Safety and Immunogenicity of TG4050: a personalized cancer vaccine in head and neck carcinoma

ASCO 2023
Abstract # 6082

C. Ottensmeier[1], JP Delord[2], C. Jamet[3], A. Lalanne[3], O. Lantz[3], C. Jamet[3], G. Lacoste[4], A. Tavernaro[4], M. Brandely[4], B. Grellier[4], B. Bastien[4], H. Makhloufi[4], T. Huss[4], Y. Yamashita[5], K. Onoue[5], N. Yamagata[5], Y. Tanaka[5], B. Malone[6], O. Baker[7], E. Quemeneur[4], K. Bendjama[4], C. Le Tourneau[3]

[1]University of Liverpool, Liverpool, UK; [2]IUCT Oncopole, Toulouse, France; Institut Curie, Paris, France; [4]Transgene SA, Illkirch-Graffenstaden, France; [5]NEC Corporation, Tokyo, Japan; [6]NEC Oncoimmunity, Oslo, Norway; [7]NEC Laboratories Europe GmbH, Heidelberg, Germany

Transgene

BACKGROUND

Immunotherapy had limited impact on Head and Neck cancer care (HNSCC) so far and while current treatments achieve significant rates of initial success through surgery and adjuvant chemo/radiotherapy, patients remain at high risk of relapse in both indications. While tumor antigen reactive T cells are associated with a better outcome and a higher response rate to immune checkpoint inhibition, it has been shown that priming of adaptive response against tumor antigens is impaired in HNSCC. 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).

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. PBMC were collected at Baseline and after 7 doses of vaccine. 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

SAFETY

SYSTEM ORGAN CLASS Preferred Term	Grade 1 N(%)	Ev	Grade 2 N(%)	Ev	Overall (N=18) N(%)	Ev
Patient with a least one Adverse Reaction	**17 (94.4%)**	**68**	**5 (27.8%)**	**9**	**17 (94.4%)**	**77**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**1 (5.6%)**	**2**	**0 (0.0%)**	**0**	**1 (5.6%)**	**2**
Lymphopenia	1 (5.6%)	2	0 (0.0%)	0	1 (5.6%)	2
GASTROINTESTINAL DISORDERS	**2 (11.1%)**	**2**	**1 (5.6%)**	**1**	**2 (11.1%)**	**3**
Diarrhoea	1 (5.6%)	1	1 (5.6%)	1	2 (11.1%)	2
Vomiting	1 (5.6%)	1	0 (0.0%)	0	1 (5.6%)	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**15 (83.3%)**	**58**	**4 (22.2%)**	**7**	**15 (83.3%)**	**65**
Injection Site Reaction	**15 (83.3%)**	**52**	2 (11.1%)	5	**15 (83.3%)**	**57**
Oedema peripheral	1 (5.6%)	3	1 (5.6%)	1	1 (5.6%)	4
Fatigue	2 (11.1%)	2	0 (0.0%)	0	2 (11.1%)	2
Influenza like illness	1 (5.6%)	1	1 (5.6%)	1	2 (11.1%)	2
INVESTIGATIONS	**1 (5.6%)**	**1**	**0 (0.0%)**	**0**	**1 (5.6%)**	**1**
Blood alkaline phosphatase increased	1 (5.6%)	1	0 (0.0%)	0	1 (5.6%)	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**1 (5.6%)**	**1**	**0 (0.0%)**	**0**	**1 (5.6%)**	**1**
Arthralgia	**1 (5.6%)**	**1**	0 (0.0%)	0	**1 (5.6%)**	**1**
Nervous system disorders	1 (5.6%)	1	0 (0.0%)	0	1 (5.6%)	1
Headache	1 (5.6%)	1	0 (0.0%)	0	1 (5.6%)	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**2 (11.1%)**	**3**	**1 (5.6%)**	**1**	**2 (11.1%)**	**4**
Rash	2 (11.1%)	3	1 (5.6%)	1	**2 (11.1%)**	**4**

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

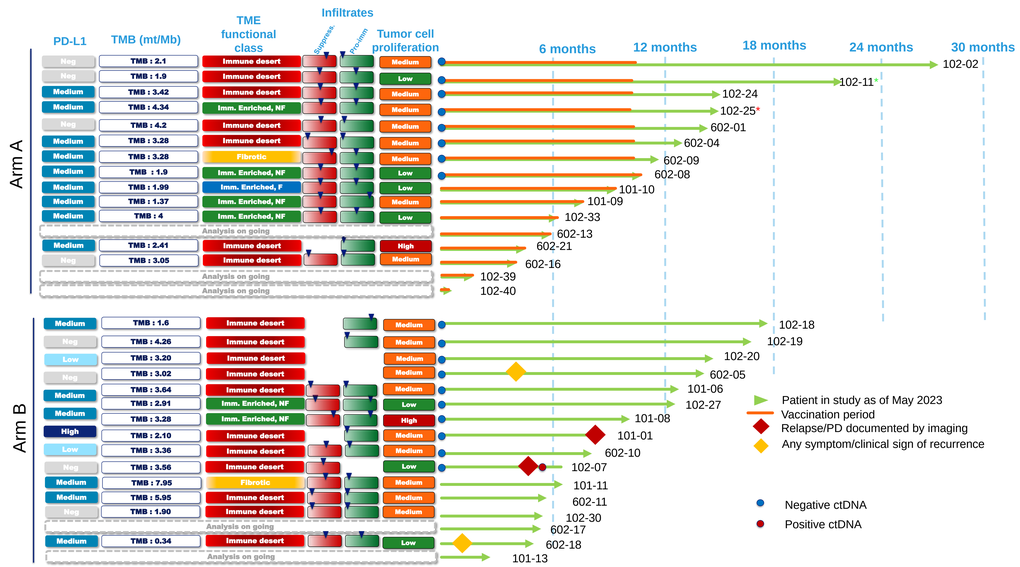
ACKNOWLEDGEMENTS

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.

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.

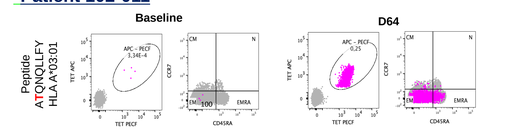


None of the 16 evaluable patients randomized to the arm A (early vaccination arm) has experienced relapse. In the arm B (scheduled to receive the vaccine at relapse only) 2 out of the 16 randomized patients have experienced relapse. The median follow-up time (prior to relapse) is 10.4 months in both arms.

KEY MESSAGES

- ✓ **Vaccination was well tolerated and no relapse was observed in the vaccinated arm after a median of 10,4 months of follow-up.**
- ✓ **All patients developed a polyepitopic response regardless of HLA and TME immune features against a mean of 10 targets.**
- ✓ **NGS data confirmed low TMB in these patients. Regardless, sufficient candidate antigens were identified to design a vaccine. Identification of immunogenic mutations was unaffected by TMB.**
- ✓ **Robust manufacturing conditions; 86% of eligible patients were provided with vaccine in due time.**

*Patient 102-011

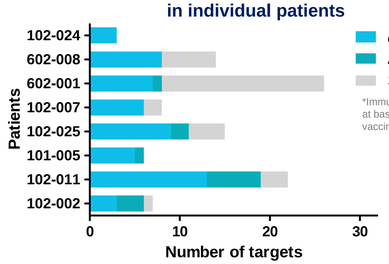


Peptide	ELISPOT Baseline	ELISPOT D64	Sequence 9mer	netMHCpan prediction & HLA	Tetramer response D64
1	-	++	GSASFGTVY	SB A2902	
2	+	++		Not tested	
3			TIGKLEPYY	SB A2902	Not tested
			RTIGKLEPY	SB A2902	No response
4			Not tested		
5	+	++	TQNQLLFYM	WB A2902	Not tested
			ATQNQLLFY	SB A2902	RESPONSE
6	-	-	REEQKELQW	SB B4403	No response
7	-	-	AYYQSADPY	SB A2902	No response
8	-	-	SEDPSLTSV	SB B4403	Not tested
9	-	-	REIHSHSLL	SB B4403	No response
10	-	-	TEKVFLSTF	SB B4403	No response
11	-	-	ERIEGVRHW	WB B4403	No response
12	+	+	HLFNEQNFY	WB A2902	Not tested
13	-	+	RAYETKNRY	WB A2902	Not tested
14	-	+++	SEQRASILH	WB B4403	Not tested
15	-	+++	SSTESSPEY	SB A2902	Not tested
16	+	+++		Not tested	
17			REPKHLLAF	SB B4403	No response
18	-	+		Not tested	
19	+	+	GQHQEVFFY	SB A2902/WB B4403	No response
20	-	+			
21	-	+++	ASPTQEEFY	WB A2902	

Patient 102-011 remains disease free 20 months after initiation of initial treatment. One response was detected by tetramer staining with a remarkably high frequency of positive cells. Vaccine-expanded T cells primarily exhibit an antigen-experienced phenotype within the effector memory gate (CCR7-, CD45RA-), and their lack of CD27 expression allows for more precise classification as effector cytotoxic cells.

ADAPTIVE IMMUNE RESPONSE

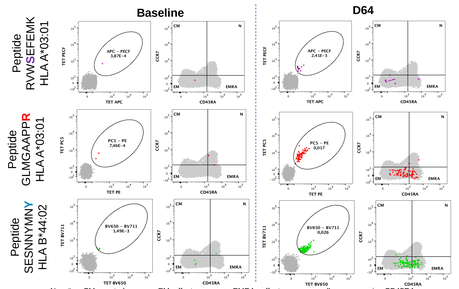
Number of responses against vaccine targets in individual patients



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.

Further to *ex vivo* ELISPOT testing, we have characterized T cell response using tetramer staining whenever it was feasible to obtain a stable multimer/peptide complex and characterized these cells for CD45RA and CCR7 and compared tetramer and ELISPOT data. We report herein tetramer staining data for selected patients.

*Patient 102-025



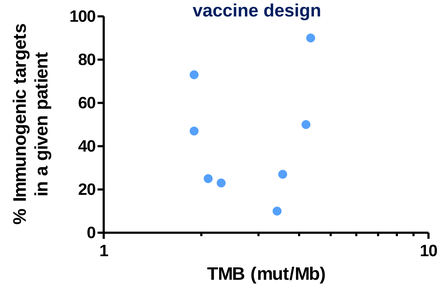
Peptide	ELISPOT Baseline	ELISPOT D64	Sequence 9mer	netMHCpan prediction & HLA	Tetramer response D64
1	+	+++	SGIDTMYY	SB A2902	No response
2	-	+++	RLGEAGLRR	SB A0301	No response
3	-	-	VFSKWTWPY	SB A2902	No response
			WEWPTPYLL	SB B4402	No response
4	-	-	NVTHFIWLK	WB A0301	
5	-	++	SLNRANFRK	SB A0301	No response
6	+	+	SVTGLLSQF	WB A2902	
7	-	+	GQVVKTLAH	WB A0301	No response
8	-	-	RVWSEFEMK	SB A0301	Small response
9	-	++	YVDDRRAF	WB A2902 /WB B4402	Not tested
10	-	-	DWFRARYSY	SB A2902	Not tested
11	+	+	KESLWVCSK	WB B4402	Not tested
			KVSKSDLGR	WB A0301	No response
12	-	-	GTVKESLWK	SB A0301	Not tested
			AQSGAVVQW	SB B4402	Not tested
13	+	+	IKEQVRHFY	WB A2902	Not tested
14	-	+	IENSGVYTK	WB B4402	Not tested
15	Not tested		SESNNYMNY	SB A2902 /SB B4402	RESPONSE
16	+	++	IFDVLFNFY	SB A2902	No response
17	-	-	CLRSHDGRY	WB A2902	Not tested
18	-	-	QPAWLCGRY	WB A2902	Not tested
			RQPAWLCGR	WB A0301	No response
19	-	-	LCDSDGPWK	WB A0301	Not tested
			FLCDSDGPW	WB B4402	Not tested
20	-	-	GLMGAAPPR	WB A0301	RESPONSE
21	-	-	HDDYSRCDY	WB A2902 /WB B4402	Not tested
22	-	-	SEVSPSFRK	WB B4402	Not tested

SB: Strong binder; WB : Weak binder

N: naive, CM : central memory, EM: effector memory, EMRA : effector memory cells re-expressing CD45RA

3 responses were detected by tetramer staining versus 7 by ELISPOT. Difference is expectable and explained by the polyclonality of ELISPOT responses and by the fact that tetramer staining is limited to CD8 responses while mixed or pure CD4 responses may represent a significant part of the overall response.

Correlation of TMB and immunogenicity of targets selected for vaccine design



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