A Phase I/II Trial of TG01 and Gemcitabine in patients with resected pancreatic cancer; Phase I results

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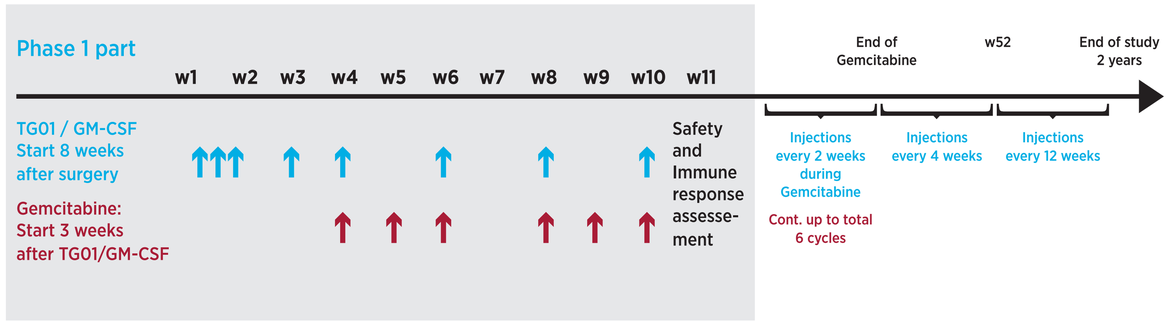
INTRODUCTION

Oncogenic RAS mutations found in 80–90% of pancreatic cancers are attractive targets for immunotherapy. It has earlier been reported that mutant RAS peptide vaccination of patients with inoperable disease induced specific T cell responses in approximately 50% of the patients[1], whereas all patients given adjuvant vaccination after resection of their tumour responded immunologically[2]. Here we report the Phase I results from an ongoing Phase I/II study investigating the safety and immunological response of adjuvant treatment of resected pancreatic cancer with RAS peptide vaccination (TG01) alone and then combined with gemcitabine adjuvant chemotherapy. TG01 covers the common RAS mutations found in pancreatic cancer.

PHASE I/II STUDY DESIGN

Patients will receive TG01, together with immune modulator GM-CSF, within 1–8 weeks after surgery. Between 3–7 weeks after TG01/GM-CSF has started, patients will also receive Gemcitabine. The patients will be assessed for safety and immune responses by week 11 after receiving at least one cycle of gemcitabine. 6 to 12 patients will be included in the Phase I part of the study. After assessment of the 6 first patients at week 11 either, if ≥4 immuneresponders and ≤ 2 DLTs, the Phase II part of study will be initiated, or if < 4 immuneresponders and/or >2 DLTs, the Phase I part is expanded to 12 patients. After completion of gemcitabine treatment, patients can continue to receive TG01/GM-CSF for up to two years.

Study Design Administration of trial treatment



Safety table

PATIENTS EXPERIENCING ADVERSE EVENTS DURING INITIAL TREATMENT PHASE (N=6)

	Grade 1/2		Grade 3/4	
	TG01/GMCSF monotherapy period	chemo combination period	TG01/GMCSF monotherapy period	chemo combination period
GASTROINTESTINAL DISORDERS	**4 (66.67%)**	**5 (83.33%)**		**1 (16.67%)**
- Nausea		4 (66.67%)		1 (16.67%)
- Vomiting		3 (50%)		1 (16.67%)
- Diarrhea	2 (33.33%)	1 (16.67%)		
- Abdominal pain	3 (50%)	1 (16.67%)		
METABOLISM AND NUTRITION DISORDERS	**2 (33.33%)**	**3 (50%)**	**1 (16.67%)**	**1 (16.67%)**
- Anorexia	2 (33.33%)	2 (33.33%)		
- Hypokalemia		1 (16.67%)	1 (16.67%)	1 (16.67%)
- Weight loss		2 (33.33%)		
BLOOD AND LYMPHATIC SYSTEM DISORDERS			**1 (16.67%)**	**4 (66.67%)**
- Neutropenia			1 (16.67%)	4 (66.67%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1 (16.67%)**	**3 (50%)**		
- Fatigue		1 (16.67%)		
- Flu like symptoms		1 (16.67%)		
- Fever		1 (16.67%)		
- Injection site reaction	1 (16.67%)			
PSYCHIATRIC CONDITIONS		**1 (16.67%)**		
- Insomnia		1 (16.67%)		
NERVOUS SYSTEM DISORDERS		**1 (16.67%)**		
- Headache		1 (16.67%)		
INFECTIONS AND INFESTATIONS		**1 (16.67%)**		
- Pulmonary infection		1 (16.67%)		

RESULTS

The Phase I part of the study was finalized with 6 patients as TG01 specific immune responses (DTH) were detected in all of the patients (6) by week 11 and no DLTs were reported.

The safety profile to week 11 of the study was as expected for patients post pancreatic surgery who received chemotherapy. There were one adverse event considered related to TG01/GM-CSF alone (injection site reaction). One patient experienced 3 events that were related to TG01/GM-CSF and gemcitabine (nausea, vomiting and flu like symptoms). Adverse events that were related to gemcitabine were as expected with grade 3/4 neutropenia being the principal related adverse event. Interruptions or reductions in dose of gemcitabine were required in these cases.

Four serious adverse events were reported in 2 patients: One patient experienced pulmonary infection and two episodes of fever all considered related to gemcitabine, and one patient had nausea also considered unrelated to treatment.

DTH Table

	W1 TG01	W3 TG01	W4 TG01/Gem	W6 TG01/Gem	W8 TG01/Gem	W10 TG01/Gem
Pt01				+	+	*
Pt02					+	
Pt03				+	+	+
Pt05		+	*	+	+	
Pt06		+	+	+	+	+
Pt07					+	

Table 2: DTH skin reactions. +; Positive with average diameter ≥ 5mm.
•; recorded response < 5mm (Pt01: 2mm, Pt05: 4mm).

References: [1]Gjertsen MK et al., Int. J. Cancer: 92, 441-450 (2001), [2]Weden S et al., Int. J. Cancer: 128, 1120–1128 (2011).

DISCUSSION

Safety

Based on the data to include the 2nd cycle of gemcitabine chemotherapy, TG01/GM-CSF was well tolerated locally with one related adverse event of injection site reaction.
In addition, 3 adverse events (vomiting, nausea and flu-like symptoms) were reported as related to TG01/GM-CSF and gemcitabine as relationship could not be excluded. The use of gemcitabine was associated with expected adverse events and for these (predominantly myelosuppression and gastrointestinal as well as a case of pulmonary infection) dose interruptions or reduction were required.

Grade 3/4 neutropenia associated with gemcitabine use, when it occurred, was most frequently seen after the first dose in cycle 1. The frequency of these events was slightly higher than reported for gemcitabine alone but, given the lack of effect of TG01 on the bone marrow prior to gemcitabine treatment it would seem unlikely that this contributed to the first dose effect of the chemotherapy.

Immune response

From none with DTH reaction at baseline (w1), 2 patients (33%) developed a DTH reaction prior to initiation of gemcitabine treatment (w3). This increased to 4 (66%) patients with positive DTH after the first cycle of gemcitabine (w6), and to all 6 (100%) patients after the first dose of gemcitabine in the second cycle (w8). This demonstrates that a Th1 polarized response to TG01 was induced in all patients after concomitant treatment with TG01 and gemcitabine. Possible causes for the observed drop in DTH responses after the second cycle of gemcitabine (w10) might be natural fluctuations[1] (also indicated for Pts 01 and 05) and/or effects of the prolonged gemcitabine treatment causing interference with cellular activity in the skin. Immune responses (DTH, in vitro T cell responses) will be further investigated in the phase II part of the study, also after ending gemcitabine treatment.