Immunogenicity and clinical activity of tipapkinogen sovacivec (TG4001), an HPV-16 cancer vaccine: a randomized phase 2 study in advanced anogenital cancers

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C. Le Tourneau[1], F. Rolland[2], O. Capitain[3], A. Daste[4], P. Cassier[5], S. Salas[6], L. Manso Sánchez[7], A. CasadoHerraez[8], G. Colon-Otero[9], L. Eberst[10], C. Jamet[11], C.Ekwegbara[11] , A. Lalanne[11],O. Lantz[11], H. Makhloufi[12], A. Tavernaro[12], K. Bendjama[12], M. Brandely[12], J.P. Delord[13]

[1]Department of Drug Development and Innovation (D3i), Institut Curie, Paris, France, [2]Institut de Cancérologie de l'Ouest - Site René Gauducheau, Saint Herblain, France, [3]Institut de Cancérologie de l'Ouest - Site Paul Papin, Angers, France, [4]Hôpital Saint André, CHU de Bordeaux, Bordeaux, France, [5]Cancérologie Médicale - Centre Léon Bérard, Lyon, France, [6]Centre d'Essais Précoces en Cancérologie de Marseille-Hôpital Timone, Marseille, France, [7] Hospital Universitario 12 de Octubre, Madrid, Spain, [8]Hospital Universitario Clinico San Carlos, Madrid, Spain, [9]Mayo Clinic Florida, Jacksonville (FL), USA, [10]Institut de Cancérologie de Strasbourg Europe, Strasbourg, France, [11]Laboratoire d'Immunologie, CIC-BT1428 et Unité Inserm 932, Institut Curie, Paris, France, [12]Transgene S.A. Illkirch –Graffenstaden, France, [13]Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

BACKGROUND

Human papillomavirus 16 (HPV-16) infection is associated with several cancer types including cervical, anal, vulvar, vaginal and penile cancers. Treatment options remain limited in the R/M setting and checkpoint blockade as monotherapy has resulted only in modest advances. In a phase Ib/II single-arm study (NCT03260023), the combination of TG4001 and PD-L1 inhibitor avelumab demonstrated a clinically relevant tumor activity in heavily pre-treated patients with HPV-16 positive cancers *(1)*. It has been shown that T-cell reactivity against tumor antigens are prerequisite for the activity of ICIs *(2)*. Herein, we study the baseline T-cell response against HPV antigens and the induction of said response by TG4001. TG4001 is a vaccine using an attenuated and modified poxvirus (MVA) as a vector expressing the HPV-16 E6 and E7 proteins (rendered non-oncogenic) and interleukin-2.

METHODS

Patients with R/M HPV-16+ anogenital cancers were randomly assigned 1:1 to receive either TG4001 plus avelumab (Combination arm, TGAve) or avelumab alone (monotherapy, Ave arm). HPV-16 positivity was centrally determined using a PCR based assay. Randomization was stratified by tumor type (cervical, anal, genital). TG4001 was administered *s.c.* at $5x10^7$ pfu, Q1w for 5 weeks, then Q2w until month 6 followed by Q12w until progressive disease. Avelumab was administered *i.v.* at 800 mg Q2w starting one week after the first vaccine dose. PBMCs were collected at baseline, day 43 and day 85 to assess T-cell responses against HPV E6 and E7 antigens using ex-vivo IFNγ ELISPOT and immunophenotyping of circulating T cells. Vaccine immune response was defined as onset of a new T-cell response against either antigen or amplification of a pre-existing response under treatment. Tumor response was assessed using RECIST 1.1.

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria

- ❑ Refractory/Recurrent or Metastatic (R/M) HPV-16+ cancer including cervical, vulvar, vaginal, penile and anal cancer
- ❑ HPV-16 positivity determined in central laboratory by nested PCR with HPV-16 specific probes and retest of negative results by sequencing.
- ❑ No more than one prior line of chemotherapy for recurrent/metastatic disease
- ❑ All levels of PD-L1 expression
- ❑ For patients with hepatic metastases
  - no more than 3 hepatic lesions in total
  - maximum size of hepatic target disease ≤ 30 mm according to RECIST 1.1

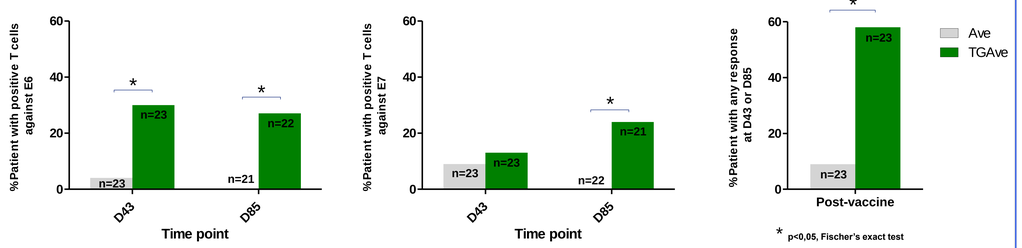
Key Exclusion Criteria

- ❑ Prior exposure to cancer immunotherapy including anti-cancer vaccines, any antibody targeting T cell co-regulatory proteins such as anti-PD-L1, anti-PD1, or anti-CTLA-4 antibodies
- ❑ CNS metastases
- ❑ ECOG Performance status ≥ 2
- ❑ Chronic treatment with systemic corticosteroids

VACCINE INDUCED PRIMING OF ADAPTIVE IMMUNITY

ELISPOT data were available for 46 patients. Baseline immunoreactivity was restricted to 3/46 patients for both E6 and E7. Adaptive response against E6 (left panel) and E7 (center panel) at D43 and D85 in the Avelumab arm (Ave) and combination TG4001 + Avelumab arm (TGAve).

% of patients with immune response at D43 or D85

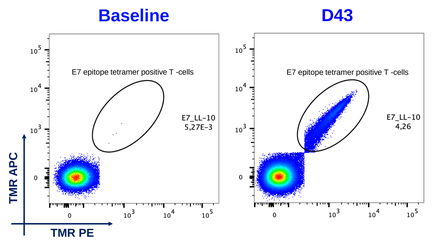


Priming was considered positive if a response was detected post vaccination while being absent prior to initiation, or if a baseline response was significantly amplified post vaccination. 58% of patients in the TGAve arm had an increased immunoreactivity post vaccination against HPV antigens vs. 9% in the Ave arm.

T –cell response

Clinical response	Negative	Positive
PD	11	2
SD/PR/CR	22	11

PD: progressive disease, SD: Stable disease, PR: Partial response, CR: Complete response



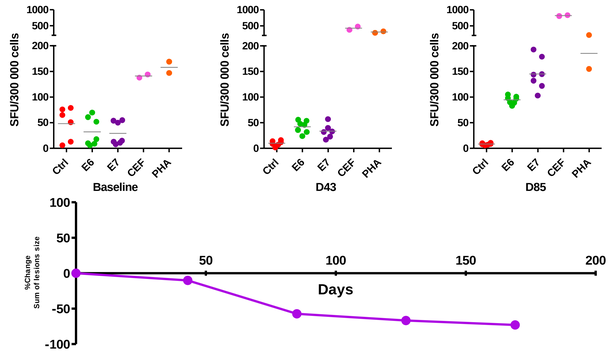
Correlation between ELISPOT response and Best Overall Response according to RECIST 1.1. Positive response is defined by de novo priming of a response or amplification after treatment. Patients with Positive antigen response were more likely to achieve a clinical response. Immune response to the vaccine was associated to a lower risk of progression.

Noteworthy, *ex vivo* ELISPOT assessment likely underestimated the prevalence of T-cell responses because of the short restimulation time and as T cell activation is solely measured using IFNγ staining. Tetramer staining for E7 epitopes revealed responses that were not detected by ELISPOT.

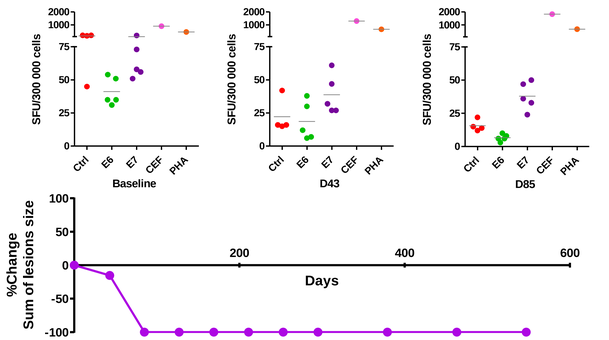
CASE REPORTS OF INDIVIDUAL PATIENTS IN CR

Patients with complete response according to RECIST 1.1 and evaluable for T-cell reactivity showed high T cell response against E6/E7 at D43 or D85.

Patient 0101048: cervical cancer, TGAve arm Correlation of ELISPOT data and anti-tumor response. (Ctrl : unstimulated cells, CEF and PHA: positive controls)



Patient 0103027: Cervical cancer, TGAve arm Correlation of ELISPOT data and anti-tumor response.



KEY FINDINGS

- ✓ **Immunoreactive T-cells against HPV antigens E6 and E7 were rare prior to vaccination**
- ✓ **TG4001 induced T cell responses against HPV16 antigens**
- ✓ **Patients with complete objective response showed strong vaccine induced immunoreactivity.**

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