The Omicron strain of SARS-CoV-2 spreads very rapidly throughout the world

Omicron, the new coronavirus variant of concern, which rapidly displaces the previous dominant strain, harbors a large number of mutations, especially in the spike protein, which make it extremely transmissible but less harmful. Preliminary data from South Africa and United Kingdom suggest that the risk of hospitalization is around one-third that for the Delta strain with even lower proportion of severe cases.1,2 Tests of Omicron neutralization by sera of vaccinated individuals indicates that the mRNA vaccines BNT162b2 (Pfizer & BioNTech) and mRNA-1273 (Moderna) protect from disease caused by this variant but only after the full three-dose course and with reduced efficacy compared to activity on the Delta strain.3–5 These results were corroborated by two preliminary field studies from Denmark and the United Kingdom suggesting that BNT162b2’s efficacy against Omicron wanes quickly and is reinstated following a booster dose.6,7 Israel now offers an additional booster dose (fourth dose overall) to individuals ≥60 years.

The US Centers for Disease Control and Prevention has recommended the use of the mRNA vaccines over that of Ad26.COV2.S vaccine (J&J) due to the rare blood clots caused by the latter.

Meanwhile the US Food and Drug Administration (FDA) has granted its emergency-use authorization for the BNT162b2 booster to include all subjects 16 years of age or older, and Evusheld (AstraZeneca) for Covid-19 prevention in immunocompromised subjects ≥12 years old. Evusheld is a mix of antibodies (tixagevimab and cilgavimab) that offer a ~ 6-month protection to people who cannot get a vaccine.

Other clinical developments for Covid-19 vaccines include:

- The two-dose inactivated vaccine COVAXIN (BBV152, Ocugen & Bharat Biotech) was safe and induced robust neutralizing antibody responses in children aged 2–18 years in a Phase 2/3 trial.
- The capsid virus-like particle vaccine ABNCoV2 (Bavarian Nordic) increased antibody responses by up to 40-fold as a booster following primary immunization with mRNA or adenoviral vaccines in >200 adults enrolled into a Phase 2 trial.
- The adjuvanted, recombinant peptide vaccine (Sanofi & GSK) also increased antibody responses by up to 40-fold as a booster following primary immunization with mRNA or adenoviral vaccines in the Phase 1/2 VAT0002 trial in >500 people.
- A homologous booster dose 8 months after primary vaccination with the adjuvanted, inactivated vaccine VLA2001 (Valneva) induced a fourfold increase in antibody titers in 77 participants (18–55 years) of a Phase 1/2 trial.

Immunotherapy combination beneficial for NSCLC patients

Combination of two immune checkpoint inhibitors tiragolumab (anti-TIGIT) and atezolizumab (anti-PD-L1, both Roche) improved progression-free survival and response rate, by 40% and 20%, respectively, compared to atezolizumab alone in PD-L1-positive metastatic nonsmall cell lung cancer. The 2.5-year follow-up in the Phase 2 CITYSCAPE trial also reported median overall survival of 23 months for the experimental group and 14.5 months for the control monotherapy group.

Tiragolumab targets the T- and NK-cell checkpoint receptor TIGIT, which inhibits antitumor responses. It is designed as an amplifier of other immunotherapies.

Fourth hepatitis B vaccine approved in US

The FDA has approved the hepatitis B vaccine PreHevBrio (VBI Vaccines) for all adults. In the Phase 3 PROTECT and CONSTANT trials, the three-antigen vaccine demonstrated safety and >90% seroprotection rate, 15% higher than that of the marketed Engerix-B (GSK).

PreHevBrio, which is also approved in Israel, consists of the S (HBsAg), pre-S1 and pre-S2 surface antigens of the hepatitis B virus.

CAR immunotherapies enter clinical trials

The allogeneic CD19-targeting chimeric antigen-receptor (CAR) cytokine-induced killer cell therapy (CARCIK-CD19, Colimmune) induced sustained responses in patients with B-cell acute lymphoblastic leukemia. The dose-escalation Phase 1/2 trial reported 13 complete responses out of 21 adult and pediatric subjects. The CAR-CIK cells, which are a mixture of T- and natural killer (NK) cells, were derived from healthy donors.

The autologous CD20-targeting CAR T-cell therapy MB-106 (Mustang Bio) was beneficial for relapsed patients with multiple types of B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia. According to interim analysis of a dose-escalation Phase 1/2 trial, 95% subjects responded including 65% with complete responses.

First volunteers enrolled for a universal influenza vaccine trial

The universal influenza vaccine candidate UFluA (Emergent BioSolutions) is being tested in 60 healthy adults up to 45 years of age. The double-blind Phase 1 EBS-UFV-001 trial investigates safety and immunogenicity of two dosage levels against a placebo.
UFuLA is an adjuvanted, intramuscular, self-assembling nanoparticle vaccine targeting the stem region of influenza A hemagglutinin. Future studies will test the technology for prevention of disease caused by influenza B as well.

**Follicular lymphoma patients benefit from bispecific-antibody treatment**

The bispecific, T-cell engaging MAb mosunetuzumab (Roche) induced complete responses in 60% of subjects with follicular lymphoma who had relapsed after at least two courses of therapy. The Phase 1/2 GO29781 trial reported median progression-free survival of 18 months with low-grade cytokine release syndrome as the most frequent adverse event.

Mosunetuzumab recognizes the B-cell receptor CD20, which is commonly overexpressed in non-Hodgkin lymphomas, and the T-cell co-receptor CD3. The MAb is designed to induce T-cell-mediated removal of malignant B cells.

**Therapeutic vaccine promising in chronic hepatitis B infection**

A two-vaccine regimen led to a decrease in hepatitis B surface antigen (HBsAg) levels in Hepatitis B chronic carriers. The Phase 1/2 HBV002 trial tests the ChAdOx1-HBV prime and MVA-HBV boost (VCT-300, Vaccitech) with and without nivolumab in six patients who have been on antivirals for at least one year.

Half of the subjects had a ≥ 10-fold decrease in HBsAg with one complete response. No safety concerns were observed.

**NK cell therapy of acute myeloid leukemia receives orphan-drug designation**

The FDA has granted its orphan-drug designation to the allogeneic NK cell therapy NKX101 (Nkarta) for acute myeloid leukemia. The treatment has shown a complete response rate of ~15% and a 3–9-month median overall survival in relapsed patients, who have no standard-of-care treatment options remaining.

NKX101 consists of NK cells derived from healthy donors that have been engineered to express membrane-bound IL-15 and CAR recognizing the NKG2D ligand on cancer cells, which synergize to induce anti-tumor activity.

**mRNA HIV vaccine shows promising preclinical results**

A multiclade mRNA vaccine candidate was safe and effectively protected rhesus macaques from SHIV. The challenge study reported successful induction of neutralizing antibodies as well as anti-Env CD4+ T-cell responses, and an efficacy against mucosal challenge of almost 80%.

The vaccine, which encodes for the Env and Gag proteins that assemble in vivo into a virus-like particle, was administered intramuscularly in multiple heterologous doses (Env from different clades).

“We are now refining our vaccine protocol to improve the quality and quantity of the VLPs produced. This may further increase vaccine efficacy and thus lower the number of prime and boost inoculations needed to produce a robust immune response,” said senior author Paolo Lusso of National Institutes of Health.

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