1.0 SCIENTIFIC ABSTRACT

Ovarian cancer is the fourth most common cause of cancer death among women in the United States. It is estimated that more than 25,500 new cases of ovarian cancer are diagnosed per year in the United States, and that over 14,500 women die per year from the disease. If diagnosed early and treated, while the cancer is still localized, the five-year survival rate from ovarian cancer is 90%. However, the overwhelming majority of the patients are diagnosed in stages III and IV, and the five year survival rate for all stages combined is only 42%. A number of factors, such as poor tumor differentiation, extension of the tumor through the capsule, and overexpression of tumor markers such as HER-2/*neu* have been associated with a worse prognosis.

In vitro studies of the early adenoviral gene, E1A, indicate that it acts as a tumor inhibitor by repressing oncogenes such as HER-2/*neu*, inducing apoptosis, and increasing the effect of other cancer treatments such as chemotherapy and radiation therapy. The E1A gene can be transferred to cells using E1A-Lipid Complex, which consists of the E1A plasmid complexed to the cationic lipid gene delivery system comprised of DC-Cholesterol* and DOPE**.

Pre-clinical studies using a murine models of ovarian cancer both with and without HER-2/*neu* overexpression have demonstrated that intraperitoneal infusion of E1A-Lipid Complex leads to tumor inhibition and increased survival relative to control/vehicle animals. No meaningful toxicities were seen in mouse toxicology studies performed in support of human clinical trials of E1A-Lipid Complex.

A multi-site, dose-escalation, open-label study of E1A-Lipid Complex has been completed. Eighteen patients were enrolled and received E1A Lipid Complex by infusion into either the abdominal cavity for treatment of intraperitoneal metastatic ovarian cancer (12 patients) or the pleural cavity for treatment of intrapleural breast cancer (six patients). Dose limiting toxicity, a syndrome of fever, nausea, vomiting and abdominal pain, was identified. A maximum tolerated dose of 3.6 mg DNA/m^2 was established for intraperitoneal administration of E1A-Lipid Complex. Biological activity, as measured by detection of E1A protein in tumor cells and down-regulation of HER-2/*neu*, was noted at all doses tested. A Phase I trial is currently underway to define the maximum tolerated dose of E1A-Lipid Complex in combination with chemotherapy.

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* 3β[N', N'-dimethylaminoethane)-carbamoyl] cholesterol

** 1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine

In this Phase II trial, up to 30 patients with advanced ovarian cancer with HER-2/*neu* overexpression will be treated with six cycles of E1A-Lipid Complex. Each cycle will consist of three weekly intraperitoneal infusions of 3.6 mg/m^2 E1A-Lipid Complex (1:3) in a volume of 1000 mL 5% dextrose followed by one week of rest. The primary objective is to determine tumor response by two-dimensional cross products by CT scan. Secondary objectives include (1) expansion of the safety and tolerability profile of E1A-Lipid Complex, (2) measurement of time to disease progression, (3) measurement of overall survival and progression-free survival rates at one and three years, and (4) investigation of the biological effects of E1A-Lipid Complex on ovarian cancer cells. A parallel study, in which the same clinical design and parameters are being investigated, is also being initiated in women with ovarian cancers that do not overexpress HER-2/*neu*.

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