ONCOVAX®
Turning Cancer On Itself™

RESURGING CANCER VACCINES ON THE CUSP OF A RENAISSANCE

It's been four decades since the United States declared a war on cancer yet the life sciences industry is still plagued by mostly unfulfilled hopes. But the pharmaceutical industry continues to push targeted therapies for cancer despite decades of chemotherapy drugs with limited efficacy and barely tolerable toxicity. This approach has been based on the false premise that all cancer cells are identical, or homogeneous, and that a one-size-fits-all strategy could be aimed at a handful of cancer targets.

A one-size fits all drug approach is no longer practical

There is now compelling evidence from cancer genome DNA sequencing studies revealing the extreme genetic diversity, or heterogeneity, of cancer cells, including the major killers such as colon, breast, lung, is far greater than previously imagined. While the pharma industry continues to advocate for more targeted therapies for smaller patient populations, the hundreds and thousands of cancer mutations revealed over the past few years makes this approach impractical. We cannot treat a heterogeneous disease with homogeneous drugs.

The immune system is designed by nature to protect against diversity of disease

There is one evolutionary approach that already exists to address the magnitude of cancer diversity – the immune system. The immune system constantly protects humans from a diverse array of deadly foreign pathogens, viruses and proteins. With the exception of safe drinking water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth.

> By embracing the heterogeneity of cancer cells within a patient's primary tumor, and by using a cancer vaccine as a preventative measure the way vaccines are intended to be used, cancer vaccines hold tremendous promise to transform cancer treatment.
>
> — Dr. Michael G. Hanna Jr., Founder and Chairman Emeritus

Harnessing the immune system to protect against cancer

In treating cancer as a homogeneous disease, we believe the life sciences industry has failed in attempts to train the immune system to recognize cancer as foreign and defend the body against it. Still, emerging scientific literature continues to support reasoning that cancer immunotherapy can be successful. By finally embracing the heterogeneity of cancer, deploying patient-specific cancer vaccines towards earlier stages of disease, and adapting to lessons learned from 20 years of attempted clinical trials, the cancer immunotherapy field is now on the cusp of a renaissance.

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ONCOVAX OVERVIEW

We believe OncoVAX® is the first cancer vaccine that can both prevent cancer recurrence and address the diversity of cancer cells. Currently preparing for a Phase IIIb clinical trial, OncoVAX is designed to use a patient's own cancer cells to mobilize the body's immune system to prevent the return of colon cancer following surgery. Embracing the now widely recognized heterogeneity of cancer, OncoVAX uses a patient's own tumor to stimulate a broad immune response against the diversity of that patient's cancer cells. OncoVAX is comprised of sterile, live but non-dividing tumor cells obtained following standard-of-care surgical tumor resection for Stage II colon cancer. Within 35 days following surgery, patients are immunized with OncoVAX to prevent disease recurrence, which is incurable and occurs in up to 35% of patients. Patients are given three vaccinations once per week for three weeks, followed by a booster vaccination after six months. A previously completed Phase III trial published in *The Lancet* showed that OncoVAX cut the risk of recurrence by 61% in patients with Stage II colon cancer.

COLON CANCER RECURRENCE IS INCURABLE

The global incidence of Stage I-IV colon cancer is 900,000 patients, of which 269,000 patients have Stage II colon cancer. The prevalence of Stage II has grown with the emergence of more rigorous screening practices and is forecasted to be about 46% of US and EU colon cancer at diagnosis by 2020.

Complete tumor resection has been the gold standard of care in Stage II colon cancer for decades, and no therapies are approved for treatment. However, a significant number of patients — up to 35% — suffer recurrent disease despite surgery. Patients with recurrent disease are classified with Stage IV colon cancer, which is incurable.

TECHNOLOGY

OncoVAX is an active specific immunotherapeutic (ASI) stimulating a patient's immune response to autologous (patient-specific) tumor cells. To prepare OncoVAX, a patient's own tumor is excised, enzymatically dissociated to separate tumor cells from normal tissue, sterilized and gamma-irradiated to render the tumor cells non-dividing and non-tumorigenic, but still metabolically active.

The OncoVAX protocol consists of a total of four vaccines injected intradermally. The first two injections consist of live but non-dividing tumor cells mixed with fresh-frozen Mycobacteria of the TICE strain of Bacillus Calmette-Guerin (BCG). BCG is a bacterial strain proven to stimulate an immune response for the prevention of tuberculosis and for the treatment of bladder cancer. The third and fourth immunizations consist of the same live, non-dividing tumor cells as in the first two injections, but without BCG. The first three immunizations are delivered weekly approximately 30 days after surgical resection of the tumor. The fourth immunization is delivered as a booster six months later. All four vaccines are developed from the original tumor sample obtained from gold-standard surgical resection for Stage II colon cancer.

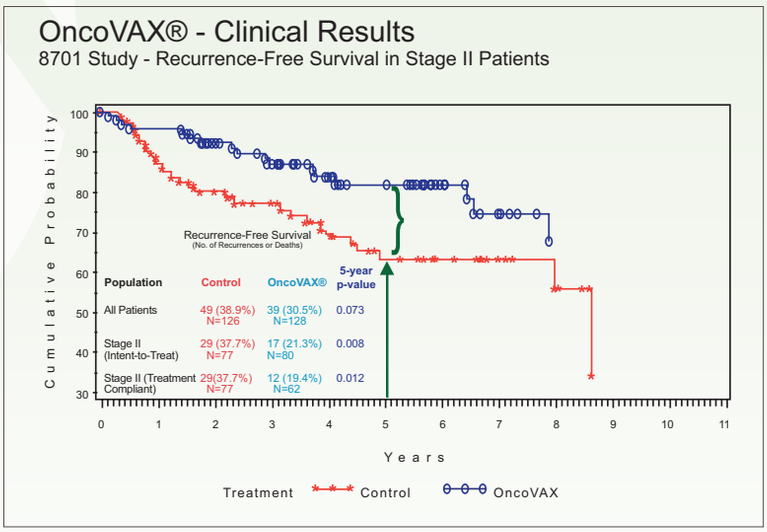
The OncoVAX Difference

- **Autologous, patient-specific live tumor as source of vaccine** – addresses the antigenic diversity of cancer cells and obviates the problem of tumor heterogeneity to trigger a broad immune response
- **Preventing disease rather than treating late stage cancer** – vaccines are intended to protect from disease, however, most cancer vaccines have been used to treat advanced stage disease. OncoVAX is designed to prevent disease after surgical resection of the colon cancer
- **Clinical trial design** – dose, schedule, route of administration all confirmed in clinical studies
- **Manufacturing logistics** – aligned with clinical practice, improved shelf life and cost-effectiveness of developing all four inoculations from a single sample

CLINICAL TRIAL HISTORY

Phase IIIa (Trial 8701)

Results from a Phase IIIa clinical trial in 254 patients with Stage I-IV colon cancer have been published in *The Lancet*. Patients were randomized 1:1 to receive surgery and then observation or OncoVAX immunotherapy. A pre-specified intent-to-treat analysis of Stage II patients reached statistical significance in overall survival at 5 years with 69% vs. 87% surviving (p=0.014). Patients with Stage II disease who received all four inoculations had superior clinical outcomes to those who received fewer than four inoculations. Relative risk of death or recurrence (disease-free survival) for all patients receiving four inoculations was 0.61 (P = 0.034) and relative risk of death or recurrence for patients with Stage II disease receiving four inoculations was 0.40 (P = 0.007). Relative risk of death from any cause in Stage II patients receiving four inoculations was 0.46 (P = 0.046). Disease-free survival in patients with Stage II colon cancer is the agreed endpoint for the Phase IIIb trial under SPA with the FDA.



Bridge Study – Sterility and Bioequivalence

Following the completion of the Phase IIIa trial, the U.S. Food and Drug Administration (FDA) requested that Vaccinogen develop a sterile drug protocol to ensure the elimination of detectable bacteria obtained during tumor resection. Vaccinogen developed patented methods to assure sterility and met compliance requirements of the FDA. The FDA requested an additional study to show the safety and immunogenicity of the new sterile vaccine and to show bioequivalence of the new formulation to the old one. Fifteen of the 15 patients in this study met the primary endpoint of indurations.

Phase IIIb Trial in Stage II Colon Cancer

Vaccinogen has coordinated with the FDA on a Special Protocol Assessment (SPA) for its Phase IIIb confirmatory trial in Stage II colon cancer. The trial will enroll 550 patients, randomized 1:1 to either receive surgery alone or surgery plus OncoVAX. The primary endpoint of the trial is disease-free survival.

Phase I/II Trial in Stage III Colon Cancer

Clinical trial sites enrolling patients with Stage II disease will also enroll up to 30 patients with Stage III disease as part of a Phase I/II pilot trial.

Manufacture and Commercial Processes

A key advantage to the OncoVAX protocol is that it is additive to routine clinical practice. A tumor sample is obtained following gold-standard surgical resection for patients with Stage II disease. Protocol requires that large tumors are obtained (3.0-3.5g) to ensure that enough tumor is available to produce four inoculations with the desired tumor count of live tumor cells. Phase III trials have indicated that the fourth inoculation, a booster at six months, is critical to sustain immune response.

Shelf life of OncoVAX also allows for improvements in logistics. Tumor samples can be transported to a central manufacturing facility within 48 hours of resection. The vaccine can be developed in six hours, sterility testing can be completed in 21 days, and product can be delivered in time for the patients follow up visit approximately 30 days after surgery. The shelf life also enables all four inoculations to be developed from the initial tumor samples to be shipped frozen to the clinical trial sites.

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