A PHASE I/II TRIAL OF TG01/GM-CSF AND GEMCITABINE AS ADJUVANT THERAPY FOR TREATING PATIENTS WITH RESECTED RAS-MUTANT ADENOCARCINOMA OF THE PANCREAS

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BACKGROUND

TG01 (a mixture of 7 mutant RAS peptides) is an injectable antigen-specific cancer immunotherapy targeted to treat patients (Pts) with KRAS mutations, found in more than 85% of pancreatic adenocarcinomas. There is scope for improvement in adjuvant treatment of resected pancreatic cancer; with 1- and 2-year published overall survival (OS) rates ranging from 56–80% and 30–54% respectively[2-5].

TG01 consists of a mixture of 7 synthetic peptides that represent 7 of the most common codon 12 and 13 mutations in p21 RAS associated with human cancer.

TG01 induces RAS mutant-specific T-cell responses which are enhanced by co-administration of GM-CSF (recombinant human granulocyte macrophage-colony stimulating factor).

TG01 was the first therapeutic peptide vaccine targeting RAS that entered clinical trials. Earlier studies demonstrate that adjuvant vaccination with TG01/GM-CSF given as monotherapy to pancreatic cancer patients after tumor resection induce mutant RAS specific immune response in 100% of patients[1].

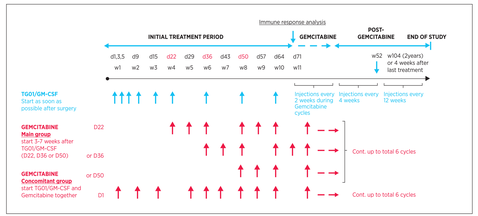
This study evaluates safety, immunological response and OS of TG01-immunotherapy with adjuvant gemcitabine chemotherapy.

METHODS

Pts were eligible after an R0 or R1 pancreatic adenocarcinoma resection. No previous radiation or chemotherapy (except for primary neoadjuvant chemotherapy, if applicable) and were expected to receive gemcitabine as adjuvant chemotherapy within 12 weeks of surgery.

As soon as possible after surgery, TG01 (0.7 mg intradermal injection) together with GM-CSF (0.03 mg id) was given on days 1, 3, 5, 8, 15, 22 and 2-weekly thereafter until the end of gemcitabine (starting within 12 weeks of surgery and given as 1000 mg/m2 for 3/4 weeks x 6 cycles). Thereafter TG01/GM-CSF were given 4-weekly up to 1 yr and 12-weekly up to 2 yrs. OS was assessed from surgery; -8 weeks before first TG01 injection. See figure 1.

Figure 1. TG01-01 Study Design



Immunological assessment

Two different antigen specific assays were used to asses the immunological response to TG01: 1) delayed type hypersensitivity (DTH-test) and 2) in vitro T-cell proliferation.

The DTH-test (up to 9 times) is a test in the skin measuring the presence of activated T cells recognizing TG01. TG01 is injected in the skin and the DTH-test is considered positive if the area of the skin reaction (redness/induration) at the injection site 48 hours after injection has an average diameter ≥ 5 mm.

The T-cell proliferation assay is an in vitro assay showing proliferation response of TG01 specific T-cells. Blood sampling and PBMC isolation is performed on day 1 (baseline), week 11, week 52 and end of study. T-cell responses are considered positive if the stimulation index (SI) is ≥ 2 indicating an increase in proliferation of TG01 specific T-cells after stimulation with TG01 compared to unstimulated cells.

RESULTS

19 pts (68% R1) from 3 sites (Norway and UK) and have been followed for 2 yrs.
18 patients discontinued study treatment prematurely due to the following reasons; 7 disease recurrence, 4 adverse events, 2 death (pneumonia and disease progression, not treatment related), 3 consent withdrawn and 2 investigator decision.
The patient's baseline characteristics are presented in table 1 below.

Table 1. Baseline characteristics

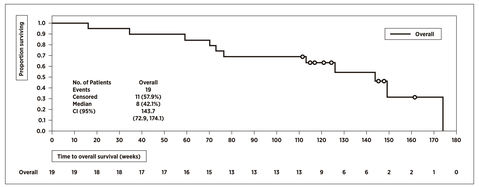
Parameters	Number of patients (N=19)
Age (Y) median (min, max)	67 (49, 79)
Gender, n (%)	
Male	10 (53%)
Female	9 (47%)
ECOG, n (%)	
0	8 (42%)
1	11 (58%)
CA19-9 (n=15) U/ml median (min, max)	16 (8, 240)
Hemoglobin (g/L) median (min, max)	124.0 (104, 153)
Disease staging at diagnosis	
T stage	
T1	1 (5%)
T2	1 (5%)
T3	17 (90%)
N stage	
N0	7 (37%)
N1	12 (63%)
M stage	
M0	19 (100%)
Resection surgical outcome, n (%)*	
R0	6 (32%)
R1	13 (68%)
KRAS mutation detected, n (%)	
Yes	16 (84%)
No	3 (16%)
Time from surgery to first IMP adm (week) median (range)	8 (7-12)

OVERALL SURVIVAL

Survival rate at 1 and 2 years were 89.5% (95% CI 75.7, 100.0) and 68.4% (95% CI 47.5, 89.3), respectively. Data showed that 13/19 patients were still alive at two years. Survival was assessed from time of resection.

While the cohort is small and there is no control arm, this rate compares favorably with the available published historical two-year survival rates of resected cancer patients treated with gemcitabine alone of between 30% and 53% [2, 3, 4, 5, 6]. Median OS measured from surgery was 143.7 weeks (95% CI 72.9, 174.1) or 33.1 months (95% CI 16.8, 40.1) see figure 2. In a recently published study (ESPAC-4) the OS in patients receiving gemcitabine alone was 27.6 months [7].

Figure 2. Overall survival from surgery



IMMUNOLOGICAL RESPONSE

An immune responder is defined as having a positive DTH response and/or a positive T-cell proliferation from a blood sample (PBMC) at least once by the end of the initial treatment period (week 11). The immune response as detected by positive DTH-test and T cell proliferation (SI ≥ 2) at either week 11 and at a later time point in the study is presented in table 2. 17/19 (89%) patients had a positive immune response by week 11 whereas 18/19 (95%) patients had a positive immune response at some time point during the study. The only patient without a detectable immune response suffered an unrelated death in study week 8 and was not fully evaluable for immune response.

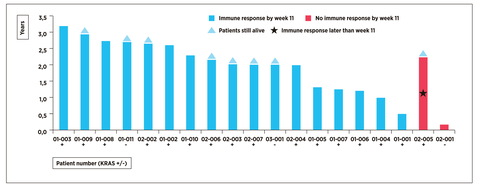
Table 2. Immune response by week 11 and through the entire study (n=19)

Study period	Immune responders	Immune responders DTH	Immune responders T-cells
By end of initial treatment (week 11)	17/19 (89%)*	16/19 (84%)	10/19** (53%)
Entire study period	18/19 (95%)*	18/19 (95%)	14/19** (74%)

* One patient (patient 02-001) died by week 8, DTH responses only assessed up to week 8. Blood sample only taken at baseline.
** Three patients (week 11) and two patients (entire study period) without blood samples for analysis.

Figure 3 gives an overview of all 19 patients showing their immune response by week 11 (17/19 patients, 89%) and later in the study period (18/19 patients, 95%). 8 patients were still alive when last patient completed the 2 years visit which is also shown in the figure. The high % positive immune responses show that the TG01 vaccination effectively induces TG01 specific T-cells.

Figure 3. Overall survival and immune response



After week 11, immune sample were collected from only 11 patients (table 3). Of these 11 patients 9 (82%) demonstrated a prevailing immune response to TG01. The results indicate that an immune response is persistent after treatment with chemotherapy and maintained during the study period. All 13 (68%) patients alive at 2 years had a positive immune response.

Table 3. Immune response after week 11 (n=11)

Study time point	No. of pts with immune monitoring after week 11	Patients with positive immune response after week 11
After week 11	11	9/11 (82%)

SAFETY

13 Serious Adverse Events were reported in 7/19 patients (table 4). Of these 8 were Serious Adverse Reactions reported in 5 pts; 4 related to gemcitabine (aneamia, pulmonary infection and 2 fever); 3 related to TG01/GM-CSF (2 anaphylaxes and 1 hypersensitivity); and 1 possibly related to all products (dyspnea). The allergic reactions only occurred after several cycles of gemcitabine and resolved within 1-2 hrs. There were no treatment related deaths. In table 5, all grade 3/4 events are presented.

Table 4. Serious Adverse Events

Serious Adverse Events Preferred term	Number of Events	Relationship to study treatment
Anaphylactic reaction	2	Related to TG01 +/- GM-CSF
Hypersensitivity	1	
Dyspnea	1	Related to Gemcitabine and TG01/GM-CSF
Lung infection	1	Related to Gemcitabine
Pyrexia (fever)	2	
Anaemia	1	
Anaphylactic shock related to a concomitant medication (Emend)	1	Unrelated to study treatments
Hyperglycemia	1	
Urosepsis	1	
Pneumonia	1	
Viral upper respiratory tract infection	1	

Table 5. Grade 3/4 Adverse Events related to any treatment

SOC	Grade 3		Grade 4	
Adverse event	**Patients**	**Events**	**Patients**	**Events**
Any adverse event	13	32	5	6
Blood and lymphatic system disorders				
Neutropenia*	6	6	1	1
Anaemia	1	1		
Gastrointestinal disorders				
Abdominal pain	2	2		
Diarrhoea	1	1		
Abdominal pain upper	1	1		
General disorders and administration site conditions				
Fatigue	1	1		
Immune system disorders				
Anaphylactic reaction			2	2
Anaphylactic shock	1	1		
Infections an dinfestations				
Urosepsis	1	1		
Investigations				
Neutrophil count decreased*	4	7	1	1
Hemoglobin decreased	1	1		
Platelets count decreased	1	1		
Metabolism and nutrition disorders				
Hyperglycaemia	1	1	2	2
Diabetes mellitus	1	1		
Hypokalaemia	1	1		
Psychiatric disorders				
Depression	1	1		
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism	1	1		
Vascular disorders				
Hypertension	3	4		

* All reported neutropenia and neutrophil count decreased were related to chemotherapy.

56 AEs in 13 patients were reported as related to TG01/GM-CSF. The majority of these AEs were as expected reported under the general disorders and administration site conditions (8 injection site reaction, 8 influenza-like symptoms, 8 fatigue, 4 injection site erythema, 3 injection site pruritus, 2 injection site swelling, 1 vaccination site pain and 1 vaccination site reaction). All related events were Grade 1 or 2, except for the two reported anaphylactic reactions that were Grade 4.

CONCLUSIONS

- TG01/GM-CSF generated early immune responses in 89% of patients with R0/R1 resected pancreatic cancer. This demonstrate that TG01 vaccination activate mutant RAS specific T cells.
- The regimen was generally well tolerated although some late, manageable allergic reactions were seen.
- OS was encouraging in view of published reports with a median OS of 33.1 months.
- We believe that the immune activation at both DTH and PBMC level is associated with the positive clinical findings.

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