AN OBSERVATIONAL CLINICAL STUDY WITH RAS PEPTIDE VACCINE TG01 EVALUATING IMMUNE RESPONSE, SAFETY AND OVERALL SURVIVAL IN PATIENTS WITH NON-RESECTABLE PANCREATIC CANCER

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BACKGROUND

TG01 is the first injectable antigen-specific cancer immunotherapy (ASCI) targeted to treat patients with KRAS mutations. TG01 consists of a mixture of 7 synthetic RAS peptides representing the 7 most common codon 12 and 13 oncogenic mutations in KRAS. Oncogenic mutations in KRAS drive cell growth and malignant transformation and is found in more than 85% of pancreatic adenocarcinomas.

Clinical efficacy of peptide cancer vaccines has generally been poor due to the short length of the peptides which are only able to activate MHC class I restricted CD8+ cytotoxic T-cells.[1] The TG01 peptides are 17 amino acids long and designed to activate both CD8+ cytotoxic T-cells as well as MHC class II CD4+ helper T-cells which is necessary to sustain the CD8+ cytotoxic T cell effect.[2-4] TG01 induces mutant-RAS (mtRAS) specific T-cell responses which are enhanced by co-administration of GM-CSF (recombinant granulocyte-macrophage colony-stimulating factor).

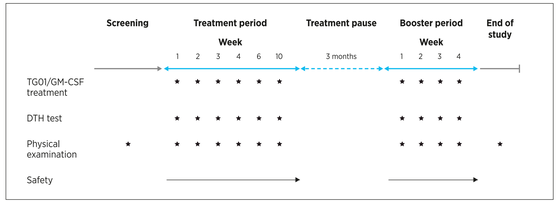
This study determined the immune response measured by Delayed Type Hypersensitivity (DTH) reaction, survival and safety of TG01/GM-CSF treatment in non-resectable pancreatic cancer patients.

METHODS

25 treatment naive non-resectable pancreatic cancer patients were administered TG01/GM-CSF at week 1, 2, 3, 4, 6, 10 (= treatment period) followed, after a three-months pause, by a booster period of one weekly administration for four weeks, Figure 1. The patients were followed up for up to 12 months from the 1st administration of TG01/GM-CSF. Immune response was evaluated by DTH reaction, survival data was estimated using Kaplan-Meier calculations and (S)AEs were recorded throughout the study.

The DTH test: a test in the skin measuring the presence of activated T-cells recognising TG01. TG01 in injected intradermally and, in this study, the DTH test is considered positive if the redness/induration of the TG01 injection site on average is ≥ 5mm in diameter measured 48 hours after administration.

Figure 1. Flowchart



RESULTS

The patients' characteristics are outlined in Table 1.

Table 1. Patient characteristics at baseline

Parameters	Number of patients
Age, median (min, max)	64 (48,77)
Gender, n (%)	
Male	13 (52%)
Female	12 (48%)
Karnofsky performance status, n (%)	
95–100	12 (48%)
90	8 (32%)
80	5 (20%)

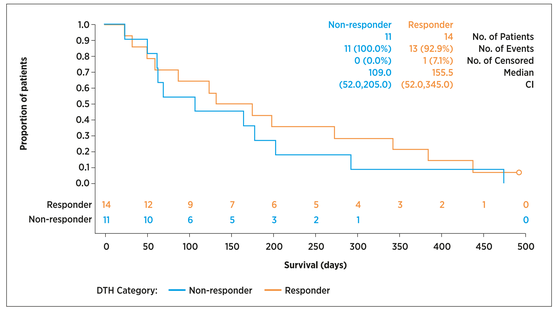
Fourteen out of 25 patients (56%) recorded at least one positive DTH reaction by week 10, Table 2. Most patients recorded the first positive DTH reaction at week 3 or 4. 12 of the 14 immune responders reported 2 or more positive DTH reactions throughout the treatment period.

Table 2. DTH responders during the treatment period (week 1–10)

	# of first time DTH responders					
Total # of DTH responders	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**
14/25	0	2	7	4	1	0

Median survival from 1st TG01/GM-CSF administration was 4.5 months for all treated patients (n=25), 5.1 months for the DTH responders (n=14) and 3.6 months for the non-responders (n=11), Figure 2. Four patients were alive after 1 year; three (21%) of the DTH responders and one (9%) of the non-responders.

Figure 2. Kaplan-Meier survival estimate for DTH responders and DTH non-responders calculated from 1st TG01/GM-CSF administration



TG01/GM-CSF was well tolerated with no reports of allergic or other hypersensitivity reactions. The majority of AEs and SAEs reported were associated with disease progression and death due to the disease, Table 3. 13 patients died during the study due to progression of the disease.

Table 3. Total number and number of treatment related AEs and SAEs

Number of patients	Total # of AEs	# of treatment related AEs	Total # of SAEs	# of treatment related SAEs
25	67	4*	19	2**

* Four patients experienced treatment related AEs; backpain, nausea, rhinitis and hypoglycaemia. ** Two patients experienced treatment related SAEs; hypoglycemia and arthritis.

DISCUSSION

In this study, DTH immune response was recorded in 56% (14 of 25) of the non-resectable pancreatic cancer patients. The result correspond with data from a phase I/II trial with a similar antigen-specific cancer immunotherapy consisting of 4 RAS peptides where 53% (16 of 36) of the non-resectable pancreatic patients showed an immune response (DTH and/or mtRAS specific T-cell response).[3] Treatment period was identical across the two studies. Patients included in the phase I/II trial with 4 RAS peptides and who showed stable disease and/or immune response during the treatment period (n=8) were administered TG01/GM-CSF during the booster period (weekly injections for four weeks).

Both studies show increased survival for the immune responders versus the non-responders, and compares favorably with untreated patients where median survival is ~ 3.7 months.[5] A randomised controlled trial is required.

CONCLUSION

- TG01 treatment is safe and tolerable in patients with non-resectable pancreatic cancer.
- Monotherapy with TG01 elicits mtRAS specific T-cell immune responses in non-resectable pancreatic cancer patients.
- Numerical indication of survival benefit for TG01 treated patients with detectable immune response measured by DTH reaction.
- DTH is a valid method for monitoring mtRAS T-cell immune responses and constitutes a potential biomarker for survival benefit in TG01 treated patients.

REFERENCES

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