

SCIENTIFIC ABSTRACT

PHASE I/II STUDY OF ALLOGENEIC HUMAN GM-CSF GENE TRANSDUCED PROSTATE CANCER VACCINES IN PATIENTS WITH METASTATIC PROSTATE CARCINOMA

This phase I/II study in patients with advanced prostate cancer is undertaken with a view toward developing an effective means of treating metastatic recurrence following surgery. No curative therapy exists for metastatic human prostate cancer (PCA). For fully informed patients with a recurrence of metastatic prostate cancer diagnosed by a serum PSA elevation after surgery, investigational therapies are a part of the standard of care for appropriate patients who give informed consent.

The scientific rationale for the design of his trial stems from 6 years of preclinical studies and early clinical studies to treat urological cancers using a new strategy of inducing specific anti-tumor immune responses. By inserting immunostimulatory genes into tumor cells, and using them as vaccines, systemic T-cell specific anti-tumor immune responses can be induced. They can eradicate implanted chemotherapy - resistant tumors of a variety of histologic types in animals of up to 1×10^4 cells. If safe and effective, this therapy is targeted for outpatient use as adjuvant therapy following surgical removal of the primary cancer. In preclinical models of hormone therapy refractory PCA, this *ex vivo* strategy of gene therapy using the GM-CSF gene can be curative. Technical limitations in this approach have not been patient toxicities, or the inability to achieve desired high level gene transfer *ex vivo*. The therapy has no dose limiting toxicities to date. It can be given to advanced cancer patients including prostate cancer patients on an outpatient basis. No safety concerns have arisen from the human use of recombinant DNA vector MFG. Instead, a limitation has been the finite numbers of autologous cancer cells that can be expanded from many primary cancers. This limits the total production yield of vaccine and evaluation of the safety and efficacy of multiple vaccinations. An estimated 4 in 5 potentially eligible prostate cancer patients for vaccination do not have enough primary tumor for the cell culture after gene transfer to achieve vaccine doses which show preliminary evidence of clinical antitumor activity. In patients who recur with metastatic prostate cancer after surgery, the primary tumor is generally not banked for gene transfer later. Thus, the use of allogeneic (immortalized human prostate cancer cell lines) which are genetically modified with the human GM-CSF gene allows the evaluation of the vaccination strategy with a virtually limitless supply of vaccine for patients who could not receive an autologous GM-CSF gene transduced PCA vaccine. The 2 allogeneic cell lines selected represent a wide spectrum of potential peptide antigens and genomic alterations represented in > 90% of clinical prostate cancers. The allogeneic vaccine (GVAX™) was manufactured by Cell Genesys Corporation. The dose of allogeneic vaccine cells and range of GM-CSF secretion are based on outpatient safety data, and preliminary evidence of efficacy of MFG-GM-CSF gene transduced irradiated autologous tumor vaccines at equivalent doses in our previous clinical trial in advanced renal cell carcinoma. Up to 30 patients will be enrolled as the study is powered to estimate efficacy. The specific aims of the study are described below.

Phase I Study Aims

1. To confirm the safety of skin injections of cultured, lethally irradiated, allogeneic GM-CSF gene transduced PCA cell lines secreting GM-CSF at $148-639 \text{ ng}/10^6/24$ hours.
2. To describe and quantitate the acute toxicities, if any, of 8 weekly injections irradiated GM-CSF gene transduced PCA cell line vaccine therapy.
3. To assay both *in vitro* and *in vivo* the contribution of PCA cell GM-CSF gene transduction to the induction of specific antitumor immune responses in men with advanced PCA.

Phase II Study Aims

1. To evaluate anti-tumor efficacy by measuring serum PSA response rates and response durations.
2. To assay both *in vitro* and *in vivo* the contribution of PCA cell GM-CSF gene transduction to the induction of specific antitumor immune responses in men with micrometastatic PCA.