

Human Vaccines: News

Lucanix greatly improves survival rates in patients with NSCLC

Long-term follow-up of a Phase 2 clinical trial showed encouraging survival in some patients with Stage 3B/4 non-small cell lung cancer (NSCLC) treated with the therapeutic cancer vaccine Lucanix (belagenpumatucel-L). The findings were recently presented at the American Association for Cancer Research (AACR) Annual Meeting 2012 in Chicago.

"This is a novel immunotherapy that appears to show unusually long survival in some patients," said Dr. Lyudmila Bazhenova, associate clinical professor at the University of California San Diego Moores Cancer Center in La Jolla.

The cell-based allogeneic vaccine Lucanix is the lead product candidate of

the clinical-stage biopharmaceutical company NovaRx, based in San Diego. Lucanix is derived from four lung cancer cell lines and was tested in an open-label study including 75 patients with NSCLC of various stages (two patients with Stage 2 disease, 12 with Stage 3A, 15 with Stage 3B and 46 with Stage 4). Patients were randomly assigned to three dose cohorts: 1.25, 2.5 or 5 x 10⁷ cells/injection.

For all patients, median survival was 14.5 months, and the five-year survival rate was 20%. The 40 patients with Stage 3B/4 cancer enrolled in the second and third dose cohorts had a median survival of 15.9 months and a one-year survival rate of 61%, a two-year survival rate of 41% and a five-year survival rate of

18%. Patients with Stage 3B/4 nonprogressive disease after chemotherapy had a median survival of 44.4 months, and a five-year survival of 50%, which is "unheard of for patients with NSCLC," according to Dr. Bazhenova. In contrast, patients who progressed after front-line chemotherapy had a median survival rate of 14.1 months and a 9% five-year survival rate.

While the results of this updated long-term survival analysis on patients treated with Lucanix are certainly intriguing, they must be confirmed in a Phase 3 clinical trial, which is under way in eight countries.

Novel HIV vaccines in early development

Inovio Pharmaceuticals recently presented positive interim results from a Phase 1 clinical study of their human immunodeficiency virus (HIV) vaccine PENNVAX-B. The vaccine demonstrated strong T-cell responses in a therapeutic trial setting. Another HIV vaccine candidate that is about to enter Phase 1 is being developed by Geovax. Their DNA/MVA vaccine protected non-human primates from multiple exposures to simian immunodeficiency virus (SIV), opening the door to a phase 1 study.

Inovio's DNA-based vaccine PENNVAX-B consists of SynCon immunogens targeting HIV gag, pol and env proteins from HIV subtype B, which is commonly found in North America and Europe. The vaccine was tested in an open label, Phase 1 study in 12 adult HIV-positive volunteers to assess safety and levels of immune responses generated. Study subjects were required to be well-controlled on highly active anti-retroviral therapy (HAART). They received four doses of PENNVAX-B (day 0, weeks 4, 8 and 16) via intramuscular electroporation. No significant adverse events were reported. 75% of the volunteers had an immune response against at least one of the three HIV antigens included in the vaccine, and 50% had a response against at least two antigens. The responses induced by vaccination were predominantly antigen-specific CD8+ T-cells, which are considered paramount

in clearing chronic viral infections and an important measurement of the performance of a therapeutic vaccine.

PENNVAX-B is unique in that it is designed to be used for both treatment and prevention. Inovio previously reported best-in-class T-cell responses to PENNVAX-B in healthy adults in a preventive setting. In that study, three doses of the vaccine delivered together with an IL-12 cytokine plasmid via electroporation resulted in over 89% of the vaccinated subjects mounting an antigen-specific CD4+ or CD8+ T-cell response against at least one of the vaccine antigens.

Geovax has mainly focused on developing a preventive HIV candidate vaccine, although they also have one ongoing trial to determine the vaccine's ability to supplant the need for continuing drug treatment in infected people currently on drug therapy. In contrast to Inovio, Geovax pursues a DNA prime/ MVA boost strategy. The DNA vaccine expresses its own adjuvant granulocyte-macrophage colony-stimulating factor (GM-CSF) as well as HIV antigens that trigger production of antibodies to stop the virus infecting the cells. The second step is a booster with MVA, a recombinant pox-virus expressing HIV proteins.

To be effective in people at a high risk of infection, an HIV vaccine needs to protect against not just one exposure but many. A

recent study in non-human primates set out to test Geovax' novel vaccine for the ability to protect against a series of 36 exposures to SIV – the primate equivalent of HIV – given in three clusters of 12 each over more than 2.5 years. The vaccination regimen consisted of two DNA inoculations at Months 0 and 2, followed by two booster inoculations at Months 4 and 6. When exposed to SIV six months after the last vaccination, five of seven vaccinated animals were protected (87%) compared to zero of nine in the unvaccinated group. The five uninfected animals were rested for one year, boosted once with MVA vaccine, rested for half a year, and again challenged. For this second series of exposures, four of five animals were protected. The four uninfected animals were rested for half a year and then challenged with yet another series of exposures. And three out of four animals were still protected.

"Repeated virus challenges in animals are used to mimic sexual transmission," explained Dr. Harriet L. Robinson, Chief Scientific Officer at GeoVax. "The hope is that the results in the non-human primate models will translate into vaccine-induced prevention of infection in humans."

No other HIV vaccine candidate currently in human clinical testing has achieved this level of preclinical success in non-human primates. Geovax has received an "allowed to

proceed" notice from the US Food and Drug Administration (FDA) to begin a Phase 1 trial of this DNA/MVA vaccine. A slightly different

version of the vaccine, which does not co-express GM-CSF, has successfully completed Phase 2a trials, and because Geovax already

has safety data from these trials, it may be possible to move straight to a Phase 2b trial after this Phase 1 study.

Peptide vaccine therapy: Immunological and clinical activity in children with gliomas

According to a recent study, peptide vaccination in children with gliomas was well tolerated with evidence of immunological and clinical responses. However, some children experienced periods of immunological pseudoprogression, where tumors appeared larger than they actually were.

"We have found that the vaccine is tolerated well with limited systemic toxicity, but we've also observed that there are some patients who have immunological responses to the vaccine target in the brain that can cause swelling and transient worsening, and subsequently, some of those children can have very favorable responses," said Dr. Ian Pollack, Professor of neurological surgery at the University of Pittsburgh School of Medicine (PA, USA) and co-director of the University of Pittsburgh Cancer Institute Brain Tumor Program. "We have also demonstrated immunological responses in the majority of the kids."

Peptide vaccine therapy had been examined in children with gliomas for the first time, and results of the study were presented at

the American Association for Cancer Research (AACR) Annual Meeting 2012.

The pilot study enrolled 27 children, including 16 with newly diagnosed brain stem gliomas, five with newly diagnosed cerebral high-grade gliomas, and six with recurrent gliomas. Researchers assigned HLA-A2-positive children to subcutaneous vaccinations with peptides for glioma-associated antigen (GAA) epitopes emulsified in the adjuvant Montanide-ISA-51 every three weeks for eight courses. They also administered intramuscular injections of the immunostimulant poly-ICLC. The GAAs included EphA2, IL13R α 2 and survivin.

Among 22 evaluable cases, four children had rapidly progressive disease, 14 had stable disease for more than three months, three had sustained partial responses, and one had prolonged disease-free status after surgery. ELISPOT analysis, which was completed in seven children, revealed responses in six children: to IL13R α 2 in five cases, EphA2 in three and survivin in three.

"These kids, who, for the most part, have intact and very robust immune systems, seem to mount an immune response against the vaccine very effectively at rates that may be even higher than have been noted in studies in adults," noted Dr. Pollack.

Pseudoprogression similar to true tumor progression was observed in some cases. For example, one child with a brain stem glioma had transient tumor enlargement and acute neurological deterioration four months after vaccine initiation. However, the tumor later regressed and the patient experienced a sustained partial response. Three other children with brain stem gliomas had symptomatic pseudoprogression, with transient neurological deterioration and tumor enlargement followed by stabilization on decreasing steroid doses.

According to Dr. Pollack, this was the first study of its type that examined peptide vaccine therapy for children with brain tumors like this. He said: "The fact that we have seen tumor shrinkage in children with very high-risk tumors has been extremely encouraging and somewhat surprising."

New oral rotavirus vaccine is developed for newborns

A new low-cost oral vaccine to protect newborn babies against rotavirus infection is being developed by collaborating research teams from Australia and New Zealand.

In January this year, researchers from the Murdoch Children's Research Institute at the Royal Children's Hospital (Melbourne, Australia) and the University of Otago (Dunedin, New Zealand) initiated a Phase 2 clinical trial for their new rotavirus candidate vaccine RV3-BB.

RV3-BB is derived from a harmless strain of rotavirus found in newborn babies. While children who have had this strain show no symptoms, they have been protected against future infection by rotavirus strains. In a previous Phase 1 study completed last year, one dose of this vaccine was well tolerated.

Dr. Pam Jackson, from the Department of Women's and Children's Health at the University of Otago said: "This oral vaccine has been shown to be well tolerated. What we now need to know is how effective the vaccine is at protecting against the disease and how long protection lasts."

The current Phase 2 study will examine the level of immunity to rotavirus generated by RV3-BB. To this end, newborn babies and infants in Dunedin will receive three doses of the oral RV3-BB or placebo. Unlike other currently available rotavirus vaccines, which are given to babies six to eight weeks of age, RV3-BB is being developed for newborns.

"This is important because we know that infection can occur very early in developing

countries and means that the vaccine has the potential to save many thousands of lives by vaccinating at birth while babies are still in a health care setting," said Dr. Jackson. "After this time, babies are often lost track of, when their risk of the severe rotavirus disease is very high. By starting vaccination from birth, we will be potentially able to offer them protection from rotavirus disease by three months of age."

The life-threatening diarrheal disease caused by rotavirus is estimated to result in the death of over half a million children under age five worldwide and two million hospitalizations each year. In many countries, the currently available rotavirus vaccines are not part of the National Immunization Programme of funded vaccines, mainly due to cost. The

research and development of RV3-BB is being led and conducted by academic institutions rather than the pharmaceutical industry with

the intention to partner with developing country manufacturers so that the vaccine will ultimately become available at lower cost for

developing countries, where they are needed most.

Allergy vaccine in Phase 2 for rhinitis/rhinoconjunctivitis

The Netherlands-based company HAL Allergy recently has successfully completed patient enrollment in a Phase 2 dose-range finding study for their allergy vaccine PURETHAL Mites.

PURETHAL Mites is a modified aluminum hydroxide-adsorbed extract of house dust mites for subcutaneous use. It is already commercially available for patients suffering from severe allergic respiratory diseases inadequately controlled despite the use of symptomatic treatments. Now, HAL Allergy is testing the vaccine for efficacy and safety in patients with allergic rhinitis/ conjunctivitis.

The current multi-center, randomized, double-blind, placebo-controlled study includes 250 patients with persistent allergic rhinitis/ rhinoconjunctivitis in five European countries. The study aims to characterize the dose-response relationship of PURETHAL Mites in order to support the optimal dose in terms of clinical efficacy and safety. Enrollment for this trial is complete, and final results are expected in early 2013.

"We are proud to have reached this important milestone according to schedule. We appreciate the commitment of our

investigators, the clinical trial team, and all the patients who have volunteered for this important study. This reinforces our confidence that our ambitions will be realized", said Dr. Harry Flore, CEO of HAL Allergy.

Allergic rhinitis is a common chronic inflammatory disease of the upper airways characterized by symptoms such as sneezing, nasal itch, rhinorrhea, and nasal congestion. The prevalence is estimated to be as high as 25% in developed countries. Besides affecting the quality of life of patients, the disease is associated with considerable direct and indirect costs.

New promising vaccine targets identified for HCV

A team of researchers led by scientists at The Scripps Research Institute in La Jolla (CA, USA) has found antibodies that can prevent infection from widely divergent strains of hepatitis C virus (HCV) in cell culture and animal models. The results of the study were recently published in the journal *Proceedings of the National Academy of Sciences*.¹

According to the World Health Organization (WHO), HCV infects nearly 3% of the world's population, and spreads to 3-4 million new people annually. In some developing countries, HCV prevalence is extremely high, but HCV infections are also a serious public health problem in the developed world. In the US and Europe, up to 14 million people are HCV positive, with an estimated 150,000 new infections each year. HCV principally infects liver cells and causes chronic, often-unnoticed liver inflammation, which eventually can lead to serious liver ailments. The virus already is responsible for about a quarter of annual US cases of liver cirrhosis and primary liver cancer, and it is the leading cause of liver transplants.

Current treatment options cause adverse side effects and are very expensive. To efficiently fight the HCV pandemic, especially in developing countries, an affordable preventive vaccine will be needed. However, an effective

HCV vaccine has so far been elusive, because the virus mutates rapidly and antibodies raised against one isolate of HCV typically will not protect against infection with another strain.

"One of the big goals of HCV vaccine development has been to find an accessible spot on the virus that doesn't change constantly," said Dr. Mansun Law, Assistant Professor at Scripps and senior author of the *PNAS* study.

To identify such vulnerable spots and see whether they could find new broadly neutralizing antibodies, Law and his colleagues used a thorough approach, known as "exhaustive panning". This is a powerful technique for finding rare antibodies that might otherwise go undetected. HCV employs a complex of two envelope glycoproteins, E1 and E2, to contact and fuse with target cells. The researchers harvested this viral E1-E2 complex from HCV-producing cells and used it as a bait for a panel of antibodies derived from the blood of a person with chronic HCV infection. The exhaustive panning technique involves exposing this bait protein to different anti-HCV antibodies in sequence, so that the known antibody-binding sites on the complex are progressively covered until only new ones are left. In this way, the researchers identified 73 new anti-HCV antibodies, which bind to

five distinct "antigenic regions" on the E1-E2 complex. Several of these antibodies demonstrated potential to neutralize infection by a wide range of HCV strains in cell culture. One antibody in particular (AR4A), showed significant neutralizing ability against all 22 HCV strains in a test panel. In collaboration with researchers at Rockefeller University (NY, USA), who recently engineered a line of HCV-infectable mice, AR4A antibodies were found to protect mice from heterologous challenge with two widely different HCV strains.

AR4A and the other newly discovered antibodies attach to sites on the viral envelope that seldom mutate. The next step for Dr. Law and his colleagues is to start making and testing prototype vaccines based on the vulnerable HCV binding sites that have been revealed in the study. Further, the new antibodies will be used to study the structure and function of HCV proteins such as the all-important E1-E2 complex. And finally, potent anti-HCV antibodies such as AR4A could have some therapeutic use, e.g., preventing new HCV liver infections in liver transplant patients.

Reference

1. Giang E, et al. *Proc Natl Acad Sci USA* 2012; 109: 6205-10.

Gardasil may also help women already infected with HPV

The human papilloma virus (HPV) quadrivalent vaccine Gardasil (Merck) is used for protecting against HPV infection. While current data show that HPV vaccination does not reduce progression to cervical precancers in women with ongoing infections at the time of vaccination, there is new evidence that the vaccine could help some women who are already infected.

According to a new study recently published in the *British Medical Journal*,¹ women who are diagnosed with and treated for HPV-related disease after they had the vaccine may have a considerably reduced risk of reoccurring disease. In two recent international, double blind, placebo controlled randomized Phase III efficacy trials of Gardasil (FUTURE I and FUTURE II), more than 17,000 women were followed for approximately four years. Participants who underwent treatment for cervical, vulvar, or vaginal disease continued to be followed until the end of the study, providing the authors of the BMJ study with the unique

opportunity to evaluate the post-treatment effect of vaccination in these women. In a retrospective analysis of data from FUTURE I and FUTURE II, the researchers looked at the subgroup of 1,350 women who were vaccinated and then diagnosed with HPV-related vaginal or vulvar diseases (including genital warts) or had cervical surgery. They found that for women who had cervical surgery after the trials, the chance of developing another bout of HPV-related disease was almost halved (46%) when compared to the placebo group. For women with vaginal or vulvar disease, the risk of another HPV disease was reduced by around a third (35%).

The study authors conclude that only long-term surveillance can determine the effectiveness of the vaccination in this population. There are a number of ongoing trials to look at the safety and impact of HPV vaccines on subsequent diseases.

In an accompanying Editorial,² Dr. Jane Kim, Assistant Professor of Health Decision Science at the Harvard School of Public Health in Cambridge (MA, USA), states: "...the current study moves us closer to understanding the full scope of benefits from HPV vaccination by showing for the first time that vaccine protection against disease can endure beyond the management of HPV related disease in women already vaccinated." However, she cautions that it is too early to generalize from these results. To find out more about the value of Gardasil in women who are already infected will take more and longer studies, but this one does show a glimmer of hope.

Reference

1. Joura EA, et al. BMJ 2012; 344:e1401.
2. Kim JJ. BMJ 2012; 344:e1544

Positive phase 1 results for hand, foot and mouth disease vaccine

The biotech company Inviragen recently reported positive results of a placebo-controlled, randomized Phase 1 clinical trial of its highly purified virus particle vaccine INV21 against Hand, Foot and Mouth Disease (HFMD).

HFMD, caused by enterovirus 71 (EV71), is typically of short duration, but there has been an increase in severe HFMD infections with sequelae that include neurological symptoms such as meningitis, encephalitis and polio-like paralysis. The disease is common in children throughout the world. However, it is endemic in the Asia-Pacific region where its incidence has been steadily increasing over the past two decades. For example, in Singapore in the first nine weeks of 2012, there were 5,568 cases of HFMD compared to 1,908 during the same period last year. In Vietnam over 7,700 children contracted HFMD during the first two months of 2012, with nine deaths. And last

year, 110,000 Vietnamese contracted the disease, resulting in 166 deaths among children. Recent reports reveal more than two million HFMD infections in 2011. No vaccines or therapeutic products exist for HFMD.

The current Phase 1 clinical study tested INV21 in healthy adults. Subjects received two immunizations each of either a high- or low-dose formulation of INV21. Study participants were monitored for safety and for immune response after each administration. Antibodies that neutralize EV71 were measured in individuals of both the low- and high-dose group. One hundred percent of vaccinated individuals had significantly increased EV71 neutralizing antibody responses after immunization, which may signify protection against infection. Further, the vaccine was safe and well tolerated.

"We were able to initiate this study rapidly and complete it in only six months through a productive relationship with the Singapore National University Health System (NUHS) and our collaboration with Duke-NUS Graduate Medical School," commented Dr. Joseph Santangelo, Inviragen's Chief Operating Officer. "Our two-dose INV21 vaccine induced neutralizing antibody responses in all of the immunized adults in this Phase 1 trial, and we look forward to exploring the vaccine's safety and immunogenicity in children in future clinical trials later this year."

Inviragen has offices in Singapore and the United States—in Colorado and Wisconsin. Besides INV21 against HFMD, the company has a vaccine against dengue fever in Phase 2 clinical testing, and several others in the preclinical stage.