Authorization of Covid-19 vaccines expand as new variant of concern emerges

The US Food and Drug Administration (FDA) has expanded the emergency-use authorization for the SARS-CoV-2 mRNA vaccines BNT162b2 (Pfizer & BioNTech) and mRNA-1273 (Moderna) to include a booster dose in adults vaccinated with any licensed vaccine. The Centers for Disease Control and Prevention’s advisory committee (ACIP) immediately recommended booster doses, especially in individuals over the age of 50.

The committee, as well as the Europeans Medicines Agency (EMA), also endorsed BNT162b2 for children 5–11 years old. Vaccination of this age cohort is underway in both US and EU.

Meanwhile, BNT162b2 was 100% effective in preventing symptomatic infection in children aged 12–15 years. In a follow-up analysis of ~2200 subjects, all 30 cases of disease were in the placebo group 7 days to 4 months after the second dose. So far, the vaccine has been used under emergency approval in this age group.

EMA has added transverse myelitis, a disorder manifested as inflammation of the spinal cord, as a rare side effect to the label of the Ad26.COV2.S vaccine (J&J). The regulator is also evaluating mRNA-1273 for risk of capillary leak syndrome, in which blood leaks from vessels into neighboring tissues.

A new variant of concern emerged in Africa. The Omicron lineage (B.1.1.529) harbors a large number of mutations in the spike protein rendering the virus more infectious. Concerns have been raised regarding the impact on vaccine effectiveness. However, epidemiologists will need to collect more data to describe the transmission dynamics of the new strain, disease severity and impact on vaccination.

Combination immunotherapy is beneficial as second-line treatment of melanoma

The CD40 agonist sotigalimab (APX005M, Apexigen) together with the PD-1 inhibitor nivolumab (Opdivo, BMS) induced stable non-progressing disease in 11 of 33 evaluable patients with PD-1-therapy-refractory, metastatic melanoma in a Phase 2 dose-escalation trial. The safety profile was acceptable with the majority of patients reporting grade 1 or 2 adverse events.

Sotigalimab has demonstrated immunogenicity in two more Phase 2 trials: as the first-line treatment, together with chemotherapy, of metastatic pancreatic ductal adenocarcinoma; and in neoadjuvant setting in combination with chemo- and radiation therapy in subjects with rectal cancer. Sotigalimab is designed to elicit both innate and adaptive immune responses in the tumor microenvironment by activating antigen-presenting cells via the CD40 co-receptor.

TGF-β-blocking immunotherapy demonstrated activity against solid tumors and Covid-19

The anti-TGF-β RNA oligonucleotide immunotherapy OT-101 (Oncotelic Therapeutics) combined with recombinant IL-2 was safe and well tolerated at all dosage levels in a Phase 1 involving subjects with advanced or metastatic pancreatic, skin and colorectal cancers. OT-101 also was safe with signs of efficacy in a small randomized trial with 32 hospitalized Covid-19 patients. Mortality reached 4.5% and 20% in the experimental and placebo cohorts, respectively.

TGF-β is exploited by Covid-19 as well as tumor cells to evade immune responses, and OT-101 is being tested for efficacy against multiple respiratory viruses and cancers.

Clinical development of checkpoint inhibitors in multiple tumor types

The PD-1 inhibitor pembrolizumab (Keytruda, Merck) combined with the Poly I:C dsRNA BO-112 (Highlight Therapeutics) achieved a 27% objective response rate, including 8% of complete responses, in 42 patients with advanced melanoma, which recurred following first-line anti-PD-1 treatment. BO-112 is designed to stimulate immune responses in a cold tumor microenvironment by activating TLR3, RIG-1 and MDA-5.

The CTLA-4 inhibitor AGEN1181, alone and together with anti-PD-1 MAb balstilimab (both Agenus), was immunogenic in heavily pretreated solid cancers with cold tumors. The responses lasted at least 24 weeks. The combination induced responses in 60% of tested subjects.

Another CTLA-4 inhibitory MAb, ONC-392 (OncoC4), was safe and well tolerated in a Phase 1 dose-escalation trial with multiple types of advanced cancers. Six of 10 enrolled patients also reported clinical activity with two complete responses. ONC-392 is designed to specifically inhibit tumor-infiltrating Tregs without compromising peripheral T cells, thereby reducing the rate of adverse events.

Five of eight patients with solid cancers achieved disease control in the Phase 1/2 EVICTION trial testing the CD277 inhibitor ICT01 (ImCheck Therapeutics) with pembrolizumab as second-line treatment following failure of checkpoint inhibition therapy. Preliminary analysis showed durable responses of >20 weeks. ICT01 selectively activates γδ T cells leading to migration of these cells from the bloodstream into the tumor tissue.
Interleukin agonist beneficial for recurrent solid cancer patients

The IL-15 superagonist SOT101 (Sotio) was well tolerated and induced stable disease in four of 30 subjects with advanced solid tumors who relapsed after previous therapy. The dose-escalation Phase 1 AURELIO-03 trial reported increased CD8+ T cells and NK cells in the responders’ tumor microenvironment.

In another arm, SOT101 combined with pembrolizumab induced partial responses in three and long-lasting stable disease in four of 13 patients, including those who failed prior checkpoint inhibition immunotherapy.

Oncolytic virotherapy was safe and immunogenic in solid cancers

The engineered virus-based immunotherapy ONCR-177 (Oncorus) was well tolerated as second-line therapy of patients with advanced breast, skin and head-and-neck cancers with no treatment options left. The open label, dose-escalation Phase 1 trial found clinical benefits in three of eight evaluable patients who received the maximum tolerated dose.

The intratumorally injected ONCR-177 is based on Herpes Simplex Virus engineered to replicate specifically in tumors and to express several transgenes and miRNAs that boost both innate and adaptive immunity and inhibit PD-1 and CTLA-4 checkpoint proteins.

Neoadtigen melanoma vaccine fast-tracked by FDA

The FDA has granted its fast-track designation to the neoantigen immunotherapy BNT111 (BioNTech) due to its potential, shown in early clinical trials, to treat inoperable, therapy-resistant advanced melanoma. BNT111 in combination with a checkpoint inhibitor is currently in a Phase 2 trial with anti-PD-1-refractory, Stage III–IV melanoma.

BNT111 is an mRNA vaccine delivered in a lipid nanoparticle, which encodes four tumor neoantigens typical for >90% of cutaneous melanoma cases.

HBV vaccine recommendations expand in US

The ACIP has unanimously recommended routine vaccination against hepatitis B for all adults 19–59 years of age and older adults with risk factors. The previous recommendation from 2005 to vaccinate all infants led to a decrease in new cases among children and adolescents.