Randomized Phase I Trial of Adjuvant Individualized TG4050 Vaccine in Patients with Locally Advanced Resected HPV-negative Head and Neck Squamous Cell Carcinoma (HNSCC)

SITC 2024
#650

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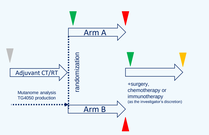
BACKGROUND

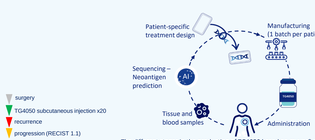
T cells targeting tumor specific mutations drive anti-tumor immune responses. TG4050 is a viral-based personalized cancer vaccine, encoding up to 30 patient- and tumor-specific DNA sequences bearing in-silico predicted class I and class II epitopes. Each epitope is designed in the vaccine as a 29mer mutation–centered neopeptide. TG4050 may prime an adaptive immune response against tumor antigens and prevent relapse in patients with locally advanced resected HNSCC. (NCT04183166)

METHODS

Study design and treatments

Multicenter, open label, randomized, two-arm Phase I trial evaluating TG4050, a vaccine engineered to carry a patient tailored antigen payload. Following curative intent treatment, HNSCC patients in complete remission were randomized to an immediate vaccination arm (Arm A) to receive weekly doses of TG4050 for 6 weeks followed by a maintenance period of one dose every 3 weeks for up to 20 doses or to a delayed vaccination arm (Arm B) where the same vaccination regimen is initiated at relapse in combination with SOC. Safety, efficacy and immunogenicity were evaluated. Longitudinal vaccine response was assessed by tetramer staining against target epitopes. In selected patients we explored tumor specificity and clonal expansion using bulk and single-cell (sc)TCR sequencing.





The different stages in the production of TG4050 based on *myvac*® platform

STUDY POPULATION

Key inclusion criteria

- Newly diagnosed stage III or IV (AJCC 8th ed.), HPV-negative, HNSCC, amenable to surgery
- Complete response 3 months after completion of adjuvant therapy

Key exclusion criteria

- Prior exposure to anti-cancer vaccines, and any antibody targeting T cell co-regulatory proteins such as anti-PD-L1, anti-PD-1, or anti-CTLA-4 antibodies

Patients

In the Phase I, 33 patients were randomized, 17 in Arm A and 16 in Arm B. Patients characteristics at baseline are presented in the tables below.

Patient characteristics	Arm A (N=17)	Arm B (N=16)	Total (N=33)
Age, years			
Median (range)	61 (26-79)	57 (47-74)	61 (26-79)
Gender, n (%)			
Male	11 (64.7%)	13 (81.3%)	24 (72.7%)
Female	6 (35.3%)	3 (18.8%)	9 (27.3%)
ECOG PS			
0	12 (70.6%)	9 (56.3%)	21 (63.6%)
1	5 (29.4%)	7 (43.8%)	12 (36.4%)

Disease characteristics	Arm A (N=17)	Arm B (N=16)	Total (N=33)
Stage on resected tumor			
I	1 (5.9%)	0 (0.0%)	1 (3.0%)
II	0 (0.0%)	1 (6.3%)	1 (3.0%)
III	4 (23.5%)	3 (18.8%)	7 (21.2%)
IVA	7 (41.2%)	5 (31.3%)	12 (36.4%)
IVB	5 (29.4%)	7 (43.8%)	12 (36.4%)
Primary Tumor Location			
Hypopharynx	1 (5.9%)	3 (18.8%)	4 (12.1%)
Larynx	0 (0.0%)	1 (6.3%)	1 (3.0%)
Oral cavity	14 (82.4%)	10 (62.5%)	24 (72.7%)
Oropharynx	2 (11.8%)	2 (12.5%)	4 (12.1%)
Extracapsular spread			
Yes	5 (29.4%)	8 (50.0%)	13 (39.4%)
No	12 (70.6%)	8 (50.0%)	20 (60.6%)
Positive Margin			
Yes	4 (23.5%)	3 (18.8%)	7 (21.2%)
No	13 (76.5%)	13 (81.3%)	26 (78.8%)
Adjuvant therapy			
Radiotherapy	7 (41.2%)	7 (43.8%)	14 (42.4%)
Radiotherapy + chemotherapy	10 (58.8%)	9 (56.3%)	19 (57.6%)

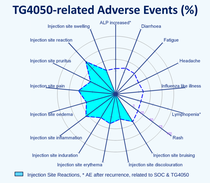
Safety

TG4050 was well tolerated. All treatment-related AEs were of mild or moderate severity. The most frequently reported were injection site reactions.

Number of patients (%)	Arm A Before recurrence (N=17) N (%)	Arm A + Arm B (N=1*) Post-Recurrence (N=3) N (%)
AE	16 (94.1%)	3 (100.0%)
AE related to TG4050	16 (94.1%)	2 (66.7%)
AE related to SOC	0 (0.0%)	2 (66.7%)
Injection site reaction	16 (94.1%)	1 (33.3%)
AE related to other study procedure	2 (11.8%)	0 (0.0%)
AE leading to treatment discontinuation	0 (0.0%)	1 (33.3%)
AE related to TG4050 leading to trt disc.	0 (0.0%)	0 (0.0%)
SAE	4 (23.5%)	1 (33.3%)
SAE related to TG4050	0 (0.0%)	0 (0.0%)
grade 3/4 AE	6 (35.3%)	1 (33.3%)
grade 3/4 AE related to TG4050	0 (0.0%)	0 (0.0%)
Fatal AE	0 (0.0%)	1 (33.3%)
Fatal AE related to TG4050	0 (0.0%)	0 (0.0%)

* Patient not evaluable for efficacy

TG4050-related Adverse Events (%)



IMMUNE CHARACTERISTICS AND PATIENT FOLLOW-UP IN RECRUITED HEAD AND NECK CANCER PATIENTS

Promising First Signals of Clinical Benefit in Adjuvant Setting

Figure 1

* ECS: Extracapsular Spread **F: fibrotic, NF: non fibrotic*

Figure 1. Patients were free of disease at the time of randomization per clinical/radiological and molecular criteria (ctDNA). Exploration of TME through deconvolution of RNAseq data reveals high prevalence of (1) low TMB, (2) tumor immune desert, (3) medium active infiltration and (4) medium tumor proliferation. PD-L1 expression was measured by CPS. **None of the 16 evaluable patients randomized to Arm A (immediate vaccination arm) has experienced relapse**. In the Arm B (scheduled to receive the vaccine at relapse only) 3 out of the 16 randomized patients have experienced relapse. The median follow-up (prior to relapse) was 24.1 months in both arms.

TG4050 INDUCES SUSTAINED NEOANTIGEN-SPECIFIC T CELL RESPONSES (*Ex vivo* IFNγ-ELISPOT)

Figure 2

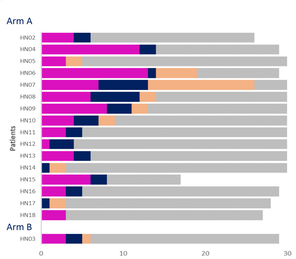
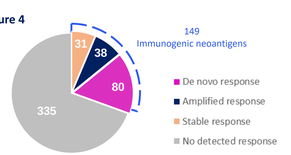


Figure 2. TG4050 induced specific CD4+ or CD8+ T-cell responses to individualized neoantigen peptides by IFNγ ELISpot without cytokine stimulation.

Figure 4



Neoantigens targeted by the vaccine

Figure 4. Of a total 484 neoantigens across 17 patients, 149 were immunogenic (31%). Of the 31% immunogenic neoantigens, 54% induced *de novo* responses, 25% amplified responses and 21% stable responses.

Figure 3

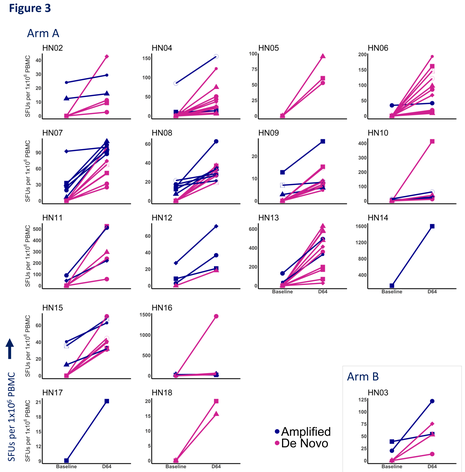


Figure 3. Variable strengths of T cell responses were detected as normalized *ex vivo* IFNγ ELISpot counts for vaccine neoantigens that induced a *de novo* response or an amplified response (20 to 1600 fold-change). Spots counts of the non-stimulated controls were subtracted. For each 29mer neopeptide in the vaccine, one or more 15mer sequence(s) were generated and tested by ELISpot. Therefore, several immune responses can be associated to a single neopeptide (same symbols).

TCR SEQUENCING IN TUMOR AND BLOOD

Figure 5

Patients	CDR3 TCR beta	Peptide	RNAseq reads Baseline Tumor	RNAseq reads Baseline Blood	RNAseq reads D64 Blood	DNA Baseline Tumor	DNA Baseline Blood	DNA D64 Blood
HN02	CASSSGLAGYNEQFF	AE (YV-9)	0	0	107	0	0	12
	CASSSKRGDEQFF	MVA KV-9	0	0	9	0	0	0
	CASRKDSGHLFYEQYF	CMV	0	57	150	0	13	18
	CASSLEGYTEAFF	CMV	0	3769	3151	0	3023	3526
	CASSSANYGYTF	CMV	0	505	411	0	266	199
HN04	CASSLMAGGPGEQFF	AE (AY-9)	55308	0	7664	8120	0	2527
	CASSGLAGGYPSSYNEQFF	AE (AY-9)	272	0	632	1	0	1

Figure 5. Tetramer reactive T cells from two patients were sorted and analyzed by single cell RNAseq to identify peptide-specific TCR clonotypes. These clonotypes were followed in bulk TCR repertoire sequencing of tumor infiltrating lymphocytes (TILs) and blood. Control CMV clonotypes were stable in the blood and not found in the tumor. MVA-specific clonotype was not found in the baseline samples but detected at D64 as expected. 2 out of 3 tumor neoantigen-reactive clonotypes were found in the tumor at baseline.

Figure 6

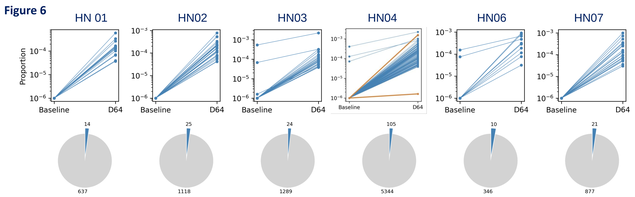


Figure 6. Bulk TCR repertoire sequencing (performed on DNA) on selected patients identified several tumor infiltrating lymphocytes (TILs) that were expanded in the blood after vaccination (top). Clonotypes identified by tetramers (Figure 5) for patient HN04 are indicated in orange. Proportion of clones found in TILs that are also found expanded in the blood after vaccination. Total number (grey) and significantly expanded (blue) (bottom).

Figure 7

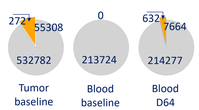
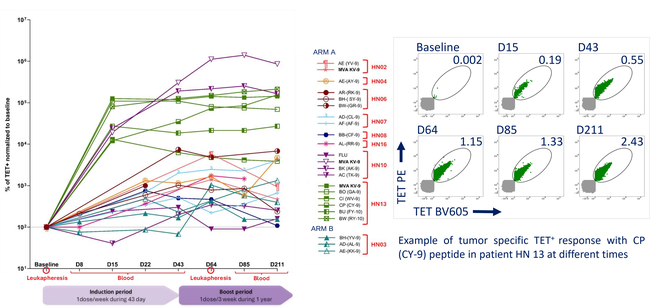


Figure 7. Abundancy of clonotypes specific for vaccine peptide AE (AY-9) in tumor baseline and blood for patient HN04. RNAseq reads are indicated. Responses observed in the blood at D64 corresponded to clonotypes found in tumor at baseline at high frequencies and stimulated by the vaccine.

TG4050 INDUCES SUSTAINED NEOANTIGEN-SPECIFIC CD8 T CELL RESPONSES

TETRAMERS staining

Figure 8



Example of tumor specific TET+ response with CP (CY-9) peptide in patient HN 13 at different times

Figure 8. Longitudinal study of antigen-specific CD8+ T-cell responses was assessed via class I MHC tetramer staining in patients showing a tetramer response at day 64 (9/14 patients). In the case of *de novo* responses for which no tetramer-reactive cells were detected at baseline, the initial frequency was assumed to be the inverse of the number of CD8+ cells analyzed by flow cytometry. The frequency of responding T cells at the other time points was normalized to the frequency at baseline.
Variable frequencies of Ag specific T cells were observed across patients increasing during the induction period, reaching a maximum at D43 or D64 and maintained during the boosting period.

KEY MESSAGES

- After a median follow up of 24.1 months, all 16 patients receiving TG4050 as adjuvant immunotherapy remained disease-free whereas 3 out of 16 patients in the control observation arm relapsed
- TG4050 was safe and well tolerated with all treatment-related adverse events mild to moderate
- Immune responses targeting selected neoantigens were identified in all patients who received TG4050, demonstrating the strong immunogenicity of the cancer vaccine, with both *de novo* and amplified responses
- Tumor antigen specific T cells detected after vaccine are either initially found at high frequency in tumor and stimulated by the vaccine, or are totally new effector T cells efficiently primed by the vaccine
- 7 months follow-up demonstrated sustained neoantigen-specific T cell responses

ACKNOWLEDGEMENTS

The authors wish to thank all patients, families, caregivers and all technical staff involved in the project.

THE STUDY WAS INDUSTRY CO-FUNDED BY NEC CORPORATION AND TRANSGENE SA.

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