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

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Transgene

BACKGROUND

Head and Neck (HNSCC) and Ovarian cancer (OC) are two indications for which immunotherapy had limited impact so far. Current treatments achieve high rates of initial success through surgery and adjuvant chemo/radiotherapy, but patients remain at high risk of relapse in both indications. Immune stimulation using a vaccine is a promising strategy to a clinically meaningful improvement. Herein we report phase I data of TG4050, a vaccine engineered to carry a patient tailored antigen payload, in patients with HNSCC (NCT04183166) or OC (NCT03839524).

METHODS

Tumor specific variants are identified using next generation sequencing of tumor and normal samples and immune relevant mutations are called using a machine learning algorithm factoring in parameters known to affect immunogenicity including MHC binding, level of expression, prevalence across clones, antigen processing. DNA sequences of the mutations of interest, up to 30 per patient, are 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 is initiated at relapse. OC patients received the vaccine upon onset of signs of relapse. PBMC were collected at Baseline and after 6 doses of vaccine. Primary endpoint was vaccine safety and secondary endpoints included feasibility and immunogenicity.

STUDY POPULATION

Ovarian cancer patients

Key Inclusion Criteria

- Stage IIIC or stage IV (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 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

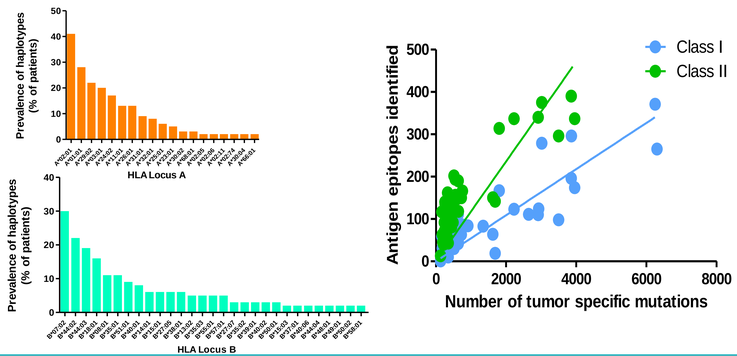
Key Exclusion Criteria

- 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

IDENTIFICATION OF NEOANTIGENS

Number of candidate epitopes correlated with overall nonsynonymous mutations. Identification of epitopes for design of the personalized vaccine was feasible in most patients across different HLA genotypes.

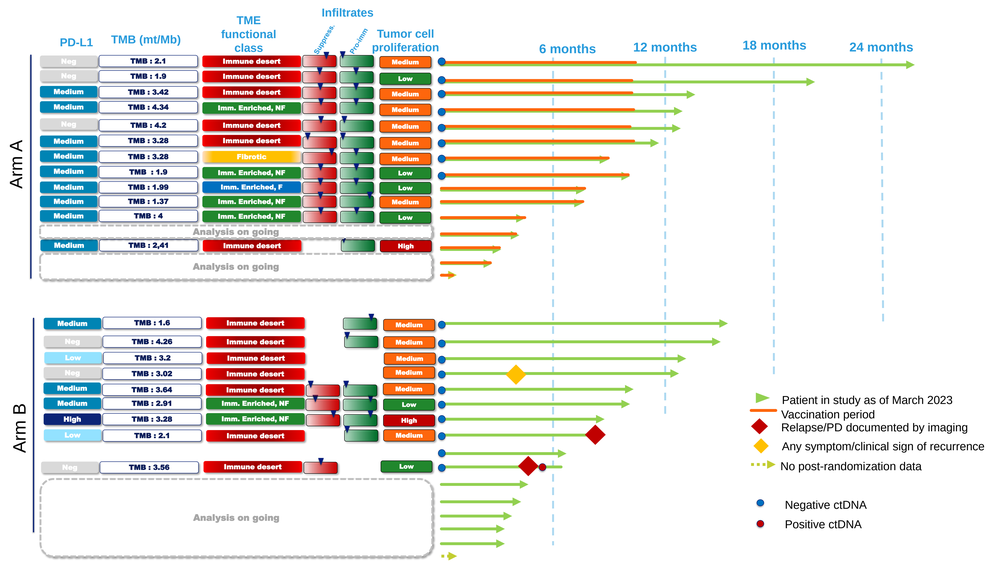
Left: HLA genotype distribution across the screened population. Right: Epitopes identified in patients screened.



The study was industry co-funded by NEC Corporation and Transgene SA.

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

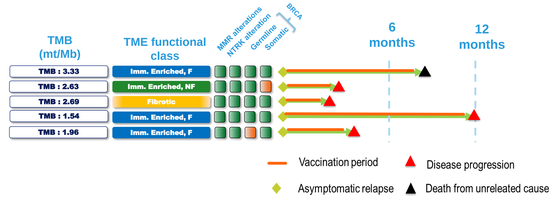
Patients were free of disease at time of randomization per clinical/radiological and molecular criteria (patient informed ctDNA). Exploration of tumor TME through deconvolution of RNAseq data reveals a challenging population with high prevalence of low/negative PD-L1 expressors and relatively poor pro-immune infiltrates.



None of the 15 evaluable patients randomized to the arm A (early vaccination arm) has experienced relapse.
In the arm B (scheduled to receive the vaccine at relapse only) 2 out of the 16 randomized patients have experienced relapse.
The average follow-up time (prior to relapse) is 9.2 months in both arms.

TME FEATURES AND CLINICAL FOLLOW-UP IN OVARIAN CANCER

Patients were treated at onset of asymptomatic relapse based on CA-125 increase or radiologic relapse. Vaccination period extended until a maximum of 20 TG4050 administrations (~1 year) or disease progression according to RECIST 1.1 whichever occurred first.



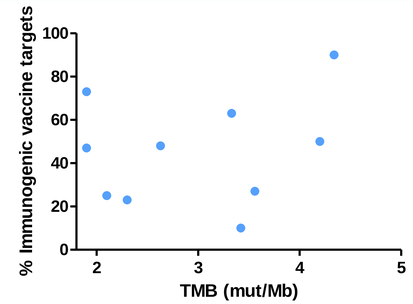
In the OvC trial, 5 patients initiated treatment.
One patient with elevated CA-125 at treatment start showed normalization after 9 weeks which has been maintained for 9 months. The remaining patients had evidence of radiological relapse at treatment start. Among them, one had stable disease for 11.4 months and the others progressed either at first or second tumor evaluation.

SAFETY

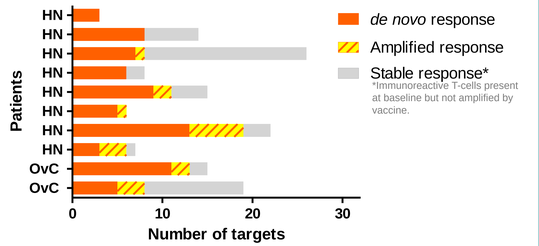
SYSTEM ORGAN CLASS / Preferred Term	Grade 1 N(%)	Grade 1 Ev	Grade 2 N(%)	Grade 2 Ev	Overall (N=22) N(%)	Overall (N=22) Ev
Patient with at least one Adverse Reaction	**21 (95.5%)**	**95**	**6 (27.3%)**	**8**	**21 (95.5%)**	**103**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**1 (4.5%)**	**2**	**0 (0.0%)**	**0**	**1 (4.5%)**	**2**
Lymphopenia	1 (4.5%)	2	0 (0.0%)	0	1 (4.5%)	2
GASTROINTESTINAL DISORDERS	**2 (9.1%)**	**2**	**1 (4.5%)**	**1**	**2 (9.1%)**	**3**
Diarrhoea	1 (4.5%)	1	1 (4.5%)	1	2 (9.1%)	2
Vomiting	1 (4.5%)	1	0 (0.0%)	0	1 (4.5%)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**19 (86.4%)**	**85**	**5 (22.7%)**	**5**	**19 (86.4%)**	**90**
Injection Site reaction	19 (86.4%)	77	1 (4.5%)	1	19 (86.4%)	78
Oedema Peripheral	1 (4.5%)	3	1 (4.5%)	1	1 (4.5%)	4
Fatigue	2 (9.1%)	2	1 (4.5%)	1	3 (13.6%)	3
Asthenia	1 (4.5%)	1	1 (4.5%)	1	1 (4.5%)	2
Influenza Like Illness	1 (4.5%)	1	1 (4.5%)	1	2 (9.1%)	2
Chills	1 (4.5%)	1	0 (0.0%)	0	1 (4.5%)	1
INVESTIGATIONS	**1 (4.5%)**	**1**	**0 (0.0%)**	**0**	**1 (4.5%)**	**1**
Blood Alkaline Phosphatase Increased	1 (4.5%)	1	0 (0.0%)	0	1 (4.5%)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**1 (4.5%)**	**1**	**1 (4.5%)**	**1**	**2 (9.1%)**	**2**
Arthralgia	1 (4.5%)	1	0 (0.0%)	0	1 (4.5%)	1
Musculoskeletal Chest Pain	0 (0.0%)	0	1 (4.5%)	1	1 (4.5%)	1
NERVOUS SYSTEM DISORDERS	**1 (4.5%)**	**1**	**0 (0.0%)**	**0**	**1 (4.5%)**	**1**
Dysgeusia	1 (4.5%)	1	0 (0.0%)	0	1 (4.5%)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2 (9.1%)**	**3**	**1 (4.5%)**	**1**	**2 (9.1%)**	**4**
Rash	2 (9.1%)	3	1 (4.5%)	1	2 (9.1%)	4

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

ADAPTIVE T-CELL RESPONSES BY EX VIVO ELISPOTS IFNγ



There was no significant difference in immunogenicity of vaccine targets across the range of patient TMB. Immunogenicity of target is defined as the presence of immunoreactive T cell prior or after vaccination.



All tested patients developed a polyepitopic T-cell response against vaccine targets (3-19 responses) as assessed by ex-vivo ELISPOT. A mean number of 9 targets per patient was observed. 80% of responses were de novo immuno-reactive T cells and 20% were preexisting responses amplified by the vaccine.

KEY MESSAGES

- ✓ **NGS data confirmed low TMB in these patient populations. Regardless, sufficient candidate antigens were identified to design a vaccine.**
- ✓ **Performance to identify immunogenic mutations was unaffected by TMB.**
- ✓ **Robust manufacturing conditions; 86% of eligible patients were provided with vaccine in due time**
- ✓ **All patients developed a polyepitopic response regardless of HLA and TME immune features**
- ✓ **Vaccination was well tolerated and associated with encouraging preliminary signs of anti-tumor efficacy**

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