

## 4. INTRODUCTION

### 4.1 Investigational Proposal

A Phase II protocol is proposed to assess safety and efficacy of intratumoral administration of Allovectin-7 in patients with recurrent or persistent squamous cell carcinoma of the head and neck. This immunotherapeutic approach is intended to stimulate an immune response by expressing HLA-B7 antigen within the tumor and potentially restoring some degree of major histocompatibility complex (MHC) class I tumor antigen presentation. Additionally, evaluation of the impact of therapy on quality of life parameters as determined by responses to standardized quality of life questionnaires is proposed.

### 4.2 Overview

Squamous cell carcinoma (SCCa) constitutes the vast majority of head and neck cancers. If identified early, these cancers can be treated relatively easily, either surgically or radiotherapeutically with an excellent cure rate. Unfortunately, most cancers are diagnosed relatively late with the disease at an advanced stage. The standard form of treatment for these patients with advanced head and neck SCCa is surgical resection followed by radiation therapy, but five year survival is under 50%. In addition, there is a significant subset of patients who are so advanced at the time of presentation that they are regarded as incurable by conventional therapy, including chemotherapy, which has yielded little improvement in survival of these patients. The average response rate for cisplatin in combination with 5-FU in recurrent or newly diagnosed squamous cell carcinoma was 50% for 365 evaluable patients in 12 trials (1). All trials considered cisplatin-based combination therapy to be more effective than single agents. The response to cisplatin plus infusional 5-FU is a 32% overall rate with 5-15% complete response. There is no improvement in the overall survival (2). The median survival for these patients is 6 months and 20% survive to one year (3).

Patients whose cancer recurs after conventional therapy have a dismal prognosis. Of equal concern, is the quality of life for these patients which can be extremely poor. Local disease often interferes with vital functions, e.g. swallowing, breathing, etc. (4). Therefore, the immunological reduction of tumor burden to improve quality of life can be a significant end point for the comfort and well-being of this patient population.

### 4.3 Allovectin-7

Allovectin-7 is a plasmid DNA encoding both the heavy and light chains of the MHC class I antigen, HLA-B7 and  $\beta$ 2 microglobulin, formulated with a cationic lipid. The plasmid DNA/lipid is administered intralesionally. The rationale for the Phase II trial was developed from the preclinical and Phase I clinical observations that gene transfer, gene product expression and the triggering of a cell-mediated immune response could

be accomplished safely and reproducibly. Clinical benefit was observed in several patients with advanced head and neck cancer in a Phase I trial and subsequent Phase II trial.

Allovectin-7's product concept is based on the observation that tumors often lose their ability to present antigens due to quantitative or qualitative deficiencies in MHC class I expression (5). Gene transfer of MHC class I HLA-B7 to tumor cells represents a form of "substitution therapy" to restore deficient antigen expression and trigger an antitumor immune response. HLA-B7 was chosen because it is a relatively infrequent haplotype and an allogeneic immune response would be triggered independently of tumor antigens in HLA-B7 negative patients.