



# Long Term Survival Analysis of Multi-Center Clinical Trial Using Endoscopy (END) and Endoscopic Ultrasound (EUS) Guided Fine Needle Injection (FNI) of TNFerade™ Biologic (TNF) in Patients with Locally Advanced Esophageal Cancer

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## Background:

Despite neoadjuvant therapy and aggressive surgical resections, the prognosis for esophageal cancer remains poor. TNFerade™ Biologic (TNF) is a second-generation replication-deficient adenovector carrying the transgene encoding human TNF-α regulated by the radiation-inducible promoter Egr-1. This is the first clinical trial using TNF in patients with esophageal cancer. Safety data have been previously presented. Updated efficacy and survival data are now reported.

## Study Design:

### Multi-center Dose-Escalating Design

**Patient Population:** Adult subjects with locally advanced (Stage 2 or 3, assessed by EUS), resectable, histologically confirmed adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction who had not received prior treatment for cancer. Metastatic patients and patients with T4 staging were excluded.

**TNF Delivery:** TNF was administered weekly x 5 via intratumoral injections by either endoscopic ultrasound-guided or conventional endoscopy (as per study site preference) during a 5½-week course of chemoradiation (45 Gy RT + cisplatin [75 mg/m<sup>2</sup> on day 1 and day 29] and 5-FU [1000 mg/m<sup>2</sup>/day via continuous intravenous infusion for 96 hours starting day 1 and day 29]). Successive dosing cohorts received TNF at 4x10<sup>8</sup>, 4x10<sup>9</sup>, 4x10<sup>10</sup>, and 4x10<sup>11</sup> PU (in 2 ml volume, divided into up to 4 injections) at each weekly administration session without intrapatient dose escalation.

## Study Objectives:

- Assess safety, feasibility, and tolerability of weekly preoperative intratumoral injections of TNF concurrent with 5-FU, cisplatin and 45Gy of external radiation therapy in patients with loco-regional esophageal carcinoma who are candidates for resection.
- Assess dose response trends and establish the dose to be used in future investigations.

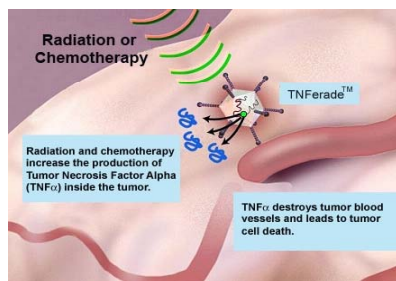
## TNFerade™ (TNF):

TNF is an adenovector containing the TNF-α gene.

- Administered intratumorally

- Causes the secretion of TNF-α protein in tumors, minimizing TNF-α levels in the bloodstream

- Has anti-tumor effects distal to local injection fields in preclinical models



**TNF is intended for use in combination with standard chemotherapy and/or radiation therapy**

## TNF-α:

- Causes collapse of tumor vasculature
- Stimulates pro-inflammatory and apoptotic pathways within the tumor
- Necrotizing action of TNF-α may create an *in situ* tumor lysate
- Activates immune system:
  - Increases expression of MHC Class I and II antigens
  - Enhances infiltration of CD8+ T cells
  - Promotes dendritic cell maturation

## Results:

Figure 1: Kaplan-Meier Graph of Overall Survival (all patients) vs. Historical Controls

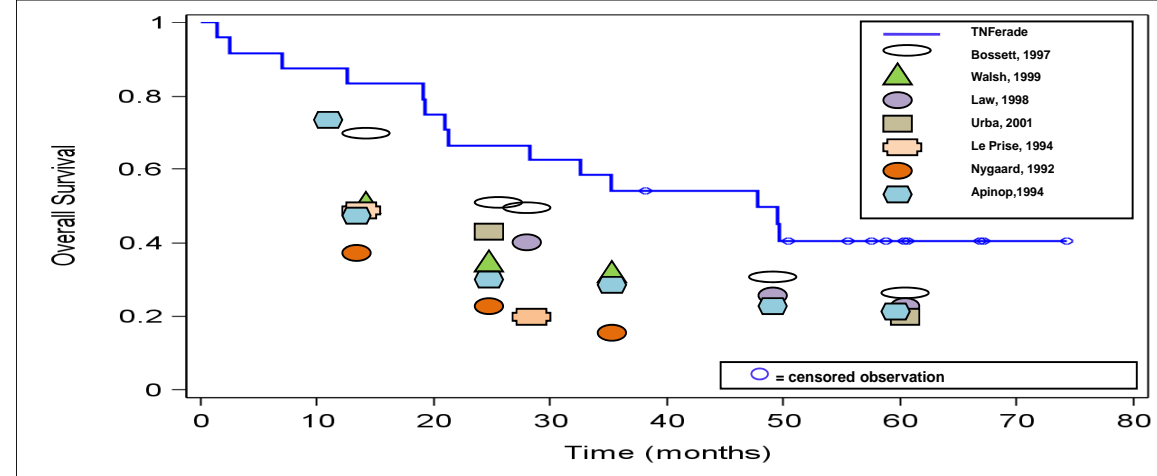


Figure 2: Kaplan-Meier Graph of Survival by Dose Group

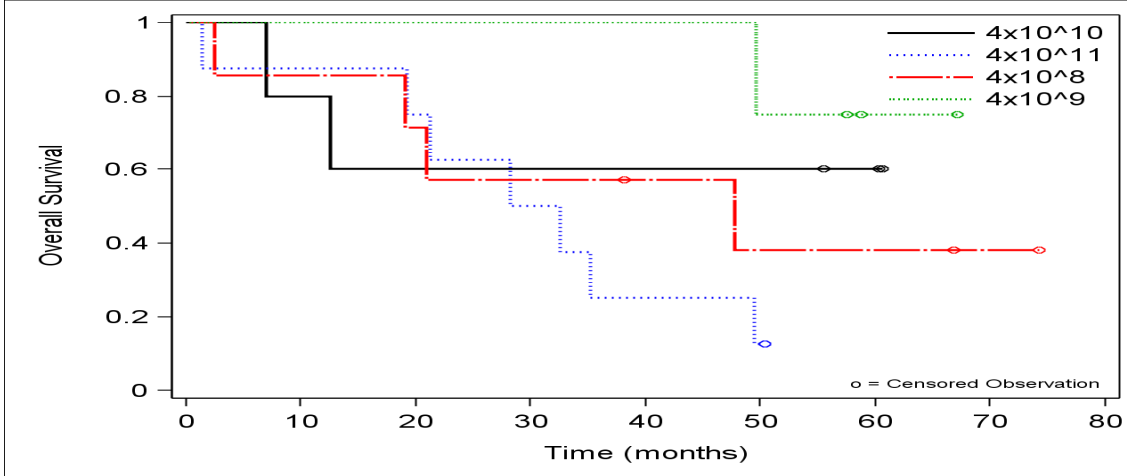


Table 1: Baseline Demographics

	4x10 <sup>8</sup> PU (n=7)	4x10 <sup>9</sup> PU (n=4)	4x10 <sup>10</sup> PU (n=5)	4x10 <sup>11</sup> PU (n=8)
Median age (years)	62	62	59	61
Male n (%)	7 (100%)	4 (100%)	3 (60%)	7 (88%)
Median KPS	90	90	90	90
Adenocarcinoma n (%)	6 (86%)	3 (75%)	4 (80%)	7 (88%)
T3 Staging n (%)	7 (100%)	3 (75%)	5 (100%)	8 (100%)
N1 Staging n (%)	5 (71%)	3 (75%)	5 (100%)	5 (63%)

Table 2: Response to TNFerade and Chemoradiation

	4x10 <sup>8</sup> PU (n=7)	4x10 <sup>9</sup> PU (n=4)	4x10 <sup>10</sup> PU (n=5)	4x10 <sup>11</sup> PU (n=8)
Resected (# patients)	6 (86%)	3 (75%)	4 (80%)	6 (75%)
Pathological Complete Response (pCR)	1/6 (17%)	3/3 (100%) <sup>1</sup>	1/4 (25%)	1/6 (14%) <sup>1,2</sup>
N1 at entry, path evaluable	4	3	4	5
N0 at pathology	2/4 (50%)	3/3 (100%)	3/4 (75%)	1/5 (20%)
T3 at entry, path evaluable	6	3	4	7 <sup>2</sup>
T3 → T2 - T0 on pathology	3/6 (50%)	3/3 (100%)	1/4 (25%)	4/7 (57%)

<sup>1</sup> Two additional patients (one treated at 4x10<sup>9</sup> PU, and one treated at 4x10<sup>11</sup> PU) who did not undergo surgical resection experienced complete responses radiographically and remain disease-free at 66 and 48 months, respectively.

<sup>2</sup> Pathology obtained via autopsy.

Figure 3: Luminal and Histopathologic Responses



Patient 3, originally staged T3N1, treated with TNFerade at 4x10<sup>8</sup> PU. Histologic analysis of resected specimen showed complete pathologic response in the primary tumor as well as lymph nodes. H&E Stains show pathology from one resected lymph node.

## Summary Results:

In the 24 patients, the majority of tumors were adenocarcinoma (20/24), T3 (23/24), and N1 (18/24). Five year follow-up was reached in 3 out of 4 groups (4x10<sup>8</sup> - 4x10<sup>10</sup> PU) and showed an overall 5-year survival rate of 56% in these three groups combined. The overall survival rate for the entire cohort was 42% and the overall median survival was 47.7 months. Literature review of historical controls indicates a range of median survival from 9.7 to 34.0 months. At the 4x10<sup>9</sup> PU dose, pCR was seen in 3/3 (100%) of resected tumors, with a radiographic CR in a fourth patient; all four (100%) remained disease-free up to 48 months. At the 4x10<sup>10</sup> PU dose, pCR was seen in 1/4 (25%) of resected tumors and the median survival has not yet been reached. The median survival for the 4x10<sup>8</sup> and 4x10<sup>11</sup> PU doses are 47.4 and 30.4 months, respectively.

## Conclusions:

- TNF was administered as weekly intratumoral injections via endoscopy in combination with cisplatin, infusional 5-FU, and radiation, with the maximally tolerated dose not reached at the 4 x 10<sup>11</sup> PU dose level.
- TNF resulted in pCR rates at 32% for the patients resected in the study and 100% in the 4x10<sup>9</sup> PU cohort.
- TNF in combination with chemoradiation in cohort of 24 pts resulted in a median survival of 47.7months (all doses combined) and a 5-year survival in the combined three lower doses of 56%.
- Encouraging increases in survival versus historical controls warrant additional evaluation.