SITC 35th Anniversary Annual Meeting during SITC 2020
Abstract ID 793

TG4001 (Tipapkinogene sovacivec) and avelumab for recurrent/metastatic (R/M) Human Papilloma Virus (HPV)-16+ cancers: clinical efficacy and immunogenicity

C. Le Tourneau[1], P. Cassier[2], F. Rolland[3], S. Salas[4], J.-M. Limacher[5], O. Capitain[6], O. Lantz[7], A. Lalanne[7], C. Ekwegbara[7], A. Tavernaro[8], H. Makhloufi[8], K.Bendjama[8], J.-P. Delord[9]

[1]Department of Drug Development and Innovation (D3i), Institut Curie, Paris, France, [2]Cancérologie Médicale - Centre Leon Bérard, Lyon, France, [3]Institut de Cancérologie de l'Ouest - Site René Gaudducheau, Saint Herblain, France, [4]CEPCM Hôpital Timone, Marseille, France, [5]Hôpitaux Civils de Colmar, Colmar, France, [6]Institut de Cancérologie de l'Ouest - Site Paul Papin, Angers, France, [7]Laboratoire d'Immunologie, CIC-BT1428 et Unité Inserm 932, Institut Curie, Paris, France, [8]Transgene S.A. Illkirch –Graffenstaden, France, [9]IUCT-Oncopole, Toulouse, France

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 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 efficacy and immunogenicity and performed a pooled analysis in the phase Ib/II population consisting of 6 patients of the phase Ib treated with the phase II dose of TG4001 and 28 evaluable patients of the phase II (NCT03260023). Additionally, we assessed immune priming effect of the regimen by analyzing tumor infiltrates, expression of PD-L1, expression of immune-related genes in the tumor and development of a specific T-cell response against the vaccine targets: E6 and E7 HPV antigens.

METHODS

Study design and treatments

- Multicenter, open label, single arm study evaluating the combination of TG4001 and avelumab in patients with recurrent/metastatic HPV-16 positive oropharyngeal squamous cell carcinoma of the head and neck (SCCHN), anal, cervical, vulvar or vaginal cancer,
- TG4001 was administered at a dose of $5x10^7$ pfu SC weekly for 6 weeks, every 2 weeks up to M6, and every 12 weeks thereafter. Avelumab was given IV at 10 mg/kg every 2 weeks starting one week after the first vaccine dose,
- PBMC and tissue samples were collected longitudinally prior to and during the treatment period (Day 43).

Study endpoints and assessments

- Safety of the combination of TG4001 and avelumab,
- Efficacy and tumor response as assessed by RECIST 1.1.
- Immune parameters: priming of specific T cell response against HPV E6 and E7antigens, expression of immune related genes in the tumor, and change in PD-L1 expression on tumor cells (22C3).

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 by nested PCR with HPV-16 specific probes and retest of negative results by sequencing.
- Up to two prior lines of systemic therapy for the management of metastatic or recurrent disease
- ECOG Performance status 0 or 1

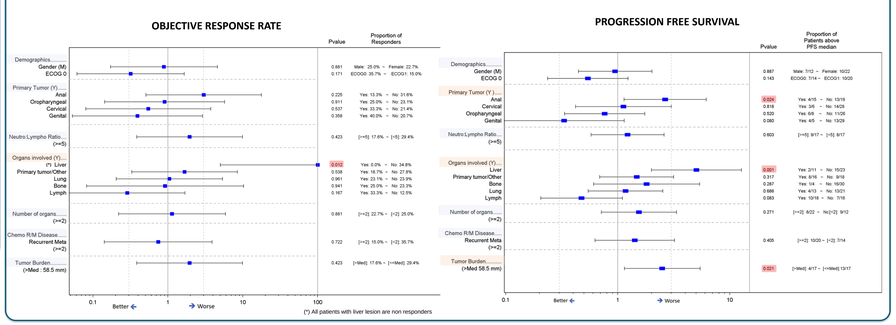
Key Exclusion Criteria

- 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

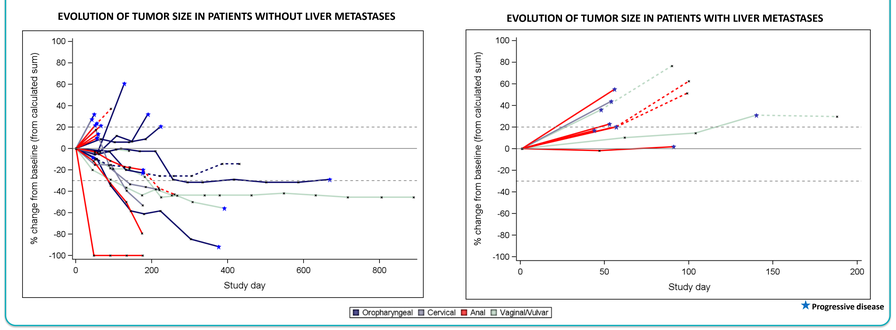
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Patients without liver metastases (N=23)	Patients with liver metastases (N=11)	Overall (N=34)
Age (years)			
Mean	61.6	52.9	58.8
Range	28 - 78	34 – 79	28 - 79
Gender			
Female	14	8	22 (64.7%)
Male	9	3	12 (35.3%)
Performance Status (ECOG)			
0	7	7	14 (41.2%)
1	16	4	20 (58.8%)
Primary tumor			
Anal	7	8	15 (44.1%)
Cervical	5	1	6 (17.6%)
Oropharyngeal	8	0	8 (23.5%)
Vaginal	2	2	4 (11.8%)
Vulvar	1	0	1 (2.9%)
Number of organs Involved			
1	9	3	12 (35.3%)
2	10	3	13 (38.2%)
3	4	5	9 (26.5%)
Number of CT lines for R/M disease			
0	4	0	4 (11.8%)
1	14	5	19 (55.9%)
2	5	6	11 (32.4%)
Tumor Burden (mm)			
Median	47.0	75.5	58.5
Min - Max	11.0 - 136.0	41.0 - 199.0	11.0 - 199.0

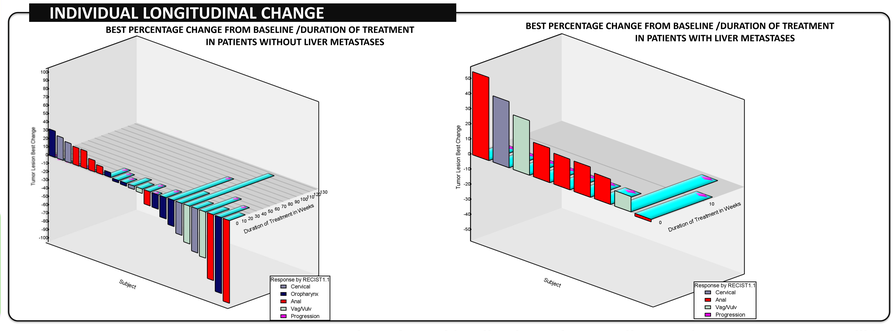
IMPACT OF DISEASE/ PATIENT CHARACTERISTICS



TUMOR SIZE EVOLUTION

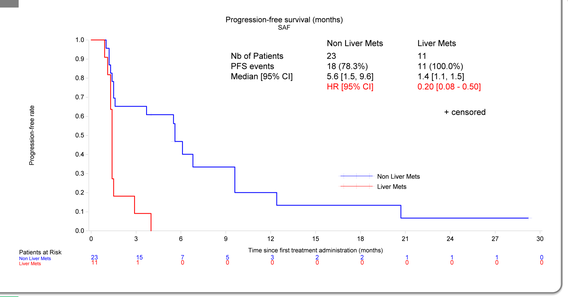


INDIVIDUAL LONGITUDINAL CHANGE



POOLED SUMMARY EFFICACY ANALYSIS

Efficacy parameters	Patients without liver metastases n=23	Patient with liver metastases n=11	Overall n = 34
Response (RECIST 1.1)			
CR : Complete Response	1 (4.3%)	0	1 (2.9%)
PR : Partial Response	7 (30.4%)	0	7 (20.6%)
ORR : Overall Response	8 (34.8%) [16.4 ; 57.3]	0 (0%)	8 (23.5%) [10.7 ; 41.2]
Disease Control Rate (DCR) at 12 weeks	13 (56.5%)	1 (9.1%)	14 (41.2%)
Progression ≤ 12 weeks	10 (43.5%)	10 (90.9%)	20 (58.8%)
Response according to primary tumor (responders/total number of patients %) :			
Anal	2/7 (28.6%)	0/8	2/15 (13.3%)
Oropharyngeal	2/8 (25.0%)	-	2/8 (25.0%)
Cervical	2/5 (40.0%)	0/1	2/6 (33.3%)
Vulvar/Vaginal	2/3 (66.7%)	0/2	2/5 (40.0%)



SUMMARY OF TREATMENT RELATED ADVERSE EVENTS (AEs)

The most commonly reported grade 1/2 TRAE (≥ 4 patients) were :

- **General disorders and administration site conditions (81%)**
  - ✓ Injection Site Erythema (26.2%)
  - ✓ Pyrexia (23.8%)
  - ✓ Asthenia (19.0%)
  - ✓ Injection Site Oedema (16.7%)
  - ✓ Injection Site Pain (16.7%)
  - ✓ Chills (11.9%)
  - ✓ Injection Site Rash (9.5%)
  - ✓ Injection Site Reaction (9.5%)
- **Gastrointestinal disorders (26.2%)**
  - ✓ Diarrhoea (11.9%)

TRAEs of grade 3/4/5

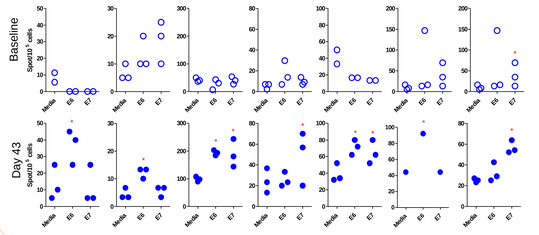
System Organ Class	Grade 3 N(%)	#AEs	Grade 4 N(%)	#AEs	Grade 5 N(%)	#AEs	Overall (N=42) N(%)	#AEs
OVERALL	3 (7.1%)	6	0 (0.0%)	0	1 (2.4%)	1	4 (9.5%)	7
Blood and lymphatic system disorders	1 (2.4%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	2
Anaemia	1 (2.4%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	2
Gastrointestinal disorders	1 (2.4%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1
Diarrhoea	1 (2.4%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1
Hepatobiliary disorders	1 (2.4%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1
Autoimmune hepatitis	1 (2.4%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1
Investigations	1 (2.4%)	2	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	2
Aspartate aminotransferase increased	1 (2.4%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1
Blood lactate dehydrogenase increased	1 (2.4%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1
Nervous system disorders	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1
Vasculitis cerebral	0 (0.0%)	0	0 (0.0%)	0	1 (2.4%)	1	1 (2.4%)	1

#AEs: Number of AEs

IMMUNE DATA

EX VIVO ELISPOT RESPONSE AGAINST E6 AND E7

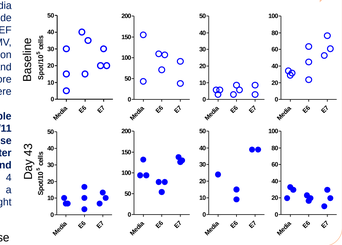
Patients with a detected response against target antigens



Cells were unfrozen and stimulated overnight with media (negative control), E6 peptide pool, E7 peptide pool or CEF (positive control: EBV, CMV, Flu). Cells were then plated on anti-IFNg coated plates and incubated ($1\text{-}10^5$ cell/well) before revelation. Three replicates were performed for each condition. **11/22 patients were evaluable for ELISPOT response. 7/11 patients had a response against E6/E7 or both after treatment with TG4001 and avelumab (left panel)**. 4 patients did not show a response upon treatment (right panel).

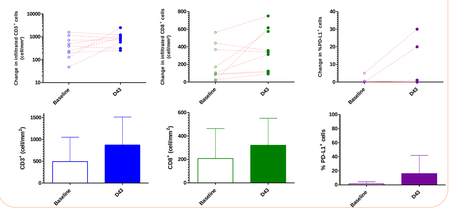
* : Positive antigen response

Patients without specific response at day 43

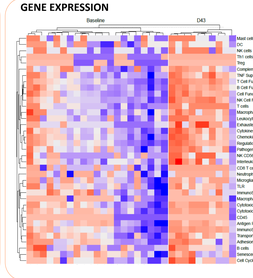


TUMOR INFILTRATES

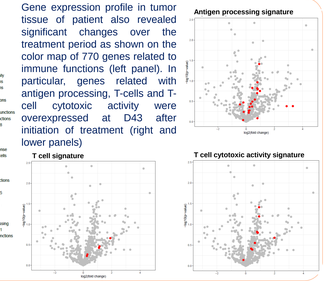
CD3 and CD8 T-cell infiltrates and expression of PD-L1 were increased in most patients after 43 days of TG4001/avelumab treatment as shown in longitudinal samples (upper panels) in patients were matched samples were available. In the overall patient population, all three parameters were higher after treatment (lower panels).



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 genes related to immune functions (left panel). In particular, genes related with antigen processing, T-cells and T-cell cytotoxic activity were overexpressed at D43 after initiation of treatment (right and lower panels)



CONCLUSIONS

- **The combination of TG4001 and avelumab demonstrates a clinically relevant tumor activity in patients with HPV-16 positive cancers having received multiple previous lines of treatment**
- **Presence of liver metastases has a profound impact on outcome in terms of ORR and PFS. In patients without liver metastases an ORR of 34.8% and median PFS of 5.6 months is achieved**
- **The treatment is associated with changes in tumor microenvironment such as increase in immune infiltrates and expression of genes associated with activation of the immune system. Increased expression of PD-L1 may be the basis of a synergy between TG4001 and avelumab**
- **These results warrant further confirmation in a larger, randomized clinical study**

ACKNOWLEDGEMENTS

We wish to thank patients and their families, care givers and study teams.
This study was financially supported by Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer.