Scientific Abstract:

Head and neck cancer (HNC) is estimated to have affected approximately 634,000 men and 227,000 women worldwide in the year 1999[1]. In the United States, approximately 37,000 cases of head and neck cancer are diagnosed on an annual basis, resulting in approximately 12,000 deaths annually[2]. Of these patients, two-thirds present with locoregionally advanced disease (AJCC stage III or IV) and one-third with early stage disease (AJCC stage I or II). Approximately 95% of all head and neck malignancies are squamous cell carcinomas. Elderly patients represent a rapidly growing number of patients with cancer in most industrialized countries[3]. The effect of age on prognosis and response to treatment remains unclear in those diagnosed with cancer and significant controversy exists on the most appropriate types of therapy for these patients.

Approximately 50% of patients diagnosed with HNC are age greater than 65[4]. Importantly, the prevalence of co-morbid medical conditions is high in this population leading to the difficulties in managing these patients. The most common conditions are those of hypertension and coronary artery disease and can impose treatment modifications or limitations. In addition, patients with HNC are at high risk for the development of second primary tumors, synchronous or metachronous, that may involve the head and neck region as well as other organs, predominantly the lung[5]. A significant number of patients are ineligible for clinical trials due to poor performance status or co-morbidities. The experience with chemoradiotherapy in these patients, as well as in the elderly, is limited.

Current management of HNC has evolved from poorly effective single modality therapy to an integrated, highly effective multidisciplinary approach over the past two decades. Still, the treatment of HNC in the elderly (patients >70) and in general patients of all ages with a poor performance status (i.e. ECOG=2) remains a clinical challenge. Despite improving cure rates on the order of 60-70% in recent studies[6-9] in locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC), the combined modality approach used (surgery + chemoradiation, or definitive chemoradiation) is frequently poorly tolerated in this patient population. Radiotherapy alone on the other hand is not sufficient to achieve similar efficacy. Given the increased toxicities encountered with aggressive therapies and the fact that radiation therapy alone may not be sufficient treatment for disease control in this patient population, strategies to enhance the efficacy of radiation therapy using other less toxic approaches is of interest. One such promising method is the use of local intratumoral therapies given concurrently with radiation that avoid the toxicities of the chemotherapy.

TNFerade™ biologic is an El-, E4-, and partial E3-deleted, replication-deficient adenovirus serotype 5 vector, including the human TNF-α cDNA with a portion of the Egr-1 chemoradiation inducible promoter ligated upstream. The use of TNFerade™ biologic gene transfer therapy provides a strategy that seems particularly appropriate in the context of TNF-a, which has documented potent anti-cancer properties, but high systemic toxicity. In addition, direct injection of the gene into the tumor provides a convenient means of delivery. TNFerade™ biologic has the additional advantage

compared to most other anti-cancer gene transfer therapy strategies that it capitalizes on a secreted protein (TNF-α). Consequently, only a certain (presumably small) fraction of the cells within the tumor need to be transfected and secrete the protein.

TNFerade™ biologic is also selected due to its synergy with radiation. Based on previous studies, local administration of TNFerade™ biologic in combination with fractionated external beam radiotherapy can result in increased response rates in solid tumors as compared with radiation therapy alone.

Thereby, the purpose of this study is to assess the safety, tolerability and "Proof of Concept" of TNFerade™ biologic combined with conventional once daily radiation therapy in elderly or frail patients with new onset locally advanced head and neck tumors. The hypothesis is that TNFerade™ biologic combined with radiation will be well tolerated in the elderly, and will demonstrate biological activity compared with historical cohorts treated with radiation alone.

References:

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