



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%. There is a desperate need for novel treatment of ovarian cancer, and gene transfer may prove to be such a modality.

E1A, a gene from adenovirus, has been shown to have potent anti-tumor activity through a variety of mechanisms, including down-regulation of *HER-2/neu* expression, potentiation of apoptosis, inhibition of metastasis, and induction of reversion of tumor cells toward a differentiated epithelial phenotype. The *E1A* gene has also been shown to have an additive effect *in vitro* and *in vivo* on the apoptosis induced by chemotherapy and radiotherapy.

E1A can be transferred to cells using tgDCC-*E1A*, which consists of the *E1A* plasmid complexed to the cationic lipid gene delivery system comprised of DC-Cholesterol (3 β [N-(N'-dimethylaminoethane)-carbonyl] cholesterol hydrochloride) and DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine). tgDCC-*E1A* can be injected directly into tumors or infused into body cavities, such as the peritoneum, where cancers can spread. Preclinical studies performed at Targeted Genetics Corporation (TGC) have demonstrated the safety and efficacy of tgDCC-*E1A* alone and in combination with chemotherapy in animal models.

Clinical trials have been conducted at TGC to evaluate the safety and biological activity of tgDCC-*E1A* alone and in combination with chemotherapy for treatment of ovarian cancer. Two phase I single agent clinical trials (Protocols E1A-9601 and C LF 16 0519 9602) have shown that intraperitoneal tgDCC-*E1A* infusions are safe and well-tolerated with a defined dose-limiting toxicity. A phase I trial of tgDCC-*E1A* in combination with chemotherapy (Protocol 09A01) is currently nearing completion, and shows that intraperitoneal tgDCC-*E1A* is well-tolerated when administered with intraperitoneal cisplatin and intravenous paclitaxel at doses up to 9 mg (~5 mg/m²).

The standard of care for recurrent ovarian cancer has changed over the past few years to revolve around intravenous chemotherapy. The chemotherapeutic regimen depends upon the interval between prior treatment and recurrence. Patients who develop recurrent disease more than six months after prior treatment are considered to have "platinum-sensitive" disease, and are generally treated with intravenous carboplatin. Patients who develop recurrent disease less than six months after platinum-based treatment are considered to have "platinum-resistant" disease, and are treated with a variety of non-platinum based chemotherapeutic regimens with marginal success.

In response to the evolving standard of care for ovarian cancer, Targeted Genetics Corporation is expanding its evaluation of tgDCC-E1A to include its administration with intravenous paclitaxel. The primary objective of this study (09D03) is to evaluate toxicity and define a maximum tolerated dose of tgDCC-E1A administered in combination with intravenous paclitaxel in women with platinum-resistant ovarian cancer. This study will complement the recently approved clinical trial (09D01), which proposes to evaluate and define toxicity of tgDCC-E1A in combination with intravenous carboplatin in women with recurrent platinum-sensitive ovarian cancer.

Up to 30 subjects will be treated on a weekly basis with one of four dose combinations of an intraperitoneal infusion of tgDCC-E1A at doses of 3.6, 5.0, or 7.0 mg/m² and intravenous paclitaxel at doses of 60 or 80 mg/m². Six subjects will be a comparison group, and treated only with paclitaxel 80mg/m². The dose combinations will be assigned using the Continuous Reassessment Method as described in the protocol. Both groups will be treated with six weeks of therapy, after which a restaging of the cancer will be performed. Those women who show stabilization of their disease, or improvement, will be then treated with another six weeks of the therapy they appear to be tolerating.

Elucidation of the safety profile of tgDCC-E1A in combination with paclitaxel in this Phase 1 study will pave the way for future trials to determine if the additive anti-tumor effects of tgDCC-E1A and chemotherapy seen *in vitro* and *in vivo* translate into clinical benefit for ovarian cancer patients.