, with activity in cancers including high- and low-grade glioma, biliary tract cancer and certain gynaecological and gastrointestinal cancers. Enrolment numbers and response rates were lower for some cancer types than for others.

"Physicians should consider a BRAF test as a routine diagnostic step that could enable a new option for treating patients with many solid tumours," said Vivek Subbiah, an oncologist at The University of Texas MD Anderson Cancer Center and investigator of trials of this combination.

The BRAF inhibitor dabrafenib and the MEK inhibitor trametinib were each first approved for single-agent use in 2013. The FDA approved combination use of these drugs for *BRAF*-mutant metastatic melanoma in 2014, and subsequently expanded the label to include non-small-cell lung cancer and anaplastic thyroid cancer. The new approval is the first of its kind for a BRAF plus MEK inhibitor combination.

BRAF^{V600E} mutations are particularly common in thyroid cancer, parathyroid cancer, melanoma, Langerhans cell histiocytosis and head and neck cancer, showed a recent analysis by Subbiah and colleagues of the tumour-agnostic potential of this combination.

The FDA has granted just a handful of tumour-agnostic approvals to date. Merck & Co.'s PD1 blocker pembrolizumab secured a broadened labelling for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours in 2017, and then for cancers with tumour mutational burden (TMB)-high markers in 2020. The FDA approved GSK's PD1 inhibitor dostarlimab for dMMR tumours in 2021. Loxo Oncology and Bayer's TRK inhibitor larotrectinib was approved for solid tumours with *NTRK* gene fusions in 2018, as was Genentech's TRK inhibitor entrectinib in 2019.

Asher Mullard

FDA approves fifth RNAi drug — Alnylam's next-gen hATTR treatment

The FDA approved Alnylam's vutrisiran for hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy, providing a more convenient option for patients with the rare disease.

Vutrisiran, like its predecessor patisiran, is an siRNA oligonucleotide that harnesses the RNAi pathway to degrade the mRNA encoding TTR. This lowers TTR protein levels, preventing build-up of toxic amyloid in the peripheral nerves. The newcomer uses an enhanced stabilization chemistry and is GalNAc-conjugated, improving its uptake into liver cells and enabling more convenient dosing. Whereas Alnylam's patisiran is injected intravenously every 3 weeks, the company's vutrisiran is injected subcutaneously once a quarter.

The FDA approved vutrisiran based on the phase III HELIOS-A trial, in 164 patients with hATTR amyloidosis with polyneuropathy. Volunteers were randomized to vutrisiran or to patisiran. The primary endpoint was the change from baseline in the modified Neuropathy Impairment Score + 7 (mNIS+7) at 9 months, versus the historic placebo control data from the pivotal trial that supported patisiran approval. Vutrisiran provided a 17-point