Personalized vaccine TG4050 induces polyepitopic immune responses against private neoantigens in resected HPV-negative Head and Neck cancers

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BACKGROUND

In recent years, immune checkpoint inhibitors have failed to prove their benefit in the adjuvant / maintenance setting in locally advanced Head and Neck cancer (HNSCC) to prevent relapse in resected high-risk patients. While T cells targeting tumor specific neoantigens related to point mutations drive anti-tumor immune responses and are associated with a higher response rate to immune checkpoint inhibition, it appears that the priming of adaptive responses against tumor antigens is impaired in HNSCC. Immune stimulation using a vaccine is a promising strategy for a clinically meaningful improvement. Herein, we report phase I data of TG4050, a novel viral-based cancer vaccine engineered to carry a patient tailored multi antigen payload in patients with HNSCC (NCT04183166).

METHODS

Tumor specific variants were identified using next generation sequencing of tumor and normal samples. Immune relevant mutations were called using a machine learning algorithm factoring in parameters known to affect immunogenicity including MHC binding, level of expression, prevalence across tumor clones, antigen processing and antigen presentation. DNA sequences of the mutations of interest, up to 30 per patient, were cloned in a viral vector (Modified Vaccinia Virus Ankara). Following curative intent treatment, HNSCC patients in complete remission were randomized to an immediate vaccination arm 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 where the same vaccination regimen was initiated at relapse. Leukaphereses to collect PBL were performed at Baseline and after 6 doses of vaccine for in-depth immuno-monitoring. Additional blood draws were performed at intermediary time points. Primary endpoint was vaccine safety and secondary endpoints included feasibility and immunogenicity.

STUDY POPULATION

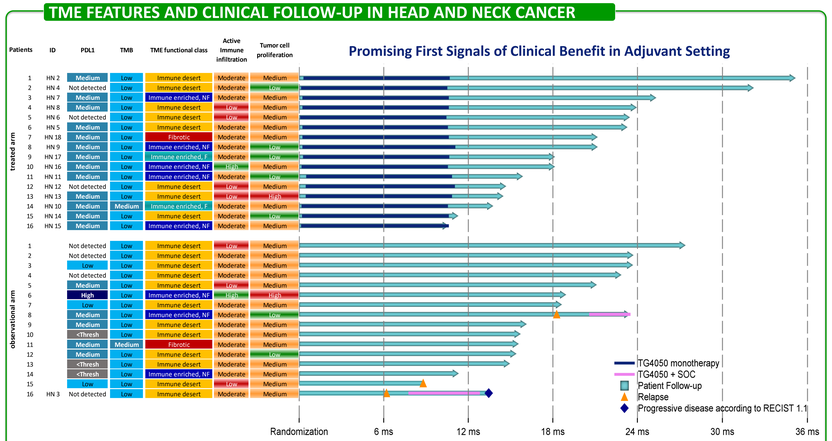
Key inclusion criteria

- Newly diagnosed stage III or IV squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx eligible for gross total resection and adjuvant therapy
- Complete response 3 months after completion of adjuvant therapy
- ECOG Performance status 0 or 1

Key exclusion criteria

- HPV-positive oropharynx primaries, carcinoma of the nasopharynx, squamous cell-carcinoma of unknown primary, squamous cell carcinoma that originates from the skin and salivary gland or paranasal sinus, non-squamous histologies
- Prior exposure to cancer immunotherapy including anti-cancer vaccines, any antibody targeting T cell co-regulatory proteins such as anti-PD-L1, anti-PD 1, or anti-CTLA-4 antibodies
- Chronic treatment with systemic corticosteroids

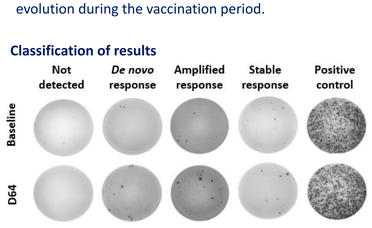
TME FEATURES AND CLINICAL FOLLOW-UP IN HEAD AND NECK CANCER

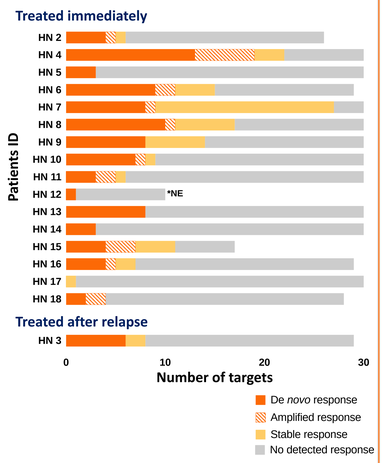


Patients were free of disease at the time of randomization per clinical/radiological and molecular criteria (ctDNA). Exploration of TME through deconvolution of RNAseq data reveals high prevalence of (1) low/medium PD-L1 expression, (2) low TMB, (3) tumor immune desert, (4) moderate active infiltration and (5) medium tumor proliferation. None of the 16 evaluable patients randomized to the treated arm (immediate vaccination arm) has experienced relapse. In the observational arm (scheduled to receive the vaccine at relapse only) 3 out of the 16 randomized patients have experienced relapse. The median follow-up time (prior to relapse) is 18.6 months in both arms.

ADAPTIVE IMMUNE RESPONSE AFTER VACCINATION

The immunological responses against vaccine peptides were classified in four categories according to their evolution during the vaccination period.





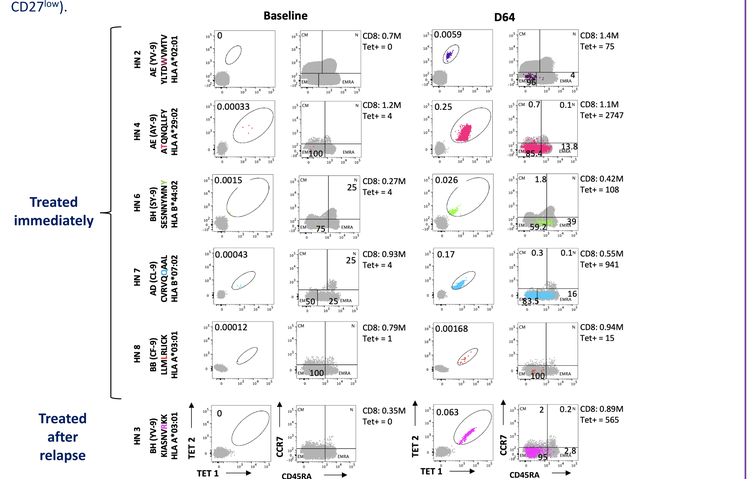
Responses were detected in almost all vaccinated patients (16/17). 33.2% of the vaccine peptides elicited an immune response including 19.1% that were not detected at baseline. Detected responses corresponded to either CD4⁺ or CD8⁺ T cells. The median number of vaccine responses was 6 (0-19).

Vaccination induced the generation and/or the expansion of tumor specific T cells detectable in the blood.

*NE: this sample will be retested against a higher number of vaccine peptides

PHENOTYPE OF TETRAMER+ T CELLS EXPANDED BY THE VACCINE

CD8⁺ T cell responses were further characterized using tetramer staining whenever stable HLA-multimer/9-mer peptide complexes could be obtained. The mutated amino acid is colored in the peptide sequence (left). A dual fluorochrome combicolor code was used to multiplex tetramer detection by flow cytometry. The phenotype of tetramer positive cells corresponded to effector/memory CD8⁺ T lymphocytes (CCR7⁻CD45RA⁻CD39⁺PD-1⁺ CD27^{low}).



We report here tetramer staining data of 6 patients. The absolute number as well as the frequency of tetramer specific T cells was greatly increased at D64 as compared with baseline. 7 patients were tested with 9 to 34 tetramers. At least one tumor-specific CD8⁺ T cell response was induced or amplified by vaccination in 6 out of 7 studied patients.

TG4050 elicited unambiguous CD8⁺ T cell responses towards tumor antigens.

ACKNOWLEDGEMENTS

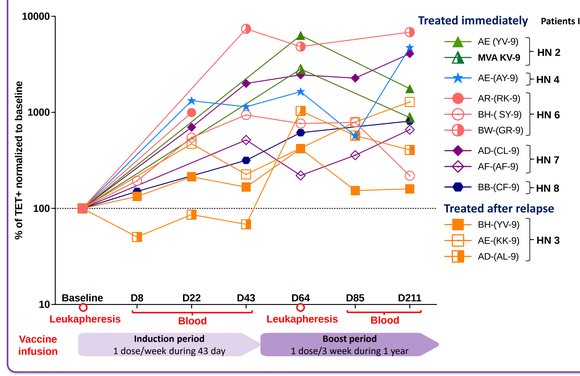
The authors wish to thank all patients, families, caregivers and all technical staff involved in the project.

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KEY MESSAGES

- Immunogenic epitopes were identified in all patients allowing the manufacturing of individualized vaccines.
- Polyepitopic responses were induced over the course of vaccination in 16/17 patients using stringent testing conditions (single peptide, ex vivo IFNg ELISPOT).
- T cell response was maintained over time beyond 211 days after initiation of treatment.
- Clinical outcome in vaccinated patients is promising with no relapse in high-risk patients receiving the vaccine post-primary treatment versus 3 relapses in patients not receiving the vaccine.

LONGITUDINAL STUDY OF TETRAMER+ CD8+ CELLS RESPONDING TO THE VACCINE

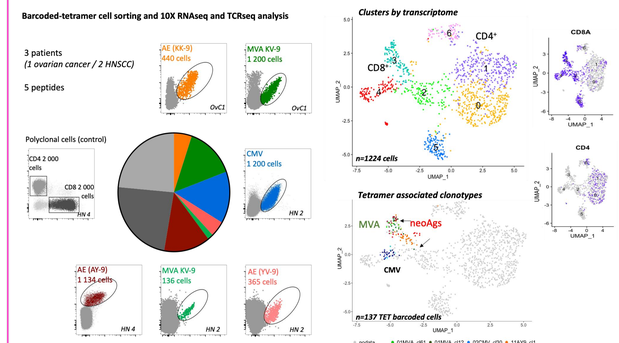


Longitudinal responses were studied for the peptides showing a tetramer response at day 64. Baseline and D64 lymphocytes corresponded to leukapheresis while the other time points were blood draws. In the case of *de novo* responses for which no cell was detected at baseline, the initial frequency was estimated as 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.

The frequency of Ag specific T cells increased during the induction period, reaching a maximum at D43 or D64 and remained at high frequency during the boosting period.

Persisting vaccine responses were observed during the whole monitoring period.

ANALYSIS OF TETRAMER+ CD8+ T CELLS BY SINGLE CELL RNASEQ VDJ

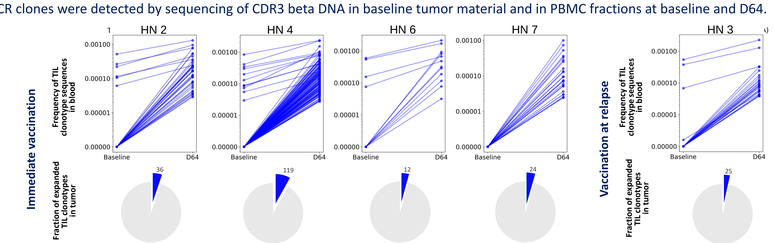


The CD8⁺ antigen specific responses were dissected using 10X single cell RNAseq-VDJ technology. Selected populations of Tetramer⁺ (TET⁺) CD8⁺ T cells were sorted using barcoded tetramers from D64 PBMC samples together with TET^{neg} CD4⁺ and CD8⁺ T cells as references. Clustering and UMAP identified 7 clusters of CD4⁺ and CD8⁺ T cells. TET barcoding allowed the projection of TET⁺ onto CD8⁺ clusters #3 and #4. CD8⁺ T cells specific for vaccine neoAgs and MVA vector mapped to cluster #3 while CMV specific T cells mapped to cluster #4 indicating a distinct differentiation states.

Some of the TCR specific for the peptides were found several times indicating that clonal expansions occurred after vaccination.

TIL CLONES EXPANSION AFTER VACCINE INITIATION

For selected patients, prevalence of clones detected in tumor at baseline were quantified in blood before vaccine treatment initiation and after 64 days. TCR clones were detected by sequencing of CDR3 beta DNA in baseline tumor material and in PBMC fractions at baseline and D64.



Pie charts show the fraction of expanded clones (blue) over the total number of clones identified in the baseline tumor.