



# Multi-Center Randomized Controlled Phase III Clinical Trial using TNFerade™ with Chemoradiation in Patients with Locally Advanced Pancreatic Cancer: Interim Analysis of Overall Survival

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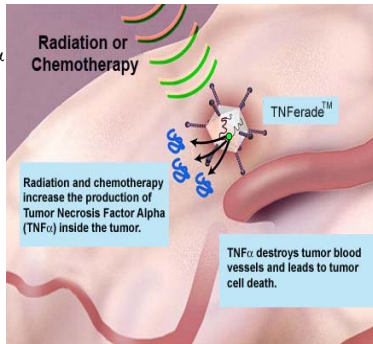
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## Background

Local control of locally advanced pancreatic cancer (LAPC) with chemoradiation (CRT) has historically demonstrated survival benefit vs. radiation therapy (RT) alone. TNFerade™ (TNF) is a nonreplicating adenovirus vector delivering human tumor necrosis factor-alpha (TNF-α). Results from a Phase II study with TNF in LAPC indicated a possible survival advantage. To confirm these findings, a randomized, open-label, controlled Phase III Pancreatic Cancer Trial with TNF, The PACT study, was developed.

## TNFerade™

- TNFerade™ 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
- In preclinical models, TNFerade™ has anti-tumor effects distal to local injection fields



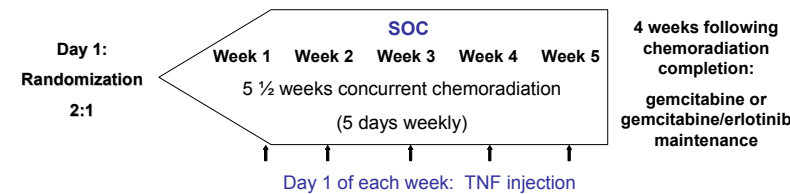
- Causes collapse of tumor vasculature
- Stimulates pro-inflammatory and apoptotic pathways within the tumor
- Necrotizing action of TNF-α may create an *in situ* tumor lysate
- Activates immune system:
  - Increases expression of MHC Class I and II antigens
  - Enhances infiltration of CD8+ T cells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

TNFerade™ is intended for use in combination with standard chemotherapy and/or radiation therapy

## TNF-α

## Study Methods

The TNF arm received a 5 week treatment of weekly intratumoral injections of 4x10<sup>11</sup> PU TNF, continuous iv 5-FU and 50.4Gy radiation. The standard of care (SOC) arm received CRT alone. Both groups received adjuvant gemcitabine (G) with the option of erlotinib (E).



## Statistical Methods

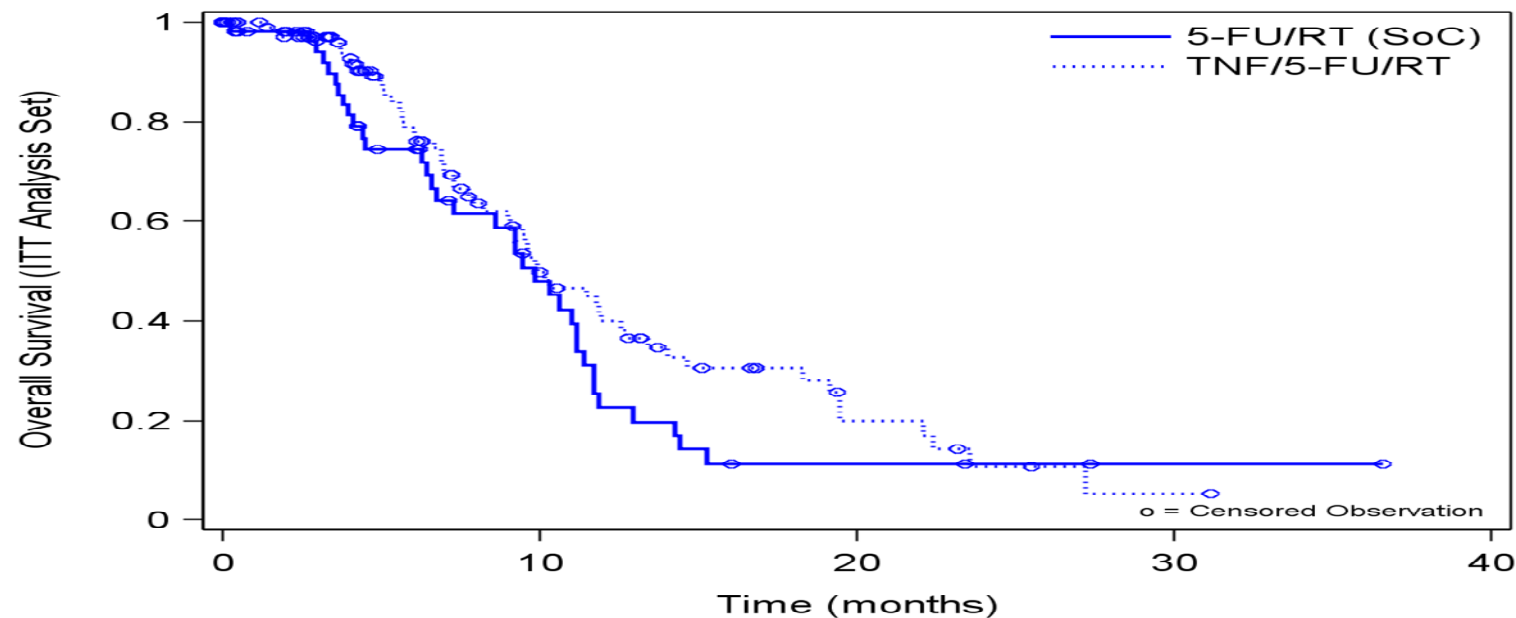
This interim analysis (IA) of overall survival (OS) (primary efficacy endpoint) was planned after the first third (92) of the expected 276 total death events (from a total patient n=330) occurred. Nonparametric log-rank of OS was planned per protocol. In addition, a log-normal model was used to account for an evident separation of the survival curves after the median.

Per protocol, secondary endpoints were not analyzed during the interim analysis but will be analyzed at the completion of the study.

## Efficacy Results

**Summary:** 185 patients were available for OS analysis (117-TNF+SOC and 68-SOC). Survival analysis after the first 92 events (deaths) in the TNF+SOC group demonstrated a hazard ratio (HR) of 0.753 (CI [0.494 – 1.15]) relative to SOC. Best fit parametric log-normal analysis indicated a median survival of 11.1 months with TNF+SOC and 8.7 months with SOC; nonparametric methods indicated a median survival of 9.9 months for both arms, with a pronounced "late effect" (75<sup>th</sup> Percentile 19.4 months with TNF+SOC and 11.8 months with SOC). Prognostic information (G and E use, stage, etc) indicated similar distribution between groups.

Figure 1: Overall Survival of Randomized Pancreatic Cancer Patients by Treatment (Nonparametric Log-Rank Method)



	SOC n = 68	TNF + SOC n = 117
Mean Age (years)	63.5	63.8
% Male	54	60
KPS ≥ 80% (#pts [%])	63 (93%)	107 (91%)
Primary Tumor Staging		
T1 (#pts [%])	1 (1%)	0
T2 (#pts [%])	5 (7%)	7 (6%)
T3 (#pts [%])	21 (31%)	26 (22%)
T4 (#pts [%])	41 (60%)	84 (72%)
Nodes Staging		
N0 (#pts [%])	28 (41%)	45 (38%)
N1 (#pts [%])	28 (41%)	43 (37%)
NX (#pts [%])	12 (18%)	29 (25%)
Metastasis Staging		
M0 (#pts [%])	66 (97%)	115 (98%)
MX (#pts [%])	2 (3%)	2 (2%)

Note: No statistically significant differences were observed between the groups, per the Fisher's exact or 2-sample t-test

Parameter	Statistic	5-FU/RT (SoC) (N=68)	TNF/5-FU/RT (N=117)
Overall Survival (months) <sup>1</sup>	25th Percentile (95%CI)	4.5 (3.8, 8.6)	6.7 (5.6, 7.9)
	KM Estimator (95%CI)	9.9 (6.7, 11.2)	9.9 (9.0, 12.6)
	75th Percentile (95%CI)	11.8 (11.0, 15.3)	19.4 (12.8, 22.4)
	Hazard Ratio (95% CI)	0.753 (0.494, 1.15)	
Censored Observations	N (%)	33 (48.5)	60 (51.3)
Kaplan-Meier Survival	12 Month Survival	22.50%	39.90%
	18 Month Survival	11.30%	30.50%
	24 Month Survival	11.30%	10.60%

<sup>1</sup>Survival is defined as the time in months from date of randomization to date of death. Subjects without death are censored as of the last date known to be alive. Subjects randomized but not treated were censored as of the date of randomization.

Table 3: Overall Survival by Parametric Methods

Survival Distribution (LIFEREG)	Median Survival Time SOC	Log-Likelihood TNF + SOC	Extra Degrees of Freedom Compared to Exponential	Best Fit Based on Likelihood Ratio Test	Hazard Ratio Estimate
Exponential	8.9	11.4	-155.8	0	0.774
Weibull	10.1	11.8	-140.8	2	
Log-Normal	8.7	11.1	-139.1	1	0.789
Gamma	9.2	11.2	-137.0	2	

	SOC n = 68	TNF + SOC n = 117
Mean Duration of Gemcitabine Therapy (weeks)	5.21	5.07
Gemcitabine Therapy Min, Max (weeks)	0, 33	0, 36
Erlotinib Usage (#pts [%])	6 (9%)	15 (13%)

Note: No statistically significant differences were observed between the groups, per the Fisher's exact or 2-sample t-test

## Safety Results

Safety is monitored by both GenVec and an Independent Data Safety Monitoring Board (DSMB). To date the safety profile between the two groups has been comparable (adverse event rates similar) with the exception of pyrexia and chills. Pyrexia in the SOC arm was 16% and in the TNF arm 42%. Chills in the SOC arm were 14% and in the TNF arm 39%.

Serious Adverse Events (SAEs) between the two groups were similar with the most common (>5%) in the TNF arm being: Abdominal Pain (6.9%), Bile Duct Obstruction (5.9%), and Thrombosis (7.9%); and the most common (>5%) in the SOC arm being: Cholangitis (12%), Gastrointestinal Haemorrhage (8%), Pulmonary Embolism (8%), Neutropenia (6%), Small Intestinal Obstruction (6%), Catheter Related Complications (6%), Disease Progression (6%), Stent Occlusion (6%), and Dehydration (6%).

## Conclusions

- TNF appeared to be generally safe and well tolerated with low grade fever and chills being the most frequently reported events.
- The hazard ratio (HR) of the overall survival interim analysis indicated an encouraging trend in favor of the TNF treated group.
- By nonparametric log-rank analysis, there appeared to be a "late effect" of TNF wherein much of the survival benefit occurs following 9 months post treatment. Too few observations exist to draw conclusions regarding the tails of the Kaplan Meyer curves.
- Parametric analysis demonstrated similar HRs as non-parametric methods but varying median survival times in favor of TNF.
- Review of the demographics and prognostic variables indicated successful random allocation between the groups. No statistically significant differences were observed between the groups, per the Fisher's exact or 2-sample t-test.
- The next interim analysis is planned after 1/3 (184) total events have occurred.