Phase 1 studies of personalized neoantigen vaccine TG4050 in ovarian carcinoma (OvC) and head and neck squamous cell carcinoma (HNSCC)

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BACKGROUND

Cancer mutations are not subject to central tolerance and are attractive targets for vaccination. The use of mutation-derived neoepitopes to design cancer vaccines is an unprecedented opportunity but the stochastic occurrence of mutations implies that a tailored vaccine needs to be manufactured for each patient. We used next generation sequencing, machine learning based genomic data analysis and advances in genome editing to systematically identify private neoepitopes in high-risk HPV negative HNSCC and relapsing OvC patients (NCT03839524 NCT04183166

METHODS

Mutations were identified by DNA and RNA sequencing and putative epitopes were selected for vaccine design based on their likelihood to elicit a class I or II response using data on HLA binding, allelic frequency, prediction of processing and expression at RNA level. The vaccine is a recombinant virus of the modified Vaccinia Ankara (MVA) strain encoding for up to 30 target antigens. The viral vaccine was amplified under GMP conditions and administered to patients after completion of SOC treatment given with curative intent in two phase I trials. Monotherapy with the vaccine was started for OvC patients at relapse defined as elevation of CA-125 and/or onset of suspicious radiological findings and for locally advanced HNSCC patients following upfront surgery and adjuvant therapy. Head and Neck patients were randomized to receive the vaccine immediately after first line treatment in monotherapy (Arm A) or at relapse (Arm B) in conjunction with standard of care. In both studies, the vaccine was administered subcutaneously weekly for 6 weeks and a booster dose every three weeks over a year.

STUDY POPULATION

Ovarian cancer patients

Key Inclusion Criteria

- Stage IIIC or stage IVA (FIGO staging) high grade serous ovarian, fallopian or primary peritoneal carcinoma
- Complete response maintained at least 6 months after debulking surgery and first-line chemotherapy
- Asymptomatic relapse (elevated CA-125 and/or radiological findings)
- ECOG Performance status 0 or 1

Key Exclusion Criteria

- 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

HNSCC patients

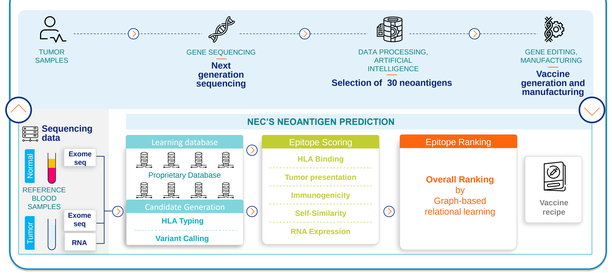
Key Inclusion Criteria

- Newly diagnosed stage III or IVA 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

DESIGN OF PATIENT SPECIFIC VACCINE



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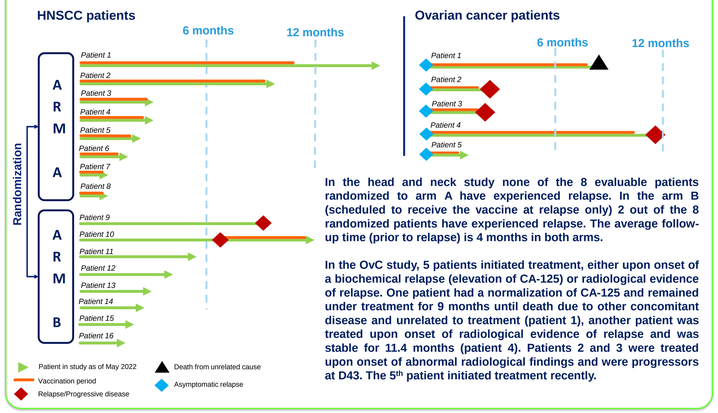
CLINICAL FOLLOW-UP

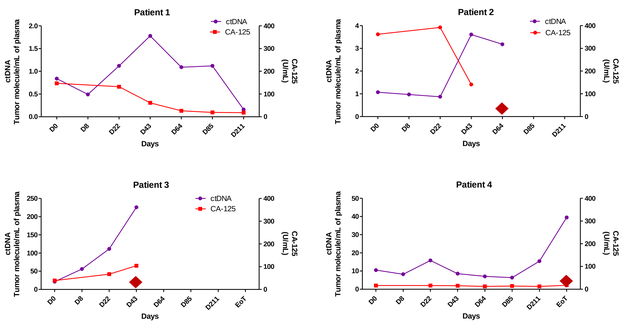


In the head and neck study none of the 8 evaluable patients randomized to arm A have experienced relapse. In the arm B (scheduled to receive the vaccine at relapse only) 2 out of the 8 randomized patients have experienced relapse. The average follow-up time (prior to relapse) is 4 months in both arms.

In the OvC study, 5 patients initiated treatment, either upon onset of a biochemical relapse (elevation of CA-125) or radiological evidence of relapse. One patient had a normalization of CA-125 and remained under treatment for 9 months until death due to other concomitant disease and unrelated to treatment (patient 1), another patient was treated upon onset of radiological evidence of relapse and was stable for 11.4 months (patient 4). Patients 2 and 3 were treated upon onset of abnormal radiological findings and were progressors at D43. The 5th patient initiated treatment recently.

MOLECULAR AND BIOCHEMICAL FOLLOW-UP

Ovarian cancer patients



To monitor disease progression in patient with subclinical disease, we designed tumor informed ctDNA monitoring panel for each patient from tumor exome sequences. Up to 16 tumor specific mutations were used to monitor the frequency of tumor DNA in cell free DNA in peripheral samples. Data were reported as mean tumor specific molecule per ml of plasma (hence large variation in value from one patient to the other).

In the OvC study, tumor informed ctDNA monitoring correlated strongly with clinical evolution of the disease.

- In patient 2, 3 and 4 ctDNA elevation was prodromal or concomitant to clinical progression.
- In patient 1, a decline in ctDNA was noted from D43 concomitantly with CA-125 normalization

Head and Neck cancer patient 1 and 2 were tested and found negative for ctDNA at all time points.

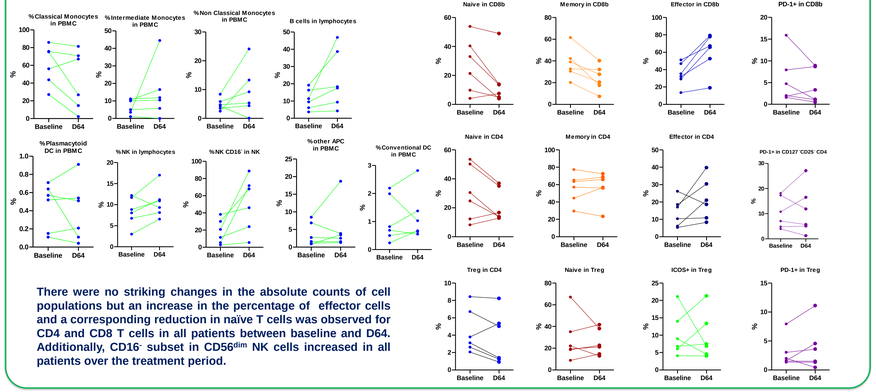
SAFETY FINDINGS

TG4050 was well tolerated. All treatment-related AEs were mild or moderate and most of them were injection site reactions. Safety data were available from 15 patients at the time of cut-off.

	Ovarian cancer (N=5)		HNSCC (N=10)		Overall (N=15)	
	N (%)	ev	N (%)	ev	N (%)	ev
Patient with at least one treatment-related AE	*4 (80.0%)*	*29*	*8 (80.0%)*	*22*	*12 (80.0%)*	*51*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**4 (80.0%)**	**28**	**8 (80.0%)**	**21**	**12 (80.0%)**	**49**
Chills	1 (20.0%)	1	0 (0.0%)	0	1 (6.7%)	1
Fatigue	1 (20.0%)	1	1 (10.0%)	1	2 (13.3%)	2
Injection Site Bruising	0 (0.0%)	0	2 (20.0%)	2	2 (13.3%)	2
Injection Site Erythema	3 (60.0%)	8	1 (10.0%)	2	4 (26.7%)	10
Injection Site Induration	0 (0.0%)	0	1 (10.0%)	2	1 (6.7%)	2
Injection Site Inflammation	0 (0.0%)	0	4 (40.0%)	9	4 (26.7%)	9
Injection Site Mass	1 (20.0%)	5	0 (0.0%)	0	1 (6.7%)	5
Injection Site Nodule	1 (20.0%)	1	0 (0.0%)	0	1 (6.7%)	1
Injection Site Oedema	0 (0.0%)	0	3 (30.0%)	3	3 (20.0%)	3
Injection Site Pain	2 (40.0%)	10	2 (20.0%)	2	4 (26.7%)	12
Injection Site Pruritus	1 (20.0%)	1	0 (0.0%)	0	1 (6.7%)	1
Injection Site Swelling	1 (20.0%)	1	0 (0.0%)	0	1 (6.7%)	1
INVESTIGATIONS	**0 (0.0%)**	**0**	**1 (10.0%)**	**1**	**1 (6.7%)**	**1**
Blood Alkaline Phosphatase Increased	0 (0.0%)	0	1 (10.0%)	1	1 (6.7%)	1
MUSCULOSKELETAL/CONNECTIVE TISSUE DISORDERS	**1 (20.0%)**	**1**	**0 (0.0%)**	**0**	**1 (6.7%)**	**1**
Musculoskeletal Chest Pain	1 (20.0%)	1	0 (0.0%)	0	1 (6.7%)	1

PHENOTYPING OF CIRCULATING CELLS

PBMC were analyzed by flow cytometry to quantify relevant immune cell subpopulations, in particular monocytes, DC, NK cells, subcells of CD8, CD4, Treg and expression of immune checkpoints ICOS and PD1.

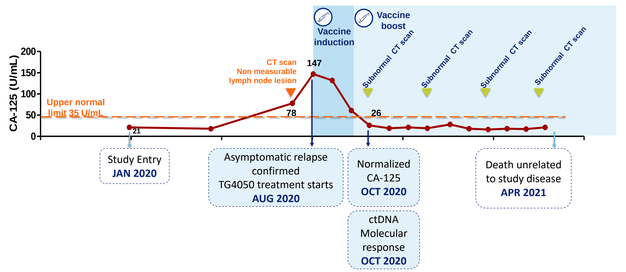


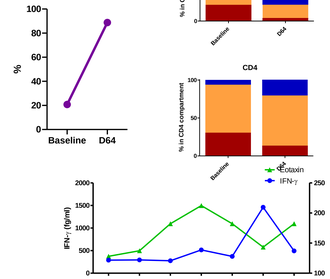
There were no striking changes in the absolute counts of cell populations but an increase in the percentage of effector cells and a corresponding reduction in naïve T cells was observed for CD4 and CD8 T cells in all patients between baseline and D64. Additionally, $CD16^{-}$ subset in $CD56^{dim}$ NK cells increased in all patients over the treatment period.

OBJECTIVE CLINICAL RESPONSE IN PATIENT 1 OF OvC STUDY

73-year old diagnosed with Grade IIIC serous carcinoma of the ovaries (No BRCA mutation but HRD score >45 and p53 mutation, Moderate TMB). Complete clinical remission after surgery and 6 cycles of paclitaxel/carboplatin as adjuvant treatment. History of heart failure.

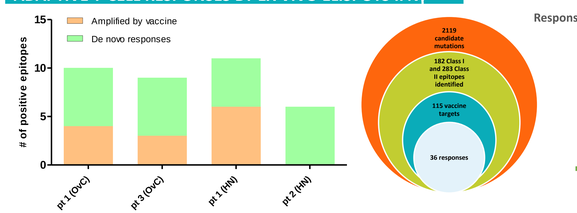
Normalization of CA-125 was observed at upon 6 weeks of vaccination. The patient remained stable over 9 months until death from an unrelated cause. Changes in immune contexture and development of T cell responses against multiple epitopes were observed concomitantly.

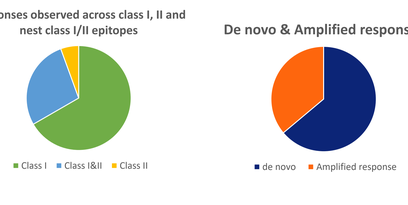




Clinical resolution (CA-125 and ctDNA response) was concomitant to an increase in CD16neg NK cells, a switch in circulating CD4 and CD8 cells toward an effector phenotype, a peak in acute phase marker Eotaxin at day 43, a peak in IFNg at day 85 and multiple antigen specific T cell response.

ADAPTIVE T-CELL RESPONSES BY EX VIVO ELISPOTS IFNγ





Data on antigen specific T cell responses were available from 4 patients at the time of the present publication, specifically OvC patients 1 and 3 and HNSCC patients 1 and 2. PBMCs were restimulated using 15-mers encoding for the mutations targeted by the vaccine. Response against each vaccine target were tested individually.

Among a total of 2119 candidates, we identified mutations associated with 182 class I epitopes and 283 class II epitopes. These sequences were used to design patient specific vaccines targeting a total of 115 mutations of which 36 elicited a response to the vaccine. ELISPOT were conducted using overnight stimulation. All tested patients had response against multiple vaccine targets (median of 10 per patient). 34% of immunoreactive peptides were amplifications of preexisting responses and 66% were *de novo*. Immunoreactive T cells were observed for both class I, II and nested class I/II epitopes. Responses are skewed toward class I epitopes but this is likely due to the priority given to class I antigens in vaccine design.

CONCLUSIONS

The viral based personalized vaccine approach was feasible: relevant targets could be identified in all patients, and time of manufacturing and drug release was compatible with the clinical course of treatment. Administration of the vaccine was safe and induced tumor specific T cell response against multiple targets. Early signs of clinical activity are encouraging with changes of tumor markers observed in a treated patient under vaccine monotherapy.