TG4001 + Avelumab vs Avelumab Single-Agent Phase II Positive Interim Analysis

Conference Call

November 2, 2022

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On Today's Call

HEDI BEN BRAHIM
Chief Executive Officer
Transgene

MAUD BRANDELY, MD, PhD
Chief Medical Officer
Transgene

Transgene – Potential Game Changing Approach to the Treatment of Solid Tumors

Customized and Off-The-Shelf Cancer Immunotherapies

Diversified pipeline

Viral vector-based immunotherapies

4 clinical-stage candidates
in Phase I and Phase II

Multiple milestones
in next 12-18 months

Two platforms in clinic

Therapeutic vaccines
- TG4001, HPV+ anogenital cancers
- TG4050, individualized vaccine

Oncolytic Viruses
- TG6002, demonstrated PoC of IV administration
- BT-001, encodes full-length anti-CTLA-4 Ab

Unique Technology based on:

- Optimized **viral vectors**
- Preclinical **Proof of Concept**
- Solid **safety** track record
- Strong **clinical data**
- Robust **IP** portfolio
- Integrated **GMP** manufacturing

Ongoing collaborations

- AstraZeneca — R&D and license deal
- MERCK, Pfizer, MSD — Supply agreements
- Orchestrating a brighter world NEC — Technology and cost sharing agreement
- BioInvent — Co-development

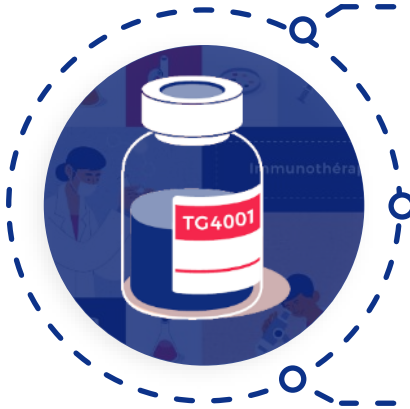
Strong Shareholder Support and Financial visibility

Financial visibility until the end of 2023

Strong shareholder support

INSTITUT MERIEUX

TG4001 | Therapeutic Vaccines Targeting HPV Positive Cancers



MVA vector
E6 and E7 HPV antigens

Targeting HPV Positive Cancers

Good safety profile
Administered
to 350+ individuals

First signals of efficacy demonstrated in previous Ph. Ib/II trial (TG4001+ avelumab)*

Advanced and heavily pre-treated patients
with HPV16-positive cancer, w/o liver metastasis (n=25)

Collaboration with MERCK Pfizer

*Single arm Phase Ib/II trial evaluating TG4001 in combination with Avelumab, in HPV16-Positive Cancers

ORR: objective response rate (RECIST 1.1); m PFS: median progression-free survival; m OS: median overall survival

Positive Outcome of Prespecified Interim Analysis of Randomized Phase II Trial

A multi-center randomized controlled Phase II clinical study comparing TG4001 in combination with avelumab to avelumab alone in patients with HPV16-positive anogenital tumors
(NCT: 03260023)

Clinical collaboration with

MERCK Pfizer

Following IDMC's recommendation

- **First efficacy signals observed - differentiation in PFS (primary endpoint) between the two arms**
- **Study to continue** to final analysis
- **Total number of patients randomized in the trial reduced to 120**
  (vs 150 previously communicated)

TG4001 + avelumab therapy well positioned in competitive landscape

Strong validation for our entire MVA therapeutic vaccine platform

Our Objective: to Establish that TG4001 Can Bring a Benefit to Patients

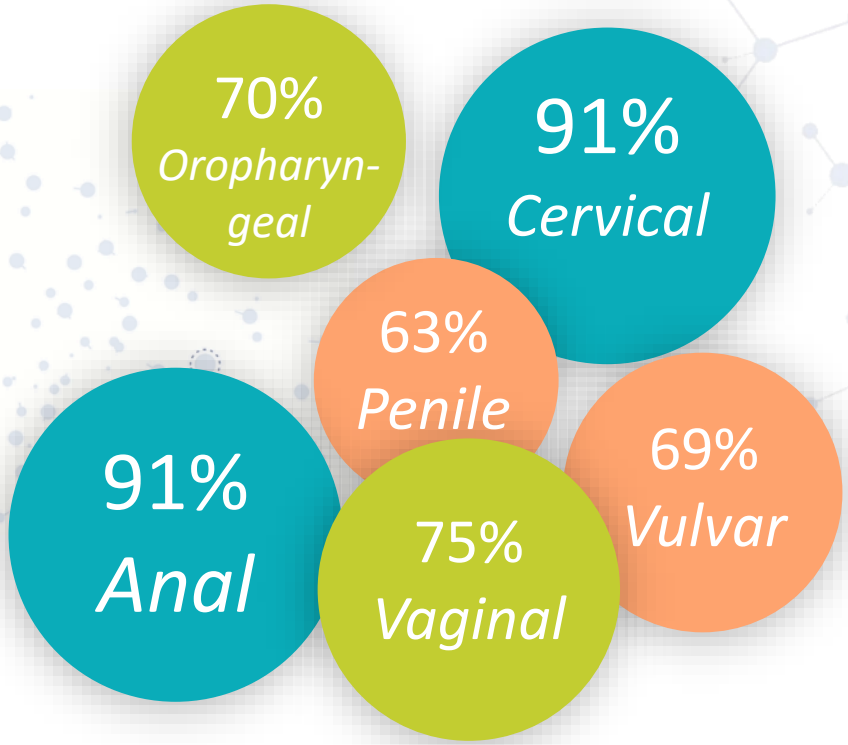
End of patient randomization expected in H1 2024

Positive final Phase II results would allow:

- to discuss with **FDA**
- to launch a **registrational trial**

HPV is Associated with a Broad Variety of Anogenital Cancers

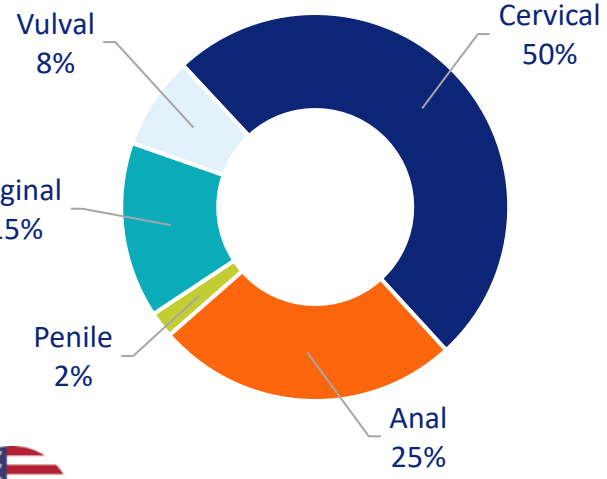
% of HPV induced cancers by localization



Incidence of anogenital HPV16 positive cancers w/o liver metastases

Newly diagnosed patients with metastatic disease and patients with recurrent disease

~ 25,000
new patients
per year



65%
EU27 + UK

35%
USA

Sources : Estimated cancer cases (2025) based on: 1. ICO/IARC – HPV Information Center> Prevention at a glance // 2. HPV-positive cervical cancer: Globocan/IARC 2020 Cancer Fact Sheets: cervix uteri (C53); ICO/IARC – HPV Information Center Statistics // 3. HPV-positive vaginal cancer: Globocan/IARC 2020 Cancer Fact Sheets: vagina (C52); ICO/IARC – HPV Information Center Statistics // 4. HPV-positive vulvar cancer: Globocan/IARC 2020 Cancer Fact Sheets: vulva (C51); ICO/IARC – HPV Information Center Statistics; CDC United States Cancer Statistics: Data Visualizations; SEER Cancer stat facts: vulvar cancer // 5. HPV-positive anal cancer: Globocan/IARC 2020 Cancer Fact Sheets: anus (C21); ICO/IARC – HPV Information Center Statistics; CDC>Cancer Home>HPV and Cancer>Statistics>Rates by Race and Ethnicity>HPV-Associated Anal Cancer Rates by Race and Ethnicity; American Cancer Society: Anal Cancer // 6. HPV-positive penile cancer: Globocan/IARC 2020 Cancer Fact Sheets: penis (C60); ICO/IARC – HPV Information Center Statistics; CDC>Cancer Home>HPV and Cancer>Statistics>Rates by Race and Ethnicity>HPV-Associated Cancers Rates by Race and Ethnicity

TG4001 | Optimized Treatment Designed for HPV-Positive Tumors

Potential to Address All HPV Positive Cancers

MVA virus
E6 and E7 HPV antigens

Designed to induce specific T cell response
MoA and first signals of efficacy demonstrated in single arm Ph. Ib/II trial

Combination with immune checkpoint inhibitor (ICI)
aims at "pressing the pedal" on the immune system with TG4001 while "removing the brakes" of the immune response with ICI

POTENTIAL TO ADDRESS ALL HPV POSITIVE CANCERS

Ongoing Phase II trial
Anogenital HPV16-positive cancers without liver metastasis
25,000 new pts/year[1]

Current SOC[2]
1L platinum-based therapy (or other chemotherapy approved) w/ or w/o ICI (cancer-dependent)

2L platinum-based chemotherapy
(+ pembro in the US and cemiplimab in EU in cervix cancer)

Collaboration with

MERCK Pfizer

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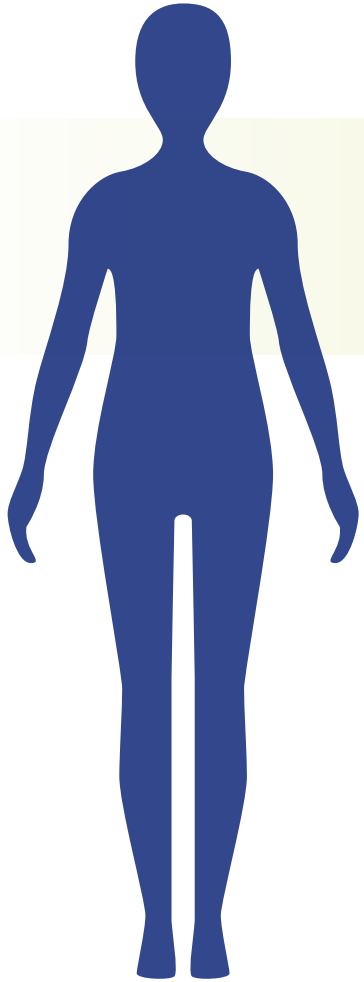
[1]Estimated cancer cases (2025) based on: 1. ICO/IARC – HPV Information Center> Prevention at a glance // 2. HPV-positive cervical cancer: Globocan/IARC 2020 Cancer Fact Sheets: cervix uteri (C53); ICO/IARC – HPV Information Center Statistics // 3. HPV-positive vaginal cancer: Globocan/IARC 2020 Cancer Fact Sheets: vagina (C52); ICO/IARC – HPV Information Center Statistics // 4. HPV-positive vulvar cancer: Globocan/IARC 2020 Cancer Fact Sheets: vulva (C51); ICO/IARC – HPV Information Center Statistics; CDC United States Cancer Statistics: Data Visualizations; SEER Cancer stat facts: vulvar cancer // 5. HPV-positive anal cancer: Globocan/IARC 2020 Cancer Fact Sheets: anus (C21); ICO/IARC – HPV Information Center Statistics; CDC>Cancer Home>HPV and Cancer>Statistics>Rates by Race and Ethnicity>HPV-Associated Anal Cancer Rates by Race and Ethnicity; American Cancer Society: Anal Cancer // 6. HPV-positive penile cancer: Globocan/IARC 2020 Cancer Fact Sheets: penis (C60); ICO/IARC – HPV Information Center Statistics; CDC>Cancer Home>HPV and Cancer>Statistics>Rates by Race and Ethnicity>HPV-Associated Cancers Rates by Race and Ethnicity [2] See Appendix

Phase II Trial Focuses on Patient Population that Showed Improved Clinical Benefit in Phase Ib/II



Patients with HPV16-positive anogenital cancer

including cervical, vulvar, vaginal, penile and anal cancers

- **With recurrent/metastatic disease**
- **Treated in first line or in second line** (with a maximum of one prior systemic chemotherapy versus two allowed in Phase Ib/II trial)
- **Without previous exposure to cancer immunotherapy**
- **Without liver metastasis** at baseline
- **Including all levels of PD-L1 expression**

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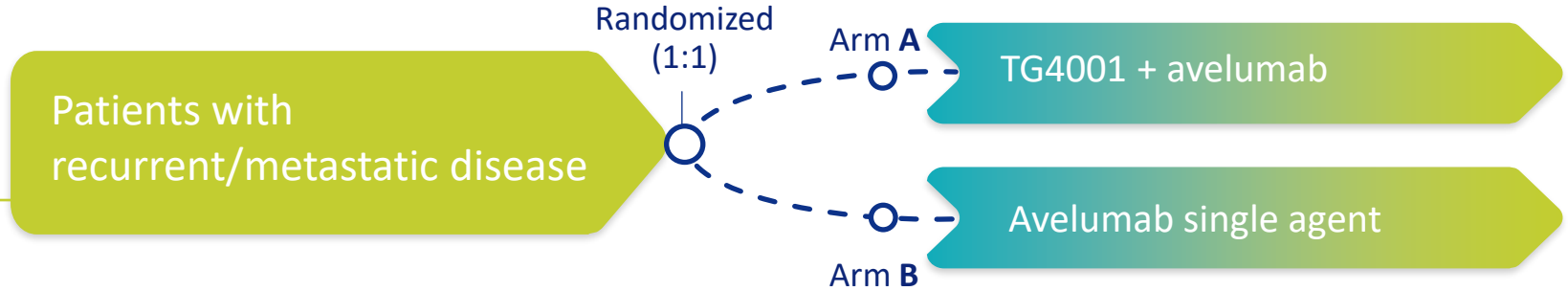
TG4001 | Randomized Controlled Phase II Trial Backed by Multiple Clinicians

Trial to enroll up 120 patients (NCT03260023)

Patients with
HPV16+ Anogenital Cancer

54 patients randomized



PRIMARY ENDPOINTS

- **Progression-Free Survival** (RECIST 1.1)

SECONDARY ENDPOINTS

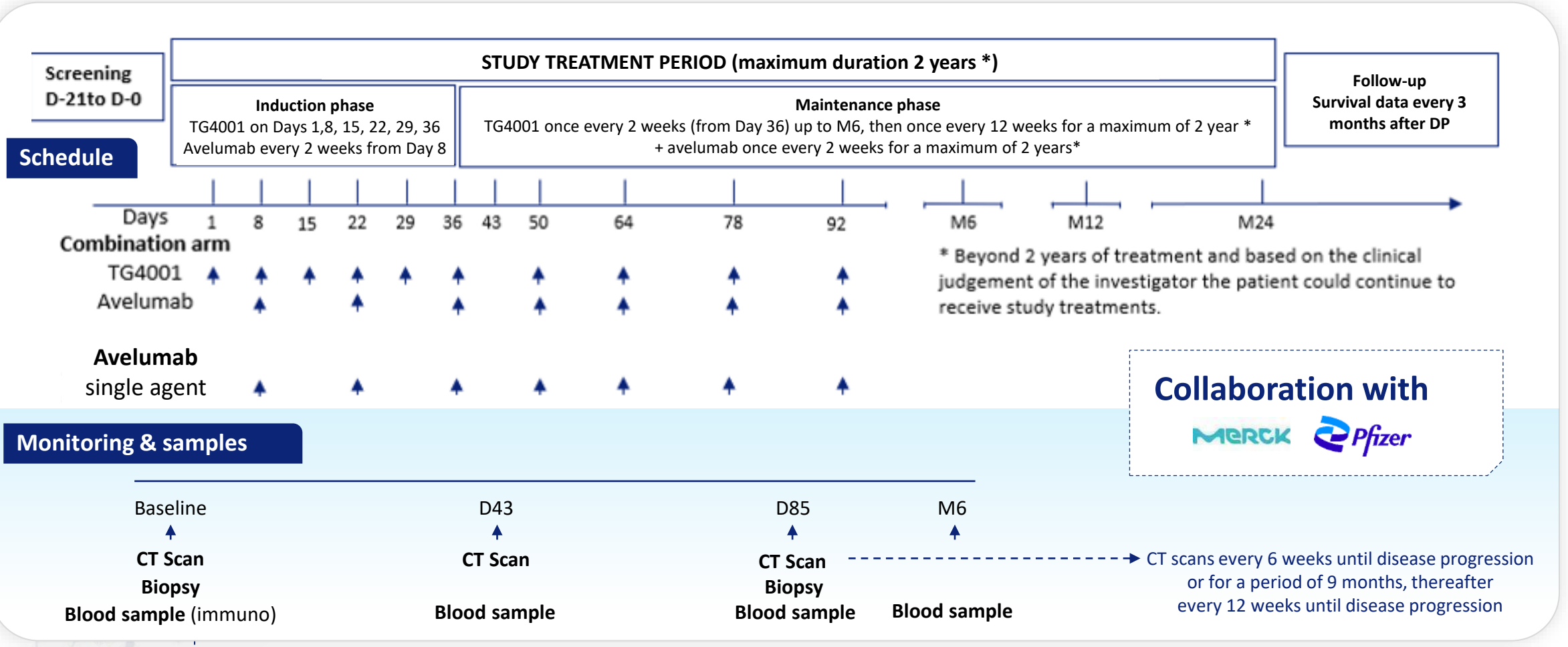
- **Overall Response Rate**
- **Disease Control Rate**
- **Overall Survival**
- **Other Immunological Parameters**

17 active sites
France, US, Spain

Clinical collaboration with

MERCK Pfizer

TG4001 + Avelumab (Randomized Ph. II) | Administration Schedule



- **TG4001:** $5x10^7$ pfu – administered SC
- **Avelumab:** 800mg – administered IV

Interim Analysis | Positive Outcome - We are Starting to See a Promising Trend

with the PFS differentiating between the two arms of the trial

PRIMARY ENDPOINT
(PFS)

SECONDARY ENDPOINTS
(ORR, DCR, safety etc)

Interim analysis based on **37 PFS events**

Trend starting to show a difference between the two arms

Consistent with **expectations** and **previous findings**

Consistent with anticipated **PFS improvement** in the ongoing randomized trial

Safety profile is good and consistent
with the MVA and avelumab safety profiles

Based on interim analysis results, IDMC recommends:

- Trial to Continue
- 120 patients total to be randomized in the study (instead of ~150 previously announced)

Positive final results
would allow to launch
a **registrational trial**

TG4001 + Avelumab (Single Arm Ph Ib/II) | Increased Benefit in Large Patient Subset

Promising results, particularly in patients without liver metastasis

Metastatic patients w/o liver metastasis (n=25)

vs patients with liver metastasis (n=11)

Compares favorably to ICIs in monotherapy and competitive landscape

In 2L, ORR is around 10–15% , median PFS is around 2 months and median OS is less than 11 months*

ORR: objective response rate (RECIST 1.1); m PFS: median progression-free survival; m OS: median overall survival

*Estimations based on the following trials
- Anal 2L: NCI9673 (Nivolumab, Phase II) [ref] ; KN028 + KN158 [ref] (pooled analysis: Phase Ib KN028 and Phase II KN158); CARACAS (Phase II) [ref]
- Cervical 2L: KN158 (Phase II) [ref]
- Cervical, vaginal vulvar 2L: CM 358 (Phase II) [ref]

1 COMPLETE RESPONSE

Patient with anal cancer and peritoneal extension that all disappeared – still followed in the trial

7 PARTIAL RESPONSES

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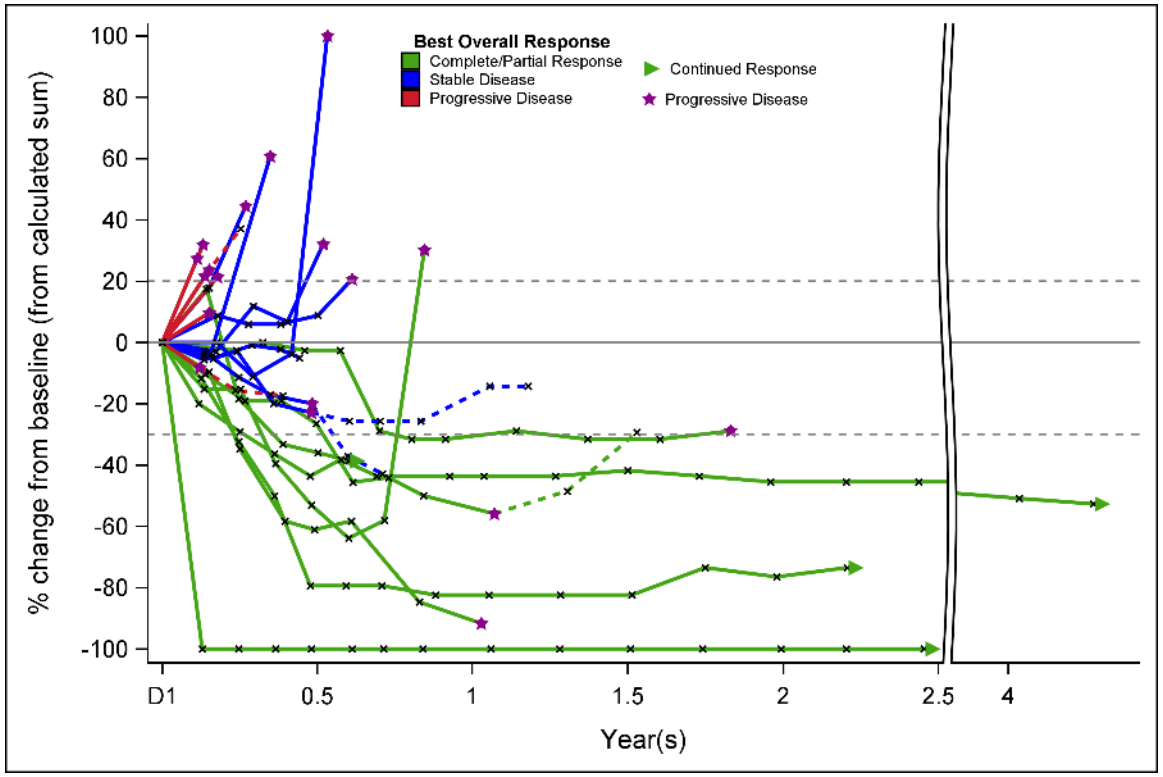
TG4001 + Avelumab (Single Arm Ph Ib/II) | Treatment Induced Long-Lasting Responses

Evolution of tumor size – End of Aug. 2022

in metastatic patients without liver metastases



- **1 patient still treated after 4+ years**
- **2 patients with 2+ years follow up**

- **Responses were also observed in PD-L1 negative patients**

Today's News is an Important Milestone for Transgene

First Phase II randomized trial with a therapeutic vaccine and an ICI to read out in HPV16+ anogenital cancers

- **Trial to continue based on potential superiority of TG4001 + avelumab** over avelumab alone
- **Last patient randomization** in **H1 2024**
- **Positive final results** would allow to **launch a registrational trial** in anogenital cancers

Strengthens our confidence in MVA platform, including TG4050

Individualized **neo-antigen therapeutic cancer vaccine**

Two ongoing Phase I trials, incl. a **randomized trial**, confirm the strong potential of this individualized cancer vaccine in ovarian and Head & Neck cancers

Additional **Phase I** Data | **H1 2023**

We would like to thank all patients, families, caregivers and all technical staff involved in the project.

TG4050 - Individualized Vaccine Based on 30 patient-specific neoantigens

2 ongoing clinical trials

TG4050 monotherapy evaluated in two ongoing Phase I trials
Head & Neck
and Ovarian cancers

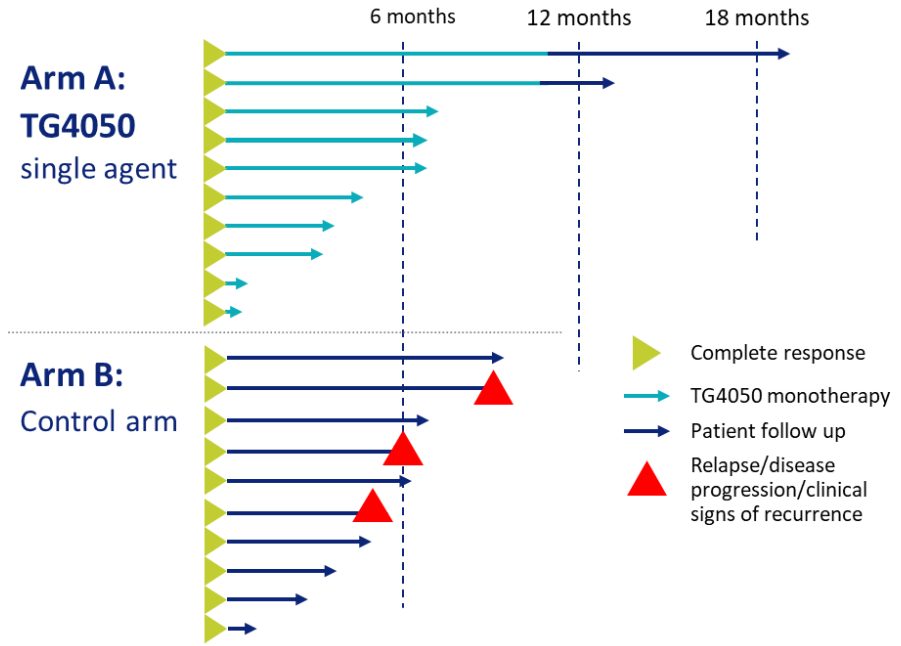
TG4050 demonstrated:

- Feasibility of process
- Safety
- First positive immunology data and encouraging clinical signs

POTENTIAL
TO **EXTEND REMISSION PERIOD**
AND **LOWER RELAPSE RATE**

Head & Neck Cancer Trial

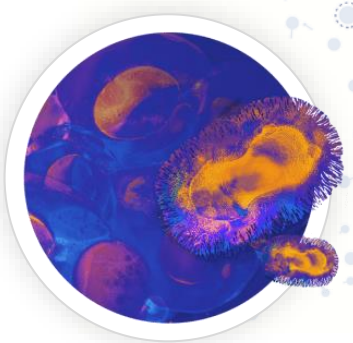
20 patients randomized - At end of August 2022



Additional **Phase I** Data | **H1 2023**

**TMB: tumor mutational burden*

Invir.IO™ oncolytic viruses | Versatile Platform Enabling Multiple Collaborations with Potential Future Value



invir.io

- **Clinical data confirm safety and feasibility of the IV route**
- **VV-IL12-X** to enter into clinical development in the IV route
- Potential expansion of our technologies through partnerships (AstraZeneca, BioInvent, PersonGen, …)

BT-001

- Signed **clinical collaboration** agreement with **MSD** for the supply of pembrolizumab
- **Positive initial Phase I data** in monotherapy

TG6002

- Demonstrated **clinical PoC of intravenous administration**

Q&A

Multiple Opportunities to Transform Solid Tumor Therapy

Product	Target/transgene	Indication	Collaboration	Preclinical	Phase I	Phase II	Next step
THERAPEUTIC VACCINE							
TG4001	HPV16 E6 – E7	Anogenital HPV+ cancers	MERCK, Pfizer				End of randomization H1 2024
myvac **TG4050**	30 neoantigens	Head and neck cancers	Orchestrating a brighter world NEC				Additional Ph. I data to be presented in H1 2023 – Ph. II expected to start in H2 2023
		Ovarian cancer					
ONCOLYTIC VIRUS (OV)							
TG6002	5-FU chemotherapy	Gastro-intestinal cancers (IV*)					New data to be presented in H1 2023
		Colorectal cancer (IHA*)					Initial Ph. I data in H1 2023
invir.io **BT-001**	Anti-CTLA4 + GM-CSF	Solid tumors	BioInvent, MSD				End of Ph. I part A in H2 2022
OV	IL12-X	Lung cancer (IV*)					Start clinical dev. in 2023
5 OVs	Undisclosed *(incl. 1 licensed product)*	Solid tumors	AstraZeneca				Potential further milestones & option exercise
OV	Undisclosed *(CAR-T combination)*	Solid tumors	博生吉 PersonGen				

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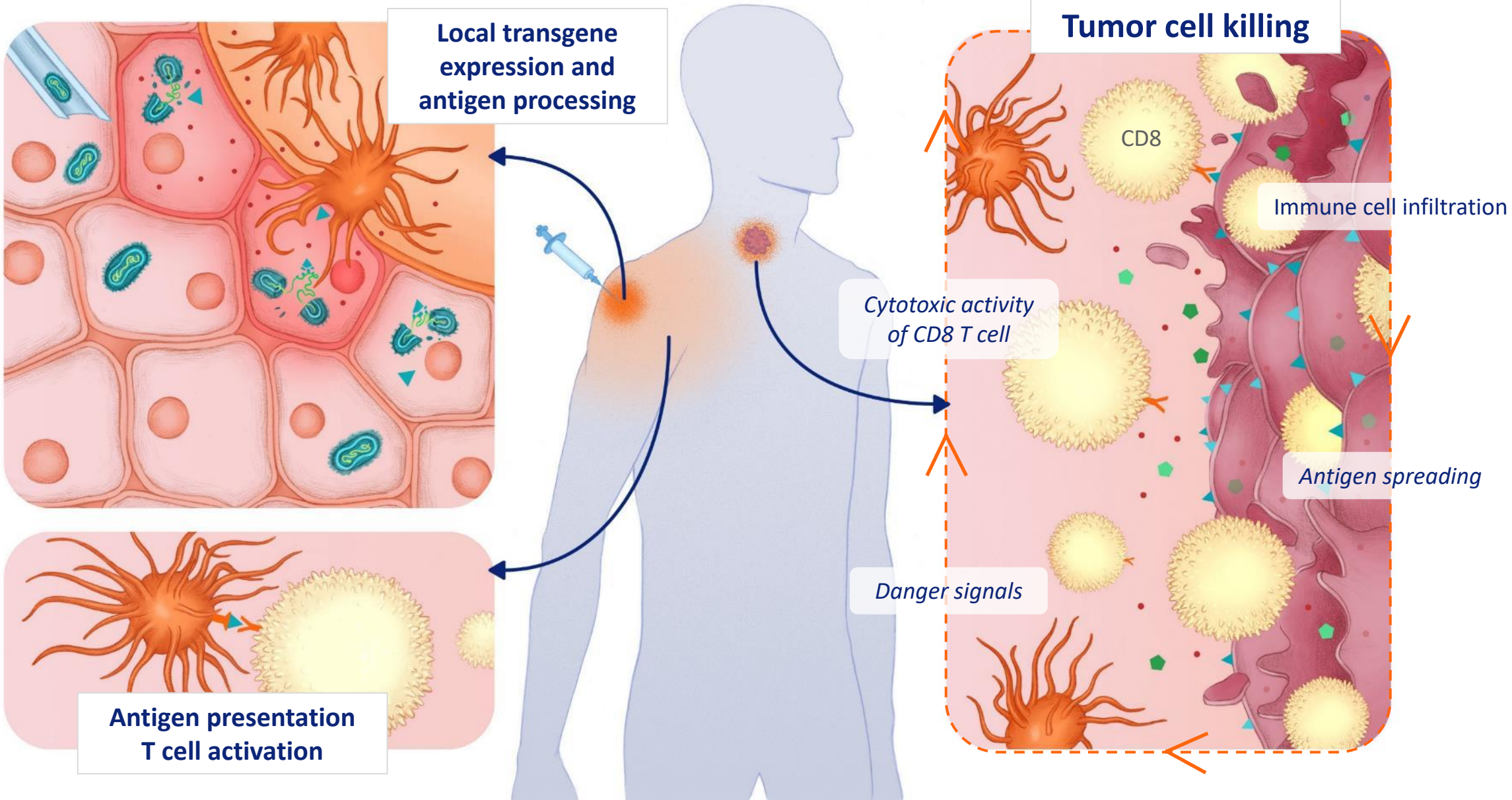
** IV: intravenous administration, IHA: intrahepatic artery administration*

Thank you for your attention

Appendix

How Virus Powered Vaccines Treat Solid Tumors

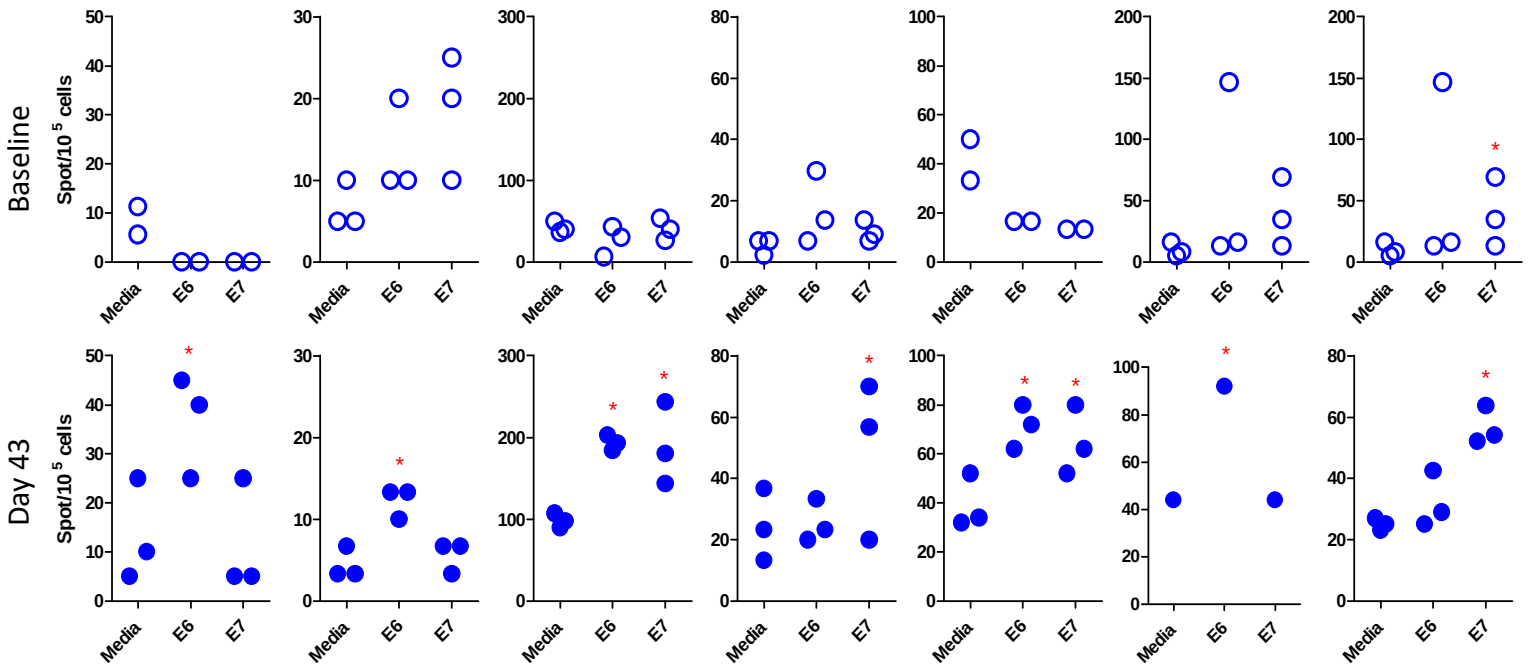
Our vaccines induce specific and strong immune response



TG4001 + Avelumab (Ph 1b/II) | Induced Specific T-Cell Response Against HPV16 E6 & E7

Patients with a detected response against target antigens

(Ex vivo ELISPOT response against E6 and E7)

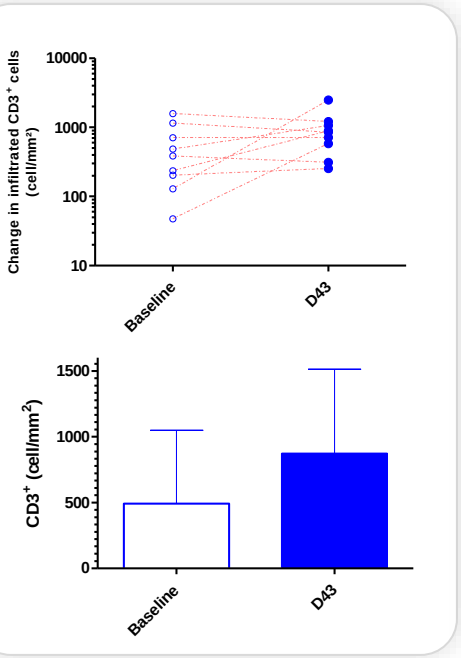


- **At baseline, no patient showed a specific response against E6 and E7**
- **7/11 patients** evaluable for ELISPOT **show specific T-cell responses against HPV16 E6 and E7 after vaccination with TG4001**
- Results support **durable control of the disease**

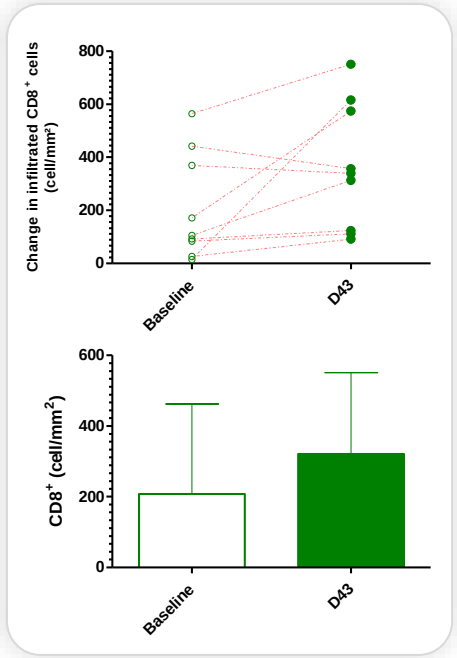
Source: Le Tourneau et al. "TG4001 (Tipapkinogene sovacivec) and avelumab for recurrent/metastatic (R/M) Human Papilloma Virus (HPV)-16+ cancers: clinical efficacy and immunogenicity." 2020 SITC Annual Meeting, 9-11 November 2020, Poster presentation

TG4001 + Avelumab (Ph 1b/II) | Treatment Shifts « Cold » Tumor into « Hot » Tumor

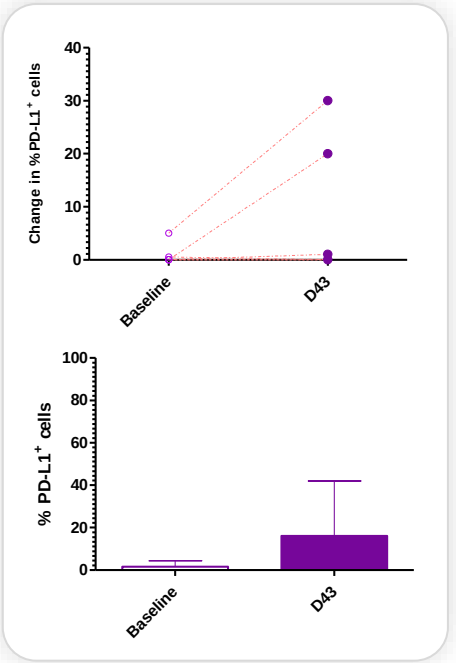
CD3+ infiltrate



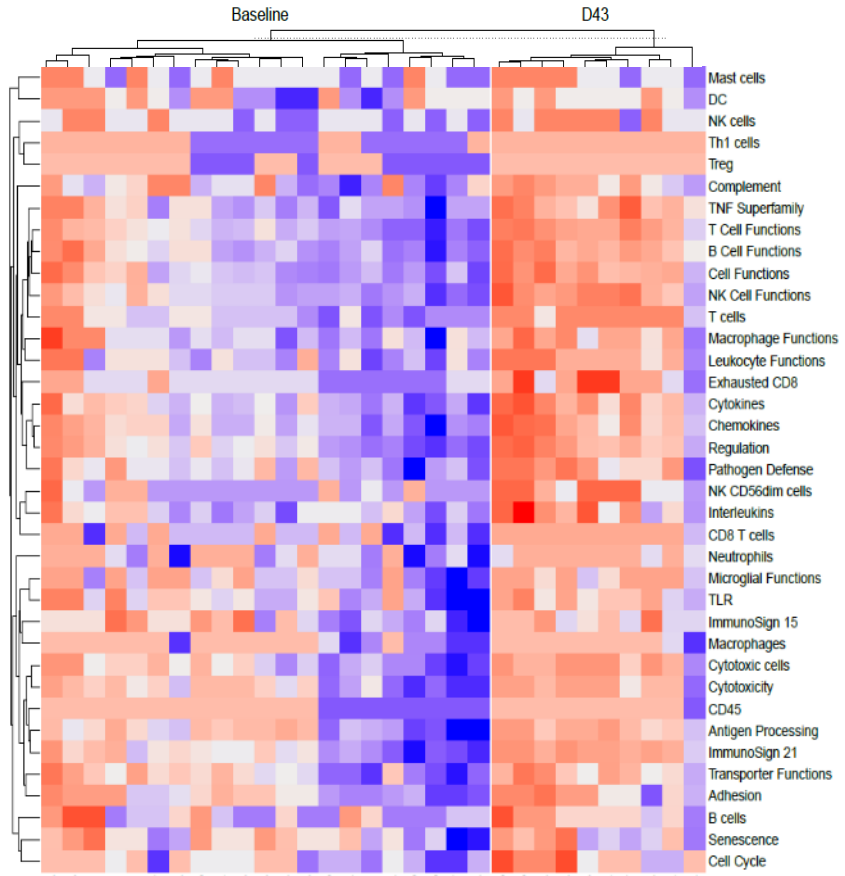
CD8+ infiltrate



PD-L1 expression



Gene expression



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Increasing Role of Immunotherapy in Standards of Care for Multiple Cancers

In first and second lines of treatment

CERVIX

1L:
platinum-based chemotherapy +/- bevacizumab + pembrolizumab in PD-L1 positive patients

2L:
Tisotumab vedotin (US)

Cemiplimab (EU)

ANAL

1L:
platinum-based chemotherapies

2L:
platinum-based chemotherapies, PD-L1 inhibitors may be considered where possible in patients who have progressed on first-line therapy (Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up- NCCN Clinical Practice Guidelines for anal cancer)

VULVAR / VAGINAL

1L:
platinium single agent, platinum-based chemotherapies

2L:
chemotherapy, pembrolizumab included in NCCN guidelines for PD-L1 positive, TMB-H or MSI-H tumors. Nivolumab for HPV-related advanced or recurrent/metastatic vulvar cancer

PENILE

1L:
platinum-based chemotherapies

2L:
chemotherapy, CT, Pembrolizumab (MSI-H) (NCCN guidelines)

TG4001 - Anogenital cancer patients undergoing 2nd line treatment still have poor prognosis

Overview of clinical trials in anogenital cancers – 2nd line of care

	H&N+ Anogenital	Anal Cancer			Cervical, Vaginal and Vulvar Cancers		Cervical
Therapy	TG4001	Nivolumab	Pembrolizumab	Avelumab	Pembrolizumab	Nivolumab	Cemiplimab
Study	Phase Ib/II	Phase II[ref]	Phase Ib and Phase II[ref]*	Phase II[ref]	Phase II [ref]	Phase II[ref]	Phase III [ref]
Number of patients	N = 34	N = 37	N = 137	N = 30	N = 98	N = 19 cervical N = 5 vaginal/ vulvar	N=608
Indication	Head and Neck + anogenital Cancers	Anal Cancer	Anal Cancer	Anal Cancer	Cervical Cancer	Cervical, vaginal and vulvar Cancer	Cervical Cancer
Line of Care	2nd Line	2nd Line	2nd Line	2nd Line	2nd Line	2nd Line	2nd Line
Overall Response Rate	35%	24%	10.9%	10%	12.2%	26.3% 20.0%	16.4%
Median Progression Free Survival (months)	5.6	4.1	2.1	2.1	2.1	5.1	2.8
Median Overall Survival (months)	N/A	11.5	11.7	10.8	9.4	21.9	12.0

TG4001 Phase II clinical trial ongoing – expecting end of randomization in H1 2024

* Pooled analysis

TG4001 Well Positioned in the Competitive Landscape - Off the Shelf HPV16 Cancer Treatment

Overview of key modalities approved and in development to treat HPV+ Cancers

	In Development							Approved	
	Cancer Vaccines							Checkpoint Inhibitor	Checkpoint Inhibitor
	Viral vectors			mRNA	Peptide			Antibody	Antibody
Company	transgene	HOOKIPA PHARMA		BIONTECH	ISA Pharmaceuticals		nykode	Pembrolizumab (Merck)	Nivolumab (BMS)
Technology	MVA virus	Arenavirus		mRNA	Long peptide		DNA vaccine	mAb	mAb
Clinical stage	Phase II Randomized	Phase I/II Phase I	Phase I/II Part II	Phase II Randomized	Phase II	Phase II	Phase II	Phase II a Single arm	Approved	Approved
Indication	Anogenital cancer without liver metastasis	HNSCC	HNSCC	SCCHN	Incurable solid tumors	Cervical cancer	SCCHN	Cervical cancer	SCCHN, cervix	SCCHN
Line of Care	2L locally advanced or 1L metastatic	1L + post-standard of care (2L)	1L advanced or metastatic	1L recurrent or metastatic PDL1>0		2L recurrent or metastatic	2L recurrent or metastatic	2L advanced or recurrent	1 Line Metastatic	2 Line Recurrent or metastatic
Next milestone	Interim Analysis in Q4 22	Data in H2 2022	Data in H2 2022	Primary completion date 2025	Completed	Completion date 2024		Completion date H1 2023	n.a.	n.a

CONTACT

Lucie Larguier

Director Investor Relations
and Corporate Communication

+33 6 7624 7227
larguier@transgene.fr

@TransgeneSA Transgene

400 Boulevard Gonthier d'Andernach | Parc d'Innovation | CS80166
67405 Illkirch Graffenstaden Cedex | France
Tél.: + 33 (0)3 88 27 91 21 | **www.transgene.fr**