

Non-Technical Abstract:

This study, entitled "A Phase I/II Safety, Tolerability and "Proof of Concept" Study of TNFerade™ in Combination with Concomitant Radiotherapy, Fluorouracil, and Hydroxyurea (TNF-FHX) for Patients with Unresectable Recurrent Head and Neck Cancer", will consist of two separate parts: a dose-escalation phase (up to 18 patients), followed by a fixed dose phase (54 additional patients). Patients in both study phases will receive treatment over 7 two-week cycles (14 weeks). One treatment cycle will consist of 5 days of treatment, followed by 9 days of recovery (a "week on/week off" schedule). TNFerade™ biologic will be given as intratumoral injections once per cycle, preferably on the first day of each 14-day treatment cycle. Radiation will be given on days 1-5 per cycle, in 1.8-2 Gy fractions, up to a total dose of 63-70 Gy. Starting with the evening dose on Day 0 of each cycle, hydroxyurea (HU) and continuous infusion of 5-Fluorouracil (5-FU) will be administered. TNFerade™ biologic will only be given concurrently with radiation, on a day that radiation is administered. 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 in patients treated with the TNF-FHX regimen (TNFerade™ biologic, 5-FU, HU, and Radiotherapy) for recurrent, unresectable head and neck malignancies that were previously irradiated. Patients will be injected with TNFerade™ biologic (4×10^9 , 4×10^{10} , or 4×10^{11} PU) at the beginning of each treatment cycle, at that time they will also receive 5-FU, HU, and conventional radiation therapy. Three to six patients will be enrolled per dose cohort in the dose-escalation phase 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 54 patients will be studied at the MTD of TNFerade™ biologic (or at 4×10^{11} PU if the MTD is not reached). All patients in the fixed dose study portion will be treated with the TNF-FHX regimen. 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 60 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. Hydroxyurea and Fluorouracil are given on Days 0-5. All chemoradiotherapy is administered on a "week-on/week-off" schedule.

The primary objective of the dose-escalation phase is to determine the safety, the MTD, and dose limiting toxicity (DLT) of TNFerade™ biologic in combination 5-FU, HU, and standard daily radiotherapy in patients with unresectable recurrent head and neck cancer. For the fixed dose phase, the objective is to assess the anti-tumor activity of the combination of TNFerade™ biologic and 5-FU, HU, and radiotherapy in patients with unresectable recurrent head and neck cancer; the primary endpoint is locoregional control rate at 2 years post-treatment.

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All patients previously treated with radiation for head and neck cancer, who now have an unresectable, locoregional recurrence with no clinically measurable distant disease, or those patients in whom distant disease is of low volume and local and regional palliation, are eligible (see Protocol **Section 6.2** for additional criteria).