

## Human vaccines & immunotherapeutics news: July 2020

### Covid-19 vaccines protect against emerging variants

The Delta variant of SARS-CoV-2 is rapidly spreading worldwide. The hyper-transmissible strain has been shown to achieve >1,000-fold higher viral load in infected people than the parent Alpha strain, with symptom onset an average of 2 days earlier.<sup>1</sup> Nonetheless, vaccination does work against the disease: a study from England indicates that two doses of the BNT162b2 vaccine (Pfizer & BioNTech) prevent 88% and 94% of symptomatic disease caused by the Delta and Alpha variants, respectively. Protection was 67% and 75%, respectively, for the ChAdOx1 nCoV-19 vaccine (AstraZeneca).<sup>2</sup>

Vaccination also prevents transmission, according to three studies conducted before the onset of the Delta strain.<sup>3-5</sup> The BNT162b2 vaccine prevented 80% of infections, and although the decrease in transmission rate in vaccinated people varied from 40% to 80% in these studies, the combined effect resulted in >88% lower risk of SARS-CoV-2 transmission within households.

The mRNA-1273 vaccine (Moderna) elicits durable cellular and humoral immunity, which is comparable to that in convalescent individuals, even if just a quarter of the regular dose is administered.<sup>6</sup> The scientists, who followed 35 participants of the original dose-escalation trial 7 months after vaccine administration, hope that lower doses might ease the global shortage in vaccine supplies.

Covid-19 might also be treated via passive immunization. The antibody S2H97, which is based on a panel of antibodies isolated from people recovering from SARS-CoV-2 or SARS-CoV infection, can bind to multiple strains of SARS-CoV-2 and other related coronaviruses and prevent infection in cell culture and a hamster model.<sup>7</sup>

The whole-virion inactivated vaccine candidate Covaxin (Ocugen) demonstrated 78% efficacy against Covid-19 (93% against severe disease) in a Phase 3 trial involving 26,000 adults. Covaxin offered better protection against the Delta strain than previous infection with the parent virus.

In contrast, another mRNA vaccine CVnCoV (CureVac) failed in a late-stage clinical trial involving 40,000 people. The vaccine showed 47% efficacy following two doses.

### Development of new immunotherapeutics on multiple fronts

The PD-1 inhibitor pembrolizumab (Keytruda, Merck) has been approved by the US Food and Drug Administration (FDA) for treatment of high-risk early stage triple-negative breast cancer. The immunotherapeutic has been licensed in combination with chemotherapy prior to surgery followed by pembrolizumab-only adjuvant treatment.

The FDA has also granted Priority Review designation to another anti-PD-1 MAb, bastilimab (Agenus), which is in a Phase 2 trial for treating recurrent or metastatic cervical cancer.

Pembrolizumab further demonstrated efficacy against cervical cancer. In the Phase 3 Keynote-826 trial, the checkpoint inhibitor improved survival compared to platinum chemotherapy regardless of the patient's PD-L1 status.

A Phase 2 clinical trial has started for the therapeutic vaccine BNT111 (BioNTech) in combination with the PD-1 inhibitor cemiplimab (Libtayo, Sanofi & Regeneron) for the treatment of anti-PD-1-refractory, advanced melanoma. BNT111 is an RNA vaccine expressing four tumor-specific antigens.

The Wilms Tumor-1 peptide vaccine galinpepimut-S (Sellas) holds promise for treating ovarian carcinoma and malignant pleural mesothelioma. The vaccine in combination with pembrolizumab induced 100% survival after 9 months in 11 patients with refractory, advanced ovarian cancer, according to interim results of a Phase 1/2 trial. The expected survival in patients undergoing chemotherapy is up to 12 months.

Treatment with galinpepimut-S combined with another PD-1 inhibitor nivolumab (Opdivo, BMS) led to an average overall survival of 35 weeks in four evaluable patients with malignant pleural mesothelioma, which is longer than typical for this disease.

Other developments in the immunotherapy field include:

- The allogeneic dendritic-cell vaccine ilixadencel (Immunicum) administered with pembrolizumab was safe in the Phase 1 Iliad trial testing the immunotherapeutics in various cancer indications.
- The STING agonist SB 11285 (F-star Therapeutics), alone and combined with the anti-PD-L1 MAb atezolizumab (Genentech & Roche), was safe in patients with solid tumors.
- The AI-assisted neoepitope vaccine EVX-01 (Evaxion) along with a PD-1 inhibitor demonstrated antitumor activity in nine metastatic melanoma patients with an objective response rate of 67% and complete response rate of 22%.
- Phase 1 trial has started testing the safety of the off-the-shelf *Listeria*-based vaccine, which targets 24 frequent tumor neoantigens, in patients with early prostate cancer.
- Phase 1/2 trial is investigating the safety and activity of the autologous T-cell immunotherapy GEN-011 (Genocea) in patients with solid tumors.
- Another Phase 1/2 trial has commenced to test the lymph node-targeted, mutated-KRAS-peptide therapeutic vaccine ELI-002 (Elicio) in KRAS-driven cancers.

- Finally, the cellular immunotherapy RTX-240 (Rubius Therapeutics), which expresses the immune-stimulating 4-1BBL and IL-15/IL-15 R fusion proteins, has entered a Phase 1/2 trial testing the treatment in combination with pembrolizumab in advanced solid tumors.

### **‘Vax gap’ threatens working environments as people return to physical workplace**

80% and 56% of vaccinated and unvaccinated people, respectively, feel some stress about working with coworkers unvaccinated for Covid-19, according to a survey conducted in US. Furthermore, almost a quarter of unvaccinated individuals is comfortable returning to a workplace with <10% vaccination rate.

“We’re seeing tremendous gaps on the safety issue based on whether you are vaccinated or not [and] employers will have to give serious consideration to the high stress levels that a majority of workers are feeling about their unvaccinated colleagues. If their concerns aren’t addressed, employers could see quit rates rise even higher,” Brett Wells, director of People Analytics said.

Nearly 80% of respondents said teachers and students should be required to get the Covid-19 vaccine.

### **PCV-15 approved in US**

The FDA has approved the 15-valent pneumococcal conjugate vaccine (PCV) Vaxneuvance (Merck) for adults. In clinical trials Vaxneuvance demonstrated immunogenicity to the three serotypes responsible for the majority of invasive disease cases. The vaccine showed equivalent or superior immunogenicity relative to the licensed 13-valent PCV Prevnar-13.

### **Shingrix indication expanded to immunocompromised adults in US**

The Shingles vaccine Shingrix (GSK) can be used in all adults at high risk of developing the disease. Previous license applied only to subjects aged  $\geq 50$  years. The decision by FDA follows similar ruling in Europe. People in the risk group include patients with HIV and solid tumors, and those immunosuppressed due to transplantation or disease.

Shingles, which is caused by the varicella zoster virus reactivated in late adulthood, causes painful rash and blisters leading eventually to postherpetic neuralgia. There are ~1 million annual cases in US alone.

### **Malaria vaccine candidate was highly protective in a small trial**

The live chemo-attenuated sporozoite vaccine PfSPZ-CVac protected 88% and 78% of healthy adults from homologous and heterologous challenge, respectively.<sup>8</sup> The two cohorts consisted of 8 and 9 participants, respectively, who were infected with the same or a different strain of *Plasmodium falciparum* 3 months after receiving the vaccine.

PfSPZ-CVac was administered together with two anti-malarials that kill both liver-stage and blood-stage parasites to prevent vaccine-induced disease. The combination induced strong and durable immune responses.

### **New dengue vaccine candidate has entered clinical trials**

A double-blind, randomized Phase 1 trial has opened to test the safety and immunogenicity of the PepGNP-Dengue vaccine (Emergex) in healthy volunteers. The synthetic peptide vaccine, which is delivered by a nanogold carrier system, is designed to induce CD8<sup>+</sup> T cells.

### **A phase 1 trial is testing an mRNA influenza vaccine**

Safety, immunogenicity and optimal dose of a monovalent hemagglutinin influenza vaccine (Sanofi & Translate Bio) will be investigated in 280 healthy adults <50 years old. The vaccine consists of lipid nanoparticle-delivered mRNA encoding the A/H3N2 hemagglutinin protein. The A/H3N2 strain tends to dominate the most severe influenza season.

### **Chikungunya vaccine candidate receives breakthrough designation**

The FDA has granted its Breakthrough Designation to the chikungunya vaccine VLA1553 (Valneva). The vaccine, which is the most advanced chikungunya vaccine in clinical development, previously received priority status in US and EU.

VLA1553 is a genetically attenuated, single-dose vaccine targeting the mosquito-borne chikungunya disease, which leads to fever and debilitating joint and muscle pain with high morbidity in tropical regions.

### **Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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