

1.0 SCIENTIFIC ABSTRACT

Data obtained from the Surveillance, Epidemiology, and End Results (SEER) Program indicate that breast and ovarian cancers remain major causes of death for women in the United States. It is estimated that in 1998 more than 25,500 new cases of ovarian cancer were diagnosed in the United States and 14,500 women died from the disease. Epithelial carcinomas account for up to 90% of ovarian malignancies, largely as a result of early abdominal seeding of this neoplasm producing carcinomatosis. Diagnosis of ovarian cancer at an advanced stage (Stage III and IV) and development of resistance to chemotherapy, despite remarkable initial chemosensitivity, account for the grim overall prognosis in these patients. Thus, a newer modality of therapy is needed for these patients. One potential modality is E1A gene therapy given in combination with chemotherapy.

In vitro studies indicate that E1A interacts with cellular mechanisms to increase the sensitivity of neoplastic cells to conventional chemotherapeutic drugs. Preclinical animal studies were conducted using the E1A-Lipid Complex in combination with standard chemotherapeutic agents (paclitaxel, cisplatin, and/or carboplatin). Treatment with chemotherapy drugs and E1A-Lipid Complex resulted in tumor growth inhibition, extended survival of *nu/nu* mice bearing human ovarian SKOV3ip1 tumor cells, and no combination treatment related toxicities were observed beyond those known for the chemotherapy agents. The E1A Lipid Complex consists of the E1A plasmid complexed to the cationic lipid gene delivery system comprised of DC-Cholesterol* and DOPE**.

In a phase 1 study (E1A-9601; RAC #9512-137), eighteen patients were enrolled and received E1A-Lipid Complex (10:1) by infusion into either the abdominal cavity for treatment of intraperitoneal metastatic ovarian cancer (12 patients) or the pleural cavity for treatment of intrapleural metastatic breast cancer (6 patients). Nine of the eighteen patients were not evaluable, due to death, disease progression or voluntary withdrawal. The commonly reported adverse events were fever, nausea, vomiting and abdominal pain. None of the patients required prophylactic treatment for these symptoms. Samples of cells obtained from the pleural effusion or ascites fluid of evaluable patients were positive for E1A gene transfer (by DNA-PCR) and for gene expression (by detection of the E1A protein by immunohistochemistry). HER-2/*neu* was expressed by tumor cells from five of the six breast cancer patients and one of the 12 ovarian cancer patients. Among these six patients with tumors expressing HER-2/*neu*, downregulation was observed in all five breast cancer patients and in the ovarian cancer patient.

In this Phase I trial the E1A Lipid Complex (3:1) will be administered to 21 evaluable patients with epithelial ovarian cancer. In the dose escalation portion of the study, 15 patients will be enrolled and receive three 3-week courses of therapy consisting of an intraperitoneal infusion of E1A-Lipid Complex (3:1) on day 1, followed by intravenous paclitaxel (135 mg/m²) on Day 2, and intraperitoneal cisplatin (100 mg/m²) on Day 3. For the MTD portion of the study, up to six additional patients may then receive six similar treatment courses at the MTD of E1A-Lipid Complex (1:3).

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

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