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NEWS, POLICY, & PROFILES

Human vaccines & immunotherapeutics news: January 2022

Tenbillion Covid-19 vaccine doses have been administered worldwide

As the hyper-transmissible Omicron strain of SARS-CoV-2 spreads around the globe, the first adapted mRNA vaccines are being tested in clinical trials. Both the BNT162b2 (Pfizer & BioNTech) and mRNA1273.529 (Moderna) vaccines encoding the mutated Spike protein corresponding to the Omicron's sequence are being administered in clinical trials to healthy adults previously vaccinated with the complete two or three-dose regimens. BNT162b2 is being further tested in vaccine-naïve subjects.

Scientists are monitoring the rise of an even more transmissible Omicron subvariant, BA.2. Preliminary data from Denmark, where this strain dominates, indicate that vaccination reduces the rate of transmission.[1] Taken together with the lower severity of Omicron infections relative to previous variants, Denmark continues to lift pandemic restrictions.

Vaccination also prevents long-term consequences of infection. A study of 1,000 Israelis infected with SARS-CoV-2 from March 2020 to November 2021 reported that two vaccine doses decreased the rate of 'long Covid' symptoms by ~60% to baseline levels.[2] 'long Covid' is associated with fatigue, shortness of breath, muscle pain, and blood pressure swings.

In addition, vaccines prevent ~90% of multisystem inflammatory syndrome in children, a rare complication of Covid-19 with onset within weeks of infection, according to the US Centers for Disease Control and Prevention report.[3] None of the study subjects that required life support after hospitalization was vaccinated.

T cell-activating immunotherapy approved for uveal melanoma

The US Food and Drug Administration (FDA) has approved the bispecific T-cell receptor-based immunotherapy KIMMTRAK (Immunocore) for HLA-A *02:01-positive unresectable or metastatic uveal melanoma in adults. The decision is based on Phase 3 trial results showing increased overall survival in a first-line treatment setting compared to standard-of-care options (mostly pembrolizumab).

KIMMTRAK, which targets the melanoma-associated antigen gp100, is a chimeric polypeptide comprising a soluble T-cell receptor fused to an anti-CD3 co-receptor, which is designed to activate both $CD4^+$ and $CD8^+$ T cells

Immunotherapy beneficial for prurigo nodularis patients in a Phase 3 trial

The IL-4 Rα inhibitor dupilumab (Dupixent, Regeneron & Sanofi) was safe and reduced the rate of itch and skin lesions after 24 weeks by ~3fold compared to placebo in patients with prurigo nodularis. The Phase 3 trial reported that 60% of patients in the experimental cohort met the primary endpoint of itch reduction, corroborating an earlier trial with similar results.

The chronic inflammatory disease prurigo nodularis causes extreme itch and painful burning and stinging in the skin. Dupilumab is designed to inhibit the IL-4 and IL-13 pathways involved in the type 2 inflammatory responses.

Checkpoint-Inhibitor immunotherapy of cancer in clinical trials

The PD-L1 inhibitor cosibelimab (Checkpoint Therapeutics) achieved an objective response rate of almost 50% in 78 patients with metastatic squamous-cell carcinoma. With mostly mild adverse events and three-quarters of responses ongoing, a license application is expected to be filed later in 2022.

The first patients with advanced or metastatic solid tumors have received a combination of the CD137 agonist ADG106 and the anti-CTLA-4 MAb ADG116 (both Adagene) in a dose-escalation trial evaluating safety and tolerability of the treatment. ADG106 is designed to induce Treg depletion in the tumor microenvironment.

Another immunotherapy combination was safe in the Phase 1b KEYNOTE B84 trial in advanced, recurrent or metastatic head-and-neck squamous cell carcinoma. The PD-1 inhibitor pembrolizumab (Keytruda, Merck) was tested with the novel anti-SEMA4D MAb pepinemab (Vaccinex), which promotes infiltration and activation of DCs and CD^{8+} T cells in the tumor microenvironment. The ongoing trial is designed to define an optimal dose for further clinical development.

Microneedle delivery of influenza vaccine comparable to intramuscular injection

The trivalent split-virion influenza vaccine administered via a transdermal microneedle patch (Zosano Pharma) was safe and induced antibody levels similar to those following standard intramuscular delivery.[4] In a Phase 1 trial, 90 adults up to 40 years old were randomized to wear the vaccine patch for 5 or 15 minutes or to receive a classical injection.

Microneedle delivery might ameliorate psychological barriers to vaccination due to its lower perceived painfulness in avoiding a needlestick, thus improving acceptance rates.

Clinical progress of T-cell immunotherapies

The T-cell immunotherapy INB-200 (IN8bio) holds promise for patients with glioblastoma, according to preliminary analysis of a Phase 1 trial with four subjects. The treatment had manageable safety profile, and all participants have exceeded the progression-free survival of 4–7 months typical for the

condition. INB-200 consists of autologous gamma-delta T cells engineered to be chemotherapy-resistant. It can be administered together with temozolomide and other chemotherapeutics.

Another T cell-based immunotherapy, MT-601 (Marker Therapeutics), received the Orphan Drug designation by the FDA for treatment of prostate cancer. MT-601 is based on selectively expanded, non-engineered T cells specific for six antigens overexpressed in prostate cancer.

In vivo CAR-T cells treat fibrosis in a preclinical trial

Reduced fibrosis and restored cardiac function was observed in a mouse model of heart failure following delivery of mRNA for antifibrotic chimeric antigen receptor (CAR) and its *in vivo* expression.[5] The approach utilizes lipid nanoparticles with encapsulated mRNA, targeted to the CD5 receptor on the surface of T cells. The transient nature of the generated CAR T cells increases safety of the treatment compared to genetically modified CAR T cells, which can persist in the body for years.

α-Synuclein vaccine reduced pathology in a mouse model of Parkinson's disease

A DNA vaccine for Parkinson's disease induced antibodies and reduced neurodegeneration in a preclinical model.[6] Four different vaccines were tested in the study targeting three B-cell epitopes of the human α-synuclein and their combination. The latter one, which reduced total α-synuclein levels and overall pathology, was selected for further investigation.

Universal influenza vaccine candidate induces broad immune response in a preclinical trial

The universal influenza vaccine PDS0202 (PDS Biotech) elicited robust antibody as well as $CD4^+$, $CD8^+$ and memory T-cell responses in a preclinical study. The vaccine antigens were computationally optimized using the COBRA pipeline and designed to induce protective responses against multiple influenza strains.

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