

Non-Technical Abstract:

This study, entitled "A Phase I/II Safety, Tolerability and "Proof Of Concept" Study of Radiotherapy and Intratumoral Injections of TNFerade™ (Ad_{Gv}EGR.TNF.11D) for Elderly or Frail Patients with Head and Neck Cancer", will consist of two separate parts: a dose-escalation phase (12 to 18 patients), followed by a fixed dose phase (44 additional patients). Patients in both study phases will receive treatment over 7 weekly cycles. TNFerade™ biologic will be given as intratumoral injections once per cycle, preferably on the first day of each 7-day treatment cycle, followed by radiation therapy given on days 1-5 per cycle (1.8-2 Gy fractions, up to a total dose of 72 Gy). TNFerade™ biologic will be administered as intratumoral injection via direct visualization. Up to five lesions within the radiation field can be injected; and with each subsequent injection, the investigator will attempt to treat differing areas of the injected tumors.

The dose-escalation phase will assess the safety and tolerability of intratumoral injection of TNFerade™ biologic (4×10^9 , 4×10^{10} or 4×10^{11} PU) in up to 18 patients undergoing first-line radiation therapy for locally advanced head and neck malignancies. Patients will be injected with TNFerade™ biologic once a week for 7 weeks (weeks 1-7) during radiation therapy. Three to six patients will be enrolled per dose cohort in the Phase I dose-escalation according to the standard "3+3" design (up to 18 patients total) in order to establish the maximum tolerated dose (MTD) of TNFerade™ biologic.

In the fixed dose phase, an additional 44 patients will be studied at the MTD of TNFerade™ biologic (or 4×10^{11} PU if the MTD is not reached). All patients in the fixed dose study portion will receive TNFerade™ biologic and radiation therapy. Patients in the dose-escalation phase who are treated at the recommended fixed dose will be included in the fixed dose phase analysis, for a total of 50 patients in final analysis.

For both phases of the study, conventional radiation therapy will be administered once daily at 1.8 to 2 Gy per fraction. A total tumor dose of 68 to 72 Gy will be administered in 7 to 8 weeks (5 days per week).

The primary objective of the dose-escalation phase is to assess the safety, MTD, and the dose limiting toxicity of TNFerade™ biologic combined with radiation therapy in elderly or frail patients with locally advanced head and neck tumors. For the fixed dose phase, the objective is to assess the anti-tumor activity of the combination of TNFerade™ biologic and radiation therapy in elderly or frail patients with locally advanced head and neck cancer. The primary endpoint will be locoregional control rate at 2 years post-treatment.

Elderly (≥ 70 years of age) or frail (ECOG performance status 2 or with comorbidities) patients with newly diagnosed, previously untreated, locoregionally advanced head and neck cancer who are judged to be poor candidates for chemotherapy will be included in this study. Patients with metastatic disease are excluded (see Protocol **Section 6.2** for additional criteria).

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In conclusion, TNFerade™ biologic may enhance the efficacy of radiation therapy for head and neck cancer without significantly increasing locoregional or systemic toxicities. This combined therapy may be particularly useful for elderly or frail patients with head and neck cancer, who are at high risk for complications with chemoradiotherapy treatments and are usually excluded from chemoradiotherapy programs. Thus, radiation therapy plus TNFerade™ biologic may represent an alternative less toxic therapy for this patient population.