Oncolytic immunotherapy reduces the size of melanoma tumors in phase 3 trial

Amgen recently announced promising findings from a phase 3 retrospective analysis of patients with metastatic melanoma, treated with the oncolytic immunotherapy talimogene laherparepvec. The investigational immunotherapeutic product significantly reduced the size of injectable tumors and also non-injected tumors that had metastasized.

Melanoma is the most aggressive and serious form of skin cancer, characterized by the uncontrolled growth of melanocytes, which are the cells responsible for providing the pigment to skin. Melanoma is considered to be advanced when it has metastasized from the origin site to deeper parts of the skin or other organs such as the lymph nodes, lungs or brain. Currently, 132,000 melanoma cases occur globally each year.

The oncolytic immunotherapy talimogene laherparepvec is designed to selectively replicate in tumor tissue and to initiate a systemic anti-tumor immune response. Talimogene laherparepvec is also engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF) to help activate the immune system. Direct injection into tumor tissue can initiate a systemic anti-tumor immune response that targets tumor cells throughout the body.

The study included 295 patients with injectable unresected stage IIIb, IIIc, or IV melanoma who received talimogene laherparepvec or GM-CSF. Almost 4000 tumor lesions were tracked for this analysis, half of which were injected with talimogene laherparepvec at least once, while the rest were not injected, including visceral tumor lesions (tumors involving solid organs such as the lungs and liver). The results showed a ≥50% reduction in tumor size in 64% of injected tumors. In addition, one-third of uninjected non-visceral tumors and 15% of visceral tumors were also reduced by ≥50%. Fatigue, chills and pyrexia were the most frequently observed adverse events in the phase 3 trial. The most common serious adverse events (SAE) included disease progression in both groups, and cellulitis and pyrexia in the talimogene laherparepvec group. SAEs occurred in 26% of talimogene laherparepvec patients and 13% of control group patients. Study results were recently presented at the Society of Surgical Oncology (SSO) 67th Annual Cancer Symposium in Phoenix.

“These data add to the body of evidence supporting talimogene laherparepvec’s local and distant effect, and its potential ability to stimulate a systemic anti-tumor immune response,” said Dr. Sean E. Harper, executive vice president of Research and Development at Amgen. “Melanoma remains a devastating and difficult-to-treat disease, and talimogene laherparepvec continues to demonstrate encouraging results in this setting.”

EV71 vaccine protects children against HFMD

The Chinese company Sinovac Biotech recently announced positive phase 3 trial data for its Enterovirus 71 (EV71) vaccine. Efficacy against EV71-associated hand, foot and mouth disease (HFMD) was 94% among infants and young children. An anti-EV71 neutralizing antibody titer of 1:16 was associated with protection against EV71-associated HFMD. The vaccine also demonstrated a 100% efficacy rate against EV71-associated hospitalization and against HFMD with neurologic complications, the main cause of fatalities.

The randomized, double-blind, placebo-controlled phase 3 trial included 10,077 healthy infants and young children in China aged 6–35 mo. Study subjects were randomly assigned to receive two intramuscular doses of the vaccine or placebo on days 0 and 28. The surveillance period was 12 mo, with the primary endpoint being occurrence of EV71-associated HFMD. The results, recently published in The New England Journal of Medicine, showed that the vaccine can provide protection against EV71-associated HFMD in infants and children.

Dr. Fengcai Zhu, Director of Jiangsu Centers for Disease Control and Prevention, co-principal investigator and lead author of the NJEM paper, said: “This study showed that the EV71 vaccine provides protection to the infants and young children against EV71-associated HFMD, and the vaccine candidate has good safety and immunogenicity profile. HFMD has been an increasingly important public health issue among the young children in Asia-Pacific region, including China, and caused a significant social burden. The successful development of the EV71 vaccine is an exciting achievement by Sinovac, as it will provide an effective tool to protect infants and young children against EV71 associated HFMD, especially at the level of severe cases and potential fatalities.”

HFMD, a common and usually mild disease that occurs most frequently in children under five years of age; however, there has been an increased number of severe cases associated with neurological symptoms. Since 1997, a growing number of outbreaks of EV71 HFMD has been reported across the Asia-Pacific region, including China, Hong Kong, Singapore, South Korea, and Taiwan. HFMD has become a very serious problem in China, especially in children, given that no vaccine and specific treatment are available to protect against disease. According to statistics from National Health and Family Planning Commission of China during 2008–13, >9 million cases of HFMD have been reported, resulting in ~2700 fatalities. The majority of severe (80%) and fatal cases (> 90%) of HFMD are caused by EV71 infection.

Reference
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Influenza vaccination important for risk groups

Results from two recent studies highlight the importance of influenza immunization in two different risk groups: children with underlying chronic conditions and diabetics.

The first study set out to estimate vaccine effectiveness against flu admissions to pediatric intensive care units (PICU). Medical records of 216 children between 6 mo and 17 y, admitted to 21 PICUs in the US during the 2010/11 and 2011/12 flu seasons, were analyzed. The study, published in the Journal of Infectious Diseases, found that receiving influenza vaccine reduces a child's risk of flu-related intensive care hospitalization by ~74%. These findings show that while vaccination may not always prevent influenza illness, it protects against more serious outcomes.

“These study results underscore the importance of an annual flu vaccination, which can keep your child from ending up in the intensive care unit,” said Dr. Alicia Fry, a medical officer in CDC’s Influenza Division. “It is extremely important that all children—especially children at high risk of flu complications—are protected from what can be a life-threatening illness.”

The CDC recommends annual influenza vaccination for everyone >6 mo and especially for children at high risk of serious flu complications, i.e., asthma, diabetes or developmental delays. In the current study, vaccination was associated with a significant reduction in risk of PICU admission. Nevertheless, vaccine coverage was relatively low among the children in this study: only 18% of flu cases admitted to ICU were fully vaccinated. More than half (55%) of cases had at least one underlying chronic medical condition that placed them at higher risk of serious flu-related complications.

Diabetes is a known risk factor for developing flu-associated complications. Influenza virus can overwhelm the immune system and lead to fluctuations in blood sugar levels. A recent study found that vaccinating diabetics against influenza can cut the risk of death by 28%. Researchers from Imperial College London, led by Dr Eszter Vamos, based their investigation on the Clinical Practice Research Datalink, which included 124 503 patients with Type 2 diabetes who contributed to 623 591 person-years of observation during the course of the seven-year study. Scientists found that people with diabetes who had received influenza vaccine were 28% less likely to die in the next 12 mo than those who were not vaccinated. Furthermore, vaccinated diabetics were much less likely to be admitted to hospital with conditions such as stroke (30%) and acute myocardial infarction (21%). The findings were presented at the recent Diabetes UK annual conference in Liverpool.

Dr Eszter Vamos said: “This study suggests that people with type 2 diabetes benefit from being vaccinated against the flu. Every effort should be made to encourage uptake in this high priority group.”

Although influenza vaccination for diabetics is free in the UK and recommended by health authorities, only two-thirds under the age of 65 y are immunized against the flu.

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Bharat’s rotavirus vaccine is safe and modestly efficacious

According to a recent study published in The Lancet, a new rotavirus vaccine (116E) was found to be safe and moderately efficacious in a phase 3 clinical trial in Indian infants. Unlike other rotavirus vaccines that have 30–40% efficacy in developing countries, the 116E vaccine has demonstrated >56% efficacy.

With 75–122 000 deaths per year, India accounts for ~25% of the total number of rotavirus deaths worldwide. Rotavirus diarrhea is responsible for almost 10% of deaths in children <5 y of age and for ~39% of diarrhearelated hospital-admissions, the majority of which take place in the first year of life.

The randomized, double-blind, placebo-controlled trial enrolled >6500 infants at three centers in India. Doses of the oral vaccine were given at ages 6–7, 10, and 14 wk, with other childhood vaccines given concurrently. More than 4350 vaccinated infants and 2200 infants who received placebo were included in the efficacy analysis. Compliance to dosing was 96%. The median age of the infants at the time of analysis was 17.2 mo, and follow-up is planned to continue up to the age of 24 mo. The vaccine 116E had a modest efficacy of 54% against severe rotavirus gastroenteritis, and efficacy was 56% during the first year of life. Although 25 deaths were reported in the vaccine arm and 17 in the placebo arm, the deaths were not related to the vaccine, the paper notes.

The oral vaccine, developed by Hyderabad-based Bharat Biotech International, is based on the live-attenuated virus strain 116E. This rotavirus strain is unusual in that it rarely causes clinical disease in India and elsewhere, but it provides protection against most of the commonly circulating rotavirus genotypes in India and other parts of the world.

“The strain can provide cross-protection as the outer structural proteins are similar to other rotavirus serotypes,” said Dr Krishna Ella, Managing Director of Bharat Biotech. “It is a human neo-natal strain and very different from other rotavirus vaccines that are bovine based.

Bharat Biotech has committed to making the vaccine available at no more than $1 per dose for government procurement. According to Dr Ella, the vaccine is very close to getting licensed in India, and a dedicated manufacturing facility for rotavirus vaccine has been developed. Vaccine development was funded jointly by Bharat Biotech, the Department of Biotechnology (DBT) at the Indian Ministry of Science and Technology, and the Bill and Melinda Gates Foundation. PATH provided technical guidance and support.

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Successfully avoiding the cold-chain for vaccines

Maintaining the cold-chain is a major difficulty for vaccination campaigns in developing countries. Two recent studies on using the meningococcal A (MenA) vaccine MenAfriVac at ambient temperatures as well as one study on a new nanotechnology approach to create heat-resistant vaccines, have shown that it is feasible to use at least some vaccines without keeping them cool.

The journal *Vaccine* recently published a study showing that MenAfriVac does not require constant refrigeration to stay viable even in ambient temperatures up to 39 °C. The study was conducted as part of a 10-d MenA campaign in Benin in November 2012, after MenAfriVac had received approval from the Indian regulatory authorities and the World Health Organization (WHO) prequalification team to be kept outside of the cold chain for up to four days at up to 40 °C in a controlled temperature chain (CTC). For the first time, a vaccine for developing countries was granted authorization to be used outside the recommended temperature range of 2–8 °C. The vaccine also was kept out of direct sunlight. The pilot targeted a rural area in Benin, vaccinating 155,000 people across 150 villages. During 2013, no cases of MenA were reported across Benin, including the area where the vaccine was not kept cold. A special card with a heat-sensitive sticker in the vaccine carriers showed if temperatures reached 40 °C; during the campaign, only nine vials had to be discarded because they were exposed to temperatures >40 °C.

Vaccinators were very positive about using the CTC approach since enabled more vaccinations per day, did not force them to return from remote villages to the health centers each night to continuously freeze ice packs, and reduced the weight of vaccine carriers.

Another advantage of using the CTC approach are the associated economic benefits, as recently published in the *Bulletin of the World Health Organization*. Investigators found that the costs of administering the vaccine without keeping it cold could drop by 50%. The study looked at the costs incurred during a ten-day MenA mass vaccination campaign in three regions of Chad in December 2011, where the cold chain was used throughout. Acquiring and transporting ice packs, refrigerators, and freezers, as well as kerosene to keep the refrigerators running make the cold chain system expensive and complicated. Other logistical challenges include unreliable electricity and poorly functioning or absent equipment. The study found that costs could potentially be halved from $0.24 to $0.12 per person vaccinated, if the vaccines were kept at or near ambient temperature instead.

The successful use of MenAfriVac after storage for four days at ambient temperature is a great step forward, but a team of researchers from Iowa State University is aiming higher. They have created the first heat-resistant nanovaccines to facilitate vaccination in developing countries by packing the antigen within nano-sized non-toxic biodegradable polymer particles. The vaccines can be stored at room temperature for six to ten months. Promising preclinical data from mice immunized against influenza have recently been presented at the National Meeting of the American Chemical Society in Dallas (TX, USA).

“We’ve shown that it works with rodents, and we’re moving forward to show that [it works] in larger animals as well. The particles are made of materials that have high-term stability—the only thing that pulls them apart is water,” said Dr Balaji Narasimhan from Iowa State University. “Our nanovaccine approach could be instrumental for containing future outbreaks of recently emerged and re-emerging diseases, such as SARS, new flu strains and multi-drug resistant tuberculosis.”

While most current vaccines work by inducing antibodies, nanovaccines activate another part of the immune system, namely T cells. These nanovaccines have been shown to elicit protective immune responses in animals following a single intranasal dose. However, the way to approval is still long.

**References**

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FDA approval for Stallergenes’ sublingual grass pollen allergy immunotherapy

Stallergenes recently announced that the US Food and Drug Administration (FDA) has approved Oralair, the first immunotherapy tablet to be available in the US for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis.

Grass allergy is the most common seasonal allergy in the US, and most people are allergic to more than one type of grass. Until now, allergen immunotherapy had to be administered via a series of subcutaneous injections in the doctor’s office. The approval of Oralair provides an additional treatment option for allergy specialists and their patients. The new sublingual allergy immunotherapy contains a mix of five grass pollen: Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass. These five grass pollens are the ones to which most patients in the US are exposed. Oralair is indicated for treating grass pollen-induced allergic rhinitis with or without conjunctivitis in persons aged 10–65 y. The first tablet is taken in the doctor’s office under medical supervision, and subsequent doses can be administered once a day by the patient or the patient’s caregiver. Treatment should start four months before the expected onset of each grass pollen season and continued throughout the season. Allergy symptoms are reduced beginning with the first grass pollen season.

“We are very pleased with the US approval of Oralair as it will bring a true benefit to US patients suffering from grass pollen-induced allergy,” said Dr Christian Chavy, Chief Executive Officer of Stallergenes. “This approval is a major milestone for Stallergenes. The company not only developed Oralair but it also continues to expand the frontiers of allergen immunotherapy. I would like to congratulate my predecessor, Roberto Gradnik and his teams on this major achievement.”

Oralair has been approved in Europe since 2008 and is authorized in 31 countries, including most European countries, Canada, Australia, and Russia. Stallergenes will launch Oralair in the US with its partner Greer, a leader in the US allergen immunotherapy market. Greer will lead US sales and marketing efforts.
HPV vaccination campaign could change from three to two doses in the UK

Advisors to the UK government have been discussing whether to change the human papilloma virus (HPV) vaccination program from the current three-dose to a two-dose schedule. The associated reduction in costs could enable the vaccination program to be extended to boys.

Since 2008, all girls in the UK aged 12–13 y, but not boys, are supposed to receive three doses of Merck’s HPV vaccine Gardasil. Following the initial approval of a new two-dose schedule for Gardasil by the European Medicines Agency (EMA) earlier this year, the UK Joint Committee on Vaccination and Immunisation (JCVI) is considering to introduce a two-dose schedule if approved by the EMA.

Dr Mark Jit of Public Health England said: “We understand the JCVI is considering a two-dose schedule. The HPV vaccination programme in the UK has achieved coverage in over 80% in 12-13 year olds, and is eventually expected to prevent most cervical cancers (and some other HPV-related cancers) and genital warts caused by the HPV-types that are included in the vaccines being used.”

Several studies, including one in *JAMA*, have shown that two doses of Gardasil are as effective as the current three doses. Switching to a two-dose schedule should lower the cost of the vaccination program in the UK, which could strengthen the case for extending the program to boys.

Giving Gardasil to boys and men would make sense medically, since the vaccine can protect them against genital warts and reduce transmission of HPV. More recently, HPV has also been associated with throat cancer, another reason to include boys in HPV vaccination programs in the future.

Reference

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Valneva continues phase 2/3 trial of Pseudomonas aeruginosa vaccine

The European biotechnology company Valneva recently announced the continuation of the current phase 2/3 clinical trial of its *Pseudomonas aeruginosa* vaccine candidate IC43.

Following different assessments including analyses conducted by a Data Monitoring Committee (DMC) and consultation with two European regulatory agencies and experts, Valneva and its co-development partner Novartis decided to continue the clinical trial of IC43. The interim analysis showed a clinically meaningful reduction in all-cause mortality rates for the vaccine group as compared with placebo and no safety concerns were observed. These findings were in-line with previous phase 2 results.

Dr Thomas Lingelbach, President and Chief Executive Officer, and Dr Franck Grimaud, President and Chief Business Officer of Valneva, commented, “We are encouraged by the interim results. This study aims to deliver a major improvement for intensive-care unit patients. Continuing the trial gives us the prospect of a potential novel nosocomial vaccine that may save many lives and underpins our ambition to develop groundbreaking innovation to improve patient’s health.”

*P. aeruginosa* is one of the leading causes of nosocomial infections that patients acquire in hospitals during the course of receiving treatment for other conditions. Of the 2 million annual nosocomial infections in the US, 10% are caused by *P. aeruginosa*. The bacterium is the #1 cause of ventilator-associated pneumonia, the #2 cause of hospital-acquired pneumonia, and the #4 cause of surgical site infections. *P. aeruginosa* infections are often difficult to treat because of the increasing antibiotic resistance of these bacteria, indicating the high medical need for additional treatments or preventive measures. There is no available vaccine.

IC43 is targeted for ventilated intensive care patients, who are vaccinated after intensive care unit (ICU) admission and are at particular risk of life-threatening *P. aeruginosa* infections. Targeted patients include >700,000 patients in Europe and US.

To continue the phase 2/3 trial, Valneva plans to include another 400 ventilated ICU patients (in addition to the 394 patients already enrolled) in this second phase of the trial at 40 different sites. Recruitment of patients is expected to resume in 2Q14.