

## **PHASE II TRIAL OF CG8123, AN AUTOLOGOUS CANCER VACCINE (GVAX), IN PATIENTS WITH SELECTED STAGE IIIB AND IV BRONCHIOALVEOLAR CARCINOMA (BAC)**

### **Scientific Abstract**

#### **Background**

Bronchioloalveolar carcinoma (BAC) is a histologic subtype of non-small cell lung cancer (NSCLC) that is increasing in incidence. BAC appears histologically as a well-differentiated adenocarcinoma and is usually confined to the lung spreading along the alveolar septa. BAC represents approximately 2 - 5% of new NSCLC cases and is reported to be more common in females, non-smokers, and younger patients compared to other subtypes of NSCLC. Radiographically, it may present as discrete nodules in 85% or lobar pneumonitis / diffuse infiltrate in 15% of patients. Patients with advanced BAC are more likely to have bilateral diffuse pulmonary involvement and are less likely to develop distant metastases than other histologic subtypes of advanced NSCLC. Among patients with Stage IIIB and IV NSCLC, a median survival of 15 months in BAC compares favorably to the median survival of 10 months seen in other subtypes.

The relative infrequency of BAC has led to a dearth of clinical trials specifically evaluating this sub-group of patients and it is unclear whether chemotherapy has equal efficacy in BAC compared to other subtypes of NSCLC. The only prospective Phase II BAC trial was recently completed by the Southwest Oncology Group (**S9714**). Fifty-eight Stage IIIB and IV BAC patients were treated with paclitaxel 35 mg/m<sup>2</sup>/24 hours by 96-hour infusion on a 21-day cycle (140 mg/m<sup>2</sup> total per cycle). The median survival was twelve months and the three-year survival was 10%. While the objective response rate was 14%, the toxicity of 96-hour paclitaxel was considerable (66% of patients experienced Grade 3 or higher toxicity and there were 5 toxic deaths). Of note is that response rate was the primary endpoint of this study. The use of response rate as a primary outcome may be problematic for patients with a diffuse pattern of disease-spread as assessment of tumor response may be very difficult. Although localized BAC can be cured with surgical resection, at the present time, optimal treatment for advanced BAC remains unclear. However, **S9714** is the first trial to prospectively establish response rate and survival data for patients with unresectable BAC. This data can be used as a historical control against which future therapeutic trials can be compared.

There is clearly a need to develop other approaches to target advanced BAC. The Southwest Oncology Group is currently conducting a Phase II study of Iressa (ZD 1839), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, in patients with BAC. p53 gene transfer using an adenoviral vector delivered via bronchoalveolar lavage is being explored at the University of Wisconsin. CG8123 (formally known as GVAX), an autologous anti-tumor vaccine modified with an adenoviral vector to secrete GM-CSF, has also demonstrated efficacy in BAC. Because the vaccine is autologous, tumor tissue is required from each patient - to manufacture their individual vaccine. This usually requires a surgical procedure to remove an adequate volume of tissue. In a Phase I study of CG8123 in NSCLC, two of three BAC patients treated with CG8123 had durable complete responses lasting 9 and 16 months respectively. As a result of these findings, we are proposing that CG8123 be studied in a Phase II study in BAC. Vaccines have not been specifically studied in BAC prior to this trial.

Given that there is no curative therapy for patients with unresectable BAC and that despite its more indolent course it remains inevitably a fatal disease there is clearly a need to develop other approaches to target advanced BAC. As a result of the promising findings in the Phase I study with CG8123 we are proposing that CG8123 be studied in a Phase II study in BAC.

#### **Objectives**

The objectives of this Phase II study are:

1. To assess overall survival in patients with advanced bronchioloalveolar carcinoma (BAC) treated with CG8123 separately in patients with or without prior systemic therapy for BAC;
2. To evaluate progression-free survival separately based on prior systemic therapy, of patients response rate (confirmed plus unconfirmed, complete plus partial) in the subset with measurable disease using both the standard RECIST criteria and by computer-assisted image analysis and the frequency and severity of toxicities in this patient population treated with this regimen;

3. To evaluate patient report of functional status;
4. To investigate in an exploratory manner, the association of p27 and ERCC1 expression levels with patient outcomes.

### **Patient Population**

Stage IIIB/IV BAC, with accessible tumor to harvest for vaccine processing, measurable tumor remaining following tumor harvest. About 58 patients who have not received other treatments for BAC will take part in this study. Another 41 patients who have received prior treatments for BAC will participate. Allowing for a percentage of vaccine production failure of 25%, about 44 previously untreated and 31 previously treated patients will be eligible for analysis.

### **Study Design**

This is a Phase II multi-center, open-label study in selected patients with stage IIIB or IV bronchioloalveolar carcinoma (BAC). Eligible patients will be stratified into two groups with separate accrual goals: Group 1 - No prior systemic cancer therapy for BAC; Group 2 - Prior systemic cancer therapy for BAC. Eligible patients will also be stratified into two additional groups to determine feasibility of vaccine production: Group 1 - Diffuse pattern BAC; Group 2 - Nodular pattern BAC.

### **Dose and Schedule**

The vaccine dose is individualized for each patient based on the total vaccine yield and ranges from  $2 \times 10^6$  to  $300 \times 10^6$  cells/vaccine. The dose for each vaccination is equivalent. This variation in cell dosage is designed to maximize each patient's opportunity to receive the maximum possible vaccine dose and is not based on any expectation of significant differences in toxicity as a function of cell number. A total of five vaccines will be administered by intradermal injection at 2-week intervals. The minimum total vaccine dose required for treatment is  $10 \times 10^6$  cells ( $2 \times 10^6$  cells x 5 vaccinations).

### **Endpoints**

#### **List primary and secondary study safety and efficacy endpoints (ie. similar to objectives).**

Blood will be collected prior to vaccine administration, Week 5 and at Week 13 for: Antigen-specific ELISPOT assays to monitor immune responses to tumor-associated antigens (CEA, NY-ESO-1, MAGE-3, p53, Her2/neu and ART-4 peptides) will be performed on peripheral blood mononuclear cells (PMBC); and ELISA assays for IFN $\gamma$ , IL-10, TGF $\beta$  as mediators and inhibitors of antitumor responses will be performed on serum.

(These are not study endpoints)

Safety will be monitored by physical examination, laboratory evaluations, and assessment of adverse events. Patients will be monitored for progression-free survival and overall survival. Tumor response will be followed by radiologic evaluations. Quality of life assessments will be performed to measure improvements in cancer-related symptoms.

### **Product**

Patient tumor tissue collected at clinical sites will be shipped to a central Cell Genesys facility for vaccine production. Solid tumors are digested to a single-cell suspension using mechanical methods. Tumor cells from pleural effusions are isolated using density gradient separation. Tumor cells are then genetically modified to secrete human GM-CSF by exposure to a replication-deficient adenoviral vector containing the gene for human GM-CSF (CG6444). Following transduction, cells are washed and irradiated to prevent cell proliferation. Cells are then aliquoted into vials and frozen at  $-70^{\circ}\text{C}$  until immediately prior to administration.