The Lancet reports on Inovio Pharma immunotherapy success with HPV

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The highly respected medical journal The Lancet has reported the success of the HPV trial.

Inovio Pharmaceuticals Publishes Successful Phase 2b Trial Results of its HPV Immunotherapy in The Lancet

Distinguished medical journal reports killer T cells produced by immunotherapy regress high grade cervical neoplasia and clears HPV infection

PLYMOUTH MEETING, Pa. – September 17, 2015 – **Inovio Pharmaceuticals, Inc. {NASDAQ: INO}** announced today that The Lancet, one of the world's leading medical journals, published a peer-reviewed article detailing the successful results of its phase 2b trial with VGX-3100 in treating women with high grade cervical neoplasia.

Previously, medical researchers have tried to stimulate therapeutic immune responses against the human papillomavirus (HPV) and cervical lesions with little success. This publication details that VGX-3100, a first-in-class product for treating high grade cervical neoplasia associated with HPV, is the first therapy to demonstrate that activated killer T cells induced in the body have the power to clear neoplastic lesions as well as the virus which caused the disease.

Dr. J. Joseph Kim, Inovio's President and CEO, said, "*Inovio's SynCon® products have overcome the elusive and difficult challenge of generating activated killer T cells in the body which clear established disease as well as eradicate cancer-causing HPV virus*."

"*Building on this proof-of-concept phase 2b study, Inovio is mobilizing to initiate our phase 3 trial for VGX-3100 next year. We are also advancing our two major immunotherapy partnerships, one with MedImmune and another with Roche, as well as driving forward multiple clinical and preclinical cancer products based on our core SynCon® platform*."

Commenting on Inovio's HPV results, two senior investigators at the U.S. National Cancer Institute Division of Cancer Epidemiology & Genetics (Dr. Mark Schiffman and Dr. Nicolas Wentzensen) wrote in The Lancet: "*The current trial represents a major breakthrough and proof-of-principle that therapeutic HPV vaccination is feasible. More broadly, the trial shows that it is possible to boost immune clearance of HPV among women who initially failed to control infection*."

Dr. Mark L. Bagarazzi, Inovio's Chief Medical Officer and the senior author of The Lancet article, said, "*For women with cervical dysplasia there is no alternative treatment except for surgery – a procedure that can bring side effects such as bleeding and fertility complications. Our study of VGX-3100 provides hope for women that a safe, non-surgical option will be available to them*."

Results of the trial were reported in the article entitled, "*Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomized, double-blind, placebo-controlled phase 2b trial*," by C. Trimble, et al. Dr. Cornelia Trimble, Professor of Gynecology and Obstetrics, Oncology, and Pathology at Johns Hopkins School of Medicine, was the principal investigator for the study.

Specifically, the phase 2b trial showed that histopathological regression of high grade cervical neoplasia (CIN2/3) to low grade neoplasia (CIN 1) or no disease occurred in a significantly higher percentage of VGX-3100 recipients compared with placebo recipients. Furthermore, concomitant histopathological regression and clearance of HPV occurred in a significantly higher percentage of VGX-3100 recipients compared with placebo recipients. HPV-specific CD8+ "killer T cells" were also generated in the blood as well as a substantial infiltration of CD8+ cells in the cervical tissue of VGX-3100 recipients, underscoring the role played by Inovio's best-in-class T-cell responses. VGX-3100 was safe and generally well-tolerated.

In VGX-3100-treated women who regressed their lesion, most (43 out of 53) completely cleared their lesions to normal (complete response). Moreover, eighty percent of VGX-3100-treated women who regressed their lesion also eradicated the infecting HPV genotype (i.e. 16 or 18) in the cervix. This is an important outcome as persistence of the virus is associated with recurrence of the disease. All data analyzed per protocol or modified intent to treat were similar with equal statistical significance.

Analyses of patient immune responses showed that overall antigen-specific T cell levels in women treated with VGX-3100 were greater than those treated by placebo at all observation periods. At week 14, T cell levels in women treated with VGX-3100 were ten times greater than those in the placebo group.

Patients who regressed their lesions had higher frequencies of HPV-specific CD8+T cells which co-expressed key molecules important in T cell killing cascade and directly correlated with clinical efficacy. Specifically, we determined that higher levels of CD8+ killer T cells which co-expressed checkpoint molecule CD137 on their surface as well as the cytolytic protein perforin could be a predictive tool for efficacy. As a strong activation marker for CD8+ T cells, stimulation through CD137 has been shown in some systems to confer resistance of CD8+ T cells to the suppressive activity of regulatory T cells and its presence can identify tumor reactive T cells. Perforin is a pore-forming protein deployed by killer T cells to bore holes into the target cell’s plasma membrane and destroy the cell. In fact, the difference in frequencies of CD8+ cells expressing CD137 and perforin was greatest in patients who had both regressed their lesions and cleared HPV compared to patients who did not.

This is the first publication to our knowledge that demonstrates the correlation of antigen-specific CD8 T cells directly to clinical efficacy. Inovio has successfully identified several key biomarkers of killer T cells which can be used to predict the clinical efficacy of VGX-3100 as well as other immunotherapies in future clinical studies.

About VGX-3100

Inovio’s VGX-3100 is an immunotherapy containing two DNA plasmids targeting the E6 and E7 oncogenes of HPV types 16 and 18. These oncogenes are responsible for transforming HPV-infected cells into pre-cancerous and cancerous cells. The treatment is administered to patients by injection into muscle (typically in the arm), followed by electroporation using Inovio’s CELLECTRA® device. VGX-3100 has been shown to induce a robust immune response against the E6 and E7 oncogenes associated with HPV types 16 and 18.

About HPV and Cervical Dysplasia

Human papillomavirus (HPV) is the most common sexually transmitted disease. At any given time, approximately 11% percent of the world population is infected with HPV. Roughly 75% or less of HPV 16/18 infections are cleared by naturally occurring immune responses in women of all ages.

Persistent HPV infection can lead to dysplasia, or premalignant changes, in cervical cells. HPV types 16 and 18 cause 70% of cervical dysplasia and cervical cancer cases. Each year in the United States, 1.4 million women are diagnosed with CIN1 and 300,000-400,000 women are diagnosed with CIN 2/3. All cervical cancers arise from untreated CIN2/3.

About Inovio Pharmaceuticals, Inc.

Inovio is taking immunotherapy to the next level in the fight against cancer and infectious diseases. We are the only immunotherapy company that is generating T cells, in vivo, in high quantity that are fully functional whose killing capacity

correlates with relevant clinical outcomes with a favorable safety profile. With an expanding portfolio of immune therapies, the company is advancing a growing preclinical and clinical stage product pipeline. Partners and collaborators include MedImmune, Roche, University of Pennsylvania, DARPA, GeneOne Life Science, Drexel University, NIH, HIV Vaccines Trial Network, National Cancer Institute, U.S. Military HIV Research Program, and University of Manitoba.

For more information, visit www.inovio.com

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