

## BACKGROUND:

TNFerade is a replication-deficient adenovector containing the human Tumor Necrosis Factor Alpha (TNF- $\alpha$ ) gene, regulated by the chemoradiation-inducible promoter, EGR-1. A 50 patient, Phase II dose-escalation study in LAPC suggested a possible dose-dependent improvement in survival. To confirm these findings, the randomized Pancreatic Cancer Clinical Trial with TNFerade (P-CT) study was developed. P-CT is a 330 patient study, powered to detect a 20% absolute increase in the primary efficacy endpoint (12 month survival) compared to standard of care (SOC) chemoradiation. Patients are randomized in a 2:1 ratio to TNFerade plus standard therapy, or standard therapy alone.

## OBJECTIVES:

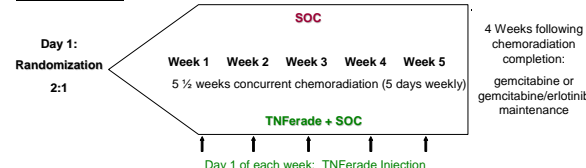
- Primary efficacy endpoint: 12-month survival rate, as compared to standard of care control.
- Secondary endpoints / measures: tumor response rates, surgical down-staging rates, duration of overall survival, change in CA 19-9 levels, and PK profile of circulating TNF- $\alpha$  following treatment with TNFerade.
- An interim analysis of objective response was planned after the first 51 patients were treated.
- As part of a risk/benefit assessment for the FDA to allow clearance to expand the methods of product delivery from the percutaneous route (PTA) to include delivery by endoscopic ultrasound (EUS), other relevant safety and secondary endpoint data (overall survival, CA 19-9, etc.) were analyzed. Note that the DSMB for the study did not initiate or recommend this assessment.

## STUDY DESIGN:

**Patient Population:** Locally advanced, unresectable adenocarcinoma of the pancreas.

**Treatment:** TNFerade is administered as 5 weekly intratumoral injections, in a total weekly dose of 4 x 10<sup>11</sup> PU in 2 ml volume, during 5½-weeks of standard chemoradiation therapy. Standard chemoradiation consists of 5½-weeks of concurrent radiation therapy (RT) (total dose 50.4 Gy in twenty-eight 1.8 Gy fractions, 5 days weekly) and fluorouracil (5-FU) by continuous infusion (200 mg/m<sup>2</sup>/day, five days weekly). Approximately four weeks after completion of chemoradiation, all patients were to receive gemcitabine or gemcitabine/erlotinib maintenance therapy.

**Treatment Schema:**



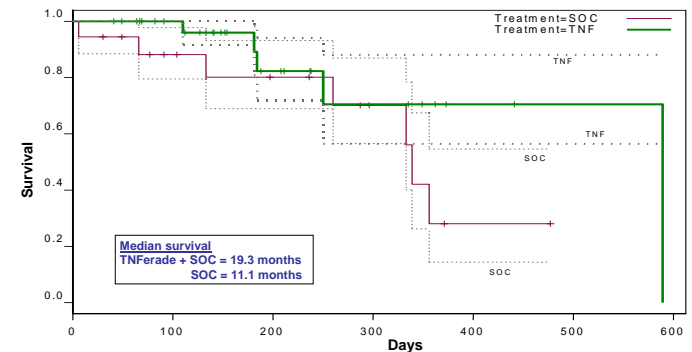
## RESULTS:

Table 1: Baseline Demographics	SOC n = 18	TNFerade + SOC n = 33
Mean age (years)	62.9	59.3
% Male	50.0	54.6
Mean Tumor size (mm) <sup>1</sup>	62.1	65.0
T4 Primary Tumor Staging (#pts [%])	10 (56%)	24 (73%)
N1 Staging (#pts [%])	6 (33%)	10 (30%)

<sup>1</sup>Measurements based on largest diameter

## RISK/BENEFIT ASSESSMENT: OVERALL SURVIVAL

Figure 1: Overall Survival of Randomized Pancreatic Cancer Patients, by Treatment (with 75% CI shown); as of 11/15/06\*



\*The logrank statistic for comparison between the two arms is  $X^2 = 2.014$  ( $p=0.16$ )

## INTERIM ANALYSIS DATA (Tables 2 and 3):

Best overall responses for the first 3 months following treatment are listed below:

Table 2: RECIST Criteria Evaluation	Statistic	SOC n = 16 <sup>1</sup> 13 (81%) <sup>2</sup> p value <sup>3</sup>	TNFerade + SOC n = 33 24 (73%) <sup>2</sup> 0.5196
Tumor Stabilization			
Response			
Complete Response (CR)	0	0	
Partial Response (PR)	1 (6%)	0	
Stable Disease (SD)	12 (75%)	24 (73%)	
Progressive Disease (PD)	3 (19%)	9 (27%)	

<sup>1</sup>Baseline CT scan not obtained or readable for 2 patients

<sup>2</sup>Follow-up CT scans not obtained due to patient death, lost to follow-up, withdrawal of consent, or surgical resection

<sup>3</sup>Based on the Cochran-Mantel-Haenszel chi-square test

## SUMMARY OF OTHER SECONDARY ENDPOINTS:

Table 4: Additional Secondary Endpoints

Treatment Group	Surgical Resections		CA 19-9 Levels (pg/mL)		TNF-α Levels (pg/mL)	
	N	Resection	N	Median AUC <sup>1</sup>	N	Median Change from Baseline at 4 Weeks Post-Treatment
SOC	18	2 (11%)	11	11.1 (range 7.0 to 47.6)	9	-1.9
TNFerade + SOC	33	5 (15%)	28	22.0 (range 4.1 to 180.2)	17	0

<sup>1</sup>Wilcoxon rank sum test  $p = 0.48$

## SAFETY RESULTS:

TNFerade injections, administered concurrently with chemoradiation, were generally well tolerated.

Table 5: Adverse events experienced by ≥25% patients in either group to date		Number of Patients Experiencing AE (%)	
Body System	Adverse Event	SOC n = 18	TNFerade + SOC n = 33
Blood and Lymphatic System Disorders	Anaemia <sup>1</sup>	39	55
	Leukopenia	11	27
	Neutropenia <sup>1</sup>	28	24
	Thrombocytopenia <sup>1</sup>	39	30
Gastrointestinal Disorders	Abdominal Pain	50	69
	Ascites	28	18
	Constipation	33	21
	Diarrhoea	56	55
	Gastrointestinal Haemorrhage <sup>1</sup>	17	0
	Nausea	67	70
	Vomiting	50	61
General Disorders and Administration Site Conditions	Chills	6	52
	Fatigue	28	42
	Oedema Peripheral	39	15
Investigations	Pyrexia	22	58
	Weight Decreased	11	30
Metabolism and Nutritional Disorders	Anorexia	22	27
Psychiatric Disorders	Hypokalaemia <sup>1</sup>	39	36
Skin and Subcutaneous Tissue Disorders	Depression	22	27
	Rash	22	27

<sup>1</sup>Adverse events that were grade 3 or higher in severity and experienced by  $\geq 15\%$  of patients in either group to date. Events that were  $\geq 15\%$  and more frequent in the SOC group were anaemia, thrombocytopenia, gastrointestinal haemorrhage and hypokalaemia. One event was  $\geq 15\%$  and more frequent in the TNFerade + SOC group, neutropenia.

**Serious Adverse Events (SAEs):** There was no statistically significant difference in the occurrence of serious adverse events between the treatment and control groups. Twenty-three patients (70%) receiving TNFerade + SOC and fourteen patients (78%) receiving SOC alone had at least one serious adverse event.

There were four SAEs where death was the listed outcome: A fatal cardiac arrest (patient received SOC alone), a fatal GI bleed (patient received SOC alone), a fatal aspiration (patient received TNFerade with SOC), and a fatal pancreatic fistula (patient received TNFerade with SOC). Events were noted as unrelated to TNFerade.

## Thrombotic Events:

The protocol defines thrombotic events as any thrombotic event occurring during or within 45 days following treatment. Eleven patients (33%) receiving TNFerade with SOC and seven patients (39%) receiving SOC alone had a thrombotic event. One medically significant thrombotic event occurred each in the TNFerade + SOC group (acute stroke secondary to aortic thrombus formation) and in the SOC group (GI bleed secondary to splenic vein thrombosis).

## CONCLUSIONS:

- TNFerade is well tolerated and is mostly associated with Grade I/II flu-like symptoms.
- Thrombotic event rates do not appear to be altered by the addition of TNFerade to SOC.
- While the data are immature and may not correlate with final trial outcome, the survival distributions support continuation of our study as planned originally.
- A second interim analysis is anticipated.