Phase Ib/II trial of TG4001 (Tipapkinogene sovacivec), a therapeutic HPV-vaccine, and Avelumab in patients with recurrent/metastatic HPV16 positive cancers

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BACKGROUND

TG4001 is a vaccine using an attenuated and modified poxvirus (MVA) as a vector expressing the HPV16 E6 and E7 proteins (rendered non-oncogenic) and interleukin-2. In a previous randomized, double-blind, placebo-controlled phase II trial TG4001 provided robust clinical response both in terms of complete histological resolution and viral DNA clearance from CIN 2/3 (Harper DM *et al.* 2019). In the ongoing Phase Ib/II trial we aimed to investigate the hypothesis that priming the immune system with TG4001 increases the clinical benefit associated with PD-L1 blockade. Thus, we assessed the combination of TG4001 and avelumab in HPV16-positive R/M cancers in terms of safety, efficacy and immunological response (NCT03260023). In this report , we present preliminary data of the Ph Ib.

METHODS

Study design and treatments

- Multicenter, open label, single arm study with a 3+3 design for the phase Ib, combining two different dose levels (DL) of TG4001 (DL1 $5x10^6$ and DL2 $5x10^7$ pfu) with avelumab at 10 mg/kg.
- TG4001 was administered SC weekly for 6 weeks, every 2 weeks up to M6, and every 12 weeks thereafter. Avelumab was given IV every 2 weeks starting one week after the first vaccine dose.

Study endpoints and assessments

- Safety and efficacy of the combination of TG4001 and avelumab, immune parameters (T cell response, changes in infiltrates and gene expression of immune related genes
- Tumor response was assessed by RECIST 1.1. PBMC samples were collected longitudinally and tissue samples were collected at baseline and D43
- PD-L1 expression was determined using the Halioseek™ assay (HalioDx, France). The assay was proven equivalent to assays based on clones 22C3 and SP263.

STUDY POPULATION

Key Inclusion Criteria

- Metastatic or refractory/recurrent HPV16+ cancer including oropharyngeal SCCHN, cervical, vulvar, vaginal, penile and anal cancer
- HPV16 positivity determined in central laboratory
- Up to two prior lines of systemic therapy for the management of metastatic or recurrent disease
- 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
- CNS metastases
- Chronic treatment with systemic corticosteroids

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

		DL1 5×10^6 pfu (n=3)	DL2 5×10^7 pfu (n=6)	Overall (n=9)
Age (years)	Mean	51.0	61.2	57.8
	Range	45 – 56	39 – 78	39 – 78
Gender	Female	2 (66.7%)	2 (33.3%)	4 (44.4%)
	Male	1 (33.3%)	4 (66.7%)	5 (55.6%)
Performance Status (ECOG)	0	0 (0.0%)	4 (66.7%)	4 (44.4%)
	1	3 (100.0%)	2 (33.3%)	5 (55.6%)
Primary tumor	Anal	2 (66.7%)	0 (0.0%)	2 (22.2%)
	Cervical	0 (0.0%)	1 (16.7%)	1 (11.1%)
	Oropharyngeal	1 (33.3%)	4 (66.7%)	5 (55.6%)
	Vaginal	0 (0.0%)	1 (16.7%)	1 (11.1%)
Histology	Adenocarcinoma	0 (0.0%)	1 (16.7%)	1 (11.1%)
	Squamous cell carcinoma	3 (100.0%)	5 (83.3%)	8 (88.9%)
Number of prior CT lines	Median	3.0	1.5	2.0
	Range	2 – 3	1 - 2	1 – 3
Locoregional relapse		1 (33.3%)	2 (33.3%)	3 (33.3%)
Distant Metastases		3 (100.0%)	6 (100.0%)	9 (100.0%)

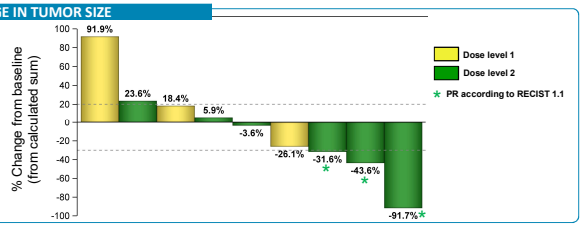
SUMMARY OF TREATMENT RELATED ADVERSE EVENTS (AEs)

System Organ Class	Preferred Term	$5x10^6$ PFU (N=3) n (%)	#AEs	$5x10^7$ PFU (N=6) n (%)	#AEs
OVERALL		3 (100.0%)	23	6 (100.0%)	45
Blood and lymphatic system disorders	Anaemia	2 (66.7%)	*3	0 (0.0%)	0
	Thrombocytopenia	1 (33.3%)	1	0 (0.0%)	0
Endocrine disorders	Hyperthyroidism	1 (33.3%)	1	0 (0.0%)	0
	Hypothyroidism	0 (0.0%)	0	1 (16.7%)	1
Eye disorders	Xerophthalmia	0 (0.0%)	0	1 (16.7%)	1
Gastrointestinal disorders	Diarrhoea	0 (0.0%)	0	3 (50.0%)	3
	Dry mouth	0 (0.0%)	0	1 (16.7%)	1
	Mouth ulceration	0 (0.0%)	0	1 (16.7%)	1
	Nausea	1 (33.3%)	1	0 (0.0%)	0
	Stomatitis	0 (0.0%)	0	1 (16.7%)	1
	Tongue coated	0 (0.0%)	0	1 (16.7%)	1
	Vomiting	1 (33.3%)	1	0 (0.0%)	0
General disorders and administration site conditions	Asthenia	2 (66.7%)	2	2 (33.3%)	2
	Chills	0 (0.0%)	0	1 (16.7%)	1
	Fatigue	0 (0.0%)	0	1 (16.7%)	1
	Injection site erythema	1 (33.3%)	3	3 (50.0%)	5
	Injection site oedema	0 (0.0%)	0	2 (33.3%)	4
	Injection site pain	0 (0.0%)	0	1 (16.7%)	2
	Injection site reaction	1 (33.3%)	1	0 (0.0%)	0
	Mucosal inflammation	0 (0.0%)	0	1 (16.7%)	1
	Pyrexia	1 (33.3%)	1	2 (33.3%)	4
Infections and infestations	Angular cheilitis	0 (0.0%)	0	1 (16.7%)	1
Investigations	Aspartate aminotransferase increased	1 (33.3%)	2	0 (0.0%)	0
	Blood thyroid stimulating hormone increased	0 (0.0%)	0	1 (16.7%)	1
Metabolism and nutrition disorders	Hypertriglyceridaemia	0 (0.0%)	0	1 (16.7%)	1
Musculoskeletal and connective tissue disorders	Arthralgia	0 (0.0%)	0	1 (16.7%)	1
	Myalgia	1 (33.3%)	1	0 (0.0%)	0
	Neck pain	0 (0.0%)	0	1 (16.7%)	1
	Sjogren's syndrome	0 (0.0%)	0	1 (16.7%)	1
Nervous system disorders	Peripheral sensory neuropathy	0 (0.0%)	0	1 (16.7%)	1
Renal and urinary disorders	Proteinuria	0 (0.0%)	0	1 (16.7%)	1
Respiratory, thoracic and mediastinal disorders	Dyspnoea	0 (0.0%)	0	1 (16.7%)	1
Skin and subcutaneous tissue disorders	Pruritus	0 (0.0%)	0	1 (16.7%)	1
	Rash	1 (33.3%)	1	1 (16.7%)	1
	Rash macular	0 (0.0%)	0	1 (16.7%)	2
	Rash maculo-papular	0 (0.0%)	0	1 (16.7%)	1
	Rash papular	1 (33.3%)	1	0 (0.0%)	0

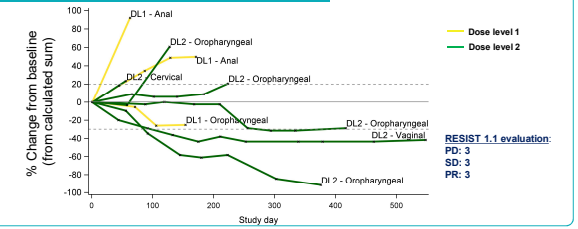
#AEs: Number of AEs

- ✓ **No treatment-related Serious AE has been observed**
- ✓ **A total of 68 adverse events in 9 patients have been observed: 23 AEs in DL1 and 45 AEs in DL2.**
- ✓ **The majority of the reported AEs were mild to moderate (grade 1 - grade 2), only two grade 3 AE were observed in the same patient of DL1 ***

BEST CHANGE IN TUMOR SIZE



INDIVIDUAL LONGITUDINAL CHANGE



IMMUNE DATA

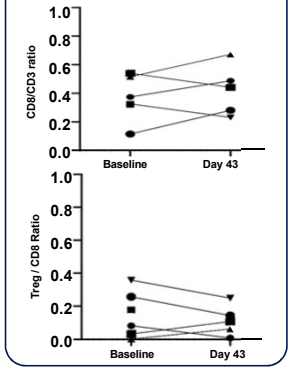
Specific T cell responses against HPV

Specific T cell response: 3 out of 4 patients evaluable for ELISPOT had E6 or E7 reactive T-cells at D43

Lines are individual patients	E6	E7
	++	+
	n/a	++
	+	=
	n/a	-

Changes in TILs under treatment

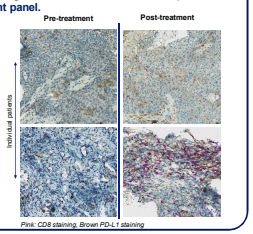
Treatment period was associated in overall increase of CD8/CD3 ratio infiltrates and decrease of Treg (CD4 FoxP3) /CD8 ratio suggesting a more favorable immune profile



PD-L1 expression on TILs and tumor cells under treatment

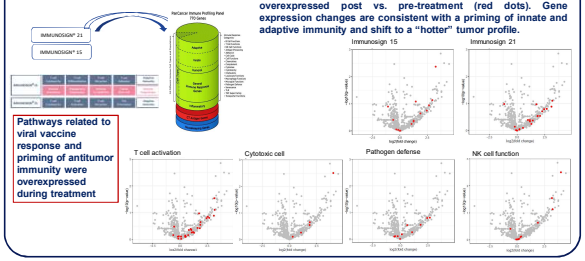
Evolution of PD-L1 expression: 4 out of 5 patients had a significant increase of PD-L1 expression in tumor (left panel); representative pathology picture on right panel.

Primary Cancer	Time point	% of PD-L1+ tumor cells	Immune cells score
vaginal	Baseline Biopsy	35	0
	Day 43 Biopsy	*NA*	0
anal	Baseline Biopsy	50	1
	Day 43 Biopsy	40	0
anal	Baseline Biopsy	0	3
	Day 43 Biopsy	*NA*	*NA*
Oropharyngeal	Baseline Biopsy	80	2
	Day 43 Biopsy	90	2
	Day 85 Biopsy	80	1
Cervical	Baseline Biopsy	40	1
	Day 43 Biopsy	80	2
Oropharyngeal	Baseline Biopsy	15-20	1
	Day 43 Biopsy	35	3
Oropharyngeal	Baseline Biopsy	20	1
	Day 43 Biopsy	40	1



Analysis of gene expression change in tumor tissue during treatment

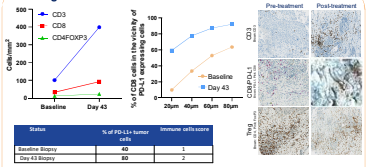
We sought to explore gene expression changes in tumor tissue induced by therapy. To do so, the expression of a panel of 770 genes related to immune response was assessed at baseline and after treatment (day 43). In particular, expression of gene signatures previously described as Immunosign 15 and immunosign 21 were studied (Gallon et al., 2013; Marabelle et al., 2017) . Volcano plots of changes in gene expression and pathways identified as overexpressed post vs. pre-treatment (red dots). Gene expression changes are consistent with a priming of innate and adaptive immunity and shift to a "hotter" tumor profile.



Pathways related to viral vaccine response and priming of antitumor immunity were overexpressed during treatment

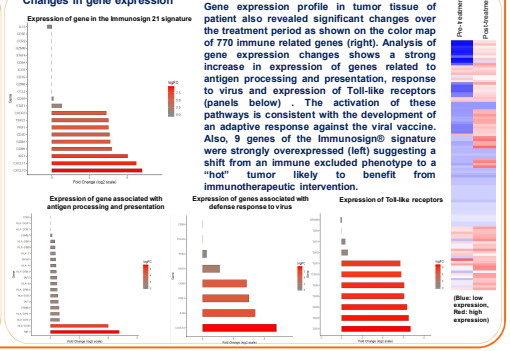
Case study on patient 0101006

Changes in immune infiltrates



Status	% of PD-L1+ tumor cells	Immune cells score
Baseline Biopsy	40	1
Day 43 Biopsy	80	2

Changes in gene expression



Gene expression profile in tumor tissue of patient also revealed significant changes over the treatment period as shown on the color map of 770 immune related genes (right). Analysis of gene expression changes shows a strong increase in expression of genes related to antigen processing and presentation, response to virus and expression of Toll-like receptors (panels below) . The activation of these pathways is consistent with the development of an adaptive response against the viral vaccine. Also, 9 genes of the Immunosign® signature were strongly overexpressed (left) suggesting a shift from an immune excluded phenotype to a "hot" tumor likely to benefit from immunotherapeutic intervention.

Patient 0101006 presented with a tumor with low level of infiltration, moderate expression of PD-L1 on tumor cells and infiltrating immune cells , and, low spatial colocalization between CD8 cells and PD-L1 expressing tumor cells. All these features are consistent with a cold tumor at baseline. At day 43, the tumor was significantly more infiltrated with more than a 4-fold increase in CD3 infiltration, a 3-fold increase in CD8 infiltration, and a doubling of tumor and immune expressing PD-L1. No significant change was observed on the level of infiltration by immune suppressive cells during treatment. Furthermore, digital pathology analysis of sample demonstrates that infiltrated CD8 are clustered around PD-L1 positive tumor cells suggesting a more favorable profile for response to checkpoint blockade.

CONCLUSIONS

- **The combination of TG4001 and avelumab is safe and well tolerated for both dose levels of TG4001 studied in patients with HPV related cancers having received multiple previous lines of treatment.**
- **The combination provides promising efficacy signals at DL2 and is being evaluated in the ongoing phase II part.**
- **The treatment is associated with changes in tumor microenvironment that are likely to change the course of the pathology by shifting tumor from a cold state to a hotter immune status even in heavily pretreated patients. This may be particularly useful in patient with "immune-excluded" tumor phenotype as shown on the individual study case.**

REFERENCES

Gallon J et al. *Immunity*, 2013, 31(1), 11-26
Harper DM et al. *Gynecologic Oncology* 2019; 153, 521 – 529
Marabelle A et al. SITC, 2017

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