Randomized phase II trial evaluating the combination of TG4001, an HPV16 therapeutic vaccine and avelumab (AV) in patients (pts) with immunotherapy-naïve recurrent and/or metastatic (R/M) HPV16-positive cervical or anogenital cancer

ID 2638

C. Le Tourneau[1], F. Rolland[2], O. Capitain[3], P. Cassier[4], JD. Fumet[5], S. Salas[6], A. Daste[7], L. Manso Sánchez[8], MJ. Bermejo-Pérez[9], A. Casado Herraez[10], L. Mansi[11], P. Pautier[12], O.Lantz[13], E. Dochy[14], C. Spring-Giusti[14], K. Bidet Huang[14], H. Makhloufi[14], C. Halluard-Thin[14], A. Tavernaro[14], JP. Delord[15]

[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]Cancérologie Médicale - Centre Léon Bérard, Lyon, France, [5]Centre Georges-François Leclerc, Early phase unit, Dijon, France, [6]Centre d'Essais Précoces en Cancérologie de Marseille-Hôpital Timone, Marseille, France, [7]Hôpital Saint André, CHU de Bordeaux, Bordeaux, France, [8]Hospital Universitario 12 de Octubre, Madrid, Spain, [9]Hospital Universitario Virgen de La Victoria, Málaga, Spain, [10]Hospital Universitario Clinico San Carlos, Madrid, Spain, [11]CHU de Besançon, Service d'Oncologie Médicale, Besançon, France, [12]Institut Gustave Roussy, Centre de Lutte Contre le Cancer, Villejuif, France, [13]Laboratoire d'Immunologie, CIC-BT1428 et Unité Inserm 932, Institut Curie, Paris, France, [14]Transgene SA, Illkirch-Graffenstaden, France, [15]IUCT-Oncopole, Toulouse, France

BACKGROUND

- Human papillomavirus (HPV) is associated with cervical and anogenital (AG) cancers. HPV-16 is the most pre-dominant high-risk subtype found in approximately 50-60% of patients with cervical cancer and despite prophylactic vaccination HPV-associated cancers will remain a high burden with unmet medical need.
- TG4001 is a therapeutic recombinant vaccine based on the non-propagative highly attenuated Modified Vaccinia virus Ankara (MVA) vector in which transgenes are inserted coding for three proteins, the HPV E6 and E7 proteins (rendered non-oncogenic), and the human interleukin-2 (IL-2) as an adjuvant.
- Anti-PD-1/PD-L1 treatment demonstrated clinical efficacy in advanced cervical and AG cancers.
- In a Phase Ib/II single-arm study, the combination of TG4001 and anti-PD-L1 avelumab (AV) demonstrated a favorable safety profile and clinically relevant tumor activity in heavily pre-treated patients with HPV-16 positive cancers (E. Borcoman *et al.*, 2023).
- The second part of this trial has been designed to investigate a potential synergistic effect of TG4001 and AV in recurrent and/or metastatic (R/M) cervical and AG cancers.

METHODS

This is a multicenter, open-label, Phase II, randomized 2-arm trial evaluating the efficacy of the combination of TG4001 and AV versus AV alone.
Between June 2021 and April 2024, 90 patients were randomized at 17 sites in France, Spain, and US.

STUDY DESIGN

- ≥ 18 years
- Refractory/recurrent and/or metastatic HPV-16+ cervical or anogenital cancer
- No more than one prior line of therapy for R/M disease
- Checkpoint inhibitors naïve
- No liver involvement

R 1:1

→ TG4001 + avelumab

→ avelumab

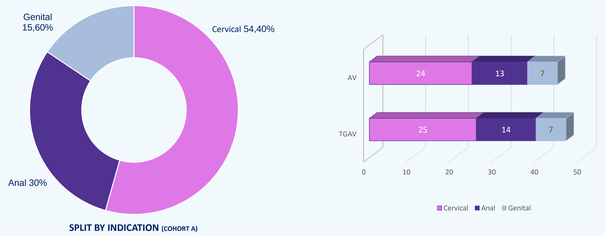
- TG4001 at a dose of $5x10^7$ pfu SC weekly for 6 weeks, every 2 weeks up to M6, and every 12 weeks thereafter
- Avelumab IV at 800 mg every 2 weeks starting one week after the first vaccine dose in the TG4001 + avelumab arm and one week after randomization in the avelumab alone arm.

STRATIFICATION FACTORS

- Primary tumor (cervical vs anal vs genital [vaginal, vulvar, penile])
- Center

KEY ENDPOINTS

- Progression Free Survival (PFS) in the overall study population (primary endpoint) and by tumor type
- Overall Response Rate (ORR)



SPLIT BY INDICATION (COHORT A)

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REFERENCE

E. Borcoman *et al*. Phase Ib/II trial of tipapkinogene sovacivec, a therapeutic human papillomavirus16-vaccine, in combination with avelumab in patients with advanced human papillomavirus16-positive cancers. European Journal of Cancer 191 (2023) 112981.

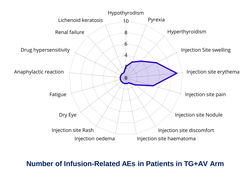
contact: christophe.letourneau@curie.fr
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DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

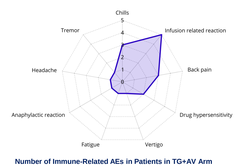
	Overall population		Patients with cervical cancer	
	TG+AV (N=46)	AV (N=44)	TG+AV (N=25)	AV (N=24)
Age at ICF signature (years)				
Median	57.0	56.5	51.0	52.0
[Min – Max]	[30.0 - 76.0]	[32.0 - 90.0]	[30.0 - 76.0]	[32.0 - 79.0]
Gender				
Female	43 (93.5%)	44 (100.0%)	25 (100.0%)	24 (100.0%)
Male	3 (6.5%)	0 (0.0%)		
Performance Status (ECOG)				
0	18 (39.1%)	11 (25.0%)	10 (40.0%)	5 (20.8%)
1	28 (60.9%)	33 (75.0%)	15 (60.0%)	19 (79.2%)
Time since initial diagnosis (months)				
Median	26.6	24.6	24.1	22.5
[Min – Max]	[3.2 - 193.1]	[1.4 - 267.7]	[3.2 - 122.3]	[9.2 - 267.7]
Number of organs involved				
1	18 (39.1%)	26 (59.1%)	12 (48.0%)	13 (54.2%)
[>1 ; ≤ 3]	28 (60.9%)	18 (40.9%)	13 (52.0%)	11 (45.8%)
Sum of diameters of lesions at baseline (mm)				
Median	42.3	42.7	43.0	40.0
[Min – Max]	[13.0 - 203.7]	[11.0 - 112.8]	[13.0 - 203.7]	[11.0 - 99.5]
Prior Surgery	21 (45.7%)	18 (40.9%)	8 (100.0%)	8 (100.0%)
Prior Radiotherapy	40 (87.0%)	34 (77.3%)	21 (100.0%)	19 (100.0%)
Prior lines of systemic anticancer therapy				
1	16 (35.6%)	24 (55.8%)	10 (41.7%)	14 (58.3%)
2	25 (55.6%)	16 (37.2%)	13 (54.2%)	8 (33.3%)
≥ 3	4 (8.9%)	3 (7.0%)	1 (4.2%)	2 (8.3%)

SAFETY

Number of patients with at least one event (%)	TG+AV (N=46)		AV (N=44)	
	N (%)	Event	N (%)	Event
AE	46 (100.0%)	781	43 (97.7%)	590
Treatment related AE	45 (97.8%)	296	37 (84.1%)	141
Injection site reaction	34 (73.9%)	96	0 (0.0%)	0
Immune-related AE	12 (26.1%)	41	3 (6.8%)	6
Infusion-related AE	10 (21.7%)	18	3 (6.8%)	4
AE leading to treatment discontinuation	4 (8.7%)	5	4 (9.1%)	4
SAE	16 (34.8%)	29	18 (40.9%)	23
SAE related to IMP	1 (2.2%)	1	0 (0.0%)	0
grade 3/4	18 (39.1%)	48	19 (43.2%)	42
grade 3/4 AE related to IMP	3 (6.5%)	3	2 (4.5%)	2
Fatal AE	7 (15.2%)	7	5 (11.4%)	5
Fatal AE related to IMP	0 (0.0%)	0	0 (0.0%)	0



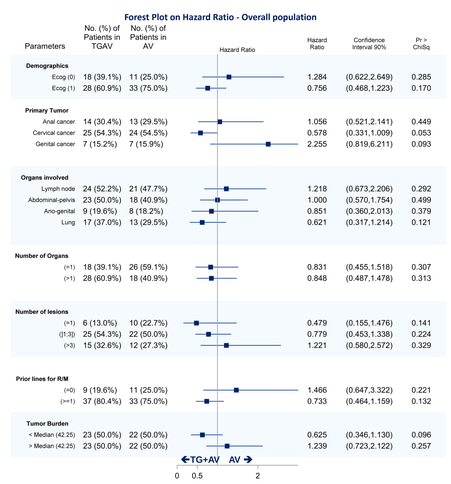
Number of Infusion-Related AEs in Patients in TG+AV Arm

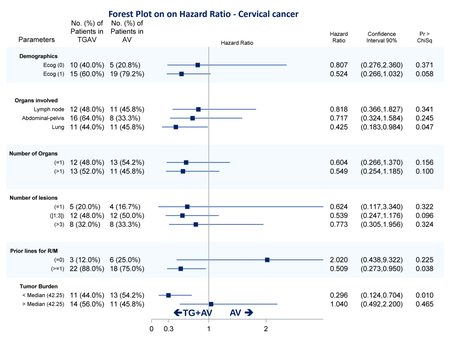


Number of Immune-Related AEs in Patients in TG+AV Arm

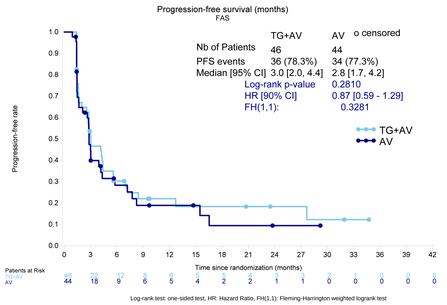
Treatment-Related AEs, Incidence ≥10% in Either Arm	TG+AV		AV	
	N (%)	Event	N (%)	Event
Patients with at least one AE related to IMP	**45 (97.8%)**	**296**	**37 (84.1%)**	**141**
General disorders and administration site conditions	**42 (91.3%)**	**166**	**18 (40.9%)**	**42**
Pyrexia	15 (32.6%)	31	7 (15.9%)	9
Injection site erythema	12 (26.1%)	29	0 (0.0%)	0
Asthenia	11 (23.9%)	16	7 (15.9%)	10
Fatigue	3 (6.5%)	6	6 (13.6%)	15
Chills	10 (21.7%)	11	2 (4.5%)	5
Musculoskeletal and connective tissue disorders	**10 (21.7%)**	**28**	**9 (20.5%)**	**17**
Arthralgia	6 (13.0%)	10	4 (9.1%)	9
Gastrointestinal disorders	**11 (23.9%)**	**17**	**9 (20.5%)**	**18**
Diarrhoea	8 (17.4%)	9	4 (9.1%)	4
Skin and subcutaneous tissue disorders	**10 (21.7%)**	**14**	**11 (25.0%)**	**20**
Pruritus	3 (6.5%)	3	6 (13.6%)	8
Nervous system disorders	**7 (15.2%)**	**13**	**6 (13.6%)**	**8**
Headache	5 (10.9%)	11	4 (9.1%)	4
Endocrine disorders	**9 (19.6%)**	**12**	**5 (11.4%)**	**7**
Hyperthyroidism	6 (13.0%)	6	3 (6.8%)	3

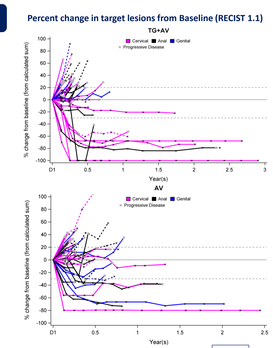
EFFICACY RESULT



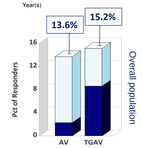


Progression Free Survival in the overall population

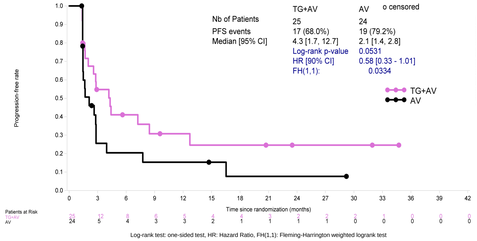


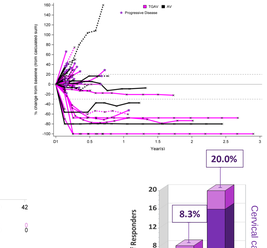


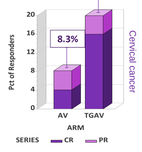
- In the overall population, this randomized phase II study of TG4001 in combination with avelumab versus avelumab did not meet the primary objective to improve PFS, an HR of 0.87 [0.59 – 1.29] has been observed.
- An ORR of 15.2% (7/46) in TG+AV and of 13.6% (6/44) in AV has been observed.
- Evolution of tumor size in target lesions shows more frequent and longer responses in patients with cervical cancer treated with the combination.



Progression Free Survival in patients with cervical cancer

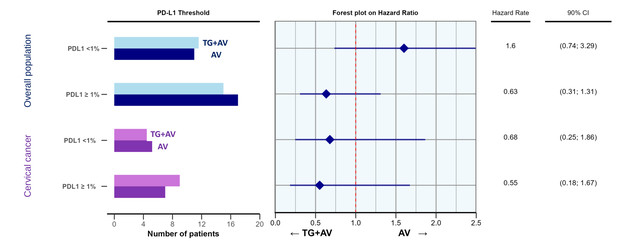




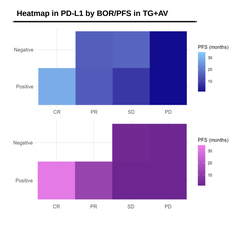


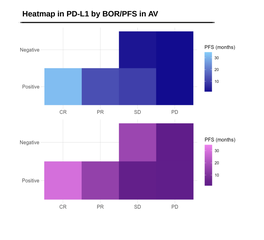
- Pre-planned subgroup analysis showed positive efficacy signal in favor of the TG4001 containing regimen in patients with cervical cancer as shown in the Kaplan-Meier curve.
- An ORR of 20% (5/20) was observed in TG+AV and 8.3% (2/24) in AV alone.

PD-L1 Analyses



	Hazard Rate	90% CI
Overall population PDL1 <1%	1.6	(0.74; 3.29)
Overall population PDL1 ≥ 1%	0.63	(0.31; 1.31)
Cervical cancer PDL1 <1%	0.68	(0.25; 1.86)
Cervical cancer PDL1 ≥ 1%	0.55	(0.18; 1.67)





- We evaluated the association between PD-L1 positivity at baseline and clinical benefit. There is a tendency for PD-L1 TPS ≥1% association with prolonged PFS and better ORR in patients treated with TG+AV.
- In patients with cervical cancer, same trends of TG4001 benefit were observed regardless of the PD-L1 status.

KEY MESSAGES

- **This randomized phase II trial in patients with HPV-16+ R/M cervical and anogenital cancers has not met the primary objective to improve PFS in TG+AV arm compared to AV alone arm.**
- **A positive trend has been observed in patients with cervical cancer in terms of PFS and ORR in a pre-planned subgroup analysis**
- **PD-L1 TPS of ≥ 1% tends to be associated with a prolonged PFS in patients treated with TG+AV in the overall population, whereas in patients with cervical cancer the TG4001 containing regimen is associated with a longer PFS regardless of the PD-L1 status.**