Virus Powered Immunotherapies against Solid Tumors

R&D Day

September 27, 2022

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Introduction

HEDI BEN BRAHIM
Chief Executive Officer
Transgene

A World-Leader in Virus Powered Immunotherapies

Remarkable progress
over the last 18 months

myvac

invir io

Positive initial data
on **all our candidates**

Unparalleled research capabilities
and
ability to engineer various products

Pioneer novel routes of administration
such as the intravenous route for oncolytic viruses

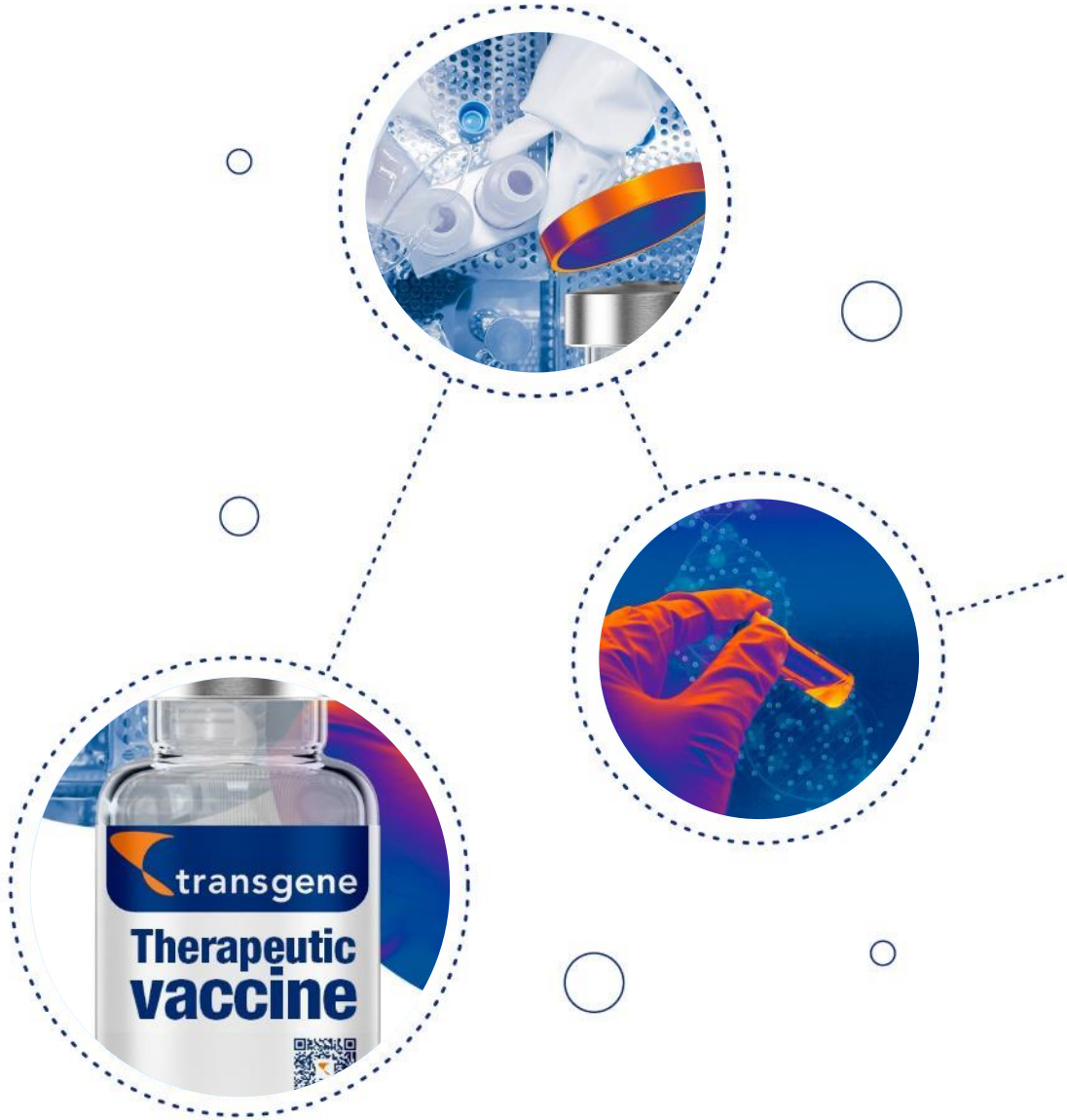
Integrated GMP manufacturing
capacity for rapid delivery of pilot scale batches

Highly productive collaborations
with AstraZeneca, NEC, BioInvent, Merck/Pfizer, MSD, PersonGene

Transgene's technologies could deliver a game changing approach
to the treatment of solid tumors

1

Therapeutic Vaccines



Agenda

THERAPEUTIC VACCINES

TIME	TOPIC	SPEAKER
2:10 pm – 2:15 pm	Therapeutic Vaccines: Potential Game Changers in Immuno-Oncology	*Maud Brandely*
2:15 pm – 2:25 pm	Viral vectors could be transformational to treat cancer	*Éric Quéméneur*
2:25 pm – 2:40 pm	TG4001, a HPV16 therapeutic vaccine in Phase II	*Jean-Pierre Delord*
2:40 pm – 2:55 pm	AI use and perspective at Transgene	*Kaïdre Bendjama*
2:55 pm – 3:30 pm	From the design of the *myvac*® platform to first immunological and clinical readouts, Update on the head and neck trial of TG4050	*Christian Ottensmeier*
3:30 pm – 3:45 pm	Personalized therapeutic vaccine in the treatment of ovarian cancer	*Matthew Block*
3:45 pm – 4:00 pm	Wrap up and Q&A	*Maud Brandely*

Therapeutic Vaccines: Potential Game Changers in Immuno-Oncology

MAUD BRANDELY, MD, PhD
Chief Medical Officer
Transgene

Vaccines Could Be Game Changers in Immuno-Oncology

Immunotherapy
has become
the 4th pilar of
cancer treatments
Along with surgery,
chemotherapy and
radiotherapy

The number of responders can still be improved
in many indications
at all stages of the
disease

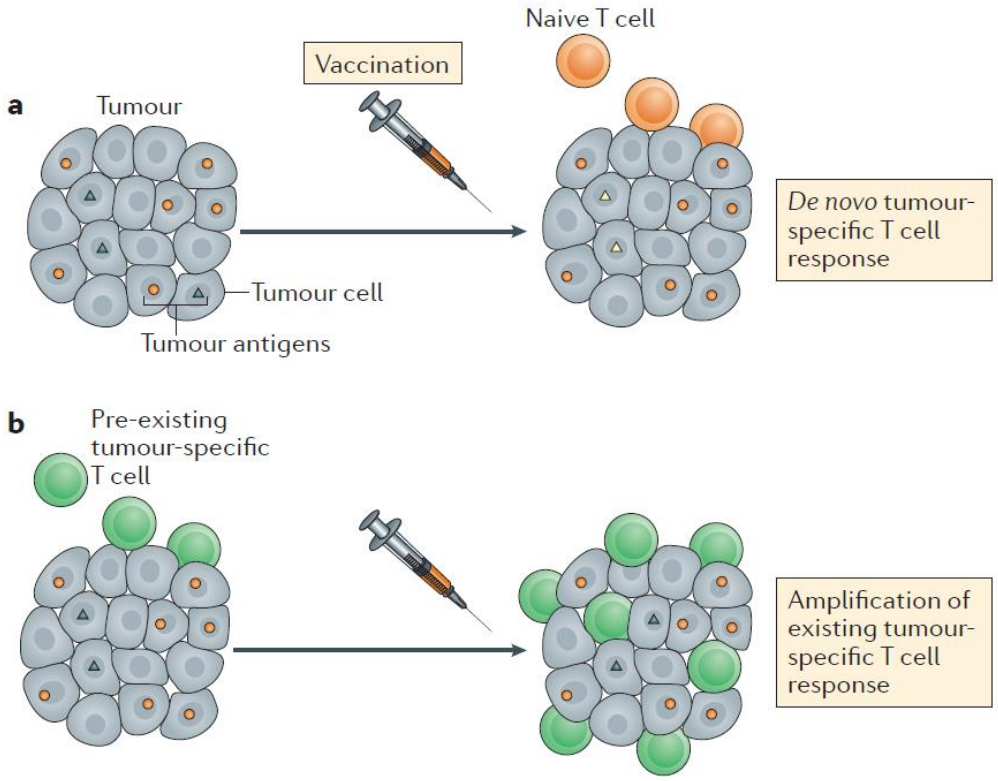
Treatment resistance could be overcome
- by better understanding the TME
- by offering the right combination of immunotherapies

Virus-based cancer vaccines are potential game changers

when targeting
the right tumor
antigens

transgene

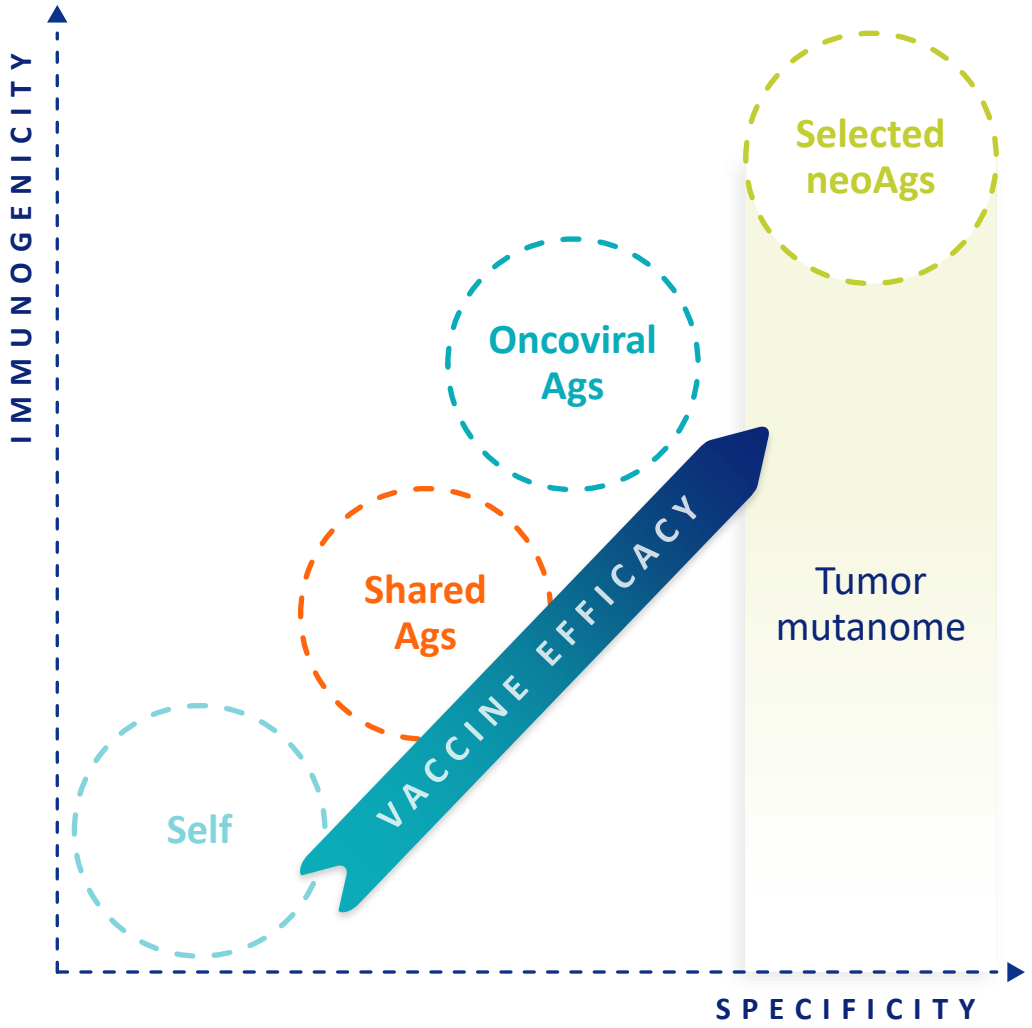
Therapeutic Cancer Vaccines: an Attractive Concept



- **Induce strong and specific immune responses**
- **Well tolerated with very good safety profile**
- **Can be used alone or in combination with most modalities**

Source : Hu Ott Wu, ''Towards personalized, tumour-specific, therapeutic vaccines for cancer'', *Nature Reviews Immunol* March 2018

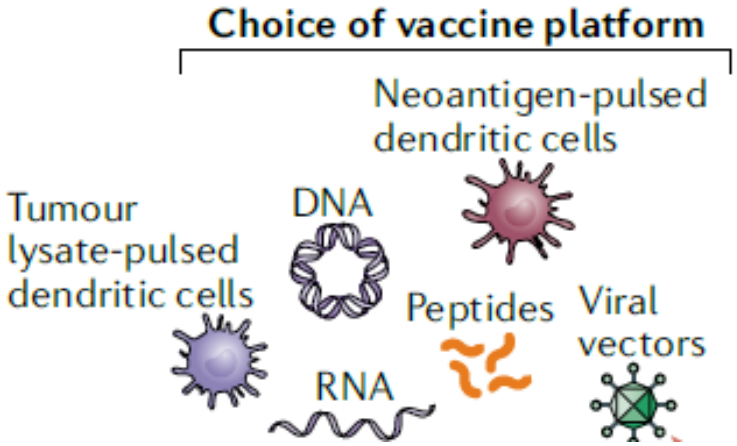
Targeting the Right Antigens to Deliver Improved Patient Outcome



Adapted from Von Witzleben, Front Imm, 2020

TYPE	EXPRESSION	PREVALENCE	EXAMPLES
Oncofetal	Physiologically expressed in fetal cells but re-expressed in cancer cells	Shared by a large number of patients in a specific histological indication or subtype	CEA, PSA, WT1, MAGE,
Overexpressed	Present in normal tissue but overexpressed by cancer cells		Mesothelin, telomerase, HER2
Post-translational modification	Present in healthy tissue but biochemical alteration in cancer tissue	Generally associated with a specific histology	Muc1
Oncoviral	Associated with infection by oncogenic viruses	Restricted to cancers with viral etiology	HPV, EBV, HBV
Neoantigen	**Specific to cancer cells, as the result of tumor-induced mutagenesis**	**Present in the majority of patients but different from one patient to another**	

Therapeutic Cancer Vaccines: Need to Select the Right Platform



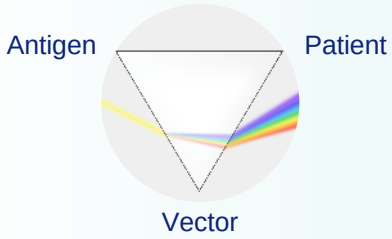
Viral vectors induce strong and durable stimulation of innate and adaptive immunity

Source : Blass and Ott, '' Advances in the development of personalized neoantigen- based therapeutic cancer vaccines, *Nature Rev Clin Oncol*, 2021

Viral Vectors Could Be Transformational To Treat Cancer

ÉRIC QUÉMÉNEUR, PharmD, PhD
Chief Scientific Officer
Executive VP
Transgene

Therapeutic Cancer Vaccines _ The Key Role of the Vector and Related Challenges



Major considerations for **designing a successful therapeutic vaccine :**

- Choice of the right antigen(s)
- Choice of the right target population
- **Choice of the right platform for antigen display**

Criteria of choice

Industrial foorprint

- Versatility, large toolbox for molecular engineering
- Manufacturing conditions and costs

Clinical use

- Safety and suitability for combination with other drugs or treatment regimens
- Pharmaceutical formulations (stability, ease of administration, etc.)

Immunological properties

- Target $CD8^+$ T cells, the main anti-tumor effector cells
  - Evidence of correlation between CD8+T cell response and clinical outcomes have accumulated
  - (Lonchay et al. PNAS 2004, Becker et al. CCI 2012, Carbone et al. JCO 2005)
- Target APCs and favor their maturation (triggering of PAMP, presentation by MHC-1, etc.)
- Activate $CD4^+$ Th cells (Th1) , and favor expansion of $CD8^+$ T cell memory response

Therapeutic Cancer Vaccines, Which Technology?

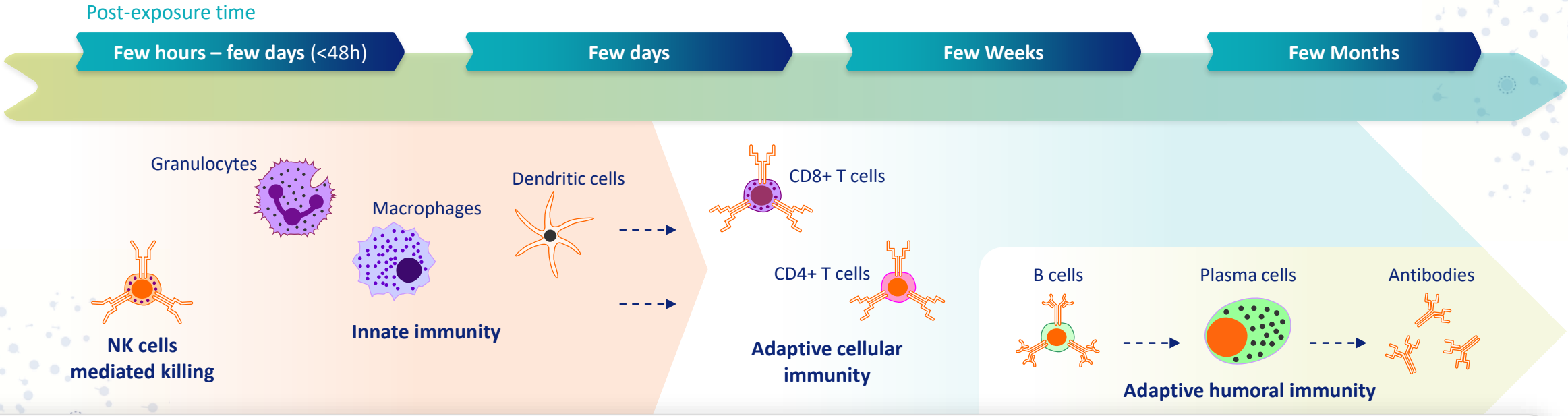
Table 1. Current vaccine formats explored for delivery of neoepitopes.

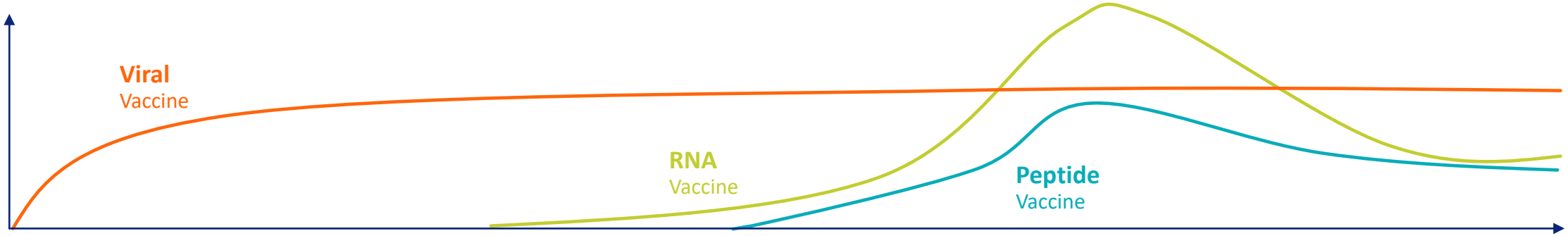
Vaccine format	Advantages	Challenges
Synthetic peptides (*45*)	Cell-free manufacturing Automated synthesis established Proven clinical activity of long peptides Compatible with a wide range of formulations to improve delivery Transient activity and complete degradation	Lack of clinical-grade manufacturability of a substantial portion of sequences High variability in the physicochemical properties of individual peptides, complicating manufacturing Irrelevant immune responses against artificial epitopes created by peptide degradation in the extracellular space
Messenger RNA (*46*)	Cell-free manufacturing Inherent adjuvant function via TLR7, TLR8, and TLR3 signaling Proven clinical activity Highly efficient systemic delivery into DCs established Transient activity and complete degradation All types of epitopes can be encoded	Fast extracellular degradation of mRNA if not protected by appropriate formulation Interpatient variability of TLR7-driven adjuvant activity
DNA plasmids (*47*)	Cell-free manufacturing Inherent adjuvant activity driven by TLR9 Cost-effective and straightforward manufacturing All types of epitopes can be encoded	Potential safety risks by insertional mutagenesis Successful transfection requires entry into nucleus, thereby limiting effective delivery of vaccines into DCs
Viral vectors (*48*) (adenoviral and vaccinia)	Strong immunostimulatory activity Extensive clinical experience with vector formats in the infectious disease field All types of epitopes can be encoded	Complex manufacturing Immune responses against components of the viral vector backbone, limiting successful in vivo vaccine delivery and efficacy
Engineered attenuated bacterial vectors (*49*) (*Salmonella*, *Listeria*)	Strong immunostimulatory activity Could be combined with plasmid DNA All types of epitopes can be encoded	Complex manufacturing and "sterility" testing Immune responses against bacterial components, limiting vaccine delivery and vaccine immunogenicity Potential safety risks due to delivery of live, replication-competent bacteria
Ex vivo antigen-loaded DCs (*50*)	Strong immunostimulatory activity Proven clinical efficacy of DC vaccines Can be loaded with various antigen formats	Higher costs and resources required for adoptive cell therapy approaches

I obviously **agree for Advantages**, but **can't agree on general statements for Challenges** considering the **large diversity of viral vectors qualified** for vaccine design

Source: Sahin U, Türeci Ö. Science, 2018. *Personalized vaccines for cancer immunotherapy.*

Viral Vaccines Prime Both Long Lasting Innate and Adaptive Immunity





Sources: Karinko K et al. Immunity, 2005; Collier ARY et al. NEJM, 2021

Lessons Learned from Two Decades of Cancer Vaccination with MVA

Proven safety in multiple routes of administration (i.e. IV, IM, IT)

- **strong safety record**: largely administered in the frame of smallpox campaigns, but also of MVA-based prophylactic vaccines
- Suitable for **use in immuno-compromized patients**, and in elderly
- Regarded as a non-genotoxic virus
- **BSL-1** environment

Versatility and flexibility

- **multiple options** for molecular engineering (del III)
- **high cargo capacity** (up to 20-25 kb)
- good knowledge of the mechanisms of virus-host cell interaction, and particularly of **immune escape mechanisms**
- moderately complex **manufacturing**

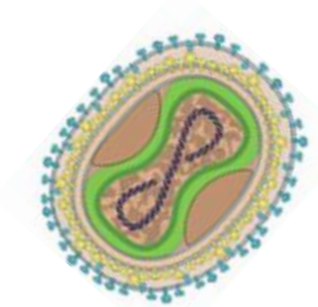
Strong immune response

- **local induction of immuno-stimulatory cytokines,** stimulating both innate and T cell responses
- **Intrinsic adjuvant properties (TLR3)**, allowing rather small Ag dosage (5 X 107 pfu)
- **Large recombinant antigens** mean large number of T cell epitopes, and less dependence to HLA restriction

Ability to disrupt immune tolerance

- Preferential **infection of APCs**, **long lasting exposure to Ags** (7 days)
- **Repeated admin.** with the same rec. virus still resulted in substantial booster induction of immune cells, even in the presence of MVA-specific immunity
- induction of **antigen spreading**

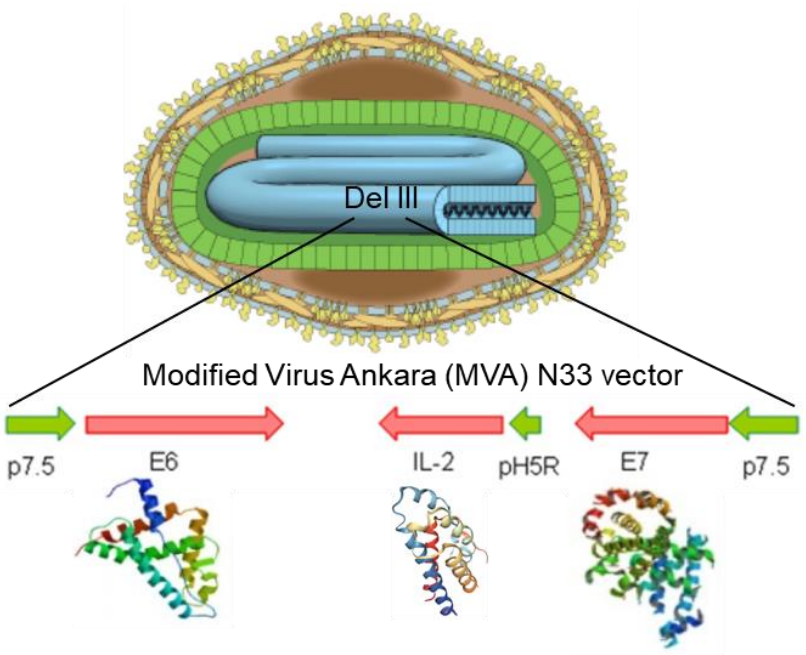
Combinable with most standards of care (CT, ICIs, RT)



Optimized antigen display| The Examples of TG4001 and TG4050

Tipapkinogen sovacivec – TG4001

MVA-HPV16(E6/E7)-IL2

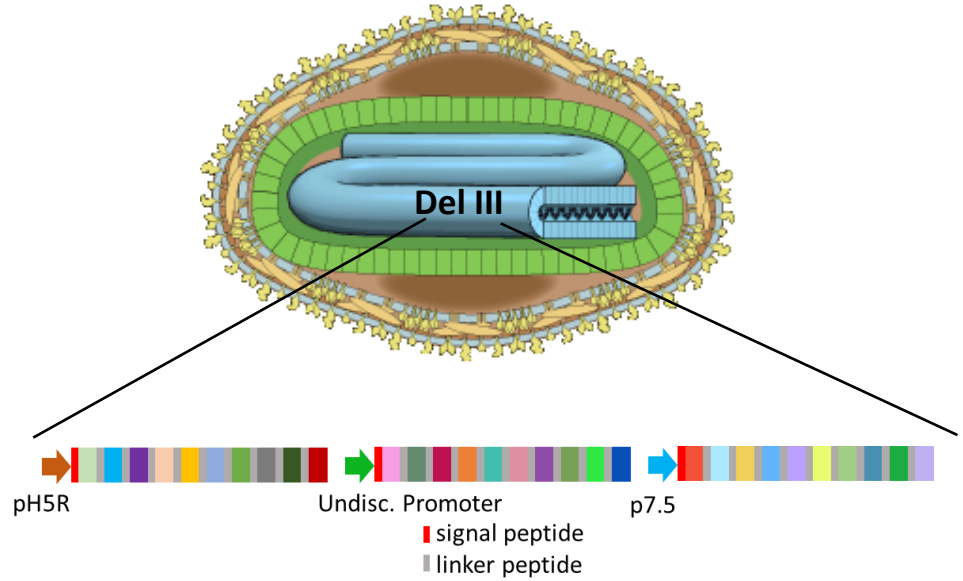


Described in US2005/0159386A1

Specific deletions in E6 and E7 proteins to eliminate their ability to bind p53 and pRb, respectively, and thus their oncogenic properties; fusions with membrane domains to enhance their immune presentation

TG4050

MVA-30 neoantigens



Described in WO2018/234506

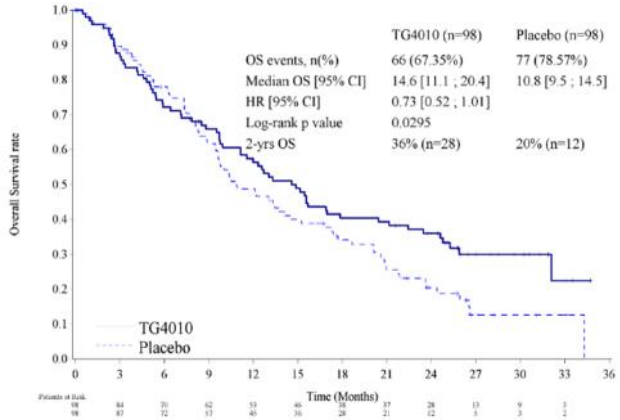
MVA viral vector designed to target up to 30 patient specific-neoantigens by 3 polyepitopic cassettes, containing each 10 neoantigens (29-mers) to induce strong immune response

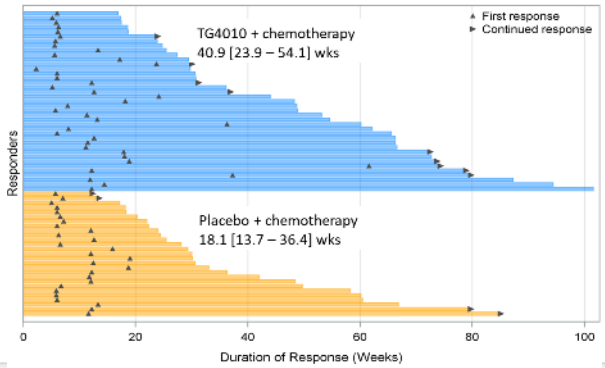
Randomized Trials Consistently Showed the Superiority of the MVA Arm

TG4010 (MVA:IL2/Muc1)

Combination with chemotherapy for 1st line treatment of NSCLC; TIME Phase II study

→ **significant increase of OS and doubling of duration of response**





Source: Quoix et al. "TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial." The Lancet Oncology, 2015

TG4001 (MVA:IL2/HPV_{16}-E6E7)

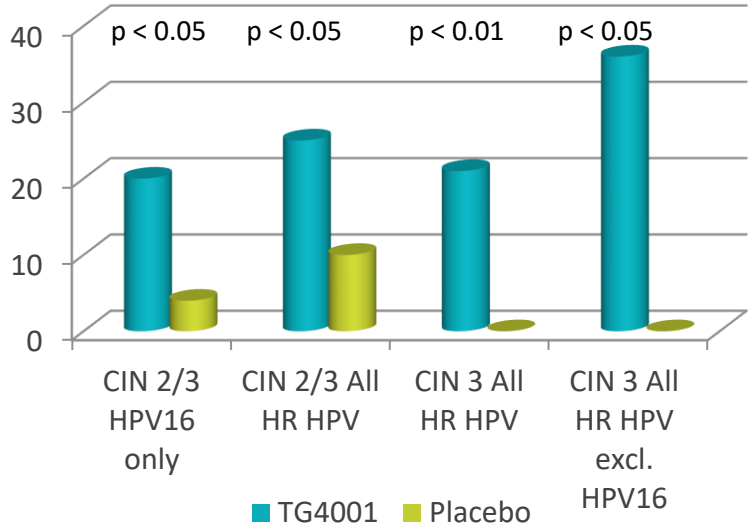
Randomized Phase II trial in CIN2/3

Monotherapy (3 weekly injections) vs placebo

→ **Single agent TG4001 is active and able to address HPV-related carcinomas**

→ **Data represent a strong POC of active immunotherapy**

Complete resolution at 6 months (%)



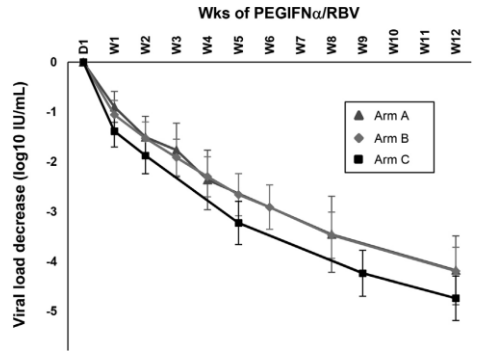
Source: Harper et al., "*The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: Randomized controlled phase II trial with 2.5 years of follow-up*", NIH, 2019

TG4040 (MVA:HCV-NS3,NS4,NS5B)

Combination with pegylated-IFNa and ribavirin in patients with chronic HCV infection (Phase II study)

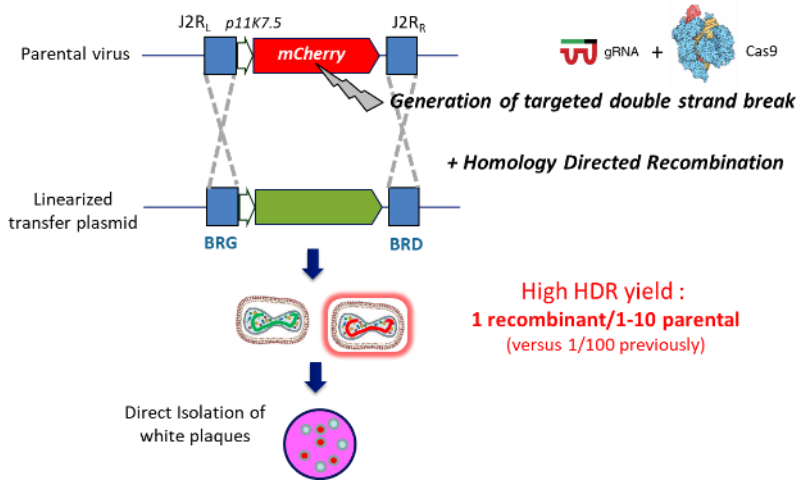
→ **doubling of cEVR* rate (64% vs 30% for SOC-treated patients)**

* cEVR, complete early virologic response , defined as HCV-RNA level less than 10 IU/mL after 12 weeks of PEG-IFNa/RBV treatment

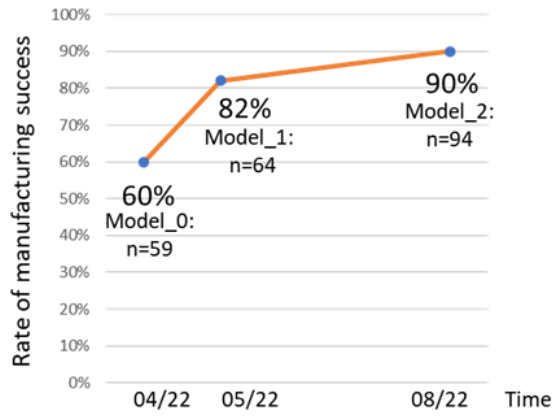


Source: Di Bisceglie et al. "*Efficacy of immunotherapy with TG4040, peg-interferon, and ribavirin in a Phase 2 study of patients with chronic HCV infection*" Gastroenterology, 2014

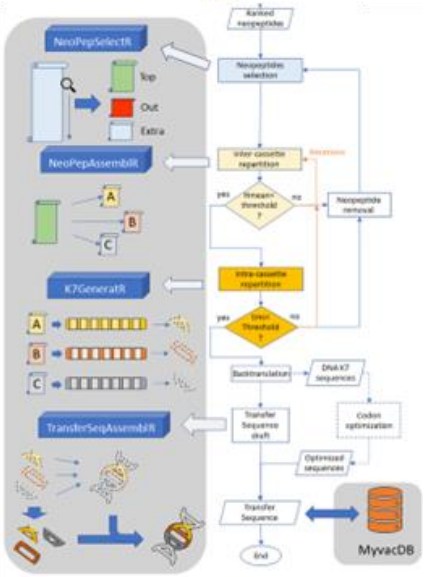
A Solid Experience in Vectorology and GMP Manufacturing, as Well as in Poxvirus Biology Makes us a Leader in Viral Vector-Based Cancer Vaccine



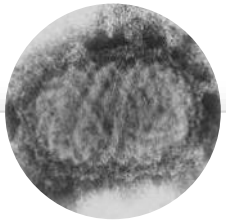
High HDR yield :
1 recombinant/1-10 parental
(versus 1/100 previously)

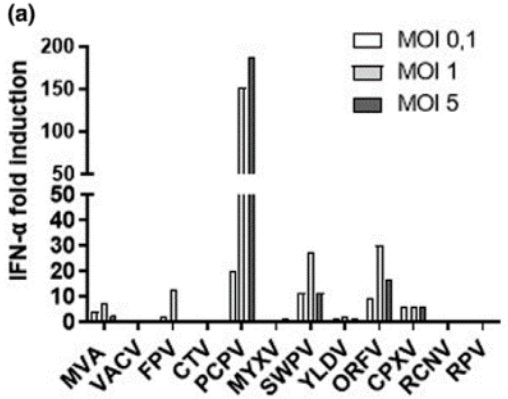


VacDesignR™



myvac





PCPV, a novel vector (...) Ramos et al. Clin Transl Immunology. 2022

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Summary

Strong arguments, both in terms of immunology, convenience of use, and industrial operations, **in favor of poxviral vectors** as platform for the design of robust cancer vaccines,

Among them, **MVA**, a non replicative poxviral vector **has been selected for two products** in our portfolio (i.e. TG4001, and TG4050),

Ongoing research opens new vistas for :

- **Further development of MVA-based products in personalized cancer immunotherapy.** (Cost and leadtime improvement for TG4050, private and/or shared neoantigens, etc.)
- Proposal of **novel vector candidate** (e.g. PCPV, armed-MVA), and of **prime/boost regimen** for hard-to-treat tumors

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE
Oncopole

TG4001, a HPV16 Therapeutic Vaccine in Phase II

JEAN-PIERRE DELORD, MD, PhD
General Manager
of IUCT Oncopole of Toulouse

transgene

IUCT- Oncopole |Leading Player at the Heart of Networks

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE
Oncopole

WORLD'S BEST HOSPITALS 2021
Newsweek

OECI COMPREHENSIVE Cancer Centre

transgene

IUCT- Oncopole | A Collective Expertise to Fight Cancer

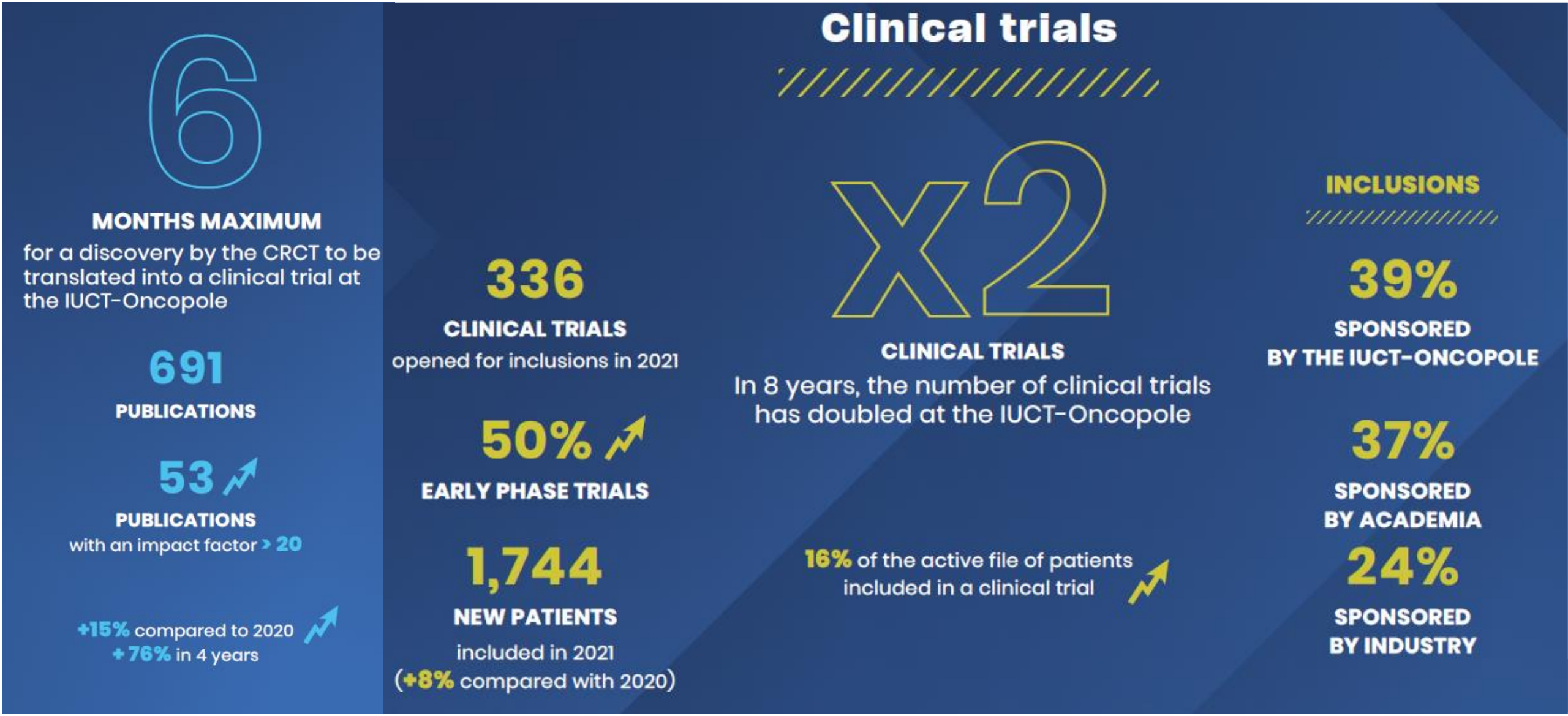
IUCT-Oncopole is:

- A referral centre within the French Expert Network for Head and Neck Cancers
- Accredited early phase trials center (CLIP2)
- Member of numerous INCa clinical research networks

The immuno-monitoring department is led by Pr Maha Ayyoub and Pr Delord with a close collaboration with CRCT Team T2i

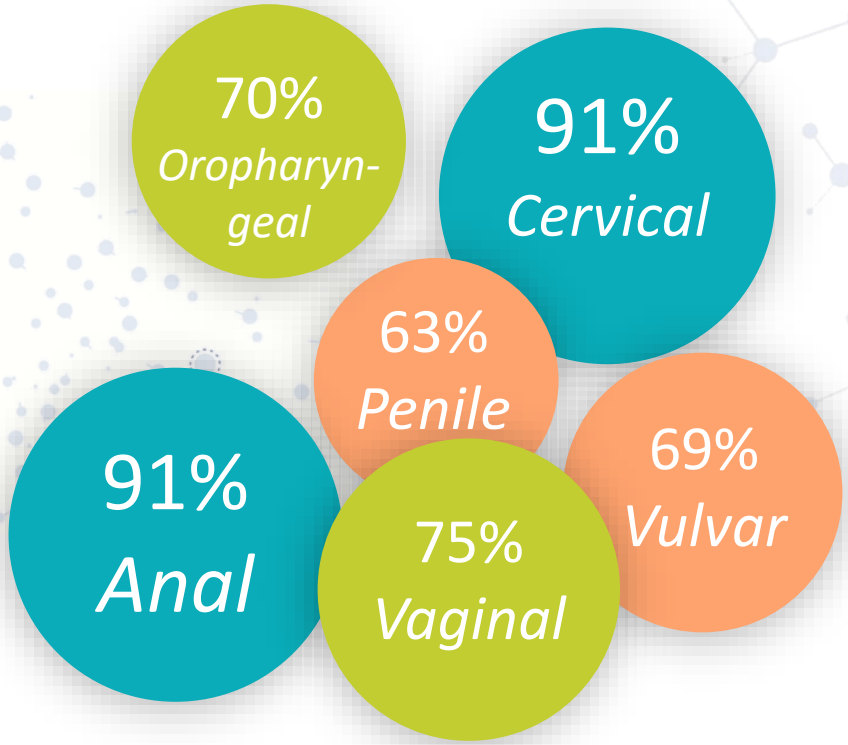
336 clinical trials opened for inclusions in 2020,
50 % in early phase

IUCT- Oncopole | Key Figures 2021



HPV is Associated with a Broad Variety of Anogenital Cancers

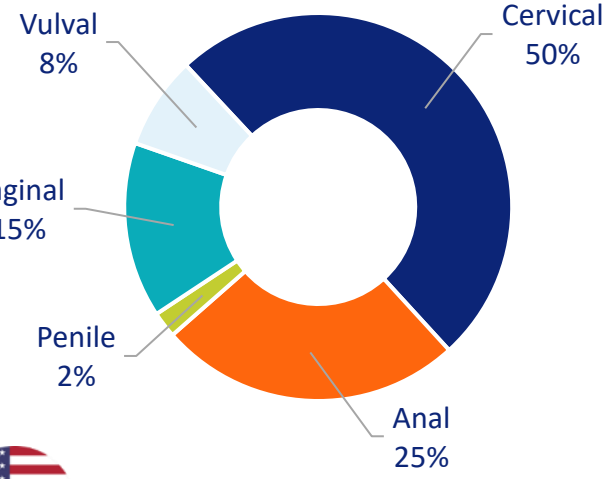
% of HPV induced cancers by localization



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

Increasing Role of Immunotherapy in Standards of Care

In first and second lines of treatment

CERVIX

- **1L:** platinum-based chemotherapy +/- bevacizumab + pembrolizumab
- **2L:** platinum-based chemotherapies (pembro in US1)

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)

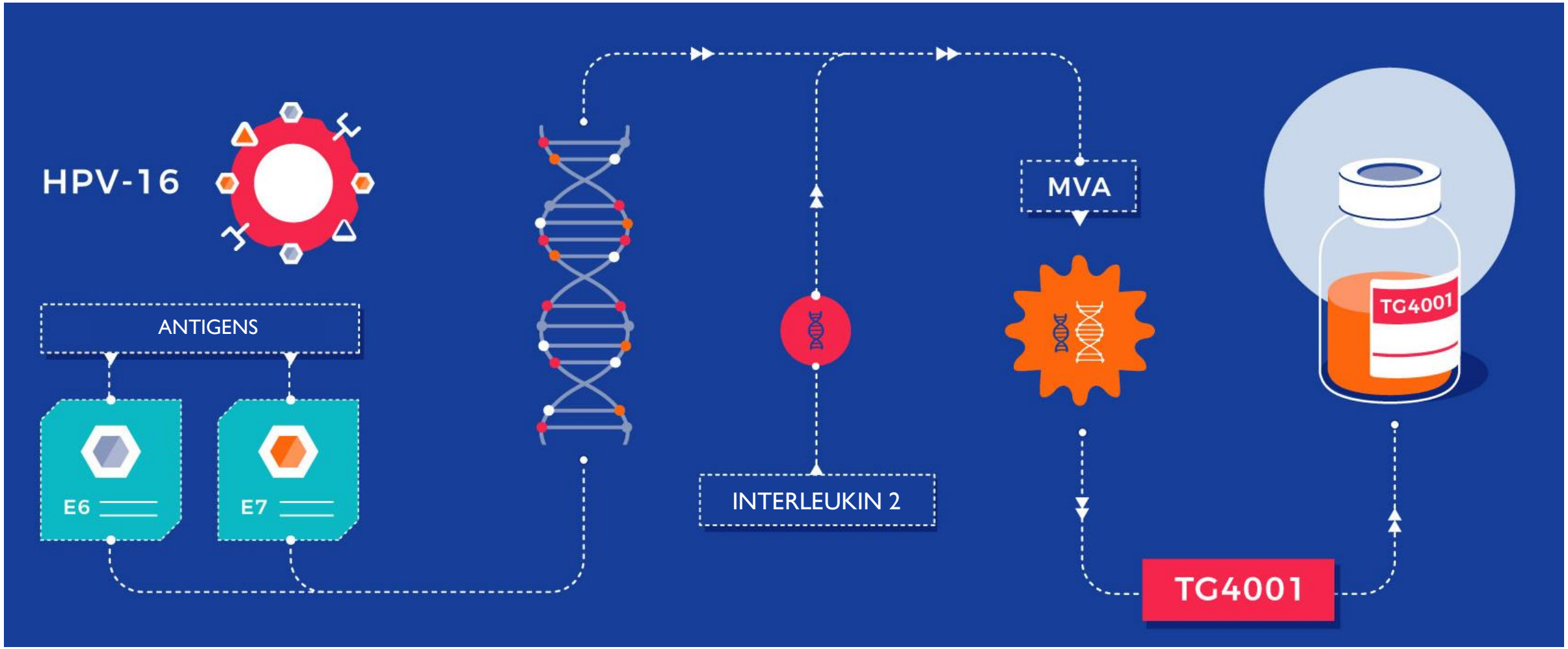
But Still, HPV16-Associated Cancer Patients Need Better Treatment Options

	Nivolumab NCI9673 [ref] Phase 2 Anal 2L	KN028 + KN158 [ref] (pooled analysis) Phase 1b (KN028) and Phase 2 (KN158) Anal 2L	CARACAS [ref] Phase 2 Anal 2L		KN158 [ref] Phase 2 Cervical 2L	CM 358 [ref] Phase 2 Cervical, vaginal vulvar 2L
Treatment N	Nivolumab N = 37	Pembrolizumab N = 137	Avelumab N = 30	Avelumab + Cetuximab N = 30	Pembrolizumab N = 98	Nivolumab N = 19 cervical N = 5 vaginal/ vulvar
ORR	24% (9)	10.9%	10% (3)	17% (5)	12.2% (12)	26.3% 20.0%
Med PFS	4.1 m	2.1 m	2.1 m	3.9 m	2.1 m	5.1 m
Med OS	11.5 m	11.7 m	10.8 m	6.8 m	9.4 m	21.9 m

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

* SOC: methotrexate, docetaxel, cetuximab

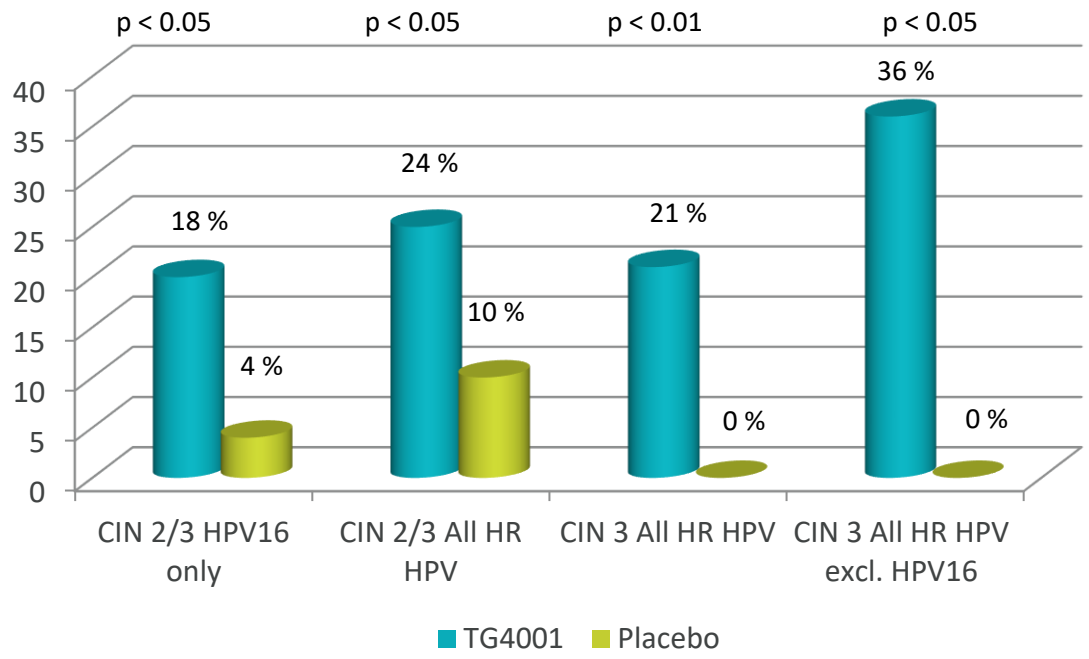
TG4001 | Therapeutic Vaccine Targeting HPV-Positive Cancers



TG4001 | Therapeutic Vaccine Targeting HPV-Positive Cancers

Randomized Phase II trial in CIN 2/3

Complete resolution at 6 months (%) [1]
TG4001 single-agent (3 injections) vs placebo



Strong data for TG4001 in CIN 2/3[1-2]

Strong and specific response against tumor cells carrying HPV16 E6 & E7 antigens

Stimulates the infection-clearing activity of the immune system

Long-lasting responses

Good combination candidate thanks to established **safety profile**

Strong rationale for testing TG4001 in advanced stage HPV-positive cancers

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[1] Harper et al., The efficacy and safety of Tipapkinogen Sovacivec therapeutic HPV vaccine in cervical intraepithelial neoplasia grades 2 and 3: Randomized controlled phase II trial with 2.5 years of follow-up, Gynecologic Oncology, April 2019 -
[2] Le Tourneau et al. "Phase Ib/II trial of TG4001 (Tipapkinogene sovacivec), a therapeutic HPV-vaccine, and Avelumab in patients with recurrent/metastatic HPV16 positive cancers" 2019 ESMO Annual Meeting, 30 September 2019, Poster presentation

TG4001 + Avelumab (Ph Ib/II) | 34 Heavily Pretreated Patients with Metastatic Cancer

Updated data – Cut-off date Sept. 2021 (NCT03260023)

	Patients without liver metastases (N=25)	Patients with liver metastases (N=11)	Overall (N=36)
Age (years)			
Mean	60.8	52.9	58.4
Range	28 – 78	34 – 79	28 - 79
Gender			
Female	16	8	24 (66.7%)
Male	9	3	12 (33.3%)
Performance Status (ECOG)			
0	7	7	14 (38.9%)
1	18	4	22 (61.1%)
Primary tumor			
Anal	8	8	16 (44.4%)
Cervical	6	1	7 (19.4%)
Oropharyngeal	8	0	8 (22.2%)
Vaginal	2	2	4 (11.1%)
Vulvar	1	0	1 (2.8%)
Number of organs Involved			
1	11	3	14 (38.9%)
2	10	3	13 (36.1%)
3	4	5	9 (25.0%)
Number of CT lines for R/M disease			
0	5	0	5 (13.9%)
1	15	5	20 (55.6%)
2	5	6	11 (30.6%)

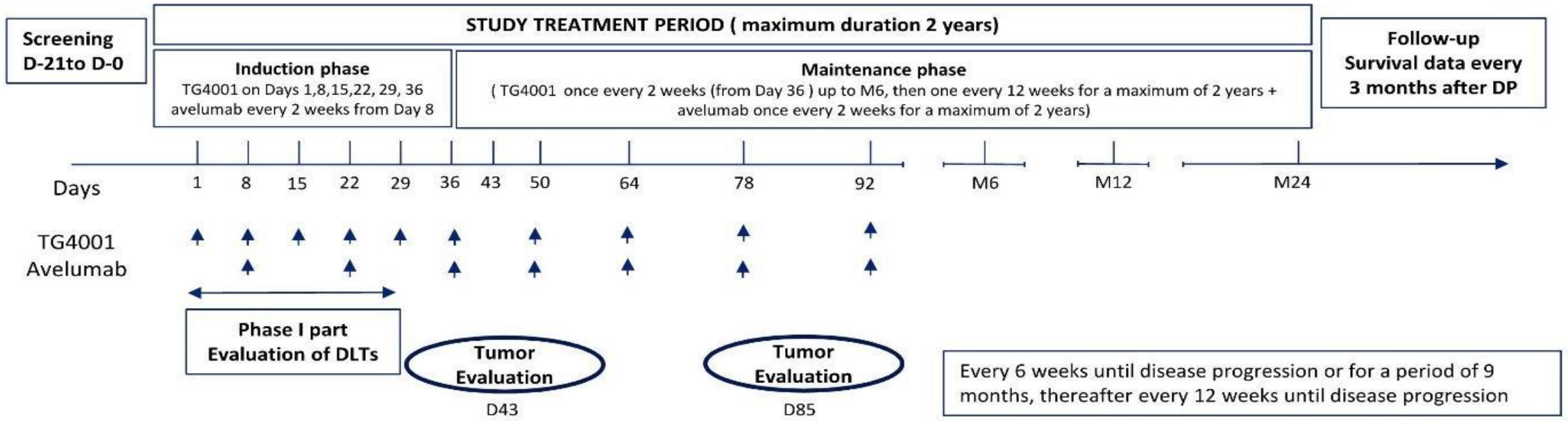
- **Patients without liver mets** identified in this trial **as better responders**
- **Still very hard to treat population**
- **Liver metastases** described as capable of **inducing immunosuppression in cancer patients**[1]

[1] Yu et al. "Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination", *Nature Medicine*, Vol 37, 152-164, Jan. 2021, doi

TG4001 + Avelumab (Ph Ib/II) | Administration Schedule

Collaboration with

MERCK Pfizer



- **TG4001:** Recommended dose for Phase 2 = $5x10^7$ pfu – administered SC
- **Avelumab:** 10mg/kg – administered IV

TG4001 + Avelumab Demonstrated Anti-Tumor Activity in Overall Patient Population

Updated data – data cut off date Sept. 2021

Overall population

36 evaluable patients

22%
ORR

42%
DCR
at 12 weeks

1 COMPLETE RESPONSE

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

7 PARTIAL RESPONSES

Two patients still followed in the trial after 2+ years

Responses were observed in **all primary tumor types** and **across all lines of prior therapy**

Compares favorably to ICIs in monotherapy and competitive landscape

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ORR: objective response rate (RECIST 1.1); DCR: disease control rate

TG4001 + Avelumab (Ph 1b/II) | Patient Population Identified from Trial Data

Promising results, particularly in patients without liver metastasis

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

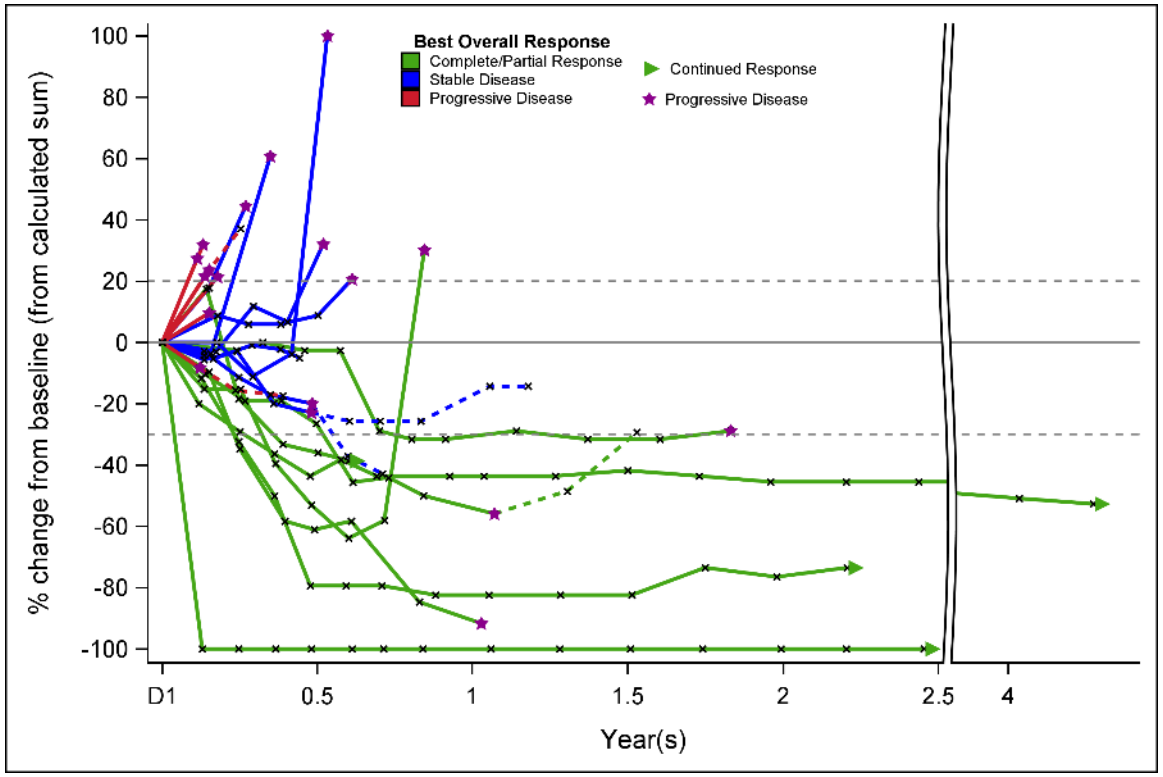
vs patients with liver metastasis (n=11)

Compares favorably to ICIs in monotherapy and competitive landscape

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

TG4001 + Avelumab (Ph 1b/II) | Treatment Induced Long-Lasting Responses

Evolution of tumor size – End of Aug. 2022
in metastatic patients without liver metastases

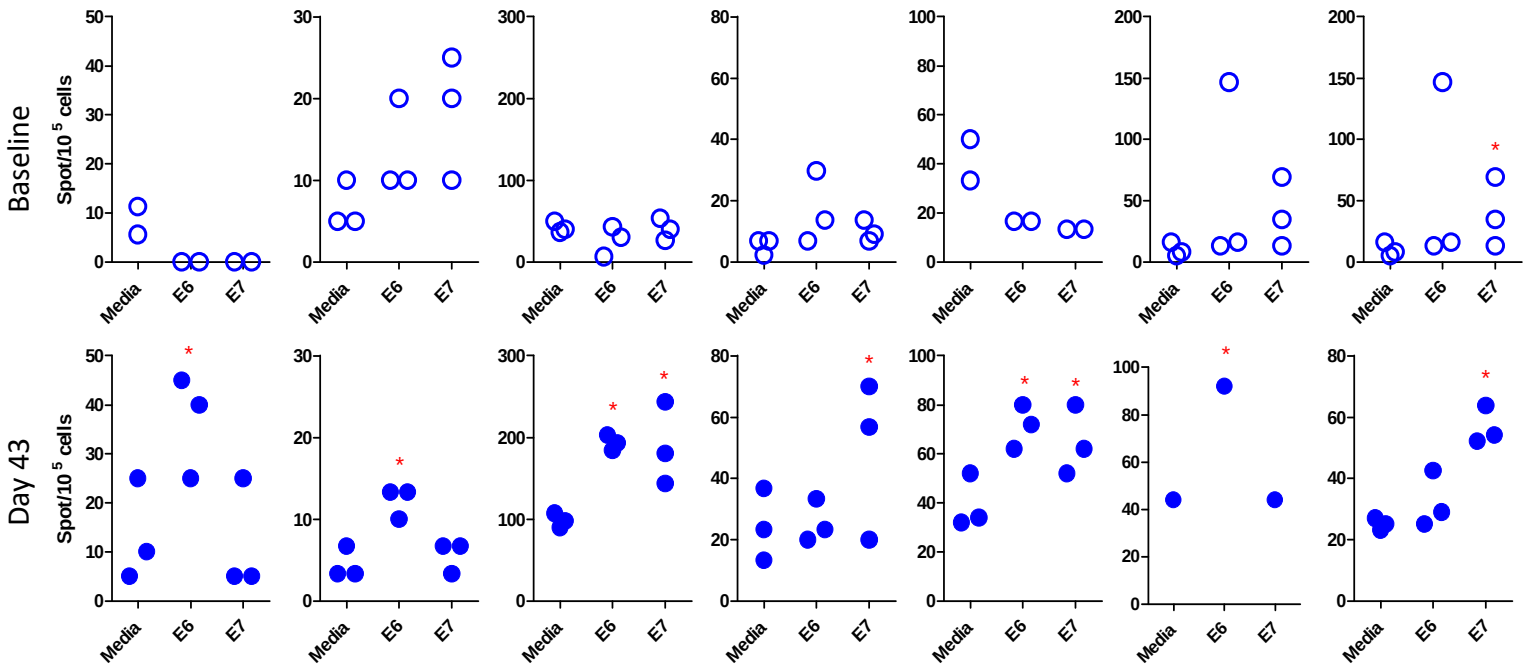


- **1 patient still treated after 4+ years**
  2 patients with 2+ years follow up
- **Responses were also observed in PD-L1 negative patients**

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

Patients with a detected response against target antigens

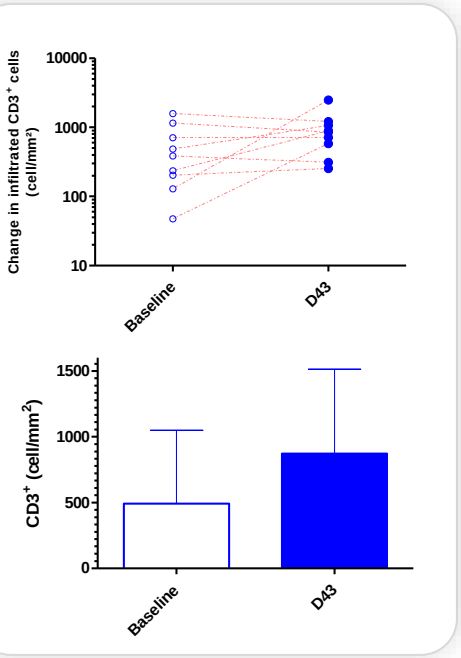
(Ex vivo ELISPOT response against E6 and E7)



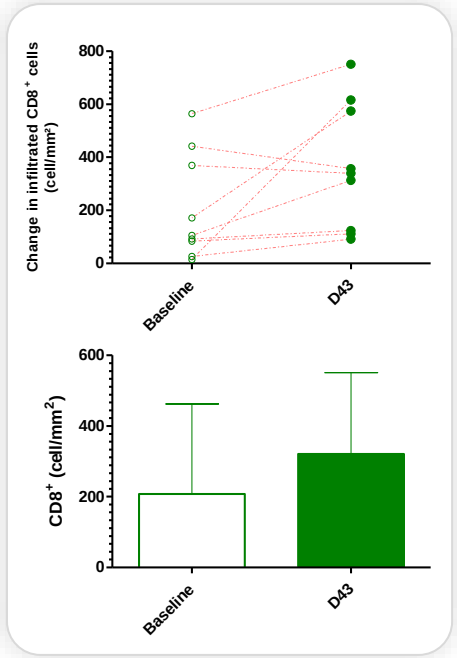
- **At baseline, no patient showed a specific response against E6 and E7**
- **7/11 patients** evaluable for ELISPOT **show specific T-cell responses against HPV16 E6 and E7 after vaccination with TG4001**
- Results support **durable control of the disease**

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

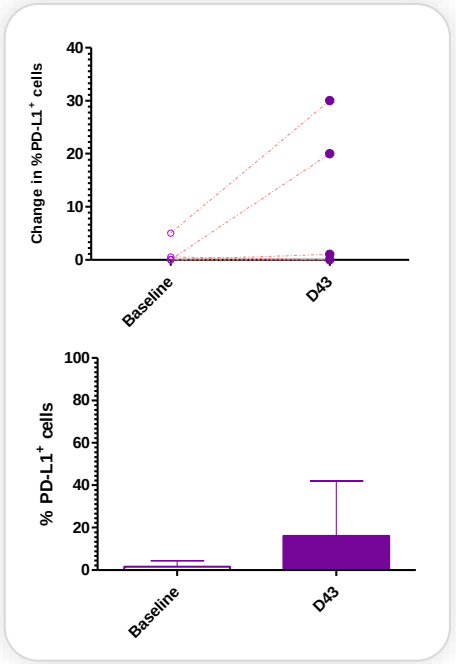
CD3+ infiltrate



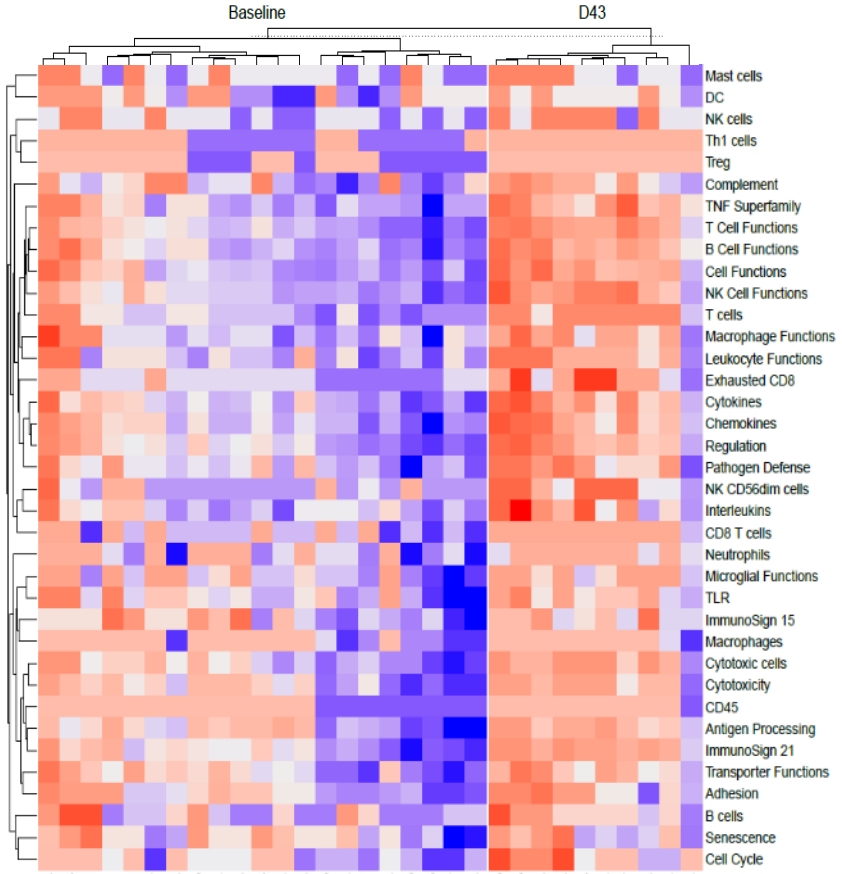
CD8+ infiltrate



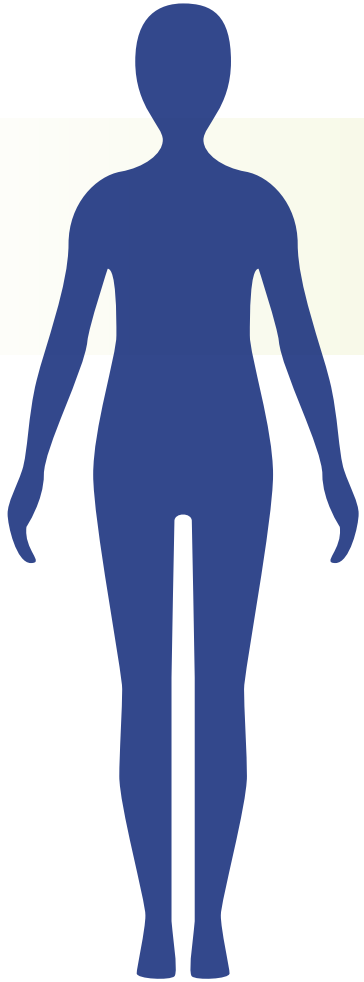
PD-L1 expression



Gene expression



Expanded Trial Focuses on Patient Population that Derived 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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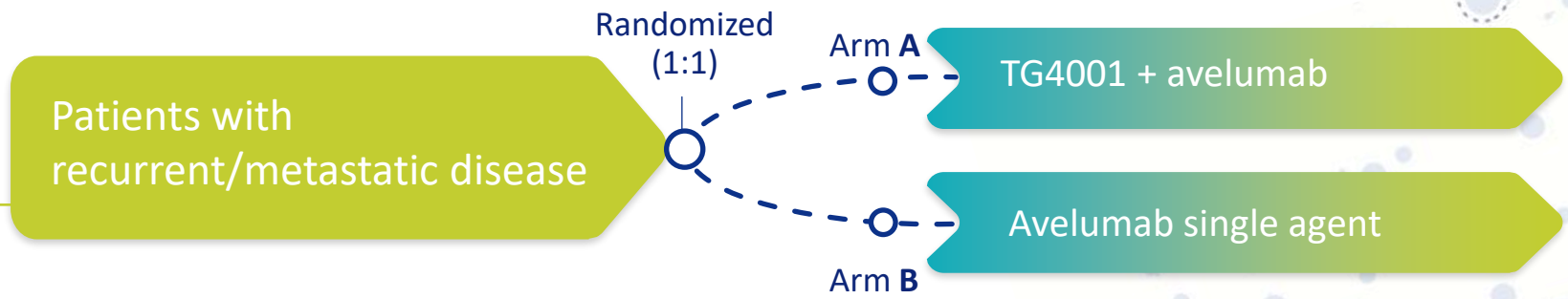
TG4001 | Randomized Controlled Phase II Trial Supported by Clinicians

Trial to enroll up to ~ 150 patients (NCT03260023)

Patients with
HPV16+ Anogenital Cancer



PRIMARY ENDPOINTS

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

SECONDARY ENDPOINTS

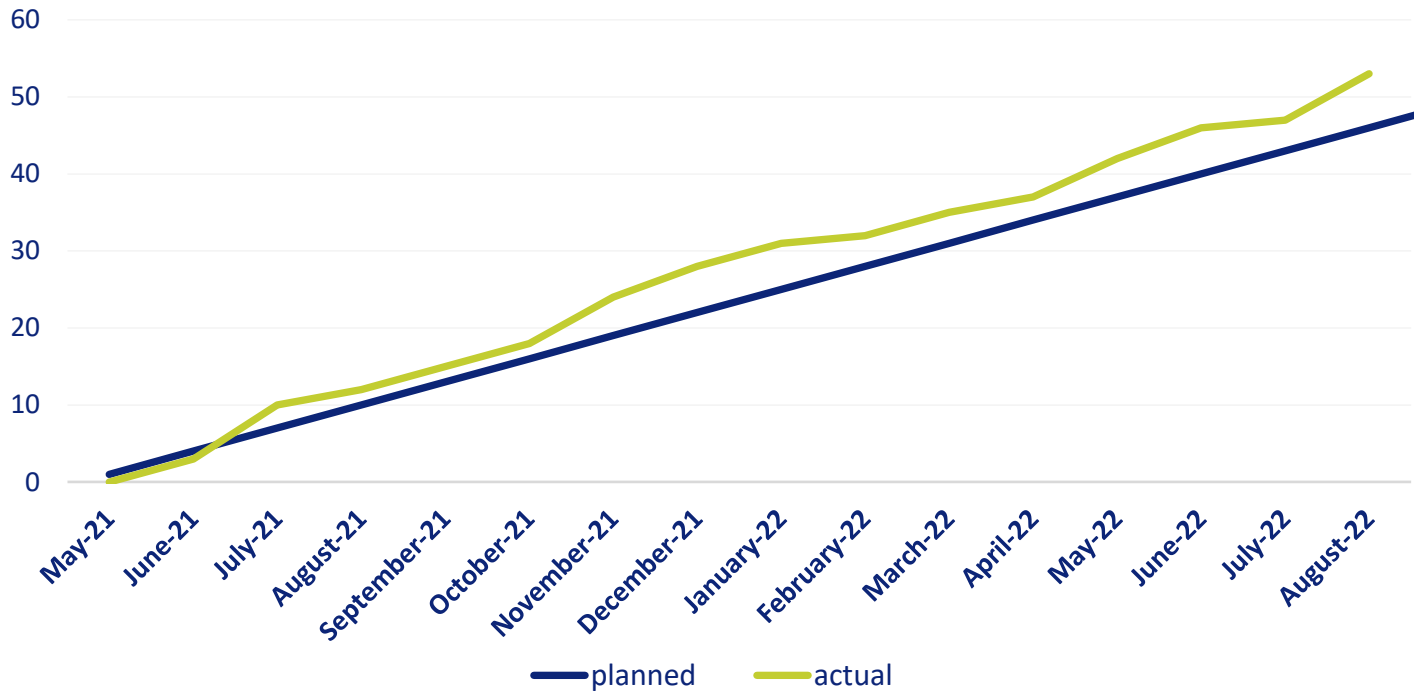
- **Overall Response Rate**
- **Disease Control Rate**
- **Overall Survival**
- **Other Immunological Parameters**

Extended clinical collaboration with

MERCK Pfizer

Inclusions in Phase II Part Were in Line with Forecast

TG4001.12 study
Phase II part 2 - Recruitment curve
Patients **without** liver mets



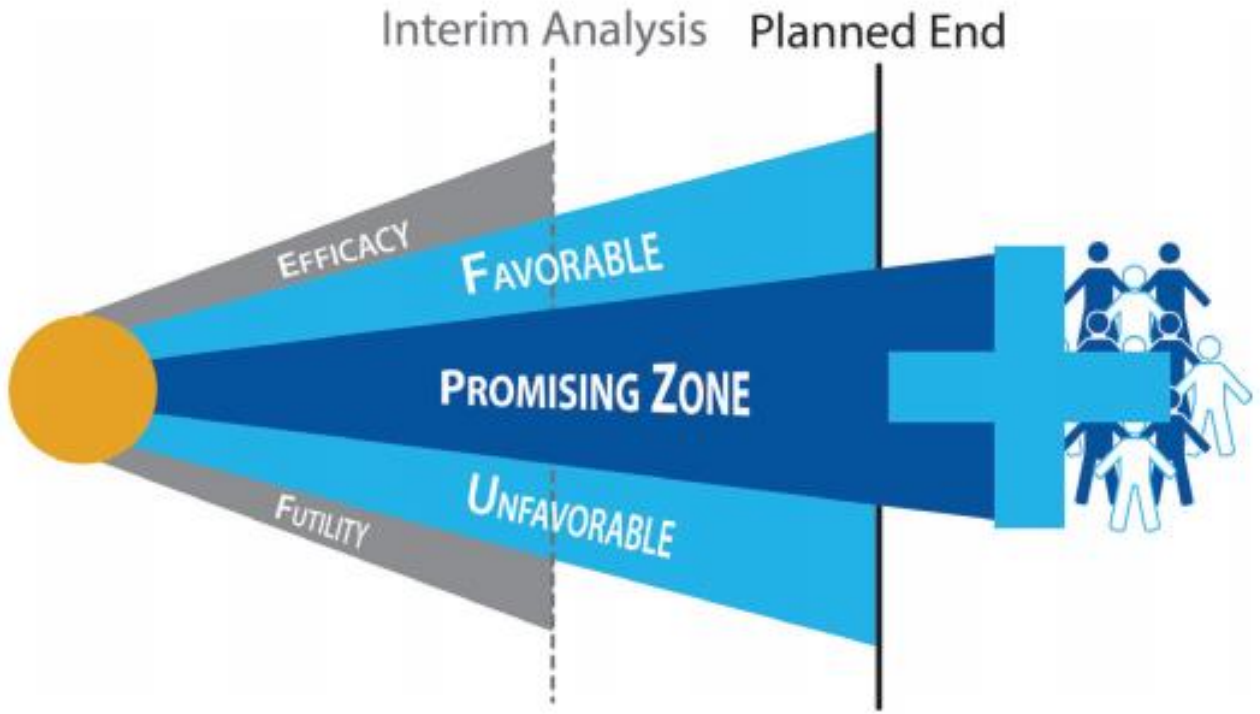
Sufficient number of patients has been enrolled to allow interim analysis in Q4 2022

17 active sites
France, US, Spain

An Adaptive Trial to Optimize Patient Inclusions

Total number of patients to be adjusted based on:

- the results obtained in the interim analysis
- the recommendations of the IDMC



A Methodologically Sound Phase II Trial to Further Validate the Potential of TG4001

Interim analysis data expected Q4 2022

Positive final results could lead to the launch of a registrational trial in anogenital cancers

MAUD BRANDELY, MD, PhD
Chief Medical Officer
Transgene

Cancer Vaccines – Demonstrating Efficacy in Several Clinical Settings

Ongoing trial will be the first Phase II randomized trial with a therapeutic vaccine to read out in anogenital cancers

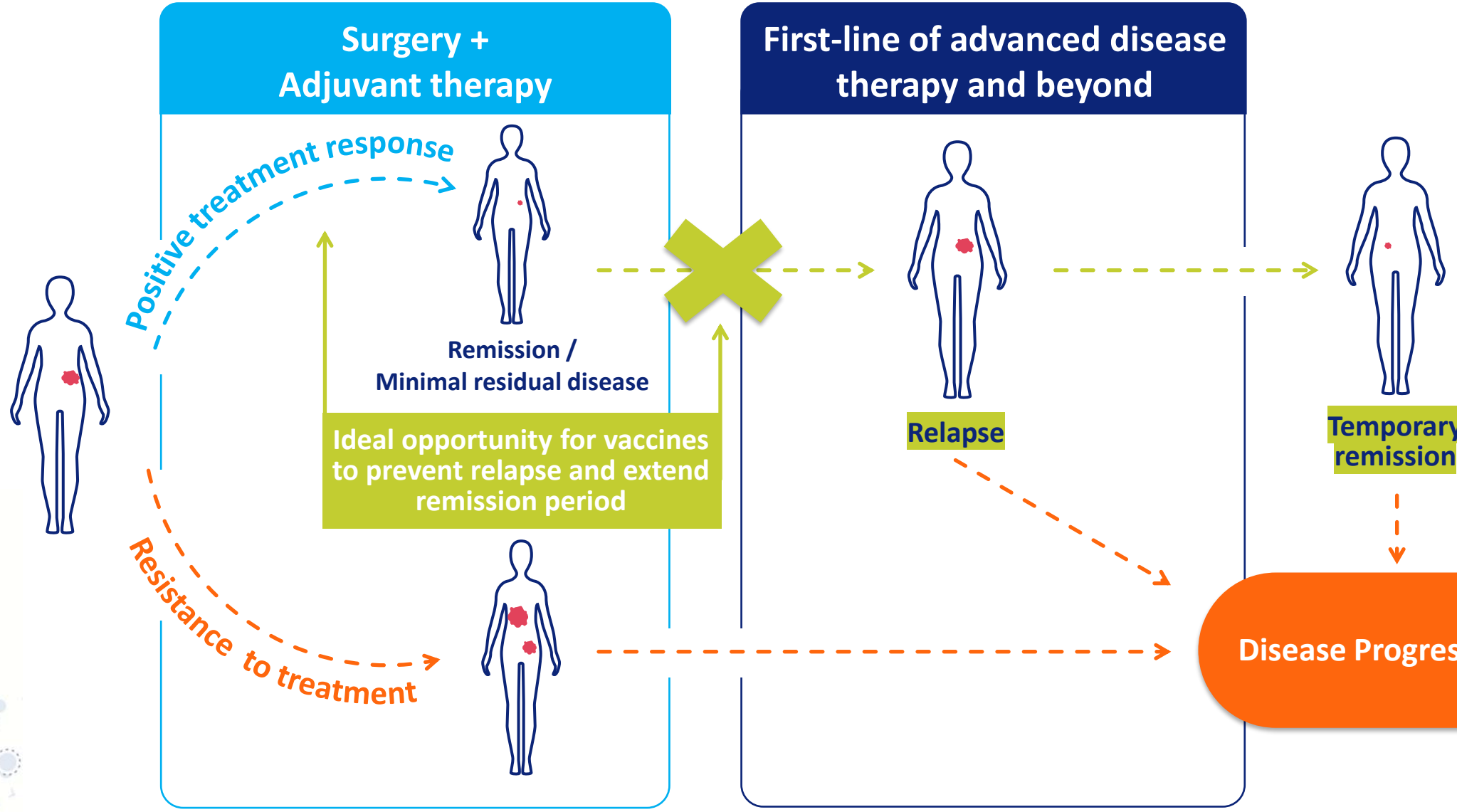
- **Phase Ib/II results are very solid proof of concept** in **advanced disease** in combination with checkpoint blocker (anti-PDL1)
- Interim analysis planned **in Q4 2022**

Based on this PoC, Transgene is progressing with a very differentiated positioning

- **Single agent vaccine**
- **Early stage** of the disease / MRD
- **Neoantigen** directed

Medical Needs and Current Gaps – Moving Therapeutic Vaccines Up Treatment Lines

Strong **NEED TO INCREASE** and **EXTEND REMISSION** periods



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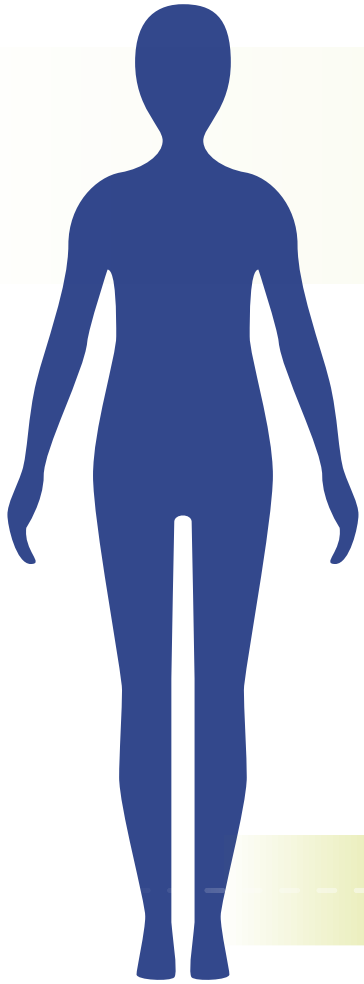
Monotherapy Administration in Patient with Residual Disease

A strategic positioning



Patients with moderately mutated tumors

Ovarian and Head & Neck cancers

- Patients in **clinical remission** with **minimal residual disease**
  that could be followed by additional biomarkers
- **Limited or absence of observed efficacy of checkpoint blockers**
- Patients with **functional immune system**
- Cancer with **low/medium TMB***

DESIGNED
TO TREAT PATIENTS WITH ESTABLISHED BUT MINIMAL DISEASE

Allows the use of TG4050 as **monotherapy**
while increasing the probability of response

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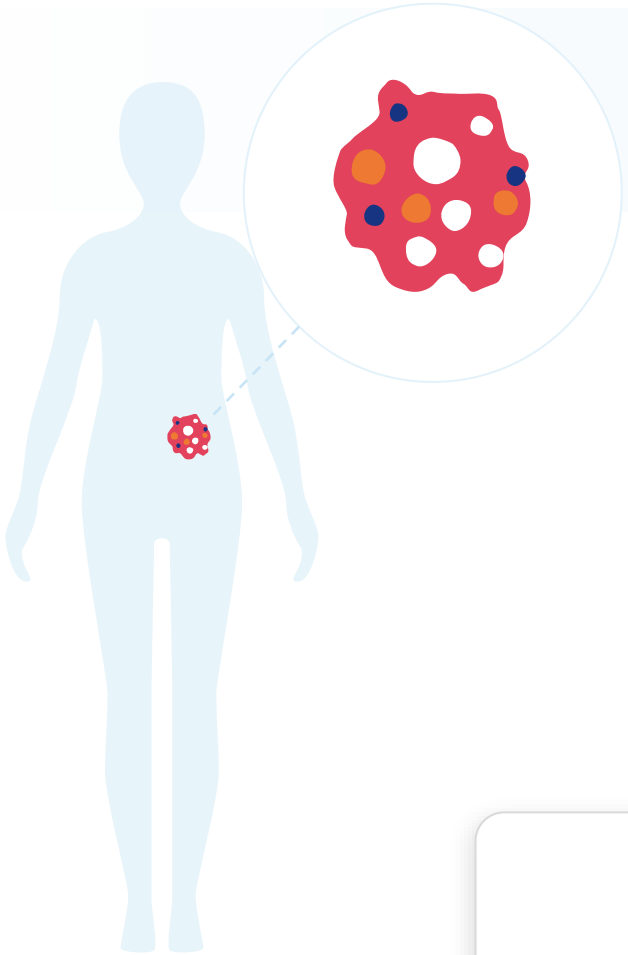
*TMB: tumor mutation burden

A Vaccine Targeting Patient-Specific Neoantigens

To stimulate strong and durable anti-tumor immune response



Patient-Specific Neoantigens are:

- **Private neoantigens** which means that the **targets are specific to each patient**, **addressing the issue of tumor heterogeneity**
- **100% tumor specific**, consequently **unlikely to be subject to central tolerance**
- **More immunogenic** than “classical” antigens, thus expected to induce **broader and stronger T cell responses**

Our individualized cancer vaccine can **target up to 30 antigens,**
maximizing efficacy and lowering the risk of tumor immune escape

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AI Use and Perspective at Transgene

KAÏDRE BENDJAMA
Program Director
Transgene

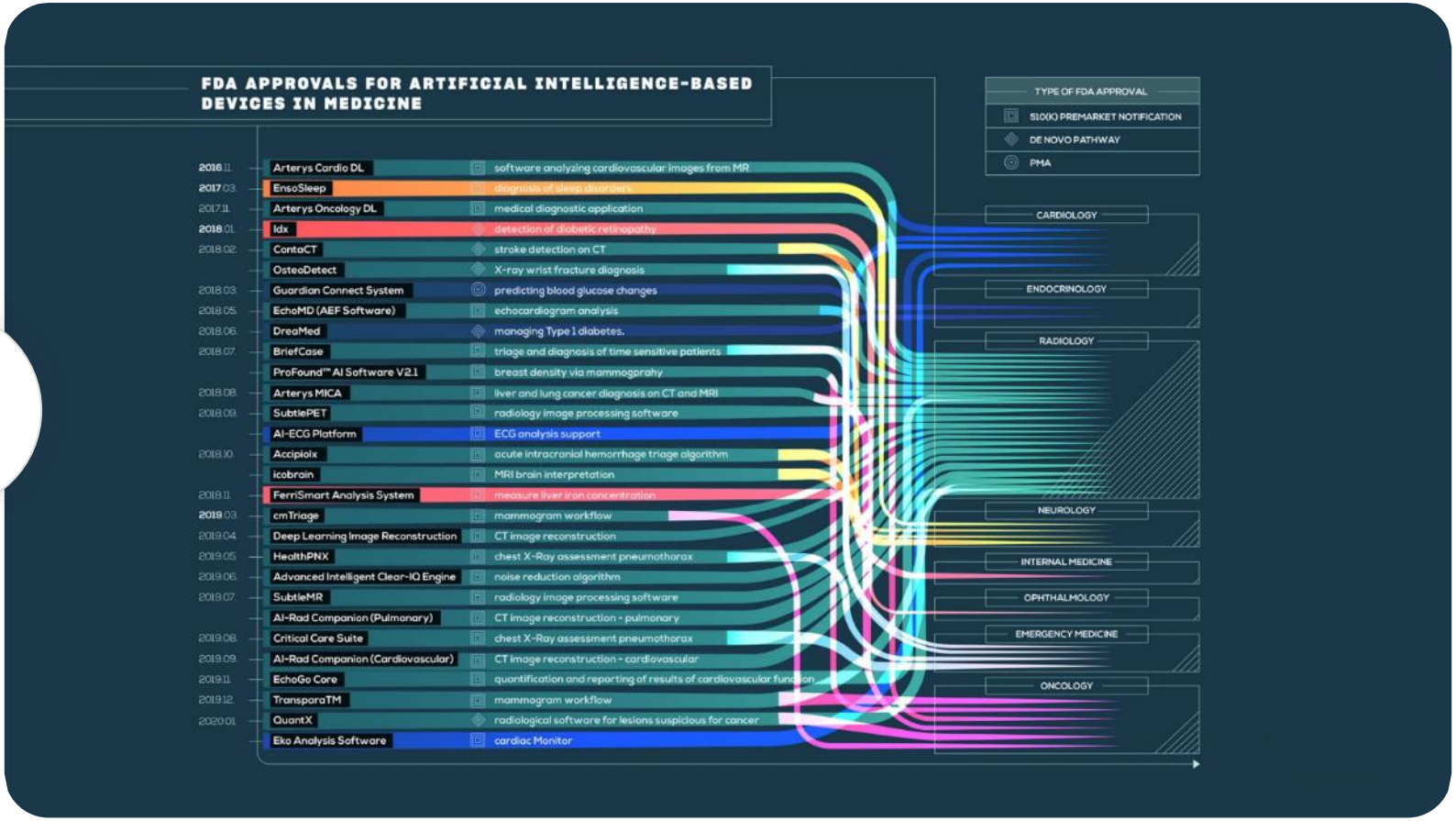
AI is More Than the Buzzword of the Decade

AI is widely developed and used in our daily lives

Over the last decade performance of AI system vastly improved allowing **implementation in low risk/low regulation application** (e.g. suggested reply on your message app), to more critical application **high risk/highly regulated environment.**

Applications of AI in Healthcare Became a Reality in the Last Years

Numerous use cases have been registered and commercialized



Sources: Benjamens S, et al. Npj Digital Medicine, 2020

AI in Oncology and Precision Medicine

Oncology progresses very fast toward increased performance and unprecedented complexity

Foundation models

Data intensity

Deep learning

netMHC
Bioinformatic "predictions"
Digital pathology

Machine learning and statistical learning

Advent of AI and Early "intelligent" machines

myvac

TG4050

Oncology 1.0

- **One indication =** one recommended approach

Oncology 2.0

- **Targeted drugs and companion diagnostics** (e.g. EGFR mutations, and PD-L1 status)

Oncology 3.0

- **Broader investigations ("multi-omics") and identification of multiple mutation** to treat with multiple drugs

Oncology 4.0

- **Mining data from large dataset;** AI based decision making; drug designed to fit patient needs

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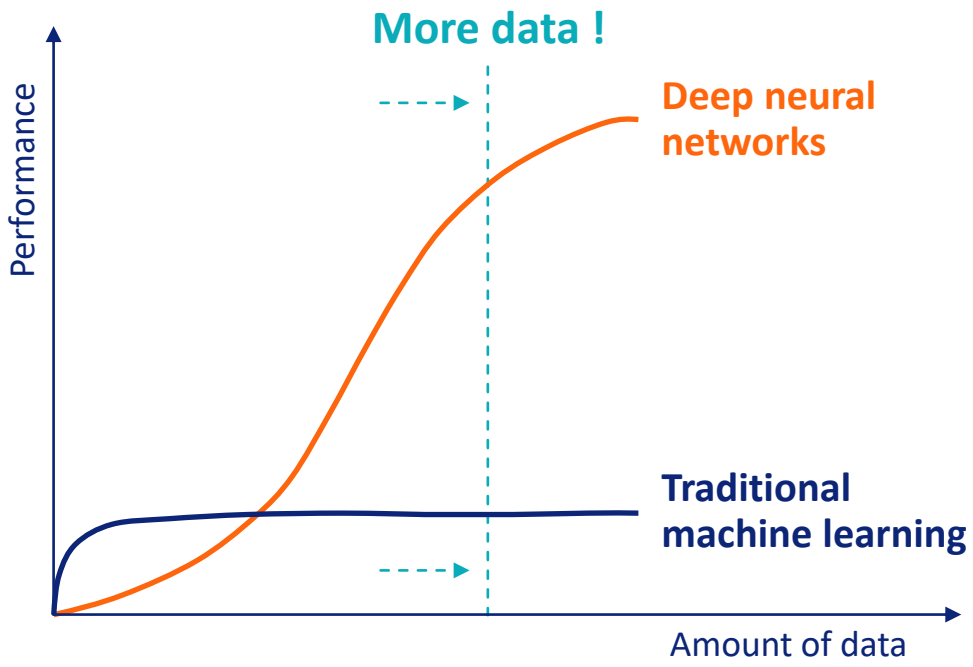
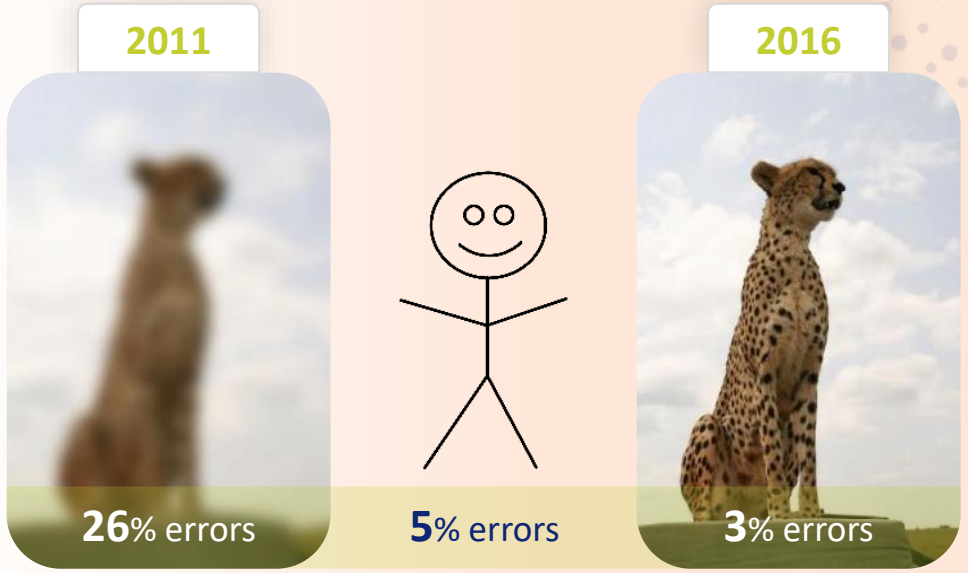
Deep Learning Has Allowed Tremendous Increase in Performance in Complex Tasks

Deep neural networks have driven performance up by using large amount of data

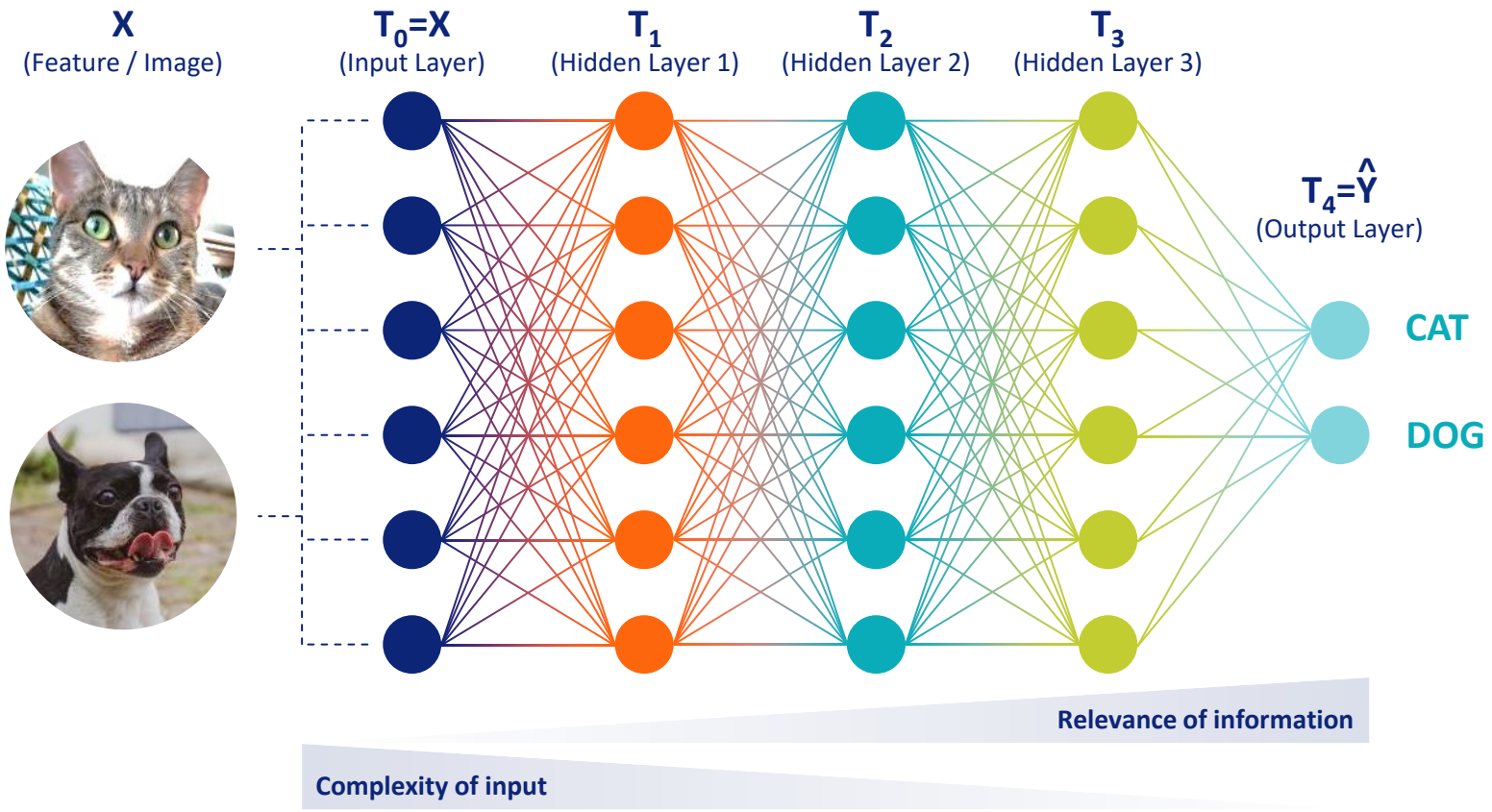




Sources: Dean J., HLF 2017

Deep Neural Network are Particularly Good at Handling Vast Amount of Data

Each layer of a neural network will filter the information to only keep data that is actually relevant to the final output



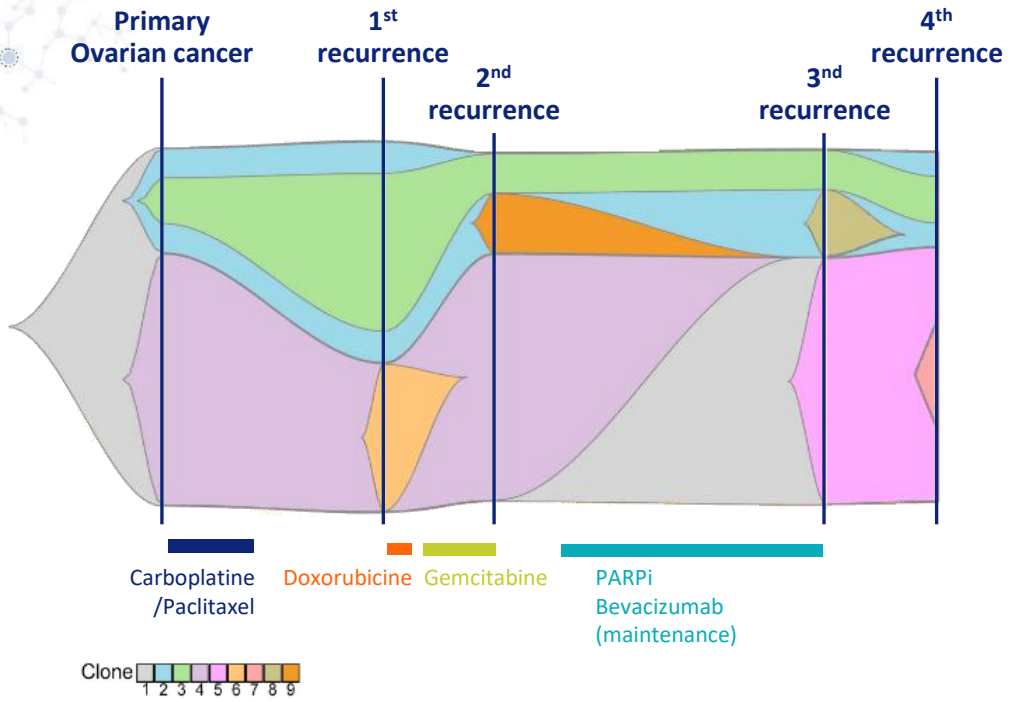
Successive layers of neurons compress the information by keeping data/feature that are relevant to a given outcome and… relevance of feature depends on the input data.

https://www.ibm.com/blogs/research/2019/06/deep-neural-networks/

Neoantigen Cancer Vaccine are a Typical Use Case for AI-Based Systems

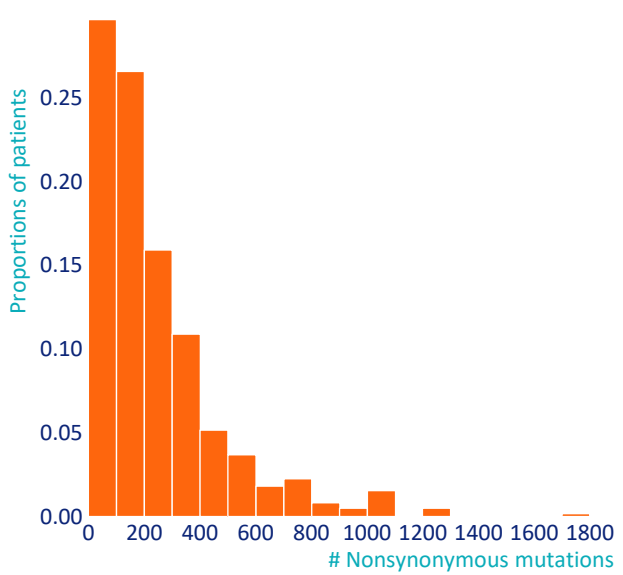
Highly parametric – High heterogeneity

Mutations vary significantly across patients, along the therapeutic journey and across cells in a given cancer:

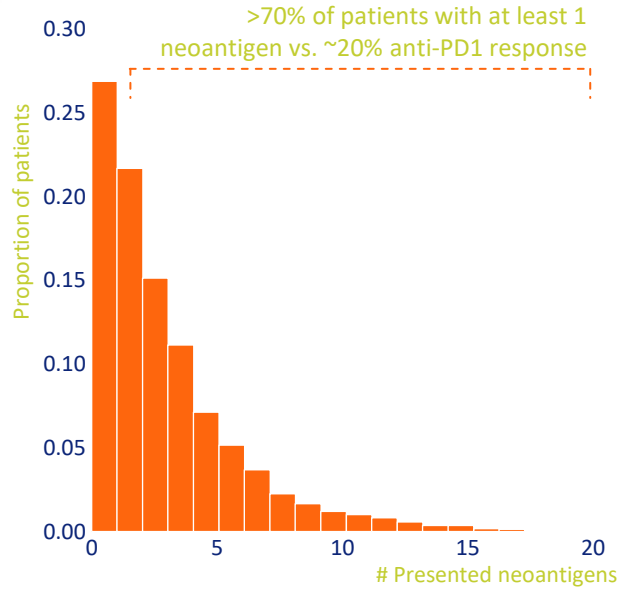


~1% of Mutations are neoantigens

Mutation Burden in TGCA NSCLC Smokers



Expected Number of Neoantigens in LUAD Smokers



Only a very minor fraction of mutations are **actual actionable antigens**

Sources: Angelova M et al. Cell, 2018; Allen A et al. Neoantigen summit, 2019

Our Vaccine Design Process Today

Deep learning allows feature agnostic antigen selection

ROUTINE TUMOR BIOPSY

Patient

Treatment administration

GENE SEQUENCING

Next generation sequencing

DATA PROCESSING, ARTIFICIAL INTELLIGENCE

Selection of 30 neoantigens

Orchestrating a brighter world

NEC

GENE EDITING, MANUFACTURING

Vaccine generation and manufacturing

Sequencing data

Normal

WXS

RNA

Tumor

WXS

RNA

NEC'S NEOANTIGEN PREDICTION

Proprietary Database

Candidate Generation

HLA Typing

Variant Calling

Feature description

HLA Binding

Tumor presentation

Immunogenicity

Self-Similarity

RNA Expression

Epitope selection

NEC

Overall Ranking by Graph-based relational learning

Vaccine recipe

Is the AI Used in our Trials Actually Doing Better Than Any Other Approach?

Method benchmark is unlikely to be achieved but AI contribution is tangible

Across 6 patients treated:

2119
vaccine target candidates

115
vaccine targets used to manufacture vaccines

36
targets confirmed in patients

We expect ~200 actual targets in the pool of 2119 mutations identified in our study patients so far

Probability to obtain more than 36 actual "working" targets with 115 targeted mutation if mutations were selected by random selection.

$$\mathbb{P}_{(k\geq 36)} = \sum_{k=36}^{115} \frac{\binom{200}{k}\binom{2119-200}{115-k}}{\binom{2119}{115}} = 8{,}5 \cdot 10^{-12}$$

Probability to have a response on 36 or more targets : $8{,}5.10^{-12}$ or **1 out 118 billions…**

From a relatively complex dataset the **AI system is capable of selecting valid vaccine targets**

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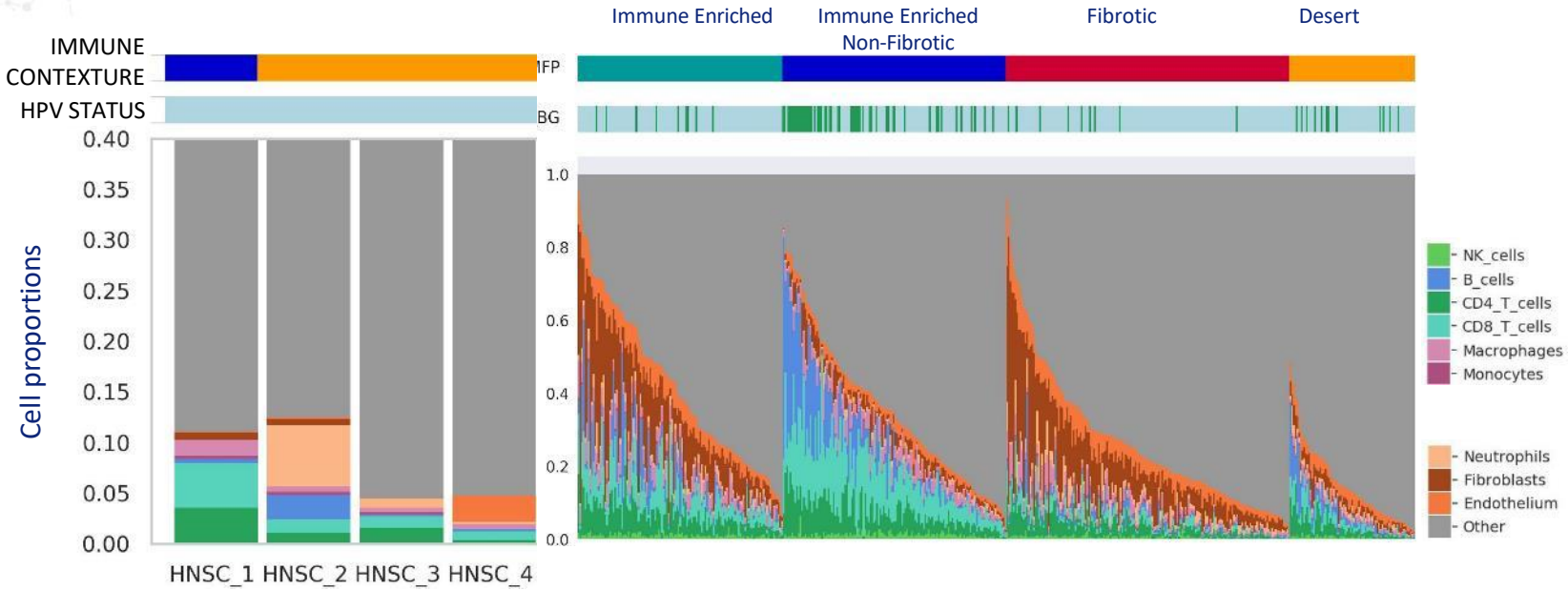
Beyond Antigen Selection & Product Design

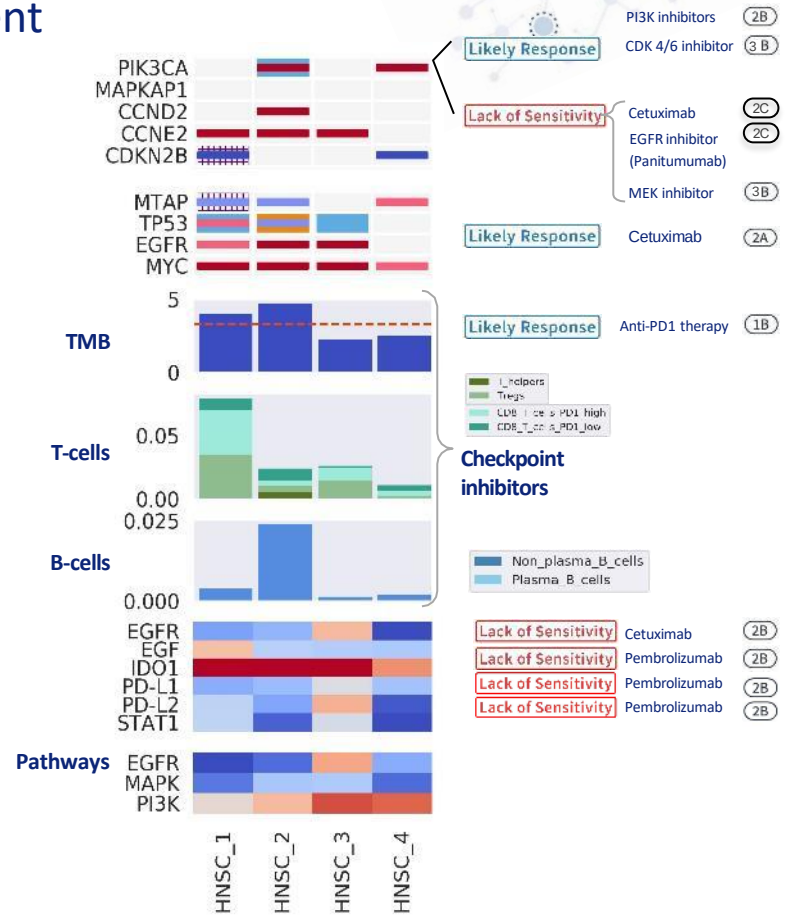
Exploitation of comprehensive genomic data and real time contextualisation in clinical knowledge pave the way to accurate patient selection

Advanced analysis of genomic information allows deep characterization of patient immune profile and profiling of patient responsiveness to registered therapy.

Study samples

Reference classification data from 1,486 patients





In a Nutshell

AI HAS THE POTENTIAL
to drive a **MAJOR IMPROVEMENT**
in **EFFICACY OF THERAPY**

- Leveraging **massive amounts of data**
- **Treating this data** without guesswork on its relevance

STILL A LONG JOURNEY AHEAD toward a definitive clinical validation
but AI based approaches show **EXCELLENT PERFORMANCE**

Further
TO VACCINE DESIGN

- AI approach will help **represent patient/TME profile** accurately
- **Contextualize findings** in regards of the existing knowledge/ literature

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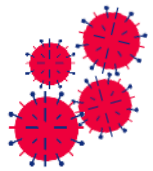
MAUD BRANDELY, MD, PhD
Chief Medical Officer
Transgene

myvac® | An Integrative Approach Capitalizing on Multiple Cutting-Edge Technologies

Taking the Treatment of Each Patient to a New Level

MVA Viral Vector: a Powerful Platform for Vaccine Development



Well-established safety profile

- Strong track record from both prophylactic campaigns, and from clinical trials in oncology
- Safe in a large variety of routes of administration

Optimal antigen display

- Demonstrated capability to express various **complex antigen structures**, and have them presented by APCs
- Ability to elicit **strong, durable and specific** immune response

GMP Manufacturing Capabilities

Production process in place

- Scaled up to **~2 batches/wk**
- Optimization in progress

Multiple Proprietary Innovative Technologies

Artificial Intelligence

- NEC's machine learning environment based on multiple parameters **to classify most immunogenic neoantigens** from whole tumor genome analysis*
- NEC covers 50% of the development cost of TG4050

Viral vector engineering

- **VacDesignR™** for **optimal design of the recombinant cassettes**
- Selection of **best promoter sequences** for optimal antigen expression, and presentation
- **Optimized pre-GMP cloning procedures** into the *myvac*® MVA backbone

*Source: Mallone et al., "Performance of neoantigen prediction for the design of TG4050, a patient-specific neoantigen cancer vaccine", AACR, June 2020, Poster presentation

From the design of the *myvac*® platform to first immunological and clinical readouts

CHRISTIAN OTTENSMEIER, MD, PhD, FRCP

University of Liverpool
The Clatterbridge Cancer Center NHS Foundation Trust

La Jolla Institute for Immunology

Cancer Immunotherapy in a Nutshell

An intriguing challenge:

If cancer develops
the immune system
must have failed

The puzzle then:

- Can we re-establish immune control
- What does ‘immune control’ look like
  - **patient level**: cancer disappears
  - **cellular level**: what does this actually mean?
  - Can we understand **‘how to get there’?**

Exploiting the Immune System for Treatment

First example:
allogeneic bone marrow transplantation

- **meaningful cure rates**
  - but much toxicity

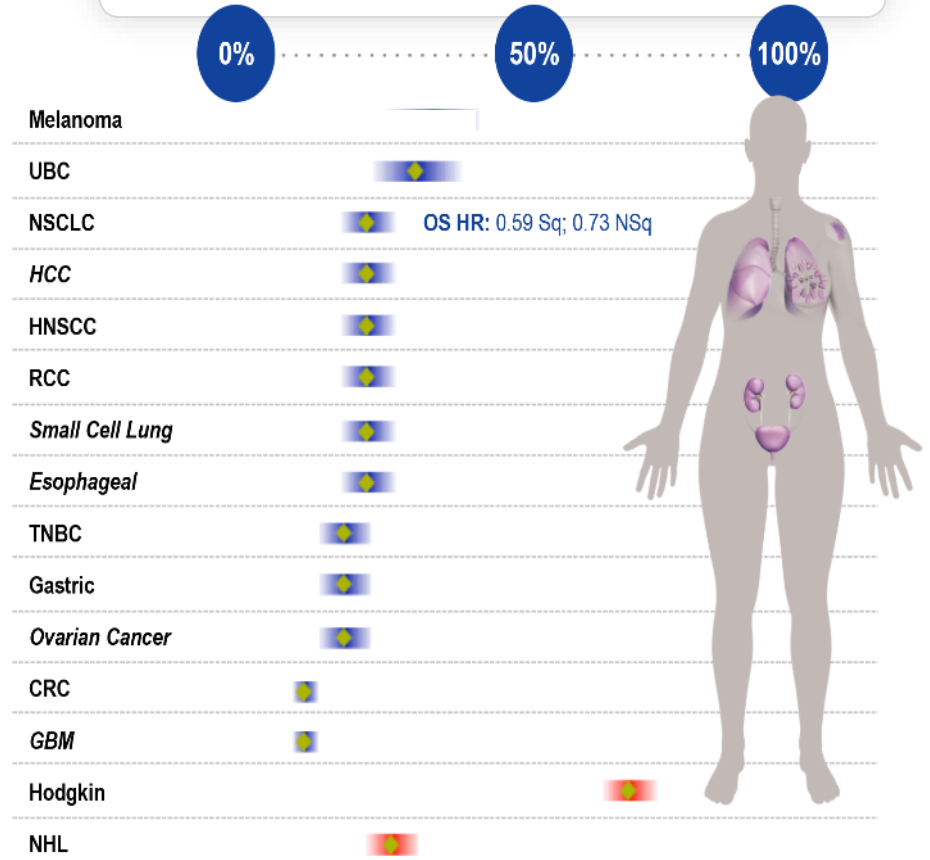
Since 2011

- **immunotherapy** has become standard treatment
- **stunning clinical benefit** in responders

Current reference standard:

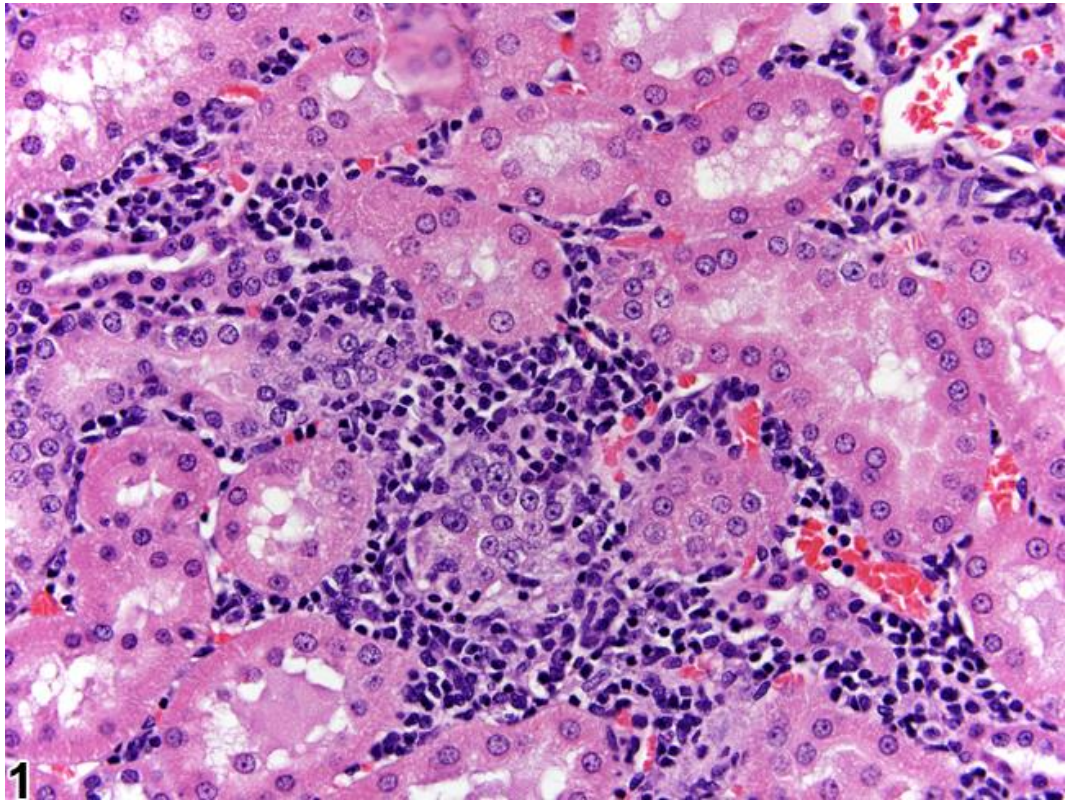
- **PD1/PDL1 inhibition**
- **single agent efficacy ~25%**

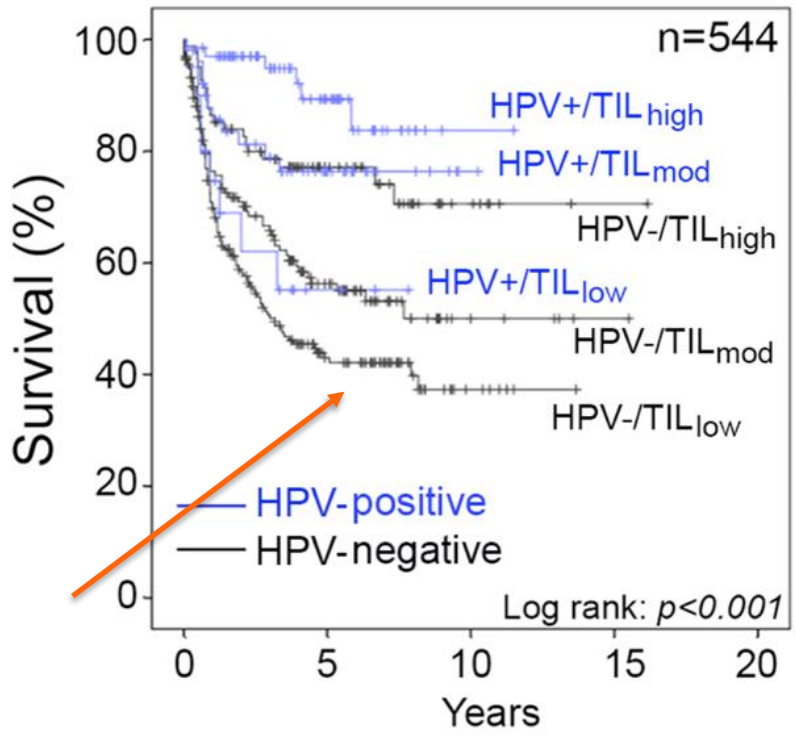
Clinical response to aPD1/aPDL1



Modified from D. Chen, BioScience Forum, 2015

‘Measuring Immune Attack’: Counting T Cells





To understand biology:

WE NEED MORE SOPHISTICATED TOOLS!

Ward et al, BJC 2014
Wood et al, Oncotarget 2016
Ottensmeier, CaRes 2016

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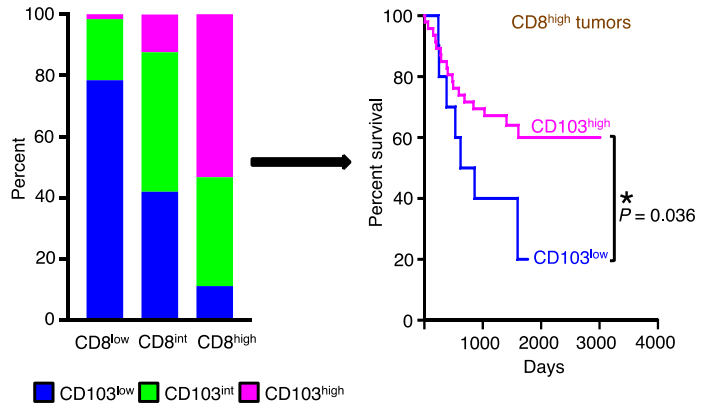
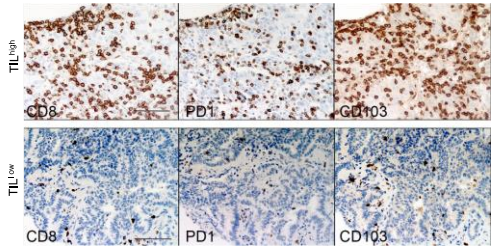
Mechanistic Insights Gained:

long lived CD8+ T tissue resident memory are:

Presence of CD103 (IHC) predicted patient survival above that of CTLs





- highly effective killers
- expand in cancer tissue
- express unique, actionable targets
- are easily quantified
- **reproduced in multiple human cancer types**
- CD8+ TRM cells underpin tumor control long lasting memory
- activated by anti-PD1 antibody induced by vaccination

In mouse models

Ganesan, Nat.Imm. 2017
Clarke, J.Exp.Med 2019

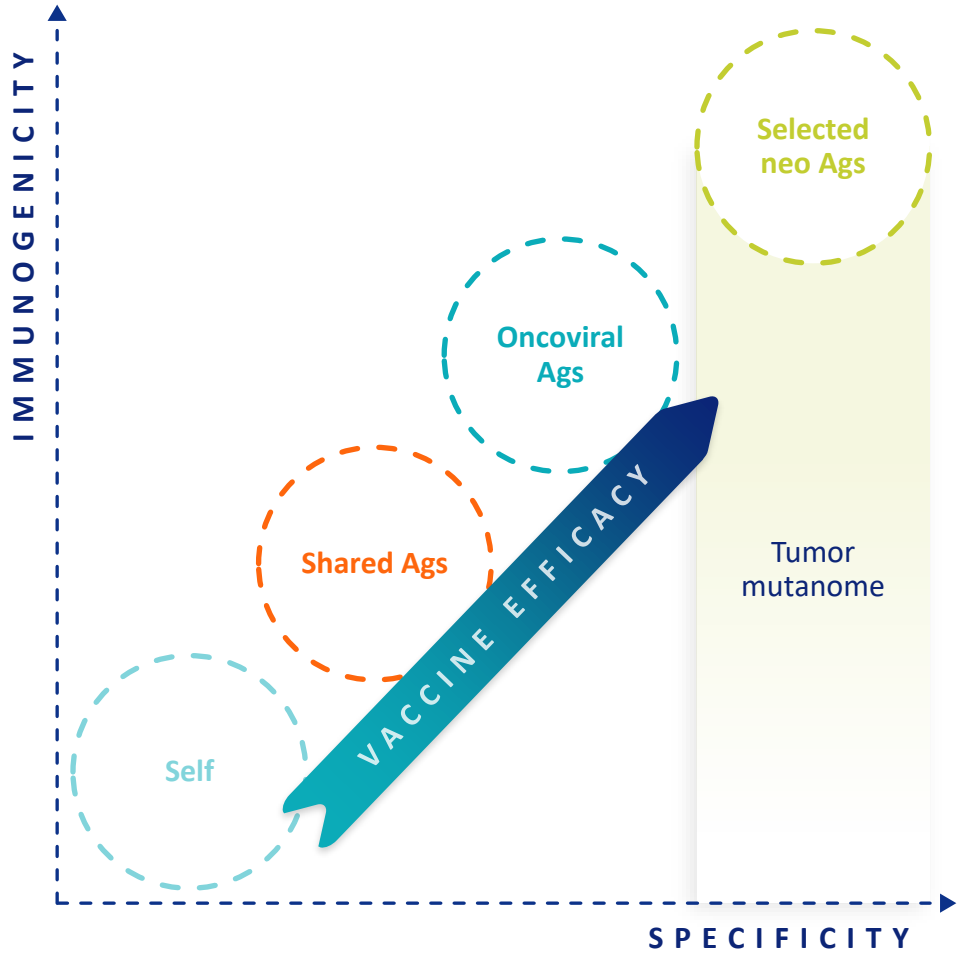
Key Questions

- What targets can immune cells recognize in cancer?
- How many cells are there that see one antigen?
- Which target is ‘most recognized’?

Immunologically appealing: **neo-epitopes:**

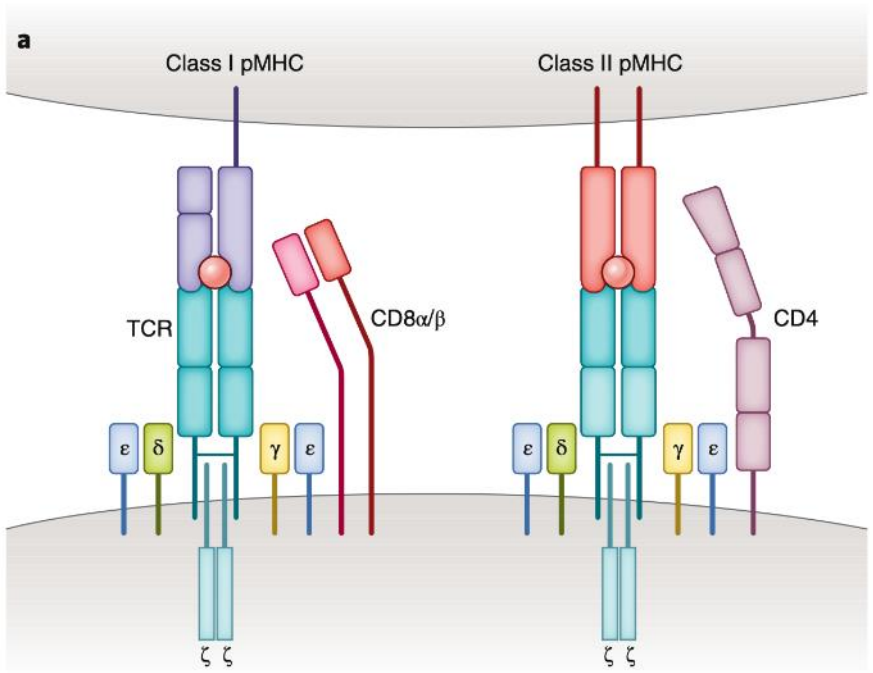
- no central tolerance
- most different from ‘self’
- immunologically ‘lowest bar’

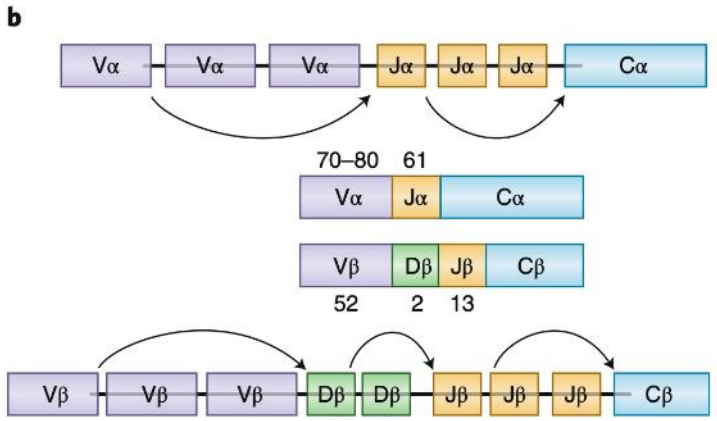
  (if technical hurdle resolved)



Von Witzleben, Front Imm, 2020

At the Heart of the Matter: TCR-MHC Interactions





Imagine the TCR as a fingerprint

It defines the identity for the individual T cell

From: Joglekar AV, Nature Methods, 2021

The Toolset

Ongoing programme of systematic probing

1 COLLECT BLOOD

(Apheresis product)

2 FIND CELLS REACTIVE

withTumour antigen

3 IDENTIFY T CELL RECEPTOR

'molecular barcode'

4 COLLECT CANCER TISSUE

5 ALL T CELLS:

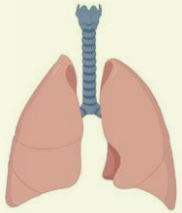
Analyse 'molecular barcode

6 DEFINE OVERLAP

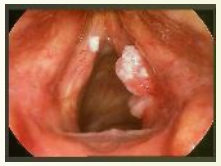
= antigen reactive T cells in tissue

- Number
- Quality
- Clonality

Molecular Profiling of Antigen-Reactive T Cells



Possible for any antigen to define T cell repertoire:



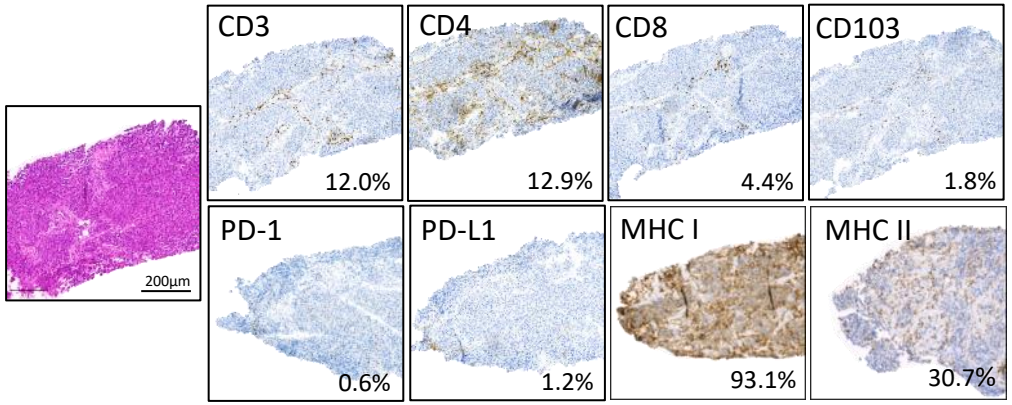
- **Viral antigens** in cancer
- **Shared antigens** in cancer
- **Neo-epitope antigens** in cancer
- **Cancer antigens** in the adjacent non cancer tissue
- **Sites of toxicity…** - any tissue (skin, bowel…)
- **Platform technology**

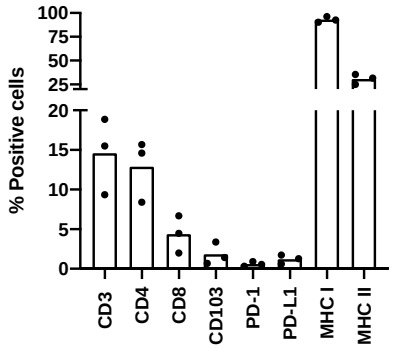
Inception of *myvac*® – Demonstration of Concept

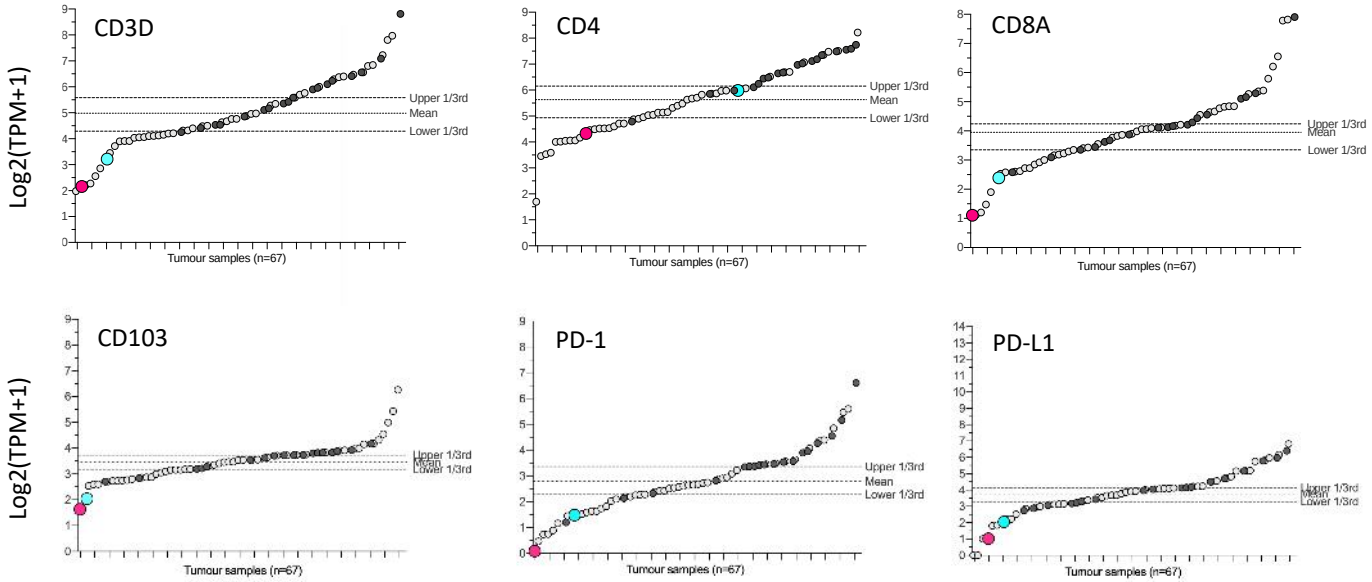
THE QUESTION:
DO IMMUNE COLD CANCERS CONTAIN NEOEPITOPE REACTIVE T CELLS?

THE PROMPT:
A PATIENT IN TROUBLE
A HUGE CLINICAL NEED

The patient:
- NSCLC
  - TMB low
  - PDL1 low
- Progressive on
  - Chemo
  - aPD1
  - RT



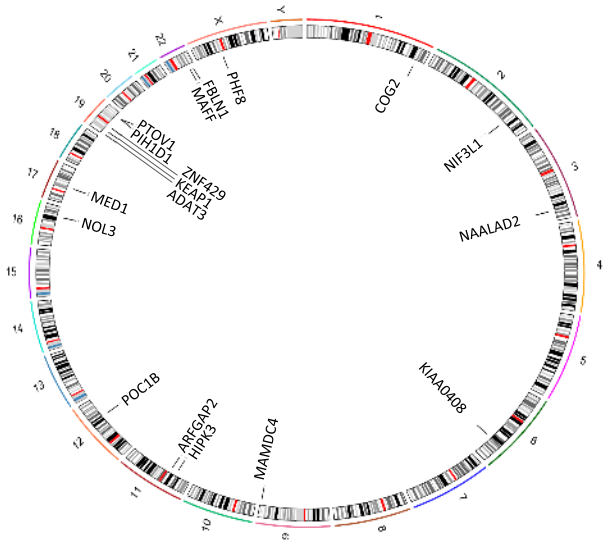




- AC003 TP01 primary lung tumor (Jun 2016)
- AC003 TP02 parasternal metastasis (Sept 2016)
- HNSCC
- Lung

transgene

Neoantigen Selection for Personalized Vaccination



TP01: 23 variants involving 18 genes: 22 missense and 1 DEL/frameshift

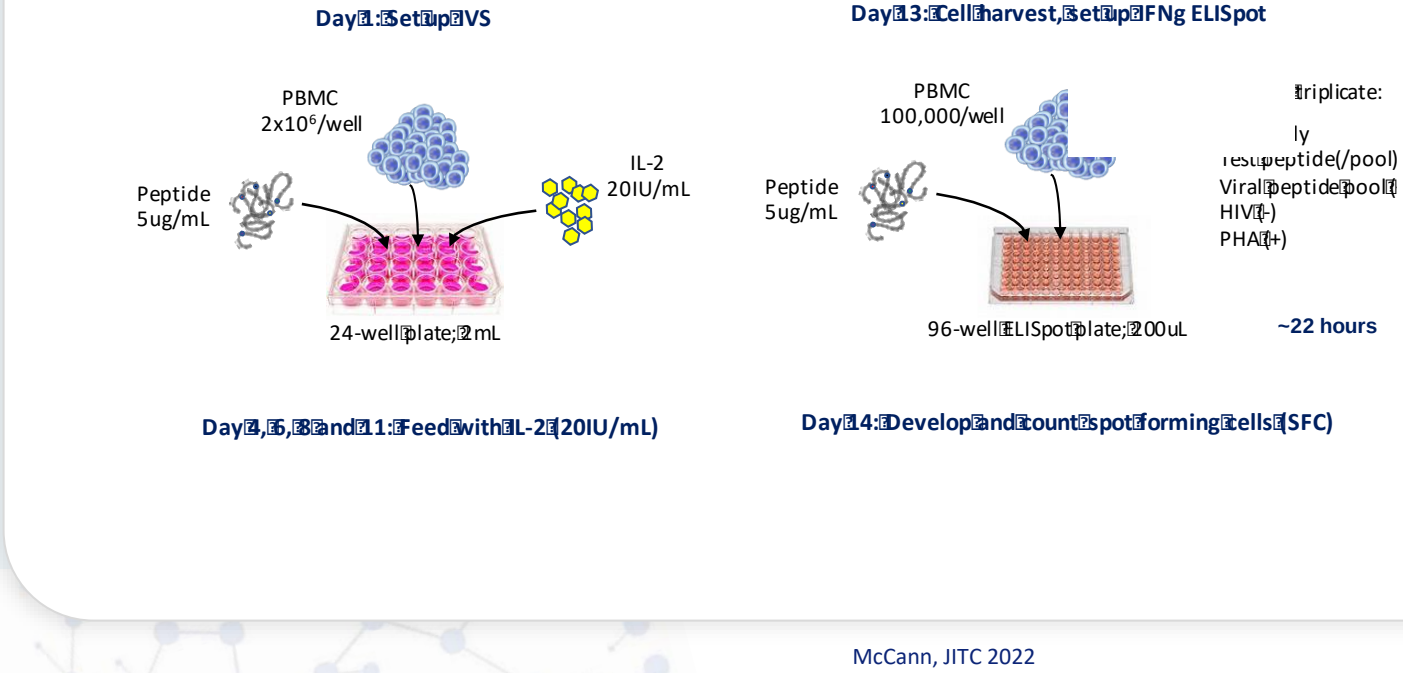
Gene Symbol	Entrez Gene Name	Somatic Mutation		Effect	Subcellular Localisation	GO Biological process
		bp	AA			
COG2	Component of oligomeric golgi complex 2	c.257T>C	p.Leu86Ser	Missense	G, C	Protein transport
HIPK3	Homeodomain interacting protein kinase 3	c.83T>C	p.Val28Ala	Missense	N, C	Transcription; Transcription regulation; Apoptosis
ARFGAP2	ADP ribosylation factor GTPase activating protein 2	c.14C>G	p.Pro5Arg	Missense	PM, G, C	Protein transport; ER-Golgi transport
POC1B	POC1 centriolar protein B	c.29G>A	p.Arg10Lys	Missense	CS	Cell proliferation; Cilium biogenesis/degradation
NOL3	Nucleolar protein 3	c.23C>T	p.Pro8Leu	Missense	N, C, M	Apoptosis; mRNA processing; mRNA splicing
MED1	Mediator complex subunit 1	c.2099C>A	p.Pro700Gln	Missense	N	Transcription; Transcription regulation
ADAT3	Adenosine deaminase, tRNA specific 3	c.832C>G	p.Leu278Val	Missense	N	tRNA processing
KEAP1	Kelch like ECH associated protein 1	c.1824delC	p.Val608fs	Frameshift	N, C, CS	Transcription; Transcription regulation; Ubl conjugation pathway
ZNF429	Zinc finger protein 429	c.220C>A	p.Pro74Thr	Missense	N	Transcription; Transcription regulation
PIH1D1	PIH1 domain containing 1	c.459G>A	p.Met153Ile	Missense	N	Transcription; Transcription regulation
PTOV1	PTOV1, extended AT-hook containing adaptor protein	c.47C>T	p.Ser16Leu	Missense	N, PM	Transcription; Transcription regulation
NIF3L1	NGG1 interacting factor 3 like 1	c.344G>T	p.Arg115Leu	Missense	N, M	Transcription; Transcription regulation; Neuron differentiation
MAFF	MAFF bZIP transcription factor F	c.98C>T	p.Ser33Leu	Missense	N, M	Transcription; Transcription regulation; Stress response
FBLN1 *	Fibulin 1	c.213G>T	p.Met71Ile	Missense	E	Host-virus interaction
NAALADL2	N-acetylated alpha-linked acidic dipeptidase like 2	c.64G>A	p.Asp22Asn	Missense	PM	Carboxypeptidase; Dipeptidase; Hydrolase; Metalloprotease; Protease
KIAA0408 *	KIAA0408	c.2063G>A	p.Arg688Gln	Missense	Unknown	Uncharacterised
MAMDC4	MAM domain containing 4	c.1486G>C	p.Glu496Gln	Missense	PM, N, E	Protein transport
PHF8	PHD finger protein 8	c.115G>C	p.Glu39Gln	Missense	N	Cell cycle; Transcription; Transcription regulator

C, Cytosol; CS, Cytoskeleton; E, Extracellular space; G, Golgi apparatus; M, Mitochondrion; N, Nucleus; PM, Plasma membrane

Immunogenicity Testing in Autologous Setting

TCR rescue,
sequences reproduced in:

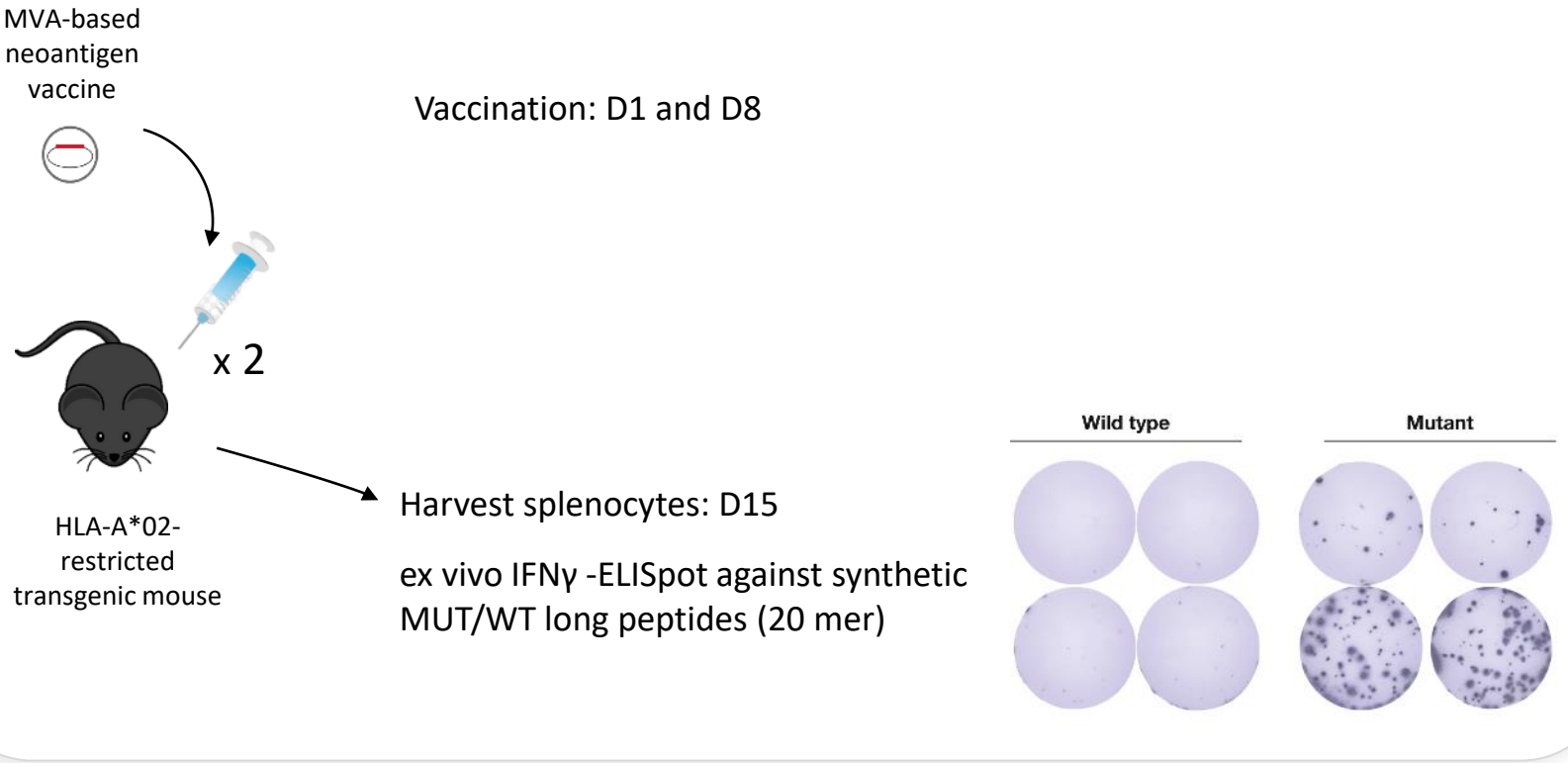
- Circulating T cells
- In the tumor
- In the metastasis
- CD4+ and CD8+ T cells



McCann, JITC 2022

Immunogenicity Testing in HHD Model

MVA-based vaccine incorporating **18 mutated gene sequences** tested in the human HLA-A*02-restricted transgenic mouse model (HHD)



Improving on ‘State of the Art’

CURRENT STANDARD

Enough of the right kind of cells

Anti-PD1 solves
the cancer problem

EXCEEDING STATE OF THE ART

**Training more
of the right cells**

TG4050 – Clinical Translation of Exemplar Data

Aim:

- To establish the relevance of cancer vaccines
- To demonstrate the power of neo-epitope vaccines

Choose optimized setting

- Minimal immunosuppression
- High unmet clinical need
  - To prevent relapse in high-risk patients
  - At relapse tx is by and large palliative

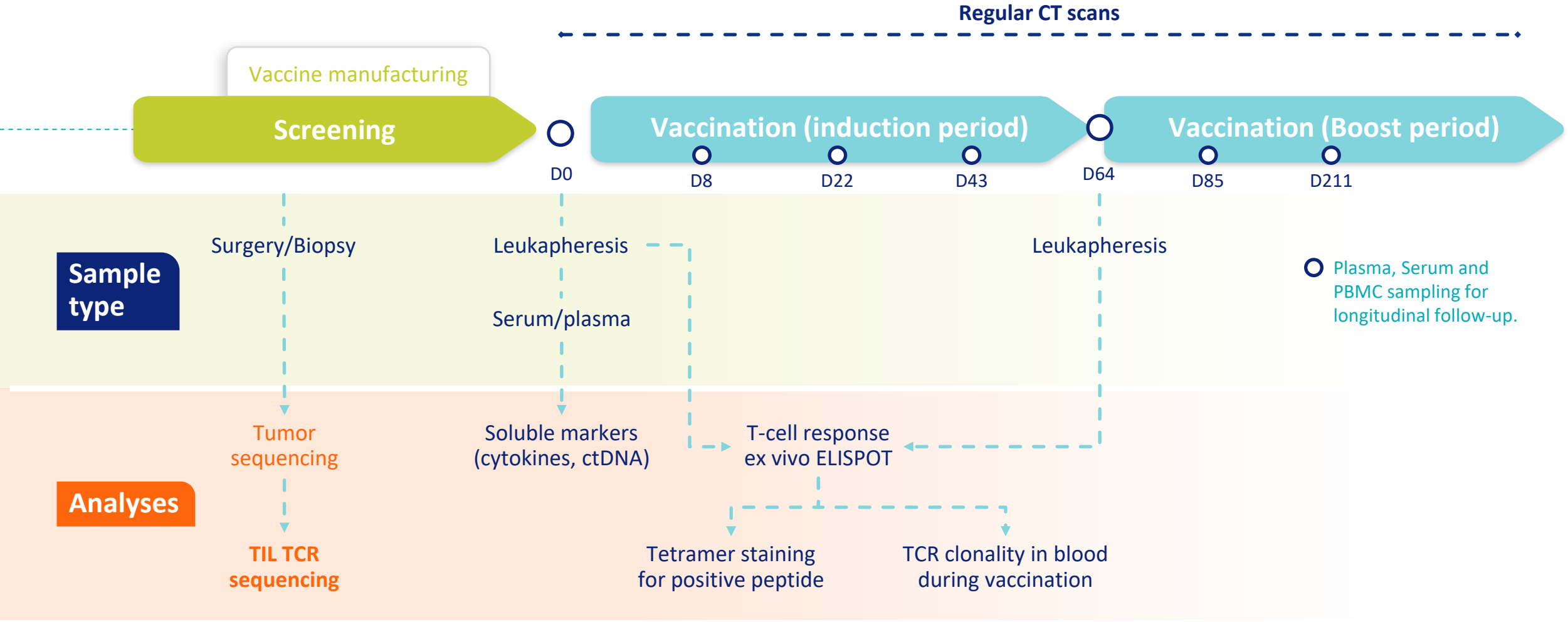
Evaluate clinical impact

- Safety
- Feasibility
- Benefit
- Option to measure impact on measurable disease

Compare immunogenicity to proof-of-concept data

An Extensive Immunomonitoring Program in the two TG4050 Clinical Trials

Sampling and analyses plan – Document immune cell responses



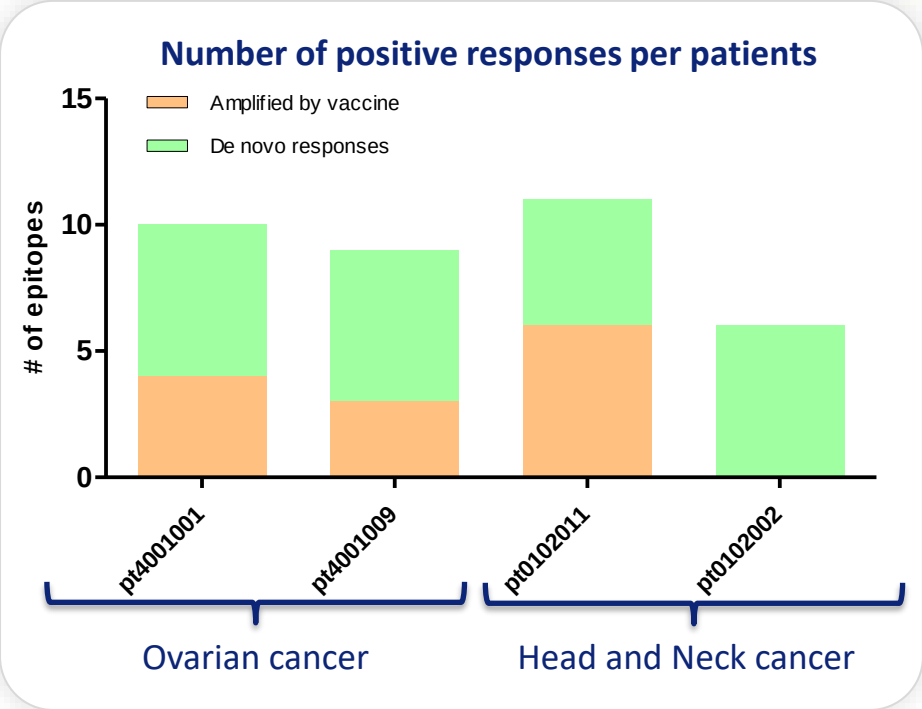
Unprecedented Rate of T Cell Response Against Tumor Specific Epitopes

Profound Remodeling of Immune Cells Consistent with Anti Tumor Response

Induction of multiple T cell responses in treated patient

Differentiation of **CD4 and CD8 into effector cells** are consistent with the **development of an active adaptive response**

NK cells phenotype suggests **ongoing antitumor activity**

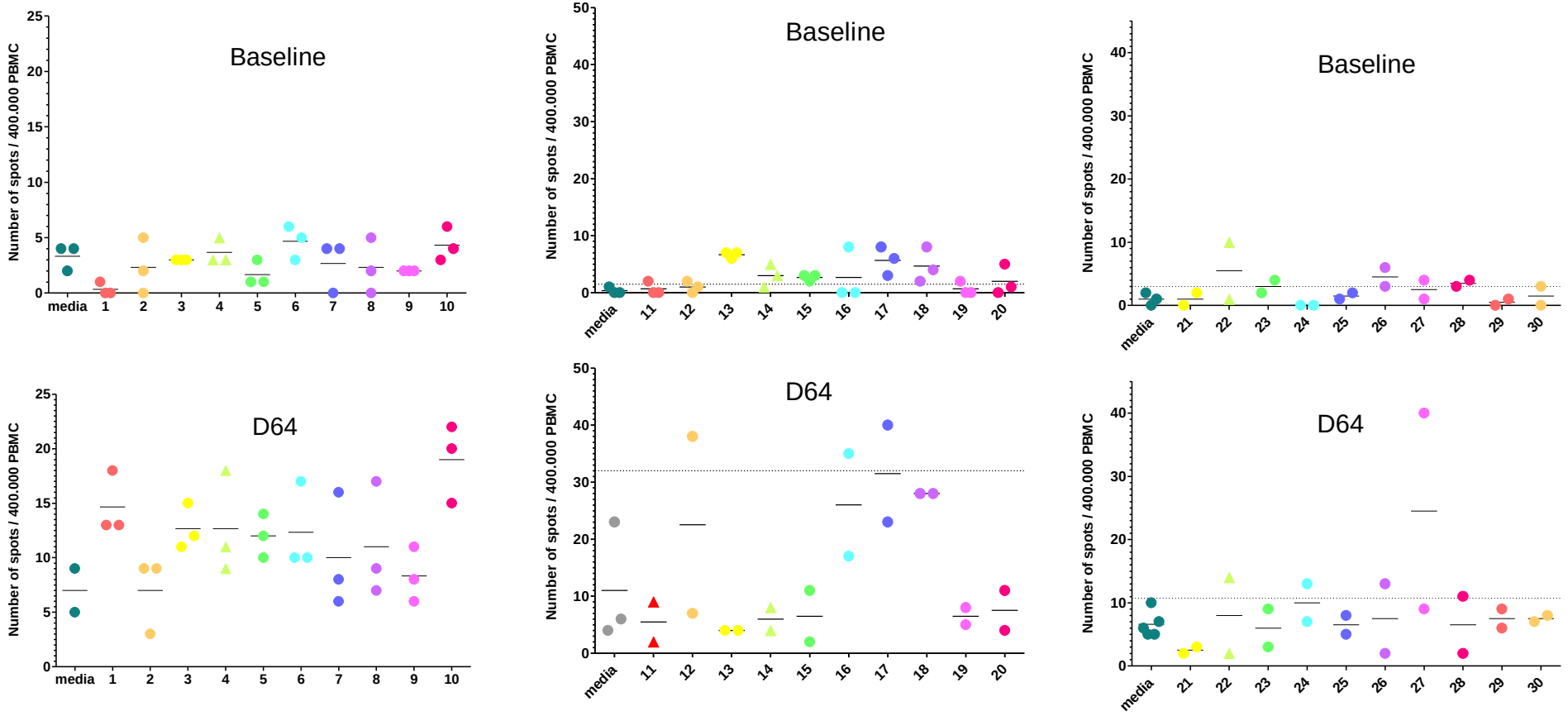


Responses were either **amplification of pre-existing responses or *de novo* responses** induced during vaccination

Responses were observed for all subjects with a **median of 10 positive responses** per patient, out of 30

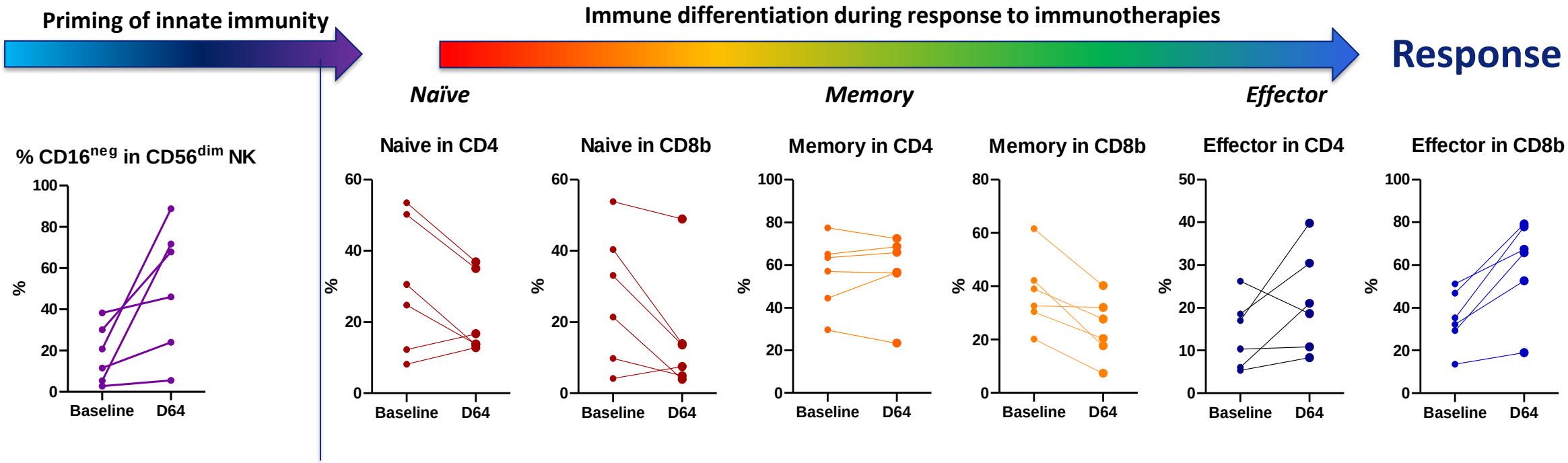
TG4050 Induces Broad and Specific T Cell Responses

PATIENT #1 - **OVARIAN CANCER TRIAL**



Profound Remodelling of Immune Cells consistent with Anti Tumor Response

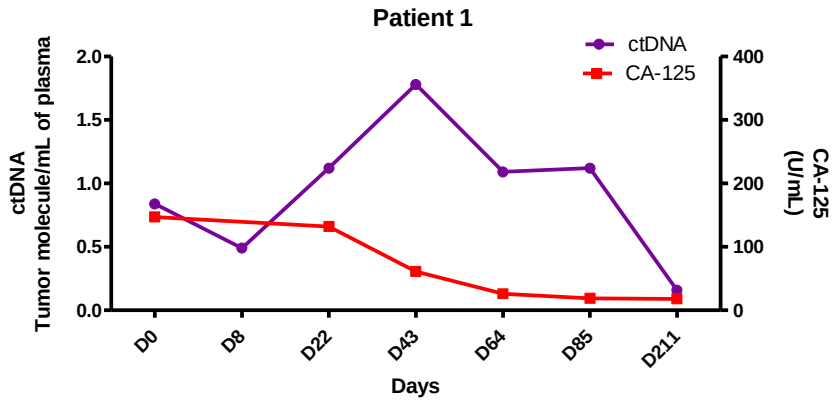
Suggesting that the Vaccine is Able to Effectively Prime the Immune System

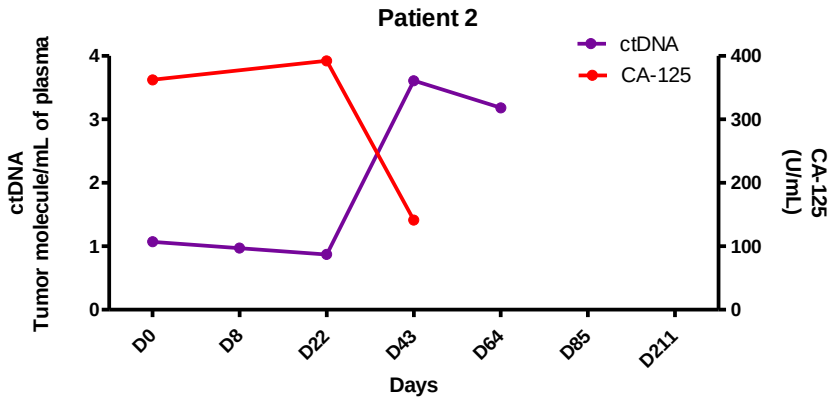


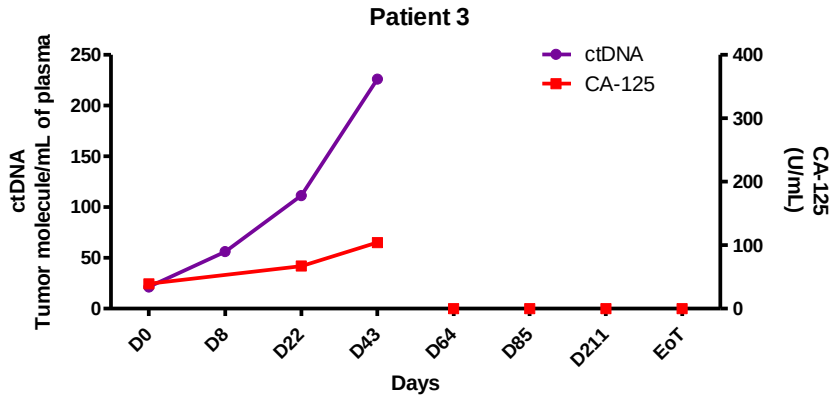
- CD27 and CD45 staining shows a **decrease in naive and memory CD4 and CD8 T-cell** over treatment
- **Effector subgroups of CD4 and CD8 T-cells are increased** at D64
- Maturation and differentiation of CD4 and CD8 into effector cells are consistent with the **development of an active adaptive response**
- Loss of CD16 on $CD56^{dim}$ NK cells suggests **ongoing antitumor activity**

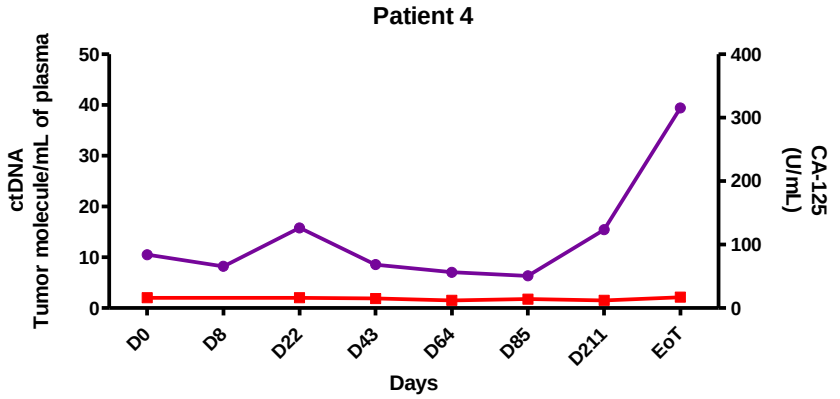
transgene

ctDNA changes are Consistent with Changes in CA-125 and Clinical Outcome







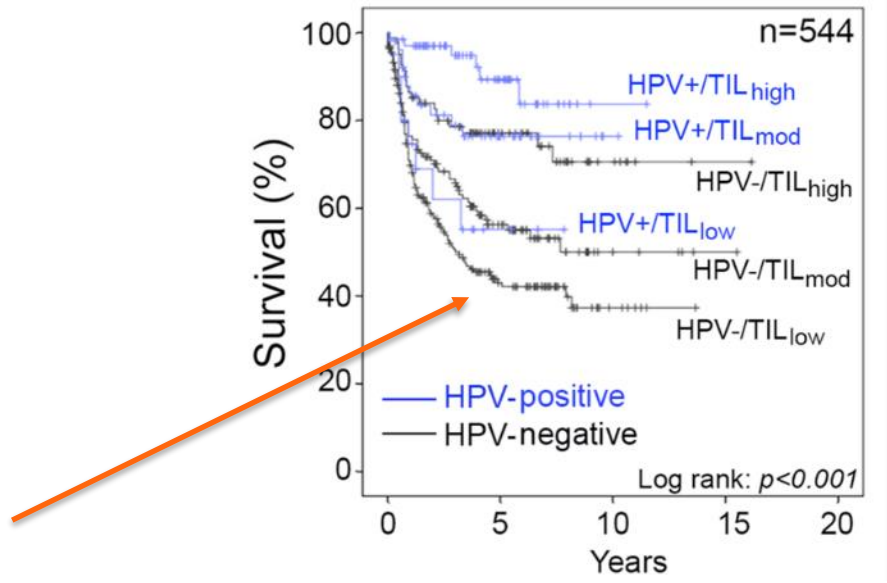


A Large Clinical Need:

HPV negative patients

- Enriched for TIL low
- (clinically ‘self declared’)
- High stage, nodal involvement, ECS

- The bad end of ‘immune cell low cancers’
- Expected median PFS ~1 year



TG4050 | HPV-Negative Head and Neck Cancer Trial after Surgery and Adjuvant Therapy

TG4050 is designed to **INCREASE** and **EXTEND REMISSION** period

Randomized Phase I Trial in **30 Patients** (NCT04183166)

Inclusions completed **Sept. 2022**

Surgery + Adjuvant chemoradiotherapy

Complete Clinical Response (approx. 90%)
RANDOMIZATION

Arm **A**

myvac **TG4050** (single agent) Repeated injections

myvac **TG4050 + SOC** (incl. checkpoint blockers)

Recurrence

Recurrence
12-month PFS is approx. 60% (w/o TG4050) [1]

Patient monitoring (no treatment)

myvac **TG4050 + SOC** (incl. checkpoint blockers)

Arm **B**

LEAD INVESTIGATOR: Pr. Christian Ottensmeier,
Clatterbridge Cancer Care Center, Liverpool

NHS The Clatterbridge Cancer Centre NHS Foundation Trust

institutCurie

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

MAYO CLINIC

transgene

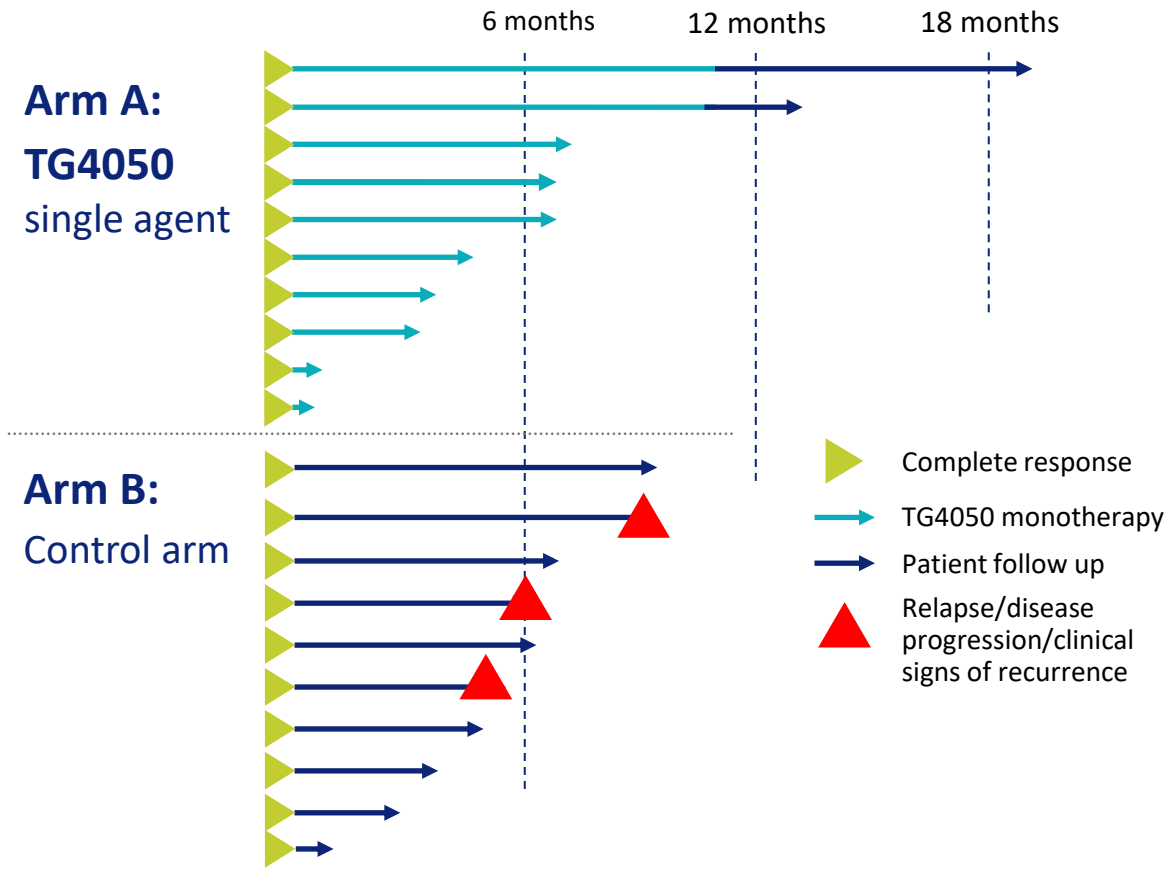
[1] Source: Bernier et al, The Oncologist,3005,10,215

Update on Extremely Promising First Signals of Clinical Activity

Repeated Injections of single agent TG4050 in patients with minimal residual disease

Head & Neck Cancer Trial

At end of August 2022



No related SAEs
Good safety profile

All 10 treated patients are stable

3 patients of the "control" arm have relapsed

Trial fully enrolled

20 patients randomized at cut off date

Effector T cells are a ‘conditio sine qua non’ for immunotherapy

CHECKPOINT INHIBITORS

- benefit a small percentage of patients
- ‘Awaken’ or ‘release’ pre-existing T cells
- Fail if there are not enough T cells
- Beyond aPD1: other targets small incremental effect

CANCER VACCINES

- The only tool to ‘train’ anti cancer T cells
- Will form the backbone of cancer immunotherapy of the future

TG4050

Combines all key features to deliver clinical efficacy

- MVA backbone
  - Immunogenic
  - Well-tolerated
- Neoantigens targeting:
  - Induce specific T cells
  - Clinically feasible

TG4050 trials

encompass decades of adaptive learning

- Optimized clinical setting to **demonstrate efficacy**
- **Randomized, multi center trial** reduces or eliminates selection bias

ASTOUNDING EFFECT in early data:

- Safe
- Immunogenic
- Early data support CLINICAL BENEFIT

Small sample size suggests LARGE EFFECT

SMART DESIGN:

We will be able to **quantify the impact on measurable disease**
HNSCC trial: at recurrence in arm B

Ovarian trial
Carefully designed **biomarker program** to **demonstrate MOA**

Outlook

Poised to deliver a landmark change

- **By demonstrating**
  - Clinical benefit of a cancer vaccine
  - Efficacy of MVA based vaccination
- **By enabling:**
  - Definiton of the ‘optimal patient setting’
  - Rational development of TG4050
    - Biomarker programme:
      - Immunologically based choice of combinatorial approaches
      - Extension to other tumor types and setting

And most importantly:

- **Offer hope to patients with terrible and fatal cancers**

Personalized Therapeutic Vaccine in the Treatment of Ovarian Cancer

MATTHEW S. BLOCK, MD, PhD

Immunologist and medical oncologist at the Mayo Clinic

Associate Professor of oncology

MAYO CLINIC

transgene

Investigator Interests

The focus of my research is to **better understand the mechanisms by which cancers interact with the immune system** and avoid immune-mediated detection and eradication.

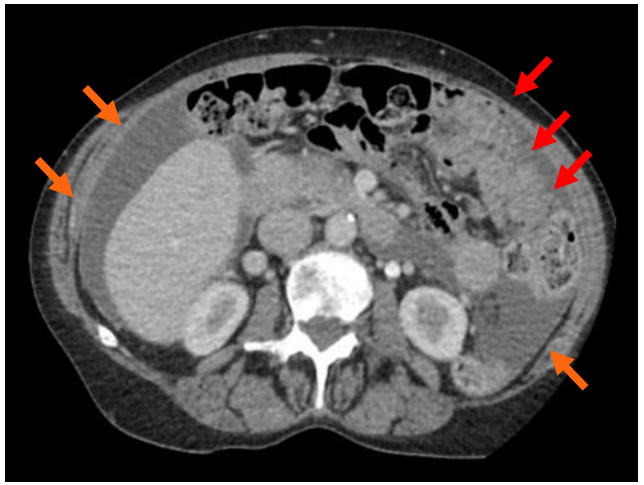
I study therapeutic vaccines and oncolytic viruses as approaches to **induce anti-tumor immune responses**, and I study immune **checkpoint inhibitor combinations** as a means to potentiate anti-tumor immune responses.

As a **medical oncologist, I treat patients** with **gynecologic cancers and patients with melanoma.**

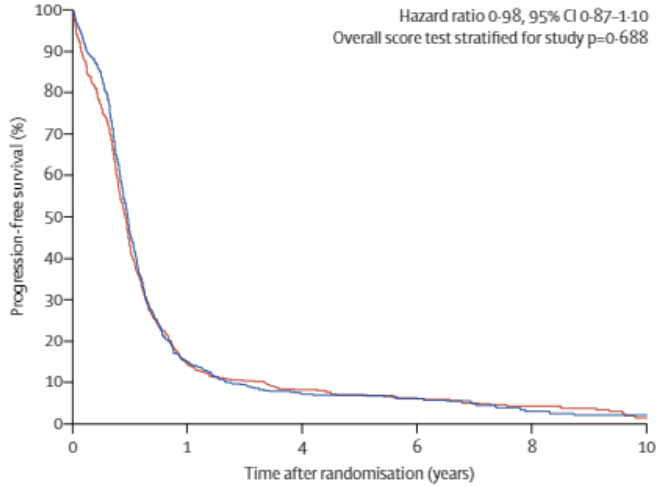
The Need For Better Treatments For Ovarian Cancer

- **Ovarian cancer is most often diagnosed at Stage III or Stage IV**, as early-stage disease is typically asymptomatic, and there is no effective screening test.
- Those **patients fit for aggressive treatment** receive cytoreductive surgery and chemotherapy with paclitaxel and carboplatin.

- Remission is common after treatment, but **cures are rare**.
- Due to its high recurrence rate, **ovarian cancer is the most lethal**.



Progression-free survival of patients with Stage III-IV ovarian cancer

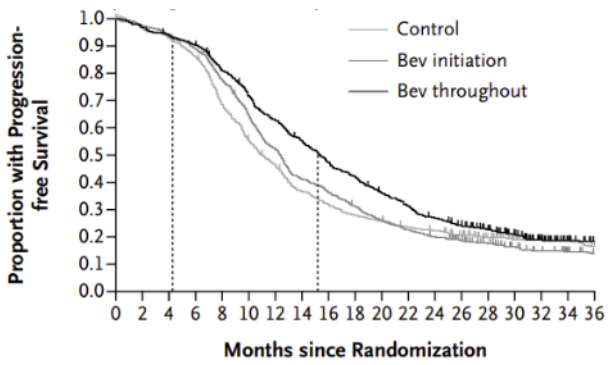


Vergote, *et. al., Lancet Oncol*, 2018

Maintenance Therapies For Ovarian Cancer

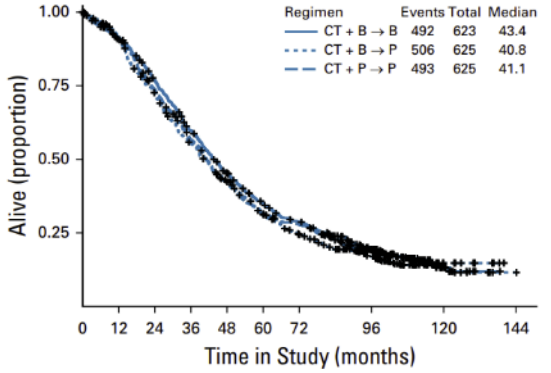
- Due to the **high recurrence rate of ovarian cancer**, **maintenance therapies** after first-line chemotherapy are commonly tried.
- **Bevacizumab (anti-VEGF) is approved** for use based on an improvement in progression-free survival, but **no overall survival benefit has been demonstrated**.
- **PARP inhibitors** have also led to improved progression-free survival.
- **Benefit from PARP inhibitors is most pronounced in patients with germline or somatic BRCA mutations**, while benefit is moderate in BRCAwt patients with homologous recombination deficiency (HRD) and marginal in patients without HRD.

Bevacizumab—PFS



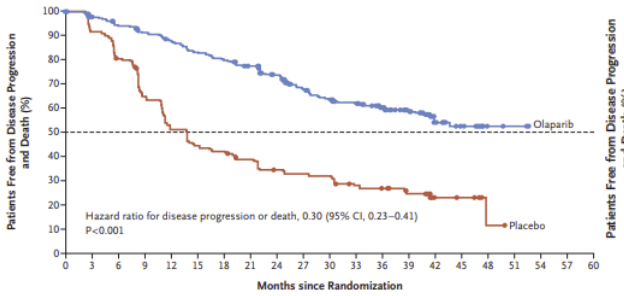
Burger, *et. al., NEJM*, 2011

Bevacizumab—OS



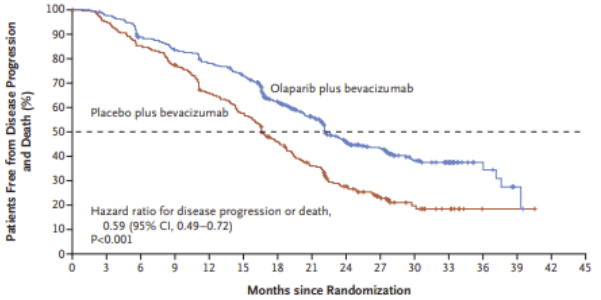
Tewari, *et. al., J Clin Oncol*, 2019

Olaparib—PFS—BRCAm



Moore, *et. al., NEJM*, 2018

Olaparib + Bev—PFS



Ray-Coquard, *et. al., NEJM*, 2019

Table 2. Improvement in disease-free survival in randomized placebo-controlled Phase III trials on PARP inhibitor use in epithelial ovarian cancer, by individual PARP inhibitors, BRCA mutation status, and tumor HRD status.

Indication	Trial (drug)	*BRCA*-mutated	*BRCA* wild-type, HRD[a]-positive	*BRCA* wild-type, HRD[a]-negative
Frontline maintenance	SOLO-1[1] (olaparib)	36 months[a]	N/A[b]	N/A[b]
	PRIMA[2] (niraparib)	11.2 months	11.4 months	2.7 months
Recurrent maintenance	SOLO-2[3] (olaparib)	13.6 months	N/A[b]	N/A[b]
	ARIEL-3[4] (rucaparib)	11.2 months	5.5 months	2.9 months
	NOVA[5] (niraparib)	15.5 months	9.1 months	3.1 months

Value in months calculated as the median disease-free survival in patients treated with PARP inhibitor minus median disease-free survival in patients receiving placebo.

[a]Median disease-free survival not yet reached in the olaparib group. Benefit listed is estimated from a sensitivity analysis.

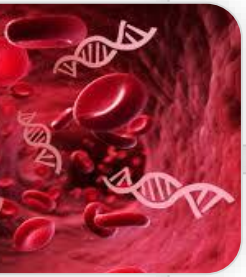
[b]Patients without *BRCA* mutated cancers were excluded from these studies.

Abbreviation: HRD = homologous recombination deficient. Numerical references to be found online.

Taylor, *et. al., Con OB/GYN*, 2020

transgene

Detecting Residual/Recurrent Disease in Ovarian Cancer



CA 125
(the secreted portion of MUC-16)

- **has long been used** as a tumor marker for ovarian cancer
- **increases** to > 2 x ULN about **3-6 months before** patients develop clinical recurrence

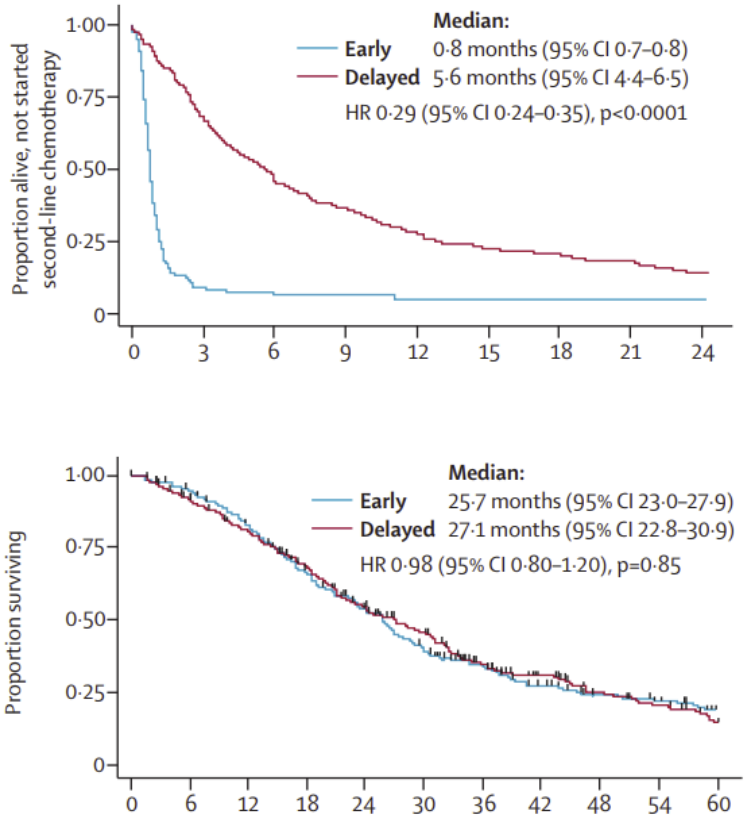
Circulating tumor DNA (ctDNA)

- **can be detected in plasma** from patients by **next generation sequencing** (NGS) or **digital droplet polymerase chain reaction** (ddPCR)
- **In some patients,** this may be **more sensitive than CA 125** for recurrent ovarian cancer.

Early initiation of **cytotoxic chemotherapy** in asymptomatic patients with elevated CA 125 has **not been shown to improve survival.**

However, this may represent a **WINDOW OF OPPORTUNITY FOR VACCINE TREATMENT**.

Onset of 2nd-line chemotherapy



Wang, *et. al., Lancet*, 2010

TG4050 | Ovarian Cancer Trial after Surgery and Adjuvant Chemotherapy

Phase I Trial in up to **13 Patients** (NCT03839524)

TG4050 is designed to **INCREASE** and **EXTEND REMISSION** periods

Complete response

Approx. 80% of patients experience CR with 12-month PFS of approx. 50%[1]

Asymptomatic relapse

(CA-125 increase or small lesions*)

First patient treated in **August 2020**

Inclusions completed **Sept. 2022**

Surgery + Adjuvant Platinum chemotherapy

Clinical remission

myvac

TG4050 (single agent) at first signs of asymptomatic relapse with **repeated injections** until disease progression

LEAD INVESTIGATOR: Matthew S. Block, MD, PhD, Mayo Clinic (Rochester)

MAYO CLINIC

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

Hôpital Pitié-Salpêtrière AP-HP

institutCurie

transgene

[1] Source: Burger et al, *New End J Med*, 2011

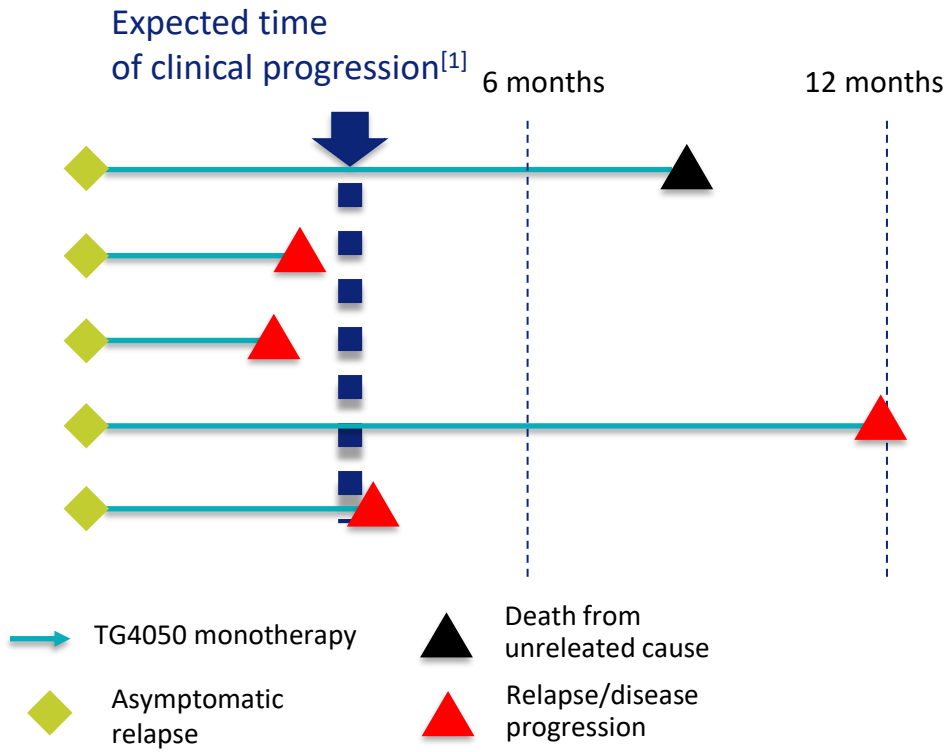
*low volume radiologic disease

AACR Update on Extremely Promising First Signals of Clinical Activity

From Repeated Injections of TG4050 as Monotherapy in Patients with Minimal Residual Disease

Ovarian Cancer Trial

Data updated end of August 2022



One patient with radiologic lesions has been **stable** for **11.4 months** after the first injection.

Another patient treated after an elevation of CA-125 **experienced a normalization of CA-125 without clinical progression for 9 months** until death from an unrelated chronic illness.

[1] Source : Wang et al. "CA-125–indicated asymptomatic relapse confers survival benefit to ovarian cancer patients who underwent secondary cytoreduction surgery", Journal of Ovarian Research, 2013

First Patient Treated with TG4050 in Ovarian Cancer Trial

Normalization of CA-125 and ctDNA without Clinical Progression for 9 Months

73-year-old female

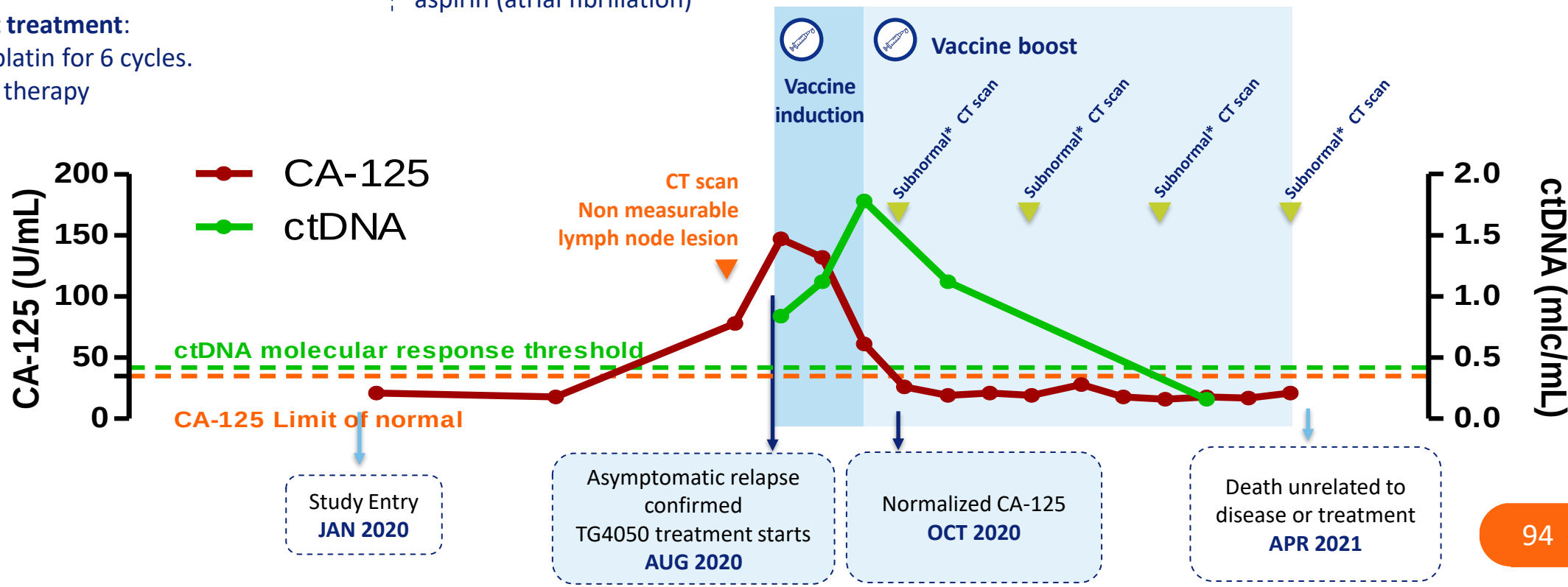
- **Grade IIIC serous carcinoma of the ovary**
- **No BRCA mutation but HRD score >45 and p53 mutation**
- **1st line/adjuvant treatment**: paclitaxel/carboplatin for 6 cycles. No maintenance therapy
- **Moderate TMB**

Relevant medical history and treatments

- Hypertension, paroxysmal atrial fibrillation, aortic valve stenosis, pulmonary embolism, obesity, dyspnea exertional
- Lisinopril, Cardia XT, Metoprolol succinate, furosemide (HTA), aspirin (atrial fibrillation)

2022 ASCO ANNUAL MEETING

Delord *et al*, "Phase 1 studies of personalized neoantigen vaccine TG4050 in ovarian carcinoma (OvC) and head and neck squamous cell carcinoma (HNSCC)" ASCO 2022, June 5, 2022, Poster presentation



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Summary

Asymptomatic patients with evidence of recurrent ovarian cancer (CA 125 or imaging) **do not benefit from immediate initiation of cytotoxic chemotherapy**,
but there is a **window of opportunity to treat these patients with a personalized vaccine**.

Personalized vaccine manufacturing is feasible, requiring approximately four months from the time of study enrollment to treatment.

While the number of patients treated is limited, **early results suggest that the TG4050 personalized vaccine given as monotherapy can delay or even reverse early findings of recurent ovarian cancer**.

MAUD BRANDELY, MD, PhD
Chief Medical Officer
Transgene

Additional data
to be communicated
in **H1 2023**

These **immune and clinical data** will serve to identify the most appropriate path **to take TG4050 to Phase II and forward**

myvac
one patient • one genome • one vaccine

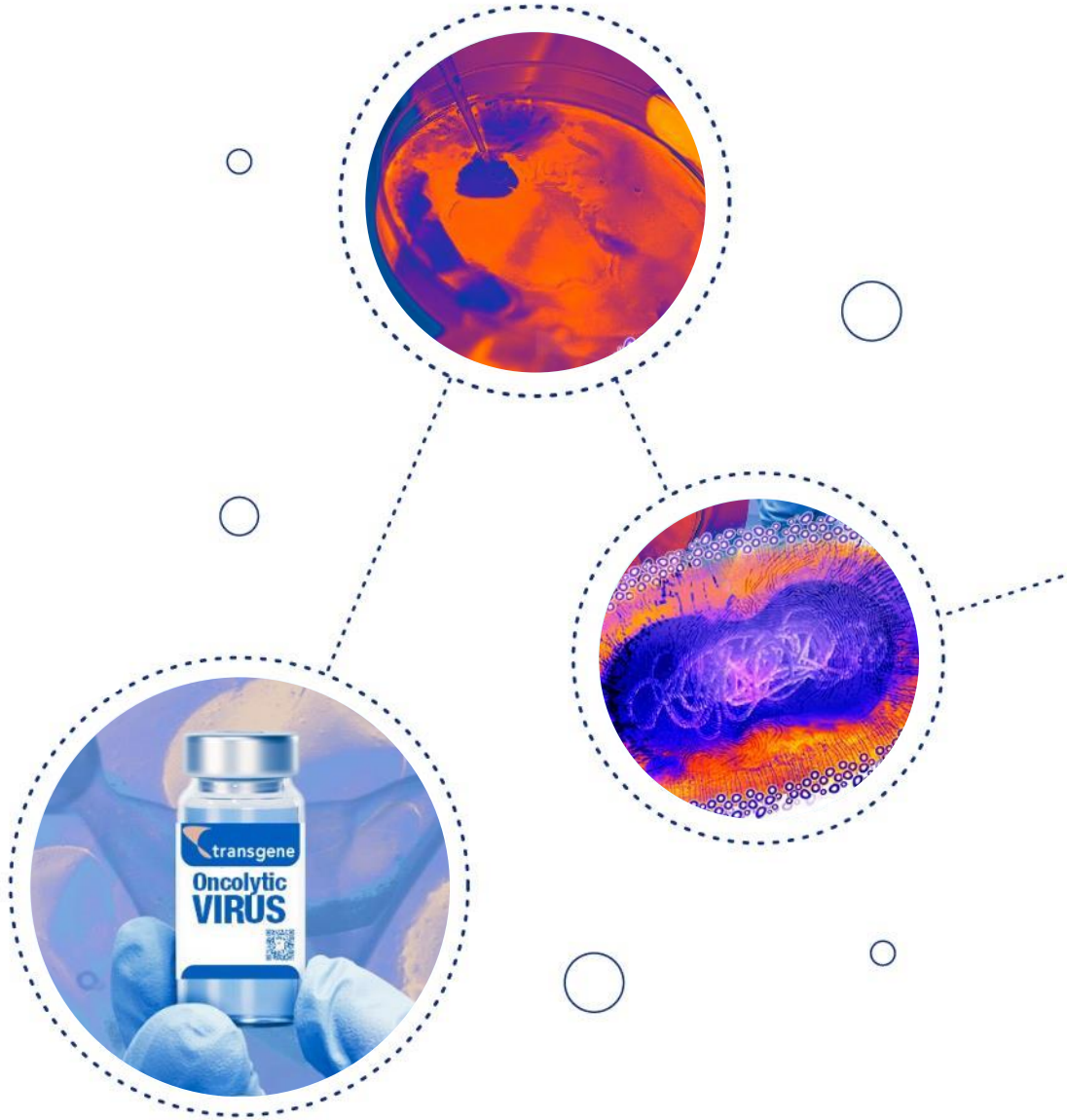
Q & A

BREAK

LET'S MEET AGAIN IN 15 MINUTES
AT 4:15 PM CET

2

Oncolytic viruses (OVS)



ONCOLYTIC VIRUSES

TIME	TOPIC	SPEAKER
4:15 pm – 4:30 pm	Clinical positioning and advantages of poxviruses	*Eric Quéméneur*
4:30 pm – 4:50 pm	Assessing novel routes of administration with TG6002	*Adel Samson*
4:50 pm – 5:05 pm	New Invir.IO™ candidate: an IL-12 Construct	*Eric Quéméneur*
5:05 pm – 5:15 pm	Invir.IO™, a versatile platform enabling multiple collaborations with potential future value	*Steve Bloom*
5:15 pm – 5:25 pm	Wrap up and Q&A	*Eric Quéméneur*

Clinical Positioning and Advantages of Poxviruses

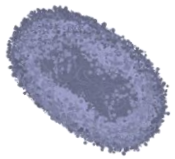
ÉRIC QUÉMÉNEUR, PharmD, PhD
Chief Scientific Officer
Executive VP
Transgene

The Two Families of Viral Vectors-based Immunotherapeutics

Turning foes into friends

Viral-vector vaccine

myvac

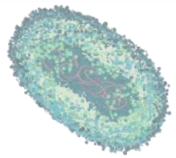


Local induction of immuno-stimulatory pathways

Expression of cancer antigens

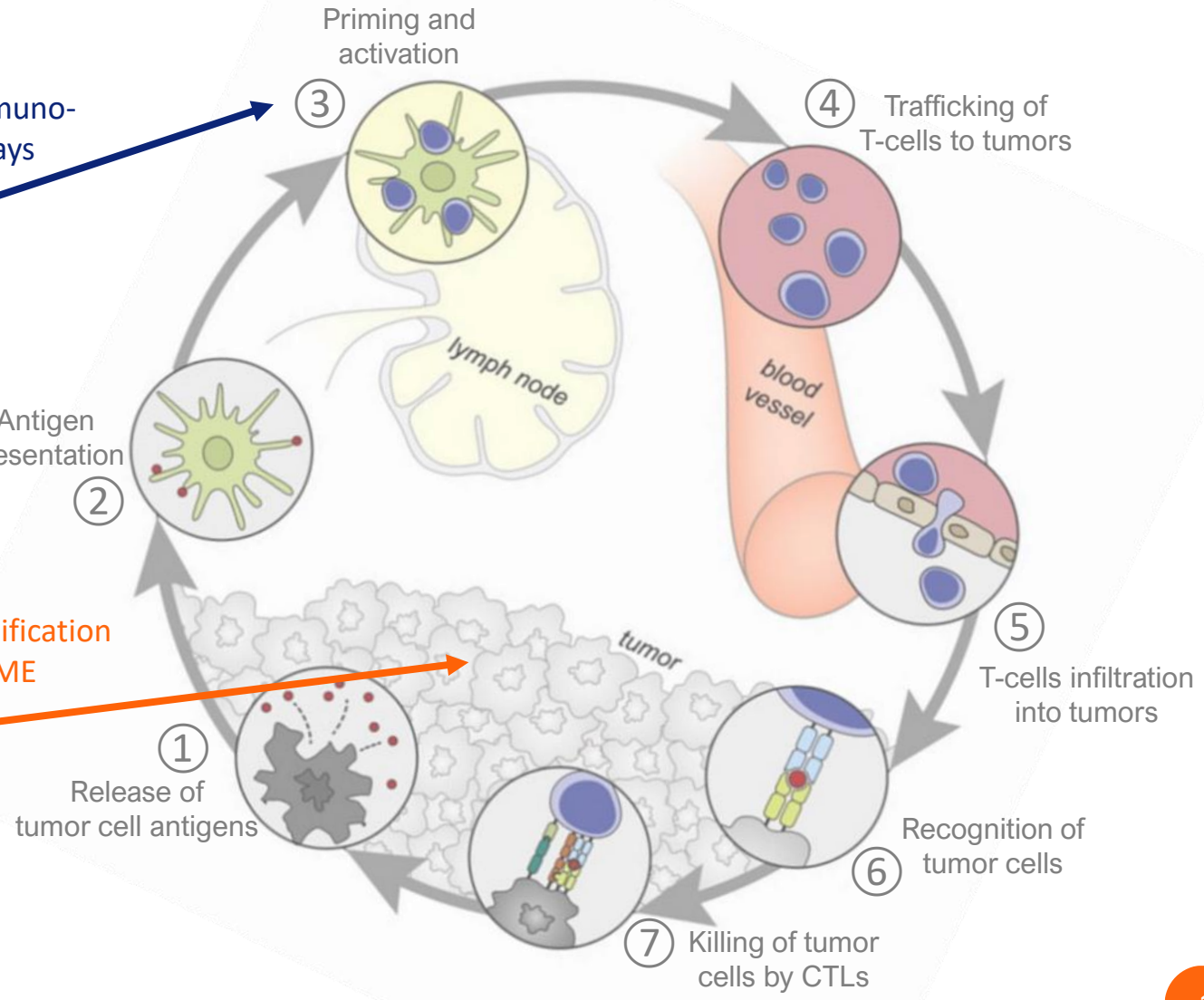
Oncolytic virus

invir io



Targeted modification of the TME

Immunogenic cell death

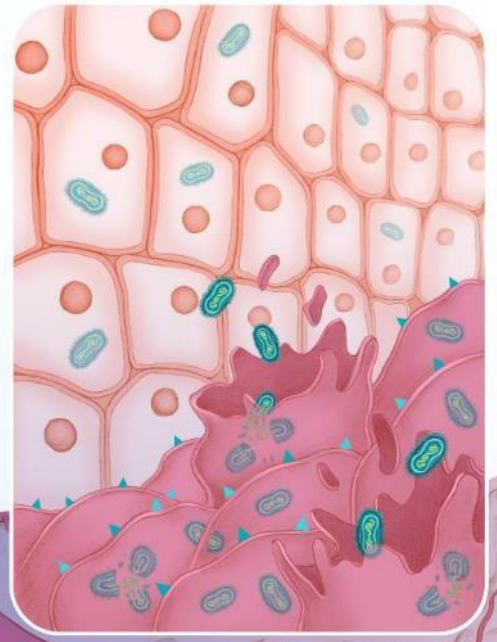


Inspired from Chen and Mellman (2013) *The tumor immunity cycle*

transgene

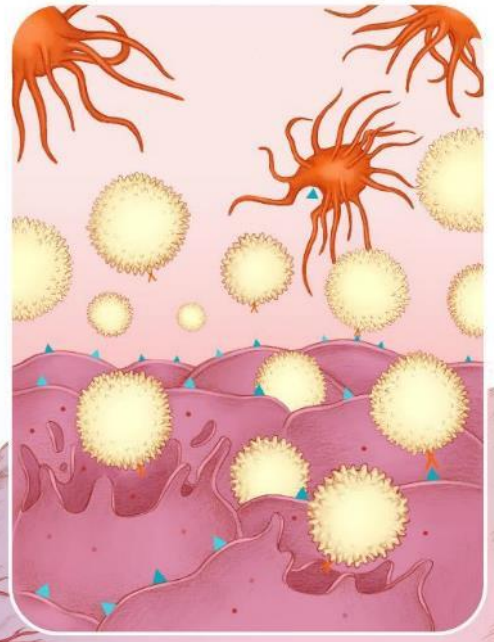
Oncolytic Vectors Combine Multiple Modes of Action in the Tumor Micro-environment

Tumor cell lysis upon viral replication



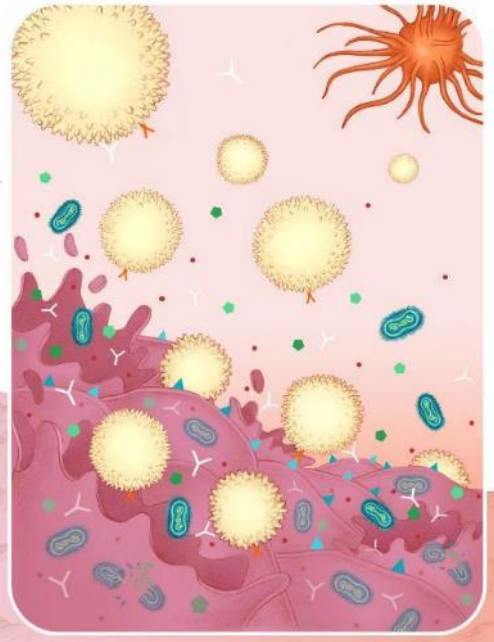
Vaccinia can infect a broad range of tumor cells in a receptor-independent mechanism.
$VV_{cop}TK^{-}RR^{-}$ replicates selectively in tumor cells, not in resting cells.

Triggering of the immune system



Infection stimulates the release of proinflammatory signals and DAMPs (immunogenic cell death), promoting immune cell infiltration and activation.

Local delivery of recombinant payload

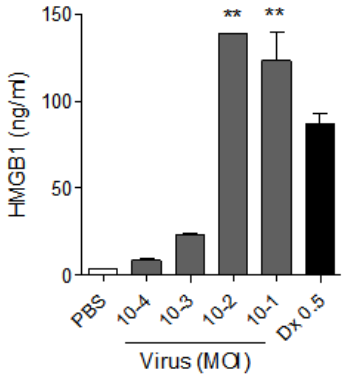


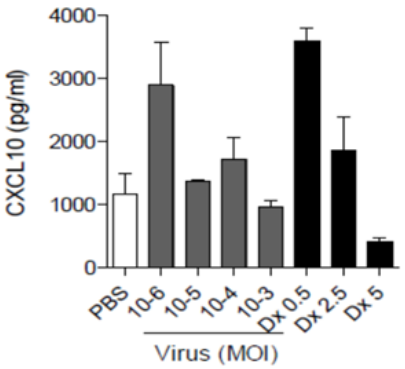
Expression and secretion of recombinant proteins that can directly act in the immuno-suppressed TME and contribute to change its phenotype.

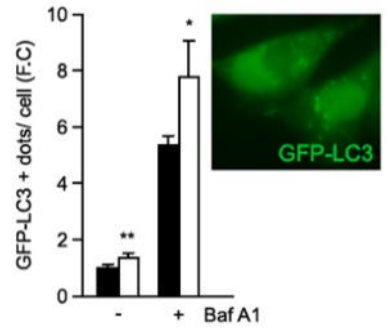
ONCOLYTIC VIROTHERAPY aims at creating a **DYNAMIC SYNERGY** in the **REMODELLING of the TME**

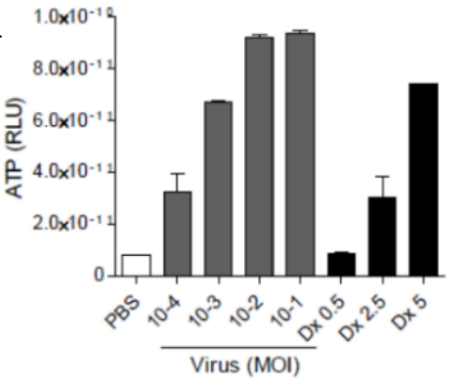
$VV_{cop}TK^{-}RR^{-}$ is a Strong Inducer of Immunogenic Cell Death

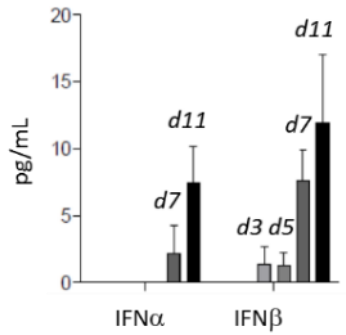
HALLMARKS OF IMMUNOGENIC CELL DEATH





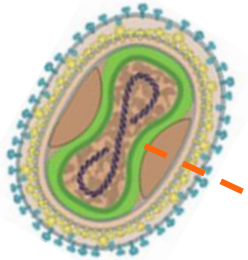




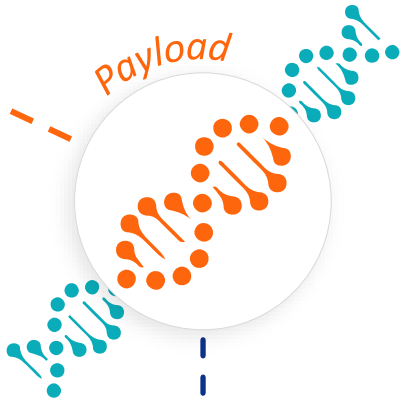


Fend et al. Cancer Research (2017)

Our technological platform for engineering innovative OVs able to address challenging tumors



Targeted insertion of recombinant payload at selected loci in the Vaccinia genome



IMMUNE BOOSTERS

- **Cytokine** (e.g. GM-CSF, interleukins, …)
- **Effector ligands** (e.g. CD40L, Flt3L, …)
- **Growth Factors** (e.g. VEGF)

PRODRUG ACTIVATOR

- *e.g.* targeted chemotherapy with **Fcu1** (TG6002), an enzyme that locally converts 5-FC into 5-FU

IMMUNE MODULATORS

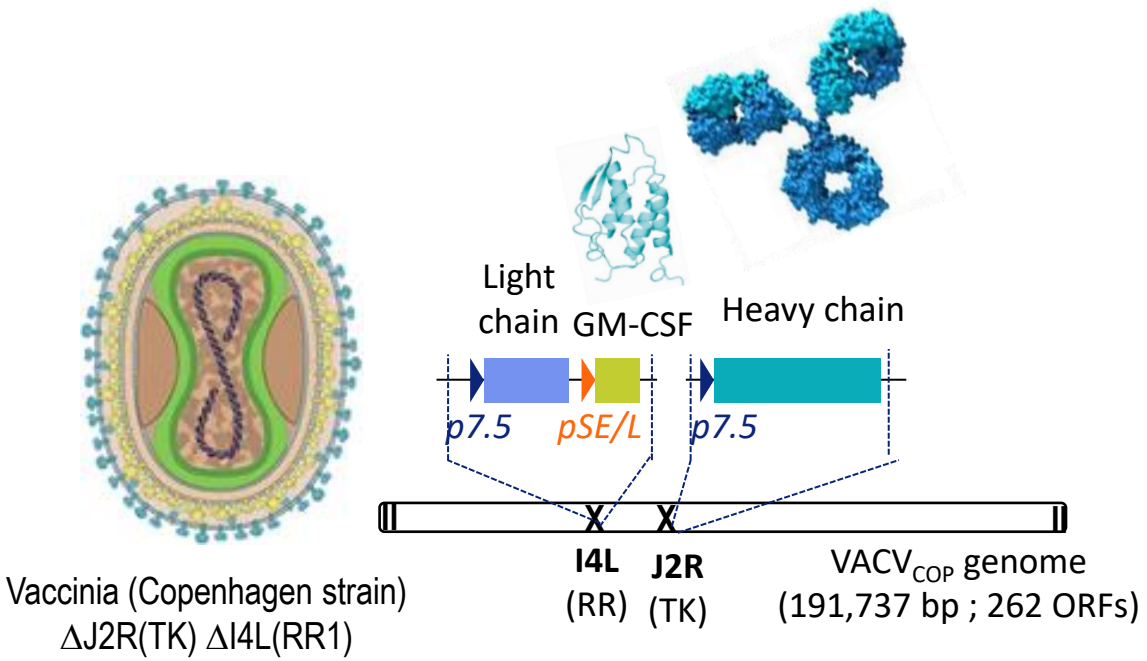
- **Monoclonal antibodies** (full length antibody, scFV, multispecific)
- **Enzymes** controlling immunosuppressive metabolites (e.g. ADA, arginase, tyrosinase)

Several payloads can be encoded in one multi-armed OV

(several permissive loci, up to 20-25 kb capacity)

Multiple payload sourcing approaches

BT-001, a Remarkable Example of the Potential of the Invir.IO™ Platform



4-E03, anti-CTLA-4 antibody

A **first-in-class anti-CTLA4 IgG1** selected from the n-CoDeR®/F.I.R.S.T™ platform at BioInvent for its potential to **deplete intra-tumoral Tregs**, cloned as a full-length antibody for FcγR engagement

GM-CSF

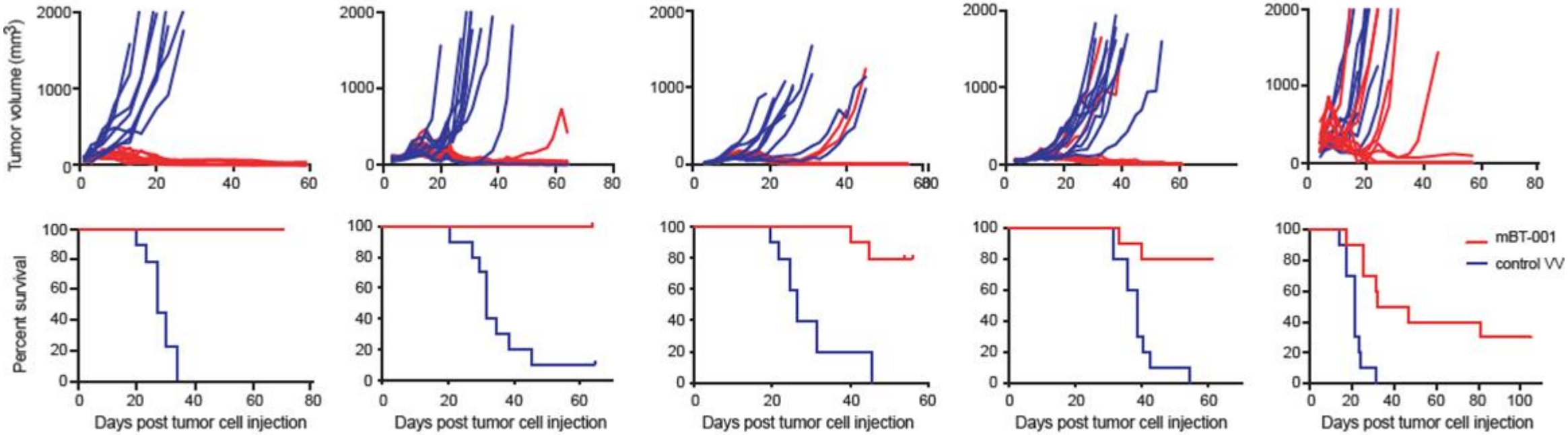
A **pleiotropic cytokine** already used in several OV products in clinic (Imlygic®, Pexa-Vec®, RP1/RP2, etc.). Incorporated into the product to **activate and mature infiltrated monocytes into macrophages and dendritic cells**. It can also promote the proinflammatory phenotype of mature macrophages (M1)

+ **mBT-001**, the product surrogate for preclinical experiments based on the same vector, encoding m5-B07, an IgG2a mAb targeting mouse CTLA-4, and mGM-CSF

mBT-001 Induces Cures Across Various Syngeneic Cancer Models

CT26	A20	EMT6	MC38	B16
Colon carcinoma, Balb/c	B-cell lymphoma, Balb/c	Breast carcinoma, Balb/c	Colon carcinoma, C57BL/6	Melanoma, C57BL/6

Hot tumor — Cold tumor

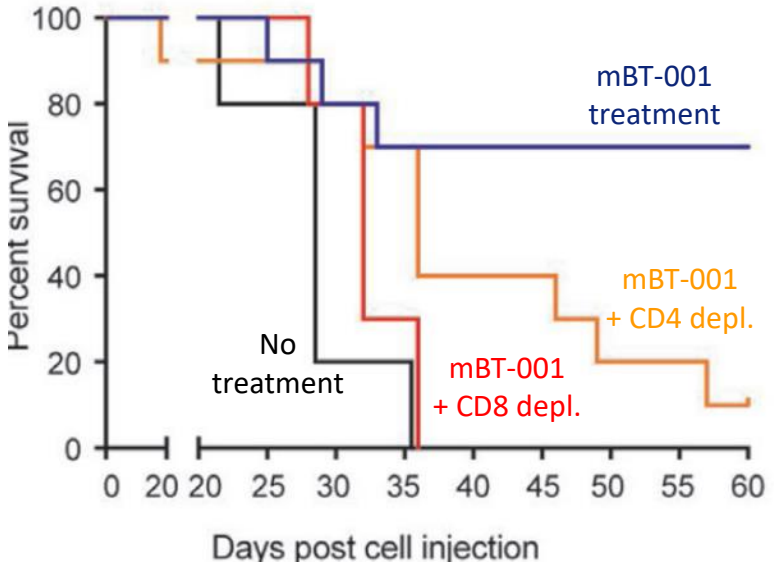


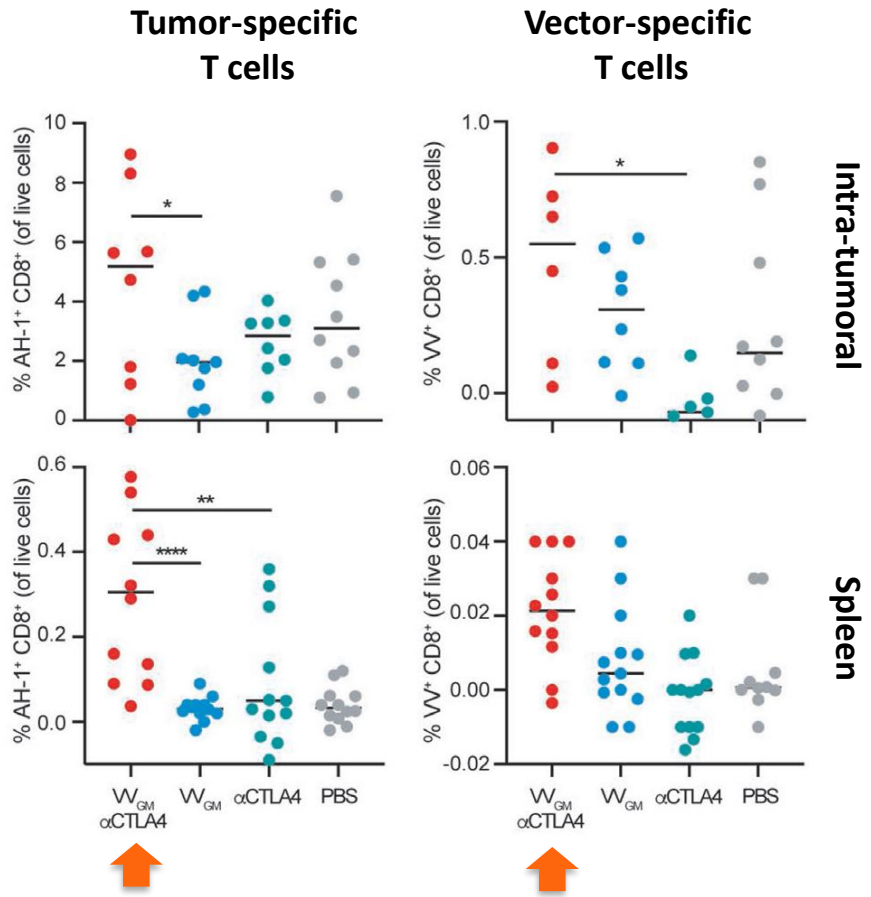
Treated / untreated with mBT-001
Treatment schedule: 3 IT administrations of 10^7 pfu

Semmrich et al. J Immunother Cancer 2022;10:e003488.

mBT-001 Elicits a Robust Systemic CD8+ T Cell-Dependent Anti-Tumor Immunity

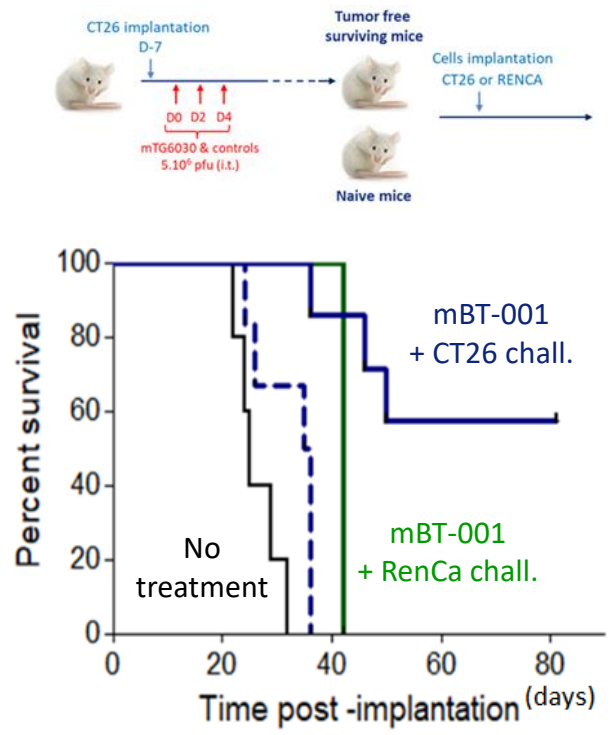
CT26 in BALB/c model





Induction of memory response

Rechallenge experiment



Semmrich et al. J Immunother Cancer 2022;10:e003488.

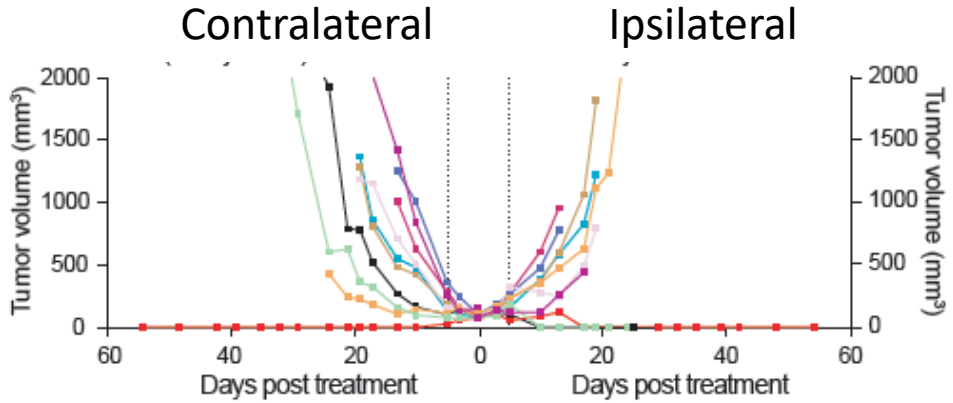
Systemic CD8+ T Cell Immunity Translates into Abscopal Response

i.t. injection

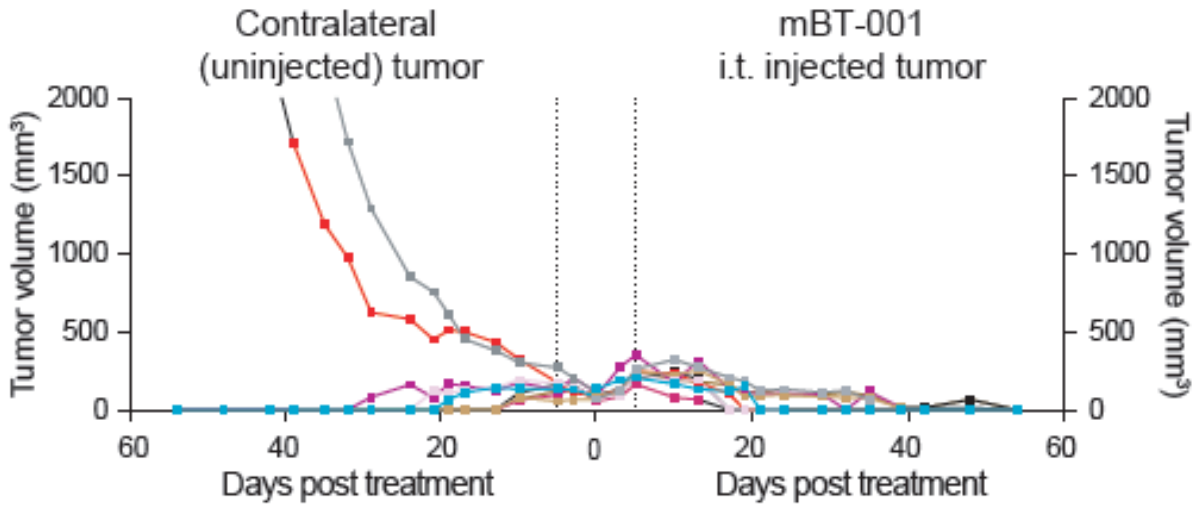
CT26

CT26 in BALB/c syngenic model

No treatment



Treatment with mBT-001

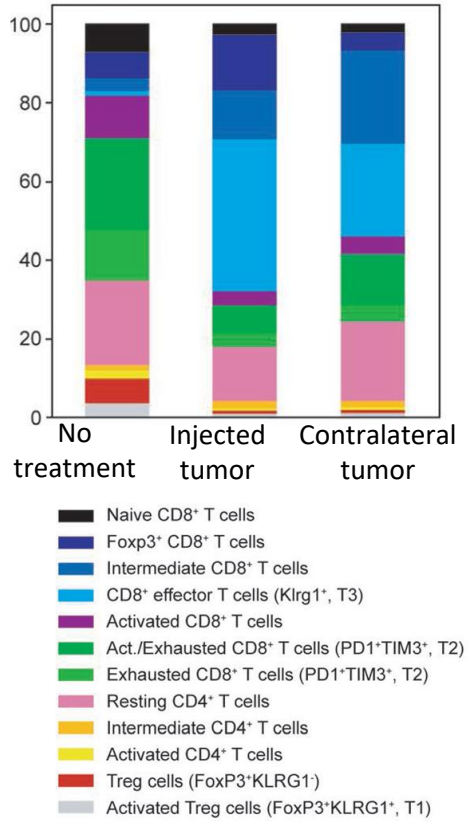


Large remodeling of TME

↑ effector CD8⁺ T cel

↓ exhausted CD8+ T cells

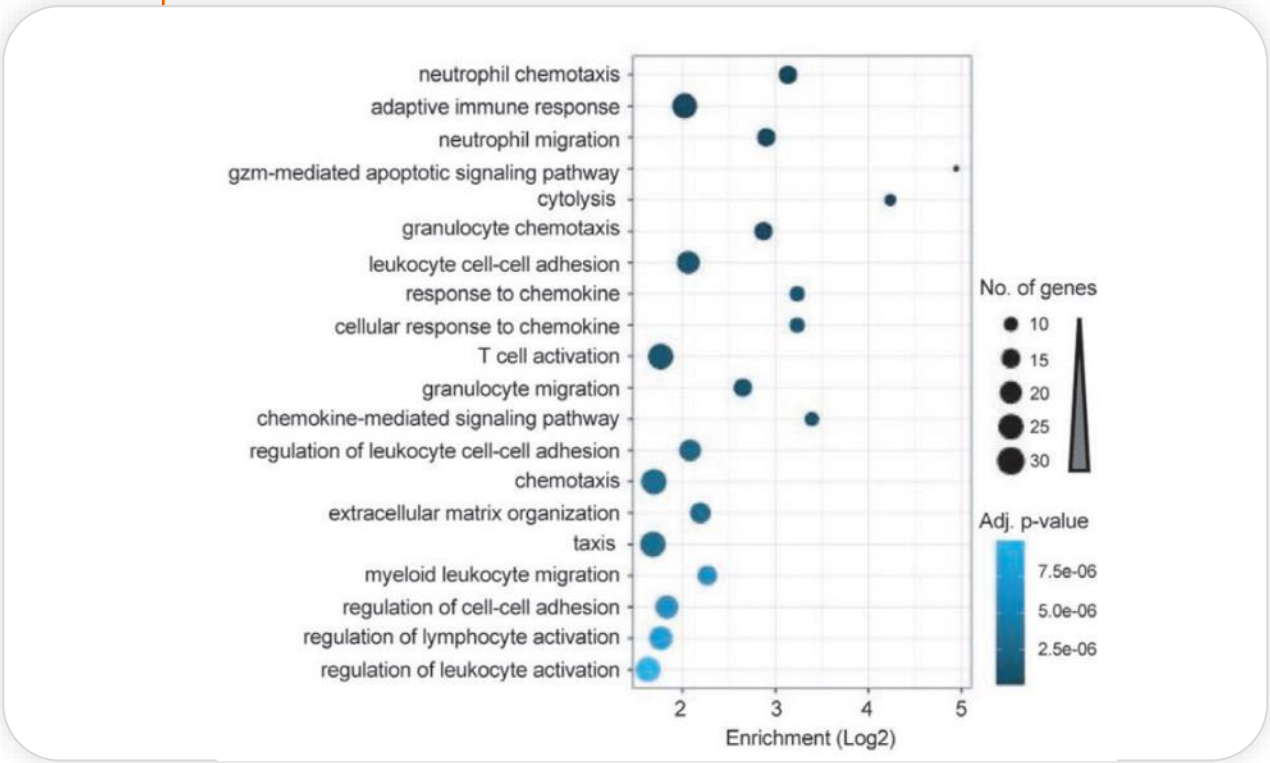
↓ intratumoral Tregs



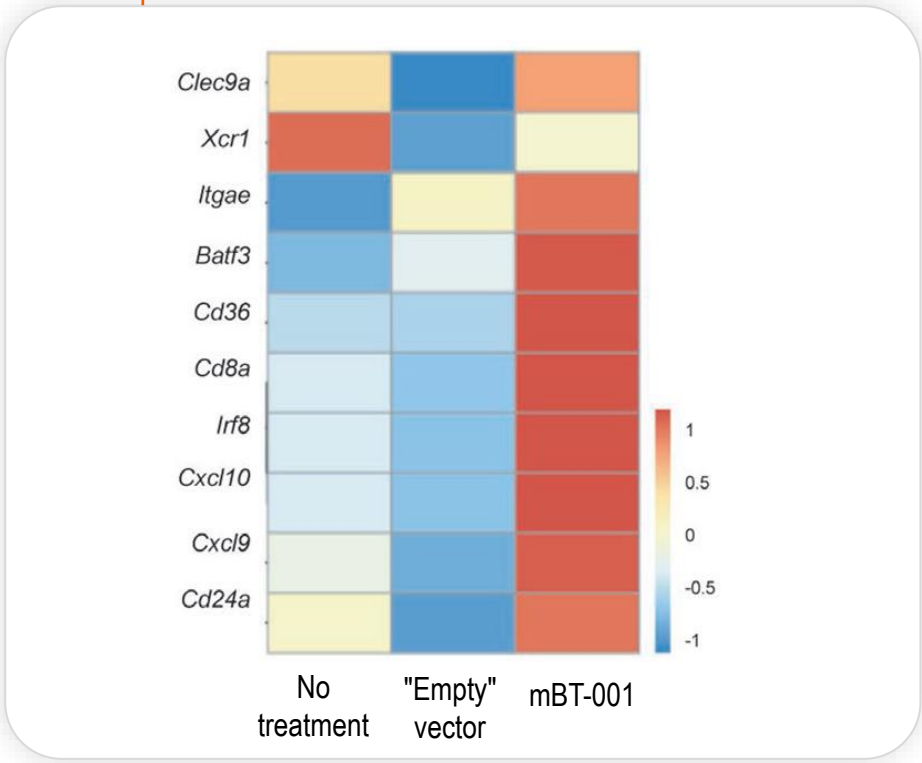
Semmrich et al. J Immunother Cancer 2022;10:e003488.

Differential Gene Expression Analysis Confirmed Large Immune Remodeling of the TME, and Induction of DC-Dependent Antigen Cross-Presentation

GO terms enriched in the set of 352 differentially expressed genes, in CT26 tumors treated with mBT-001 versus "empty" vector



cDC1-associated transcripts differentially expressed after treatment with mBT-001

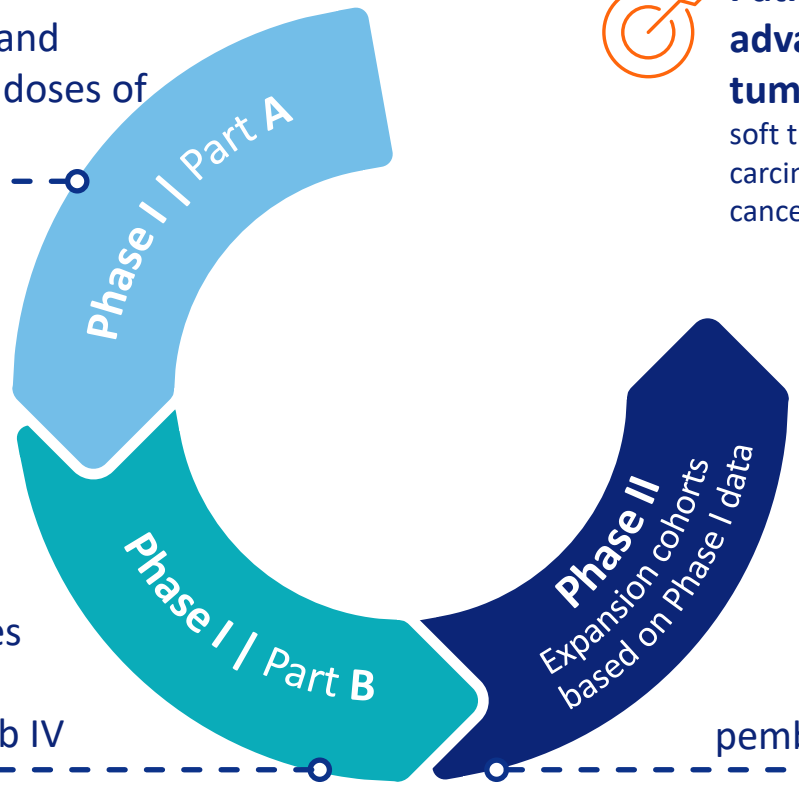


Semmrich et al. J Immunother Cancer 2022;10:e003488.

BT-001 | Ongoing Phase I/II Trial (NCT04725331)

Leverage the IT Route to Accelerate Development with Anti-PD1

Repeated and ascending doses of BT-001 IT



Repeated doses of BT-001 IT + pembrolizumab IV

Repeated doses of BT-001 IT + pembrolizumab IV**

Collaboration with MSD for free supply of KEYTRUDA®

Patients with metastatic or advanced injectable solid tumors

soft tissue sarcoma, Merkel cell carcinoma, melanoma, triple neg breast cancer, non-small cell lung cancer

Active patient enrollment in Europe, trial authorized in the US

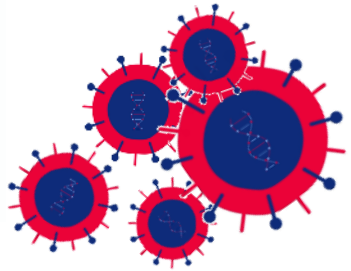
End of Phase I part A in H2 2022

Positive initial Phase I part A readout

- BT-001 alone is **well tolerated**
- BT-001 is able to **replicate** and **persist in tumor tissue**
- **Anti-CTLA-4 is expressed in the tumor** with **no detectable systemic exposure**
- **No spreading** in blood or biological fluids have been detected, suggesting **high tumor specificity**
- **Tumor shrinkage** observed in one patient **at the lowest dose level**

Transgene & AstraZeneca to Co-Develop 5 Novel Invir.IO™ OVs

Transgene and **AstraZeneca** entered into a **collaboration** and **exclusive license option agreement** in **2019**



Up to **5 new OVs**

- For **5 innovative Invir.IO™** based **armed oncolytic immunotherapies**
- Integrating **one or more transgene(s)** chosen by AstraZeneca (not disclosed)
- **Collaboration progressing well**, AstraZeneca will oversee the clinical development

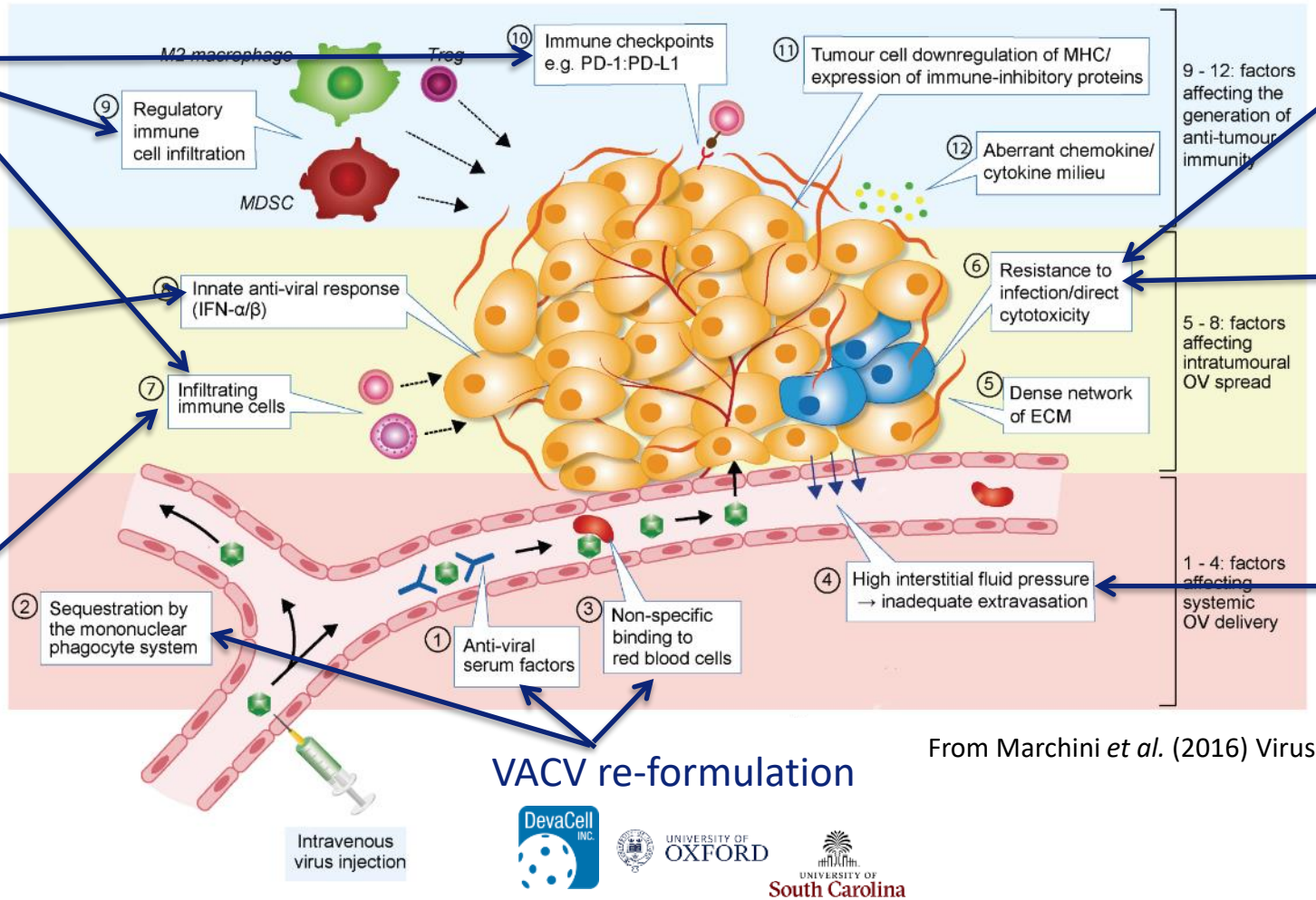
1st license option exercised by **AstraZeneca** in **Dec. 2021**

- **$8 million** option exercise payment for this 1st product
- Eligible to receive **development, regulatory and sales-based milestones payments** as well as a **royalty** based on future commercial sales

An Area of Active Internal Research and Collaboration

Supporting our strong aspiration to leadership in the IV route

CHALLENGES OF OV IN THE INTRAVENOUS ROUTE



From Marchini *et al.* (2016) Viruses

Internal projects exploring various arming of VV-COP

5 patent applications (2021, 2022)

Combination with IFNAR-targeted siRNA in Aonys technology

medesis

Joint patent application (2021)

Combination with CAR-T in solid tumor

博生吉 PersonGen

Started 2022

VACV re-formulation

DevaCell INC.

University of Oxford

University of South Carolina

Combination with nano-formulated mRNAs

COMBINED THERAPEUTICS

Internal project on shuffled viruses

Ricordel et al.
Cancers (2018)
2 patents applications (2022)

Ultrasound-induced transient permeation

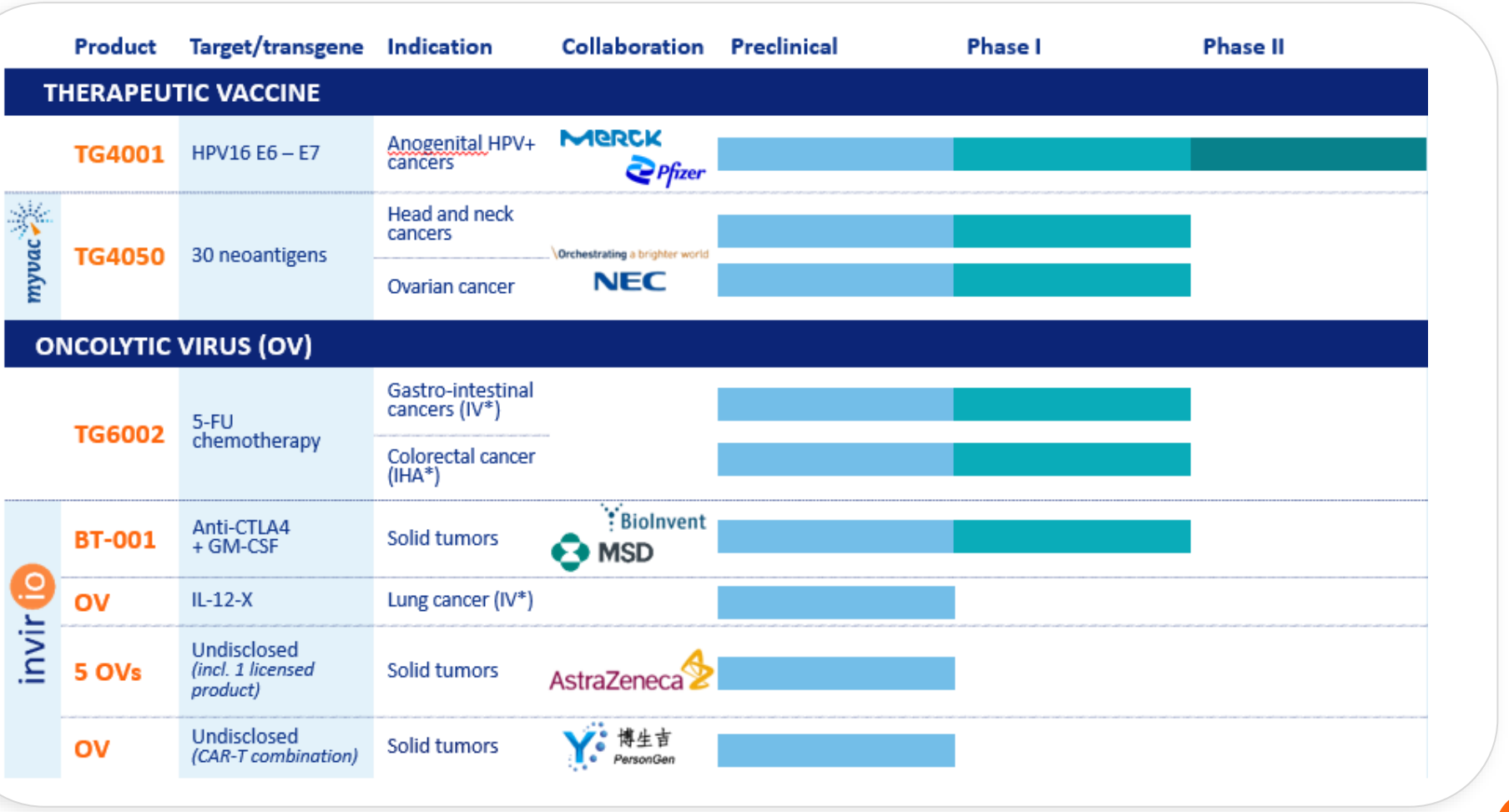
xSonics

Myers et al.
Mol. Ther. (2017)

transgene

A Strong Strategic Axis Built on Lessons Learned from Two Products in Clinical Development and Strong Preclinical Investments

THE BEST IS CERTAINLY YET TO COME



Assessing novel routes of administration with TG6002

ADEL SAMSON, MBCHB, MRCP, PHD

Consultant Medical Oncologist & Associate Professor at The Leeds Teaching Hospitals NHS Trust and The University of Leeds

transgene

UNIVERSITY OF LEEDS

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Vivek Upasani
Peter Lodge
Simon Thomson
Rob Corns
Ryan Mathew

NHS The Leeds Teaching Hospitals NHS Trust
NHS National Institute for Health Research
yorkshire cancer research
CANCER RESEARCH UK
transgene

In Which GI Cancers Could OV Make an Impact?

Colorectal cancer:

- 5FU sensitive
- dMMR Vs pMMR
- Neoadjuvant therapy pre resection of CRLM

Hepatocellular carcinoma:

- Immune sensitive cancer
- No current neoadjuvant or adjuvant therapy
- No standard second line therapy
- Could add OV to first line therapy

Cholangiocarcinoma:

- No current neoadjuvant therapy
- No standard second line therapy
- Could add OV to first line therapy

Oncolytic Viruses – Route of Delivery

Intratumoral injection

- Ensures virus reaches tumor
- BUT: Limited distribution of virus within a diffuse tumor and carries risk of bleeding

Intravenous

- Less invasive; allows easier recurrent administration
- BUT: virus sequestration in macrophages in liver and lungs

Locoregional

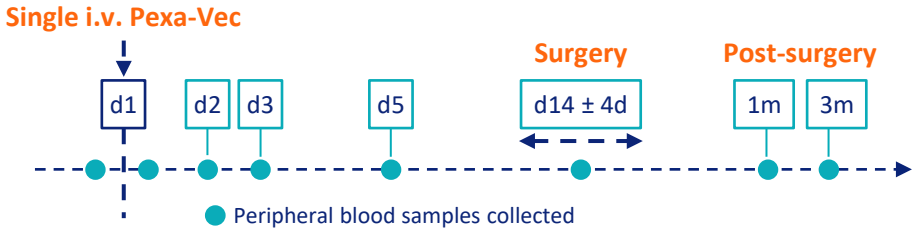
- Intrahepatic artery
- Isolated limb perfusion
- Peritoneal / pleural

Pexa-Vec | Triggers Antitumor Immunity after Single IV Administration

Prior to planned surgery of locally advanced, poor prognosis or metastatic cancers

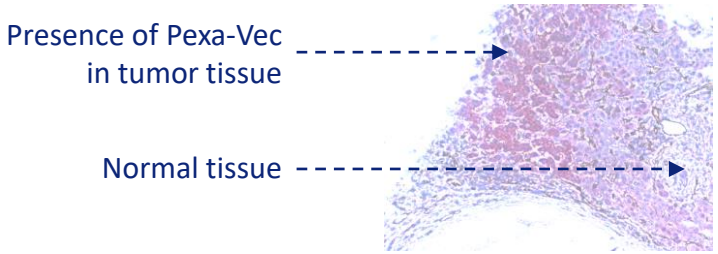
Pexa-Vec shown to:

- Selectively **target tumor tissue** after single i.v. administration
- **Stimulate the adaptive** and **innate** anti-tumor **immune response**
- Induce **expression of PD-L1 and PD-1** pathways



n = 8 ; 3 with metastatic melanoma and 5 with colorectal cancer metastases to the liver (CRLM)

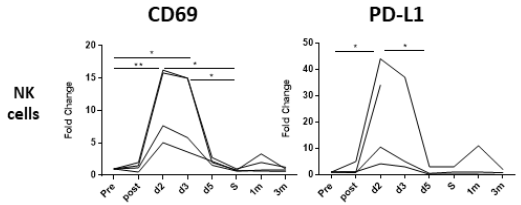
One complete and **one partial tumor pathological response** at the time of surgery on four evaluable CRLM patients

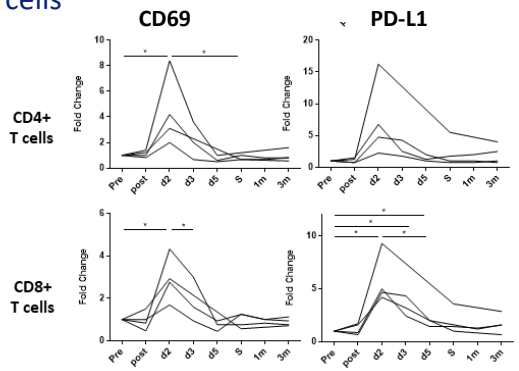


CRLM tissue showing expression of Pexa-Vec, signs of inflammation and fibrosis, necrotic cells

PBMCs exhibited robust activation by 24 hrs post-infusion

- **Expression of CD69** (an early activation marker) was enhancedon effector cell populations, notably NK & T cells
- **Expression of PD-L1** was increased





2018 ASCO ANNUAL MEETING

UNIVERSITY OF LEEDS

- **Data support ongoing development** of Transgene's Vaccinia virus-based oncolytics

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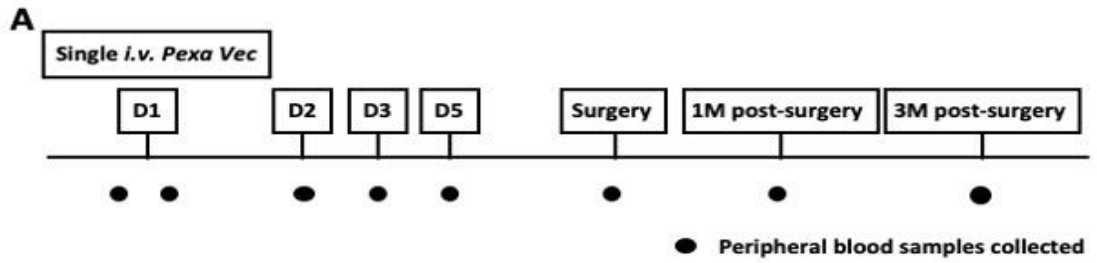
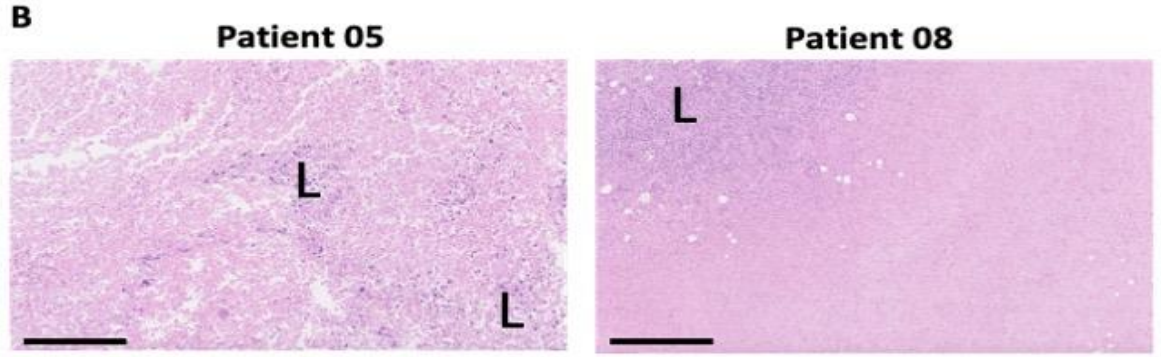
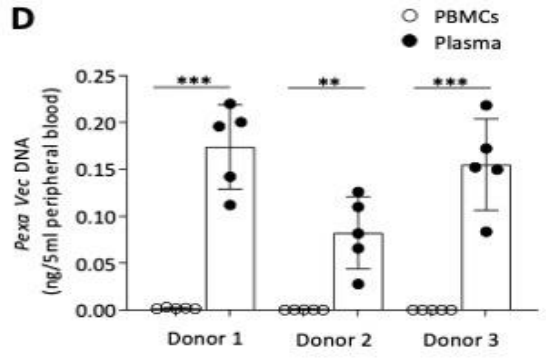
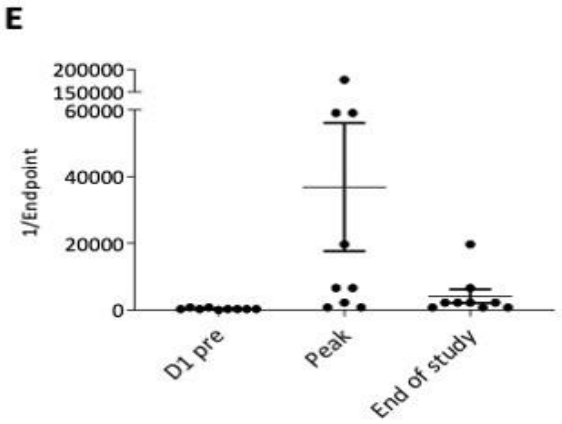
Source: Samson, A. et al, Single intravenous preoperative administration of the oncolytic vaccinia virus Pexa-Vec to prime anti-tumor immunity, ASCO 2018, June 2018

Virus Carriage in Blood





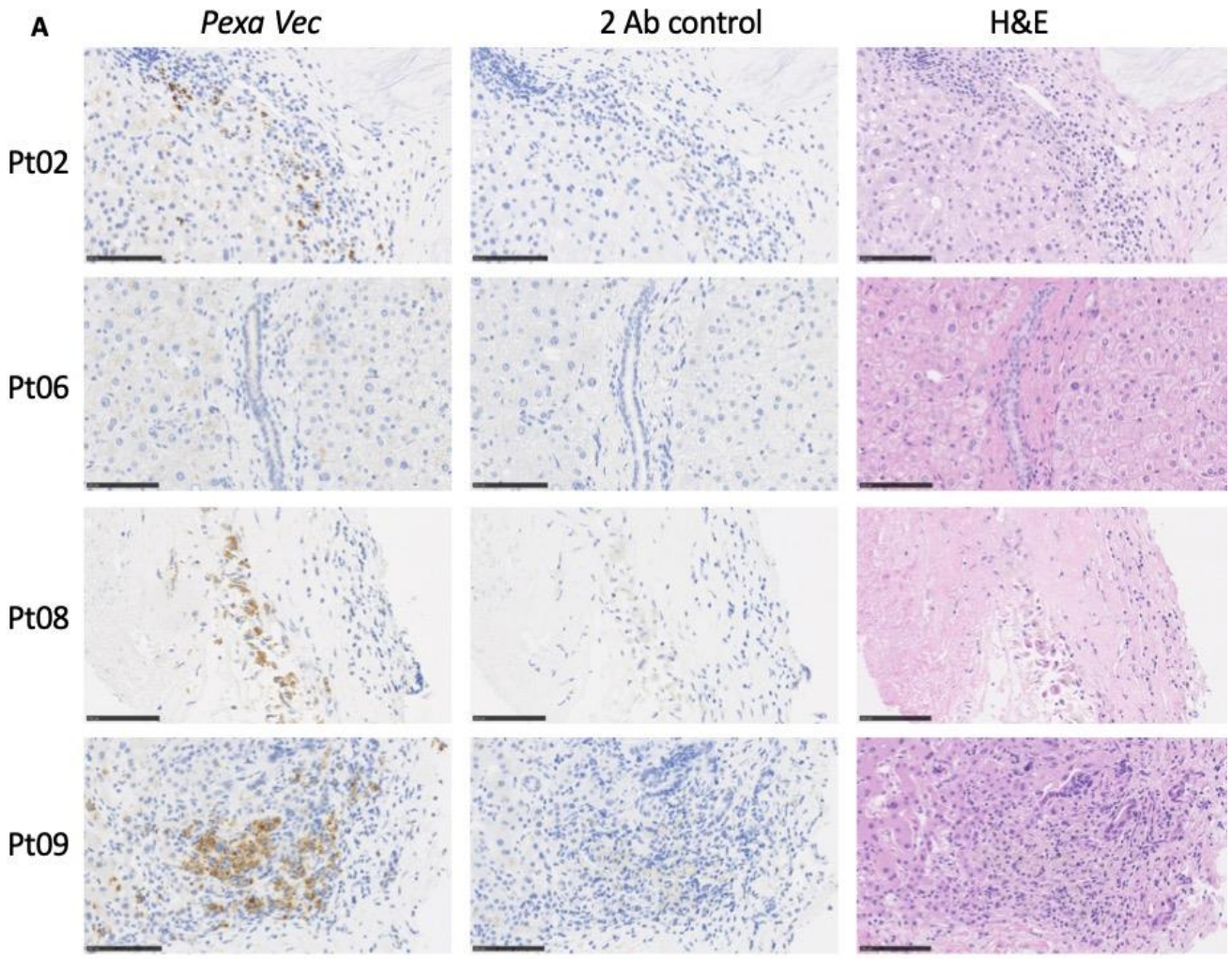


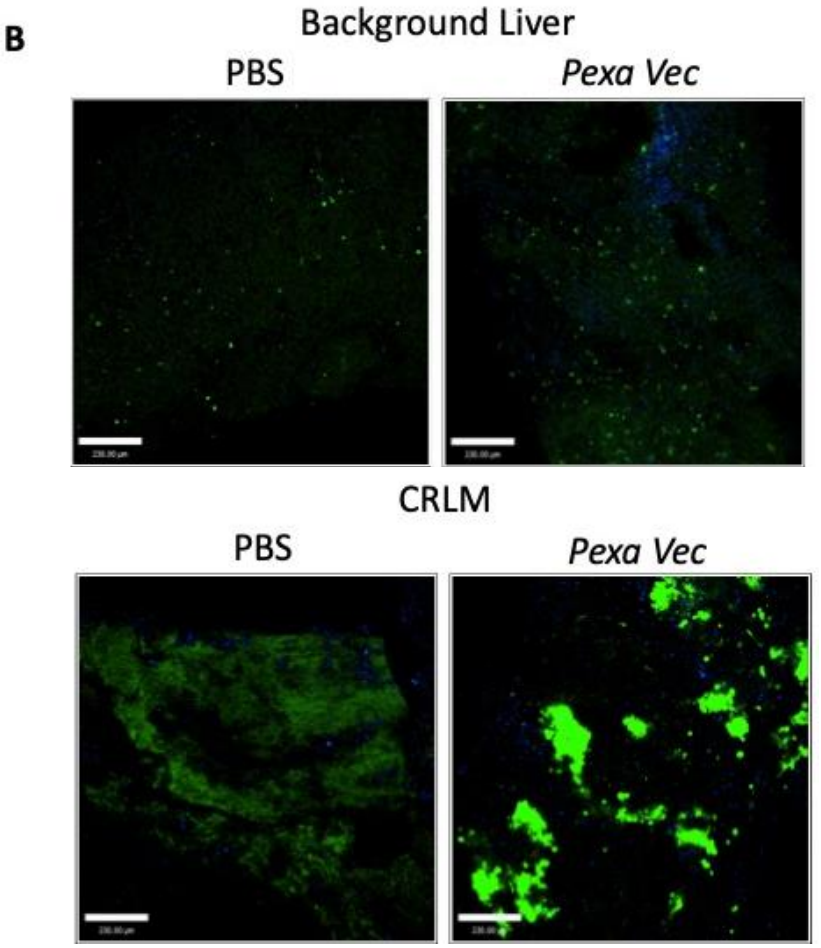


C

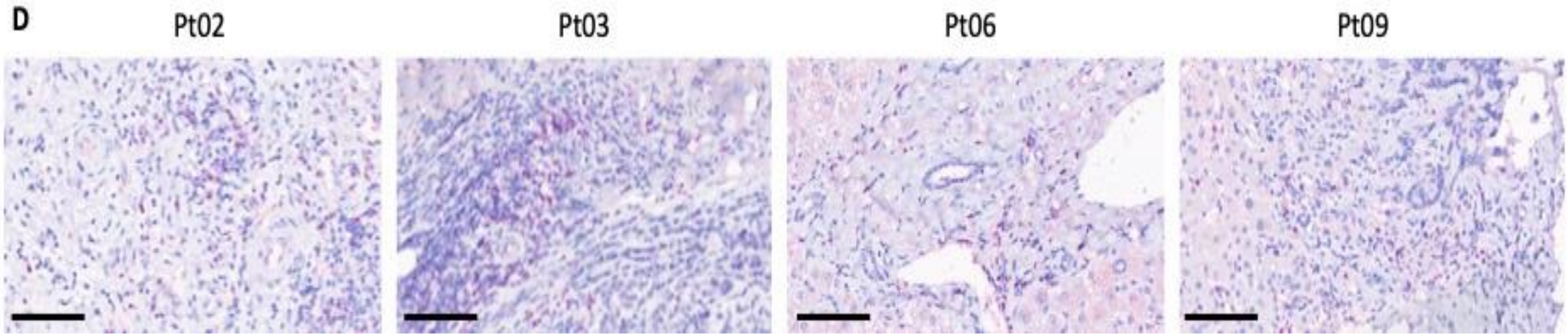
Patient	PBMC qPCR	Plasma qPCR
1	-	-
2	-	+ (1 hr post)
3	-	+ (1 hr post)
4	-	+ (1 hr post)
5	-	+ (surgery)
6	-	-
7	-	-
8	-	-
9	-	+ (1 hr post)

Virus Tumour Specificity

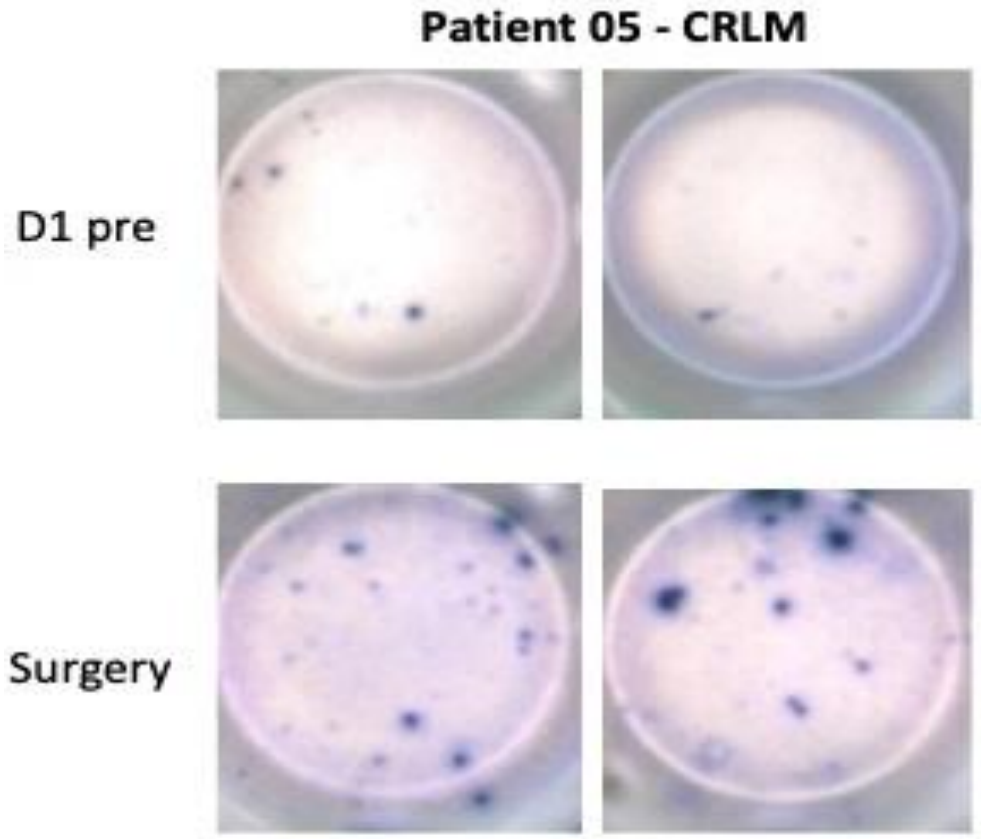


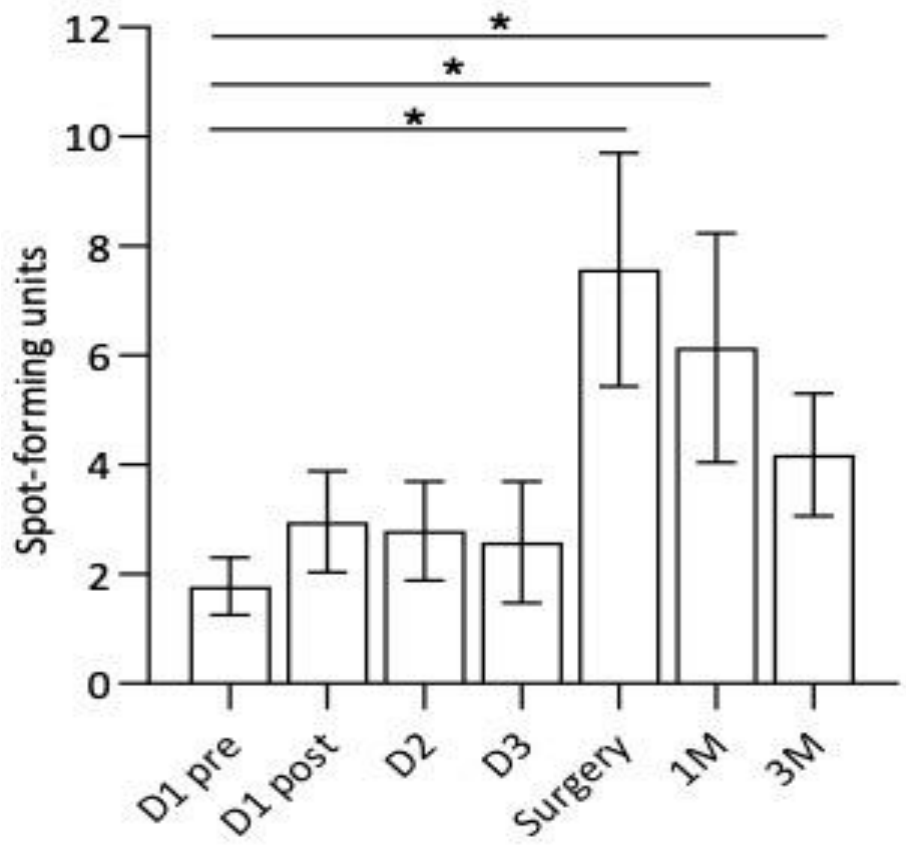


Stimulation of CD8 T-Cell Tumor Infiltration



Stimulation of Adaptive Anti-Cancer Immunity





PreOp Pexa-Vec Summary

Intravenous Pexa-Vec reaches metastatic tumors

Induction if interferon response
- Stimulates innate anti-cancer immunity
- Migration of cytotoxic T-cells to sites of virus infection/replication, i.e. to tumor

Stimulation of T-cell anti-cancer immunity

Evidence of tumor necrosis

Upregulation of immune checkpoint proteins

BUT – Hypotension common and virus delivery to tumor is limited.
- Indicates a role for locoregional delivery

TG6002 | Chemotherapy Produced Directly in the Tumor

Interim Phase I data (IV*) presented at ESMO 2022

The right virus + payload

Oncolytic armed with FCU1 gene, prodrug activator

Converts 5-FC into 5-FU, a potent chemotherapy agent

The right indication

5-FU sensitive cancers

Current SoC in 2L: bevacizumab + folfiri/folfox (3L: regorafenib, TAS-102)

OS: ~13 months

2L: 180,000 pts/year
– EU 28 & US

PoC clinical data for IV administration

After IV infusion, TG6002 was detected in the tumor and induced the production of 5-FU – no major SAE (Updated Phase I results)

The right design

Two ongoing Phase I/IIa trials
evaluating IV* and IHA** administrations

Objectives: determine the best regimen (route of administration, schedule and dose) to confirm TG6002 / 5-FC efficacy in Phase IIa

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

TG6002 | Phase I/IIa Trial to Evaluate Intravenous Administration of $VV_{cop}TK^{-}RR^{-}$ (NCT03724071)

Phase I (inclusions completed)

Patients with **advanced gastro-intestinal carcinomas**

Patients having failed and/or intolerant to standard therapeutic options

Administration schedule optimization

Arm **A**: $1x10^6$ to $3x10^9$ pfu - 3 infusions in 3 weeks (days 1, 8 and 15)

6 cohorts

Arm **B**: $1x10^9$ pfu and $3x10^9$ pfu - 3 infusions in 1 week (days 1, 3 and 5)

2 cohorts

Multicenter trial in Spain, France and Belgium

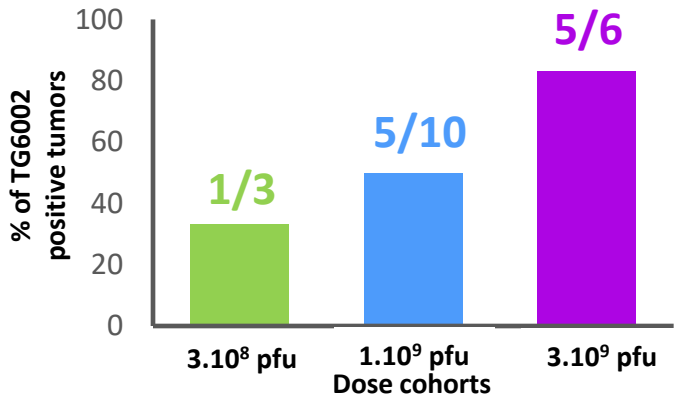
Updated Phase I data presented at ESMO 2022

TG6002 | Updated Phase I Data Presented at ESMO 2022

Clinical PoC of the Feasibility of IV Route for our Patented VV_{cop} $TK^{-}RR^{-}$ Virus

TG6002 replicates in tumor tissue without sign of widespread replication

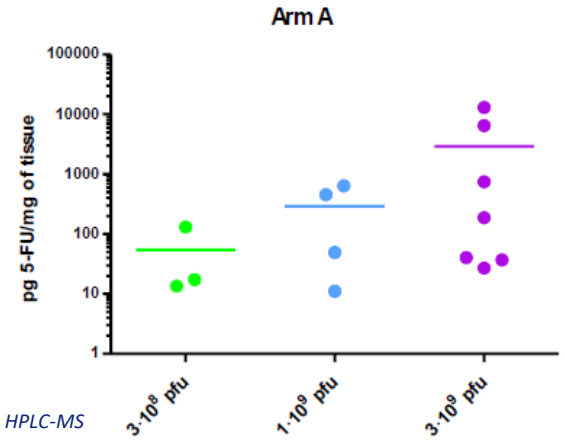
Fraction of tumor tissue positive for TG6002 by qPCR or plaque assay in arm A*



** Sensitivity of qPCR of plaque assay is impacted by scarcity of viable cells in tumor biopsies*

5-FU is expressed in tumor tissue in most of the evaluable patients (3 cohorts)

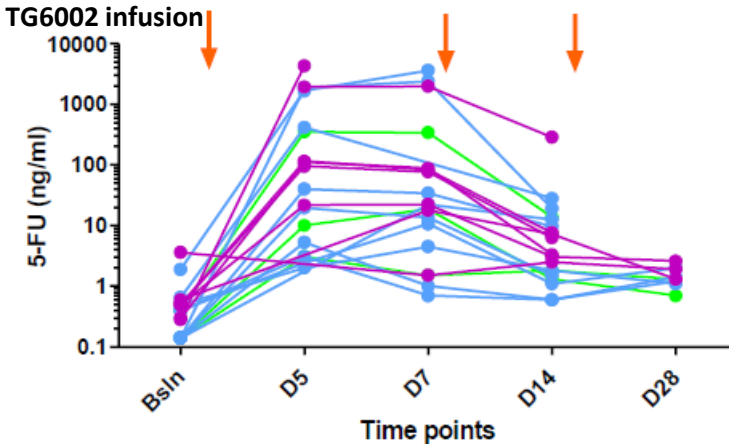
5-FU quantification in lesion biopsy on day 5*



** by HPLC-MS*

Long-lasting expression of 5-FU across the 3 dose-level cohorts

5-FU quantification in plasma (Arm A)



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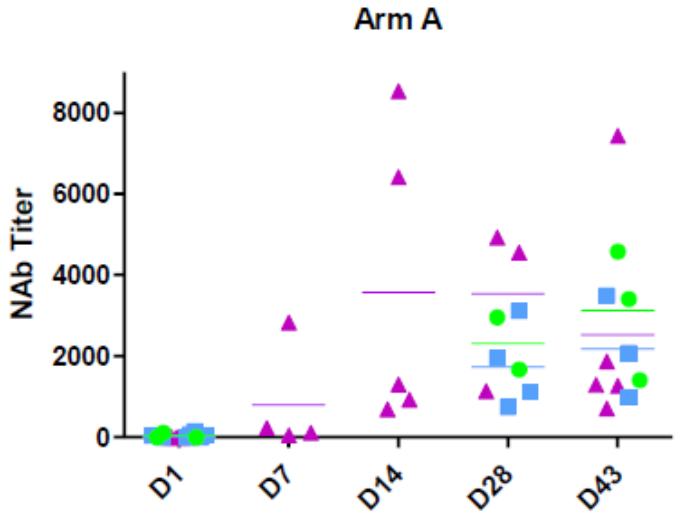
PARIS 2022 ESMO congress

Source: Moreno et al. "*Updated data of biodistribution and activity of oncolytic virus TG6002 after intravenous administration in patients with advanced gastrointestinal carcinomas*" ESMO 2022, 9–13 September 2022, Poster presentation

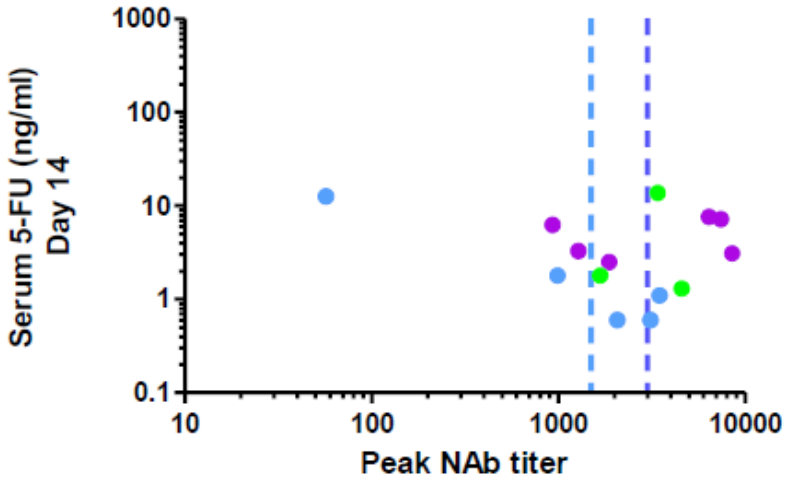
TG6002 | Clinical PoC of the Feasibility of IV Route for the $VV_{cop}TK^{-}RR^{-}$ Virus

ONSET OF **NEUTRALIZING ANTIBODY RESPONSE IS NOT ASSOCIATED WITH A DECREASED BIOLOGICAL ACTIVITY** OF THE PRODUCT

Onset of neutralizing antibodies



Absence of correlation between Peak neutralizing antibodies and serum 5-FU on day 14 (arm A)



Green: 3.10^8 pfu
Blue: 1.10^9 pfu
Purple: 3.10^9 pfu

transgene

PARIS 2022 ESMO congress

Source: Moreno et al. "*Updated data of biodistribution and activity of oncolytic virus TG6002 after intravenous administration in patients with advanced gastrointestinal carcinomas*" ESMO 2022, 9–13 September 2022, Poster presentation

Assessing a Locoregional Route | IHA Trial with TG6002

Intrahepatic Artery Route (IHA)

Routinely used to deliver therapeutic agents into patients with liver tumors

Could efficiently deliver a higher concentration of TG6002 to the liver metastases (visible or not visible with CT scan)

Phase I (inclusions completed)

Patients with **with unresectable liver metastases from colorectal cancer (CRLM)**

Patients having failed and/or intolerant to standard therapeutic options

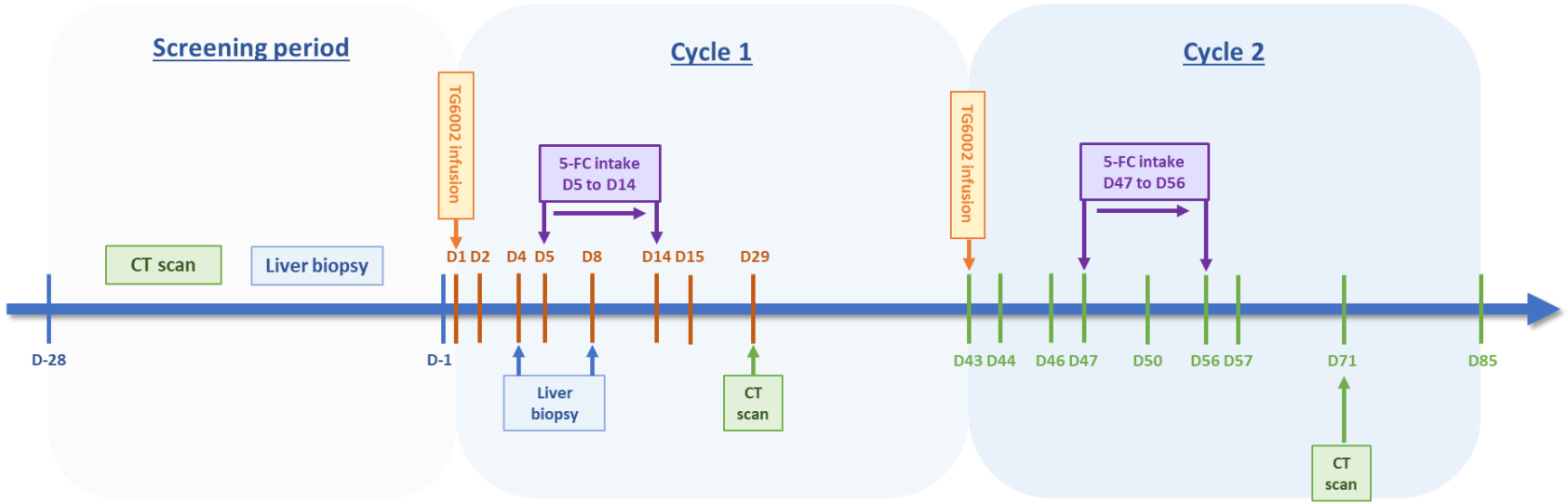
TG6002 at Day 1 and Day 43
if no PD – Oral 5-FC
$1x10^6$ to $3x10^9$ pfu

4 cohorts

TG6002.03 Intra-hepatic Artery Trial

TG6002:

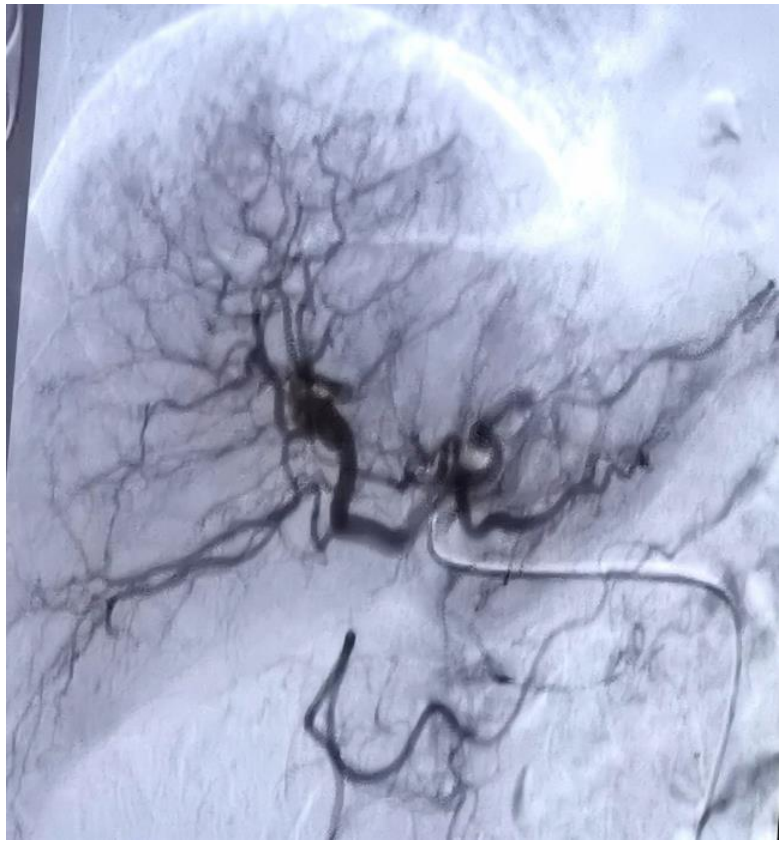
- Copenhagen strain VV, TK and RR deleted
- Encodes cytosine deaminase and uracil phosphoribosyltransferase proteins
- Conversion of prodrug 5-FC into the cytotoxic 5-FU

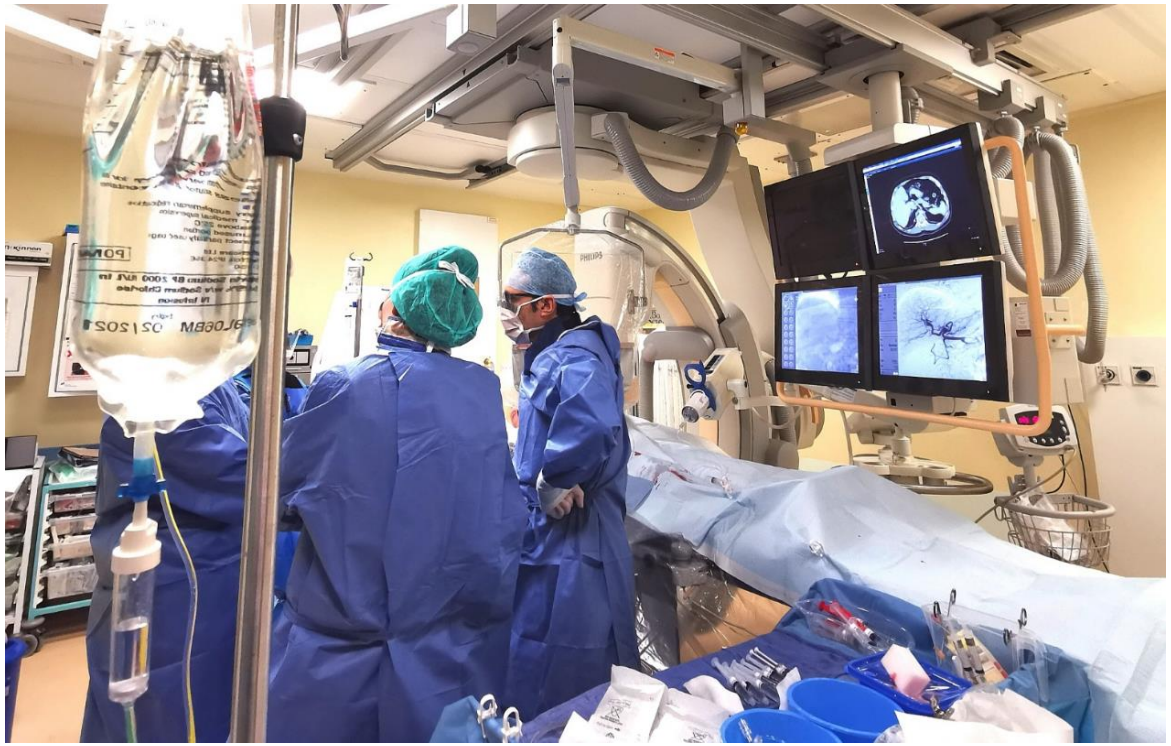


Phase I-IIa study:

- Two IHA infusions in liver-dominant advanced CRC

TG6002.03 Intra-hepatic Artery Trial





TG6002.03 Intra-Hepatic Artery Trial

Treated 15 patients
to date

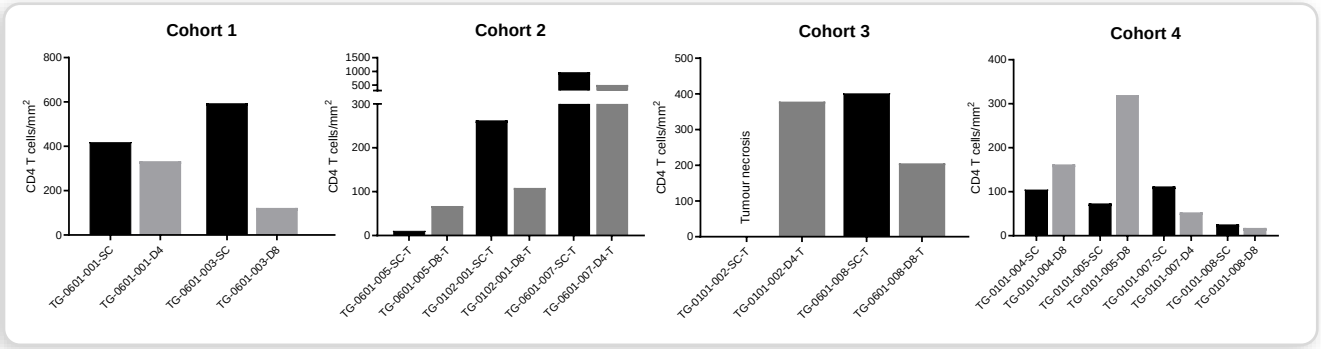
Starting dose 1x10^6 pfu,
escalating to
1x10^9 pfu

The SRC concluded that no Maximum Tolerated Dose was reached and that no further dose escalation was planned according to the protocol.

TG6002 | Effect on Immune Infiltration into Tumors

Intra-hepatic arterial infusion alters the immune environment within tumors

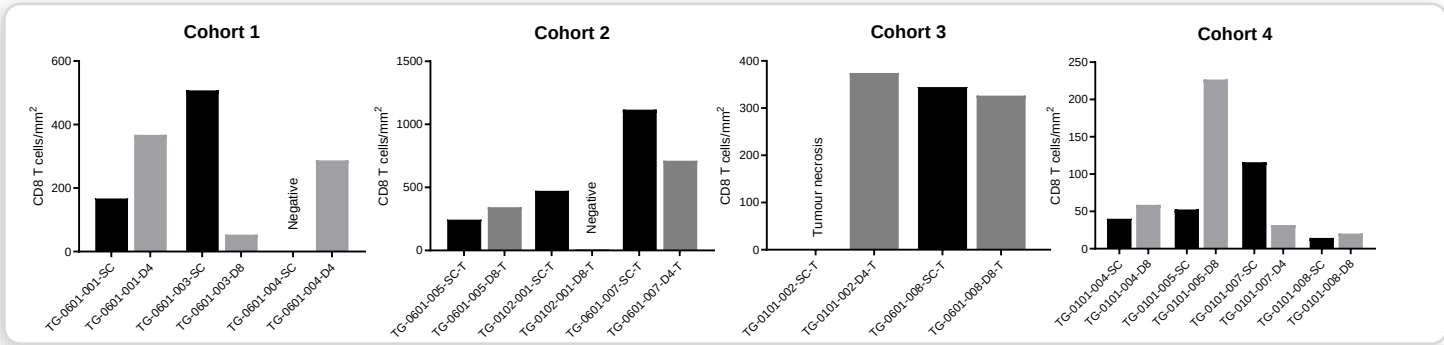
CD4 EXPRESSION



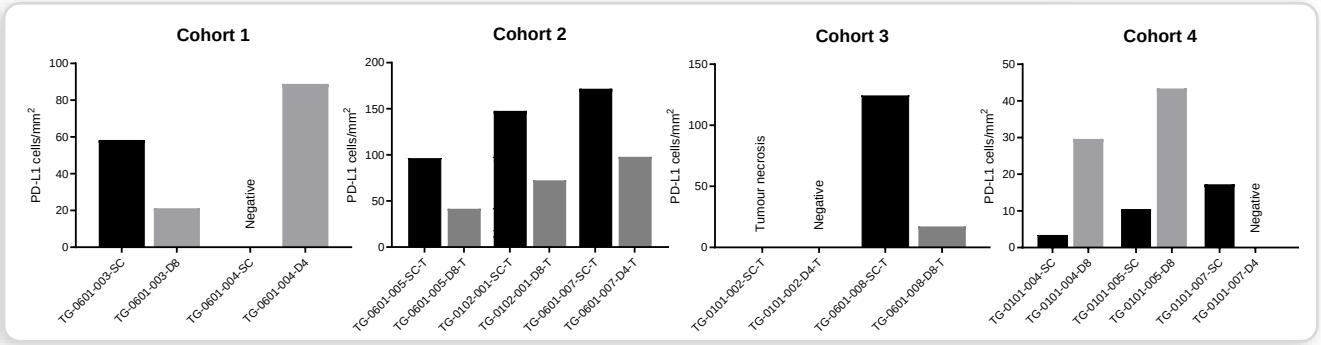
Screening tumor biopsy

Post-TG6002 tumor biopsy

CD8 EXPRESSION



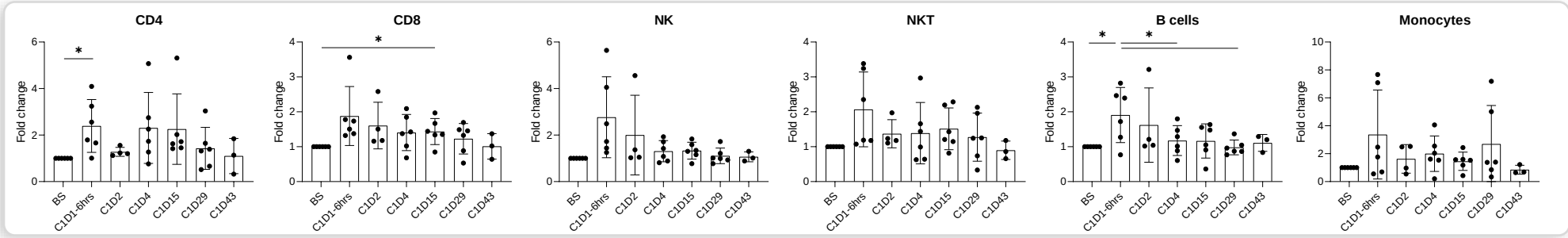
PD-L1 EXPRESSION



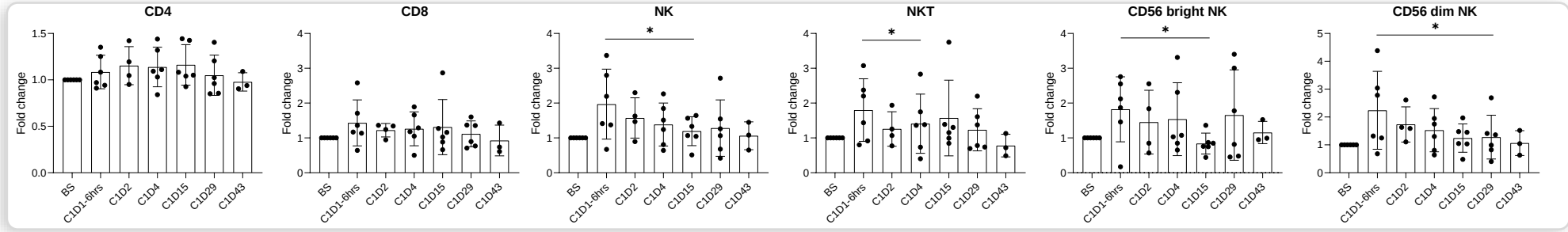
TG6002 | Peripheral Immune Cell Activation

Intra-hepatic arterial infusion stimulates immune cells within the blood

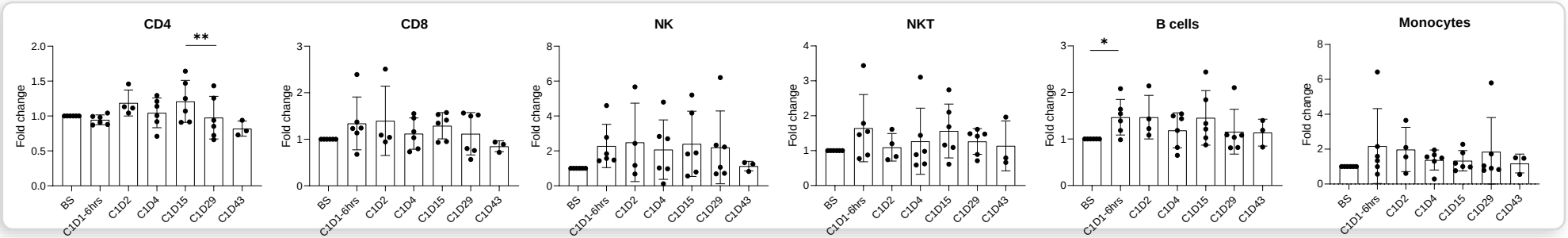
CD69



OX40



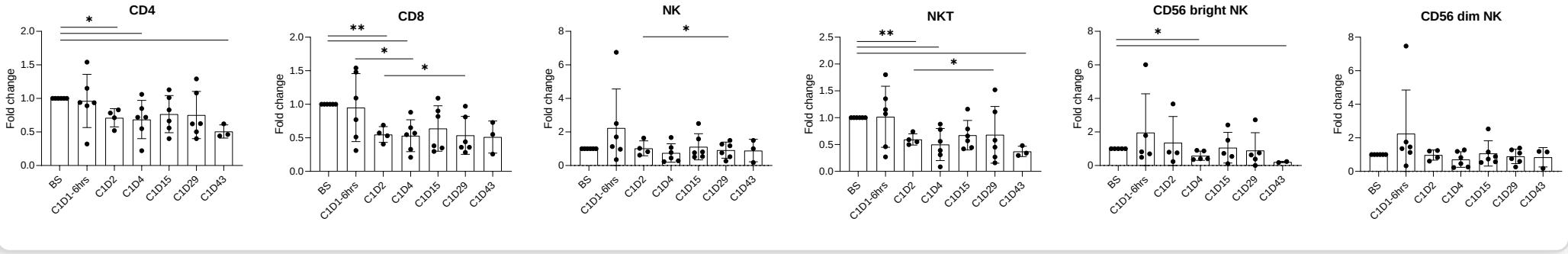
PD-L1



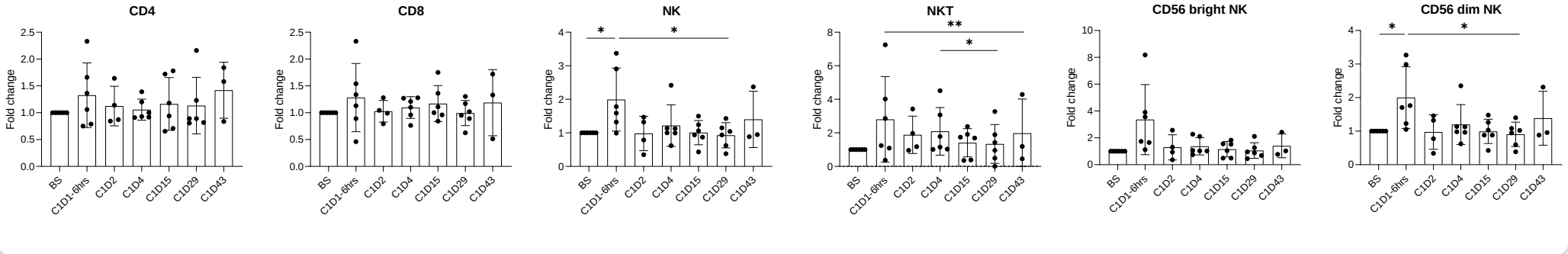
TG6002 | Peripheral Immune Cell Activation

Intra-hepatic arterial infusion stimulates immune cells within the blood

CTLA-4



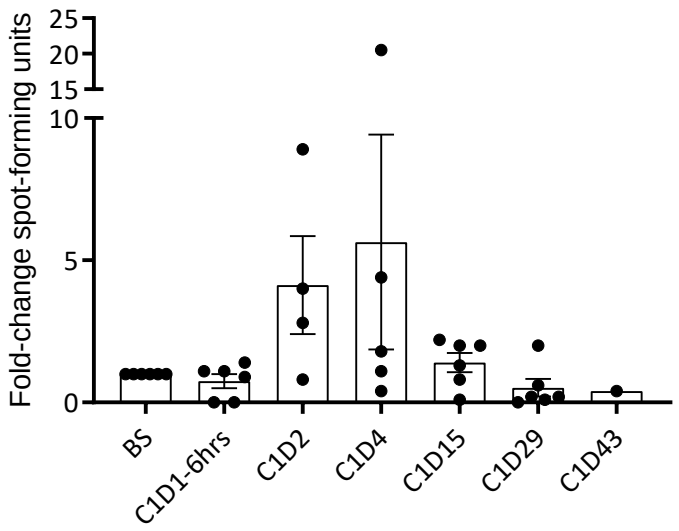
TIM-3



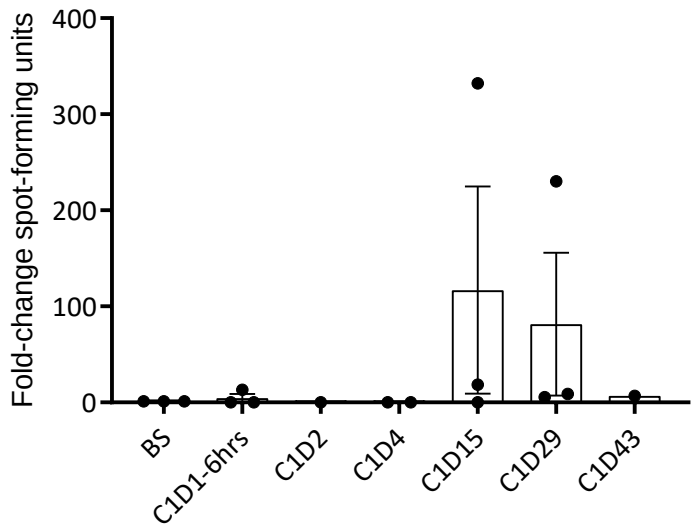
TG6002 | Antigen-Specific T Cell Recall Response

Intra-hepatic arterial infusion stimulates antigen-specific T cells against both tumor-associated antigens and virus

CEA



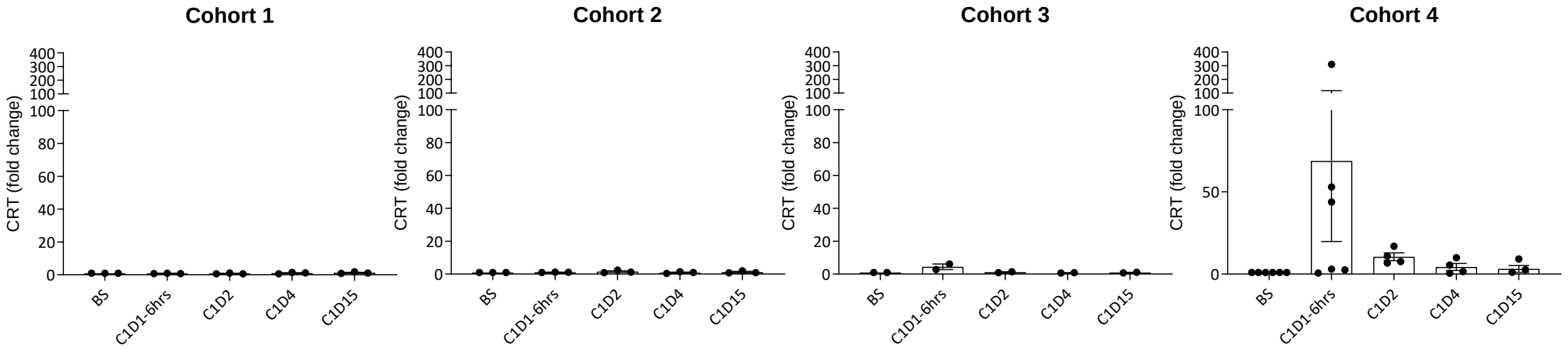
TG6002



Response to virus observed in Cohort 2, not in Cohort 1

TG6002 | Calreticulin Secretion in Response to TG6002

Intra-hepatic arterial infusion stimulates the release of calreticulin; an indicator of immunogenic cell death



Calreticulin release only observed in **Cohort 4**

TG6002 | qPCR of Patient Biopsies for Presence of TG6002

	Tumor (liver metastasis biopsy)				
	Viral DNA by qPCR (c/µg ADN) (Leeds lab)	Viral titration by plaque assay	Viral DNA by qPCR	RT-qPCR mRNA copies/total RNA	Virus IHC
$1x10^6$ pfu	C1D4: negative	C1D4: negative	C1D4: negative	C1D4: positive	C1D4: negative
	C1D8: negative	ND		ND	C1D8: negative
	C1D4: negative	C1D4: negative	C1D4: negative	C1D4: positive	C1D4: low
$1x10^7$ pfu	C1D8: negative	ND		ND	C1D8: low
	C1D4: negative	ND		ND	C1D4: low
	C1D8: positive	ND		ND	C1D8: low
$1x10^8$ pfu	C1D8: negative	C1D8: negative	C1D8: negative	C1D8: positive	IHC cancelled, biobanking only
	C1D4: positive	C1D4: negative	C1D4: negative	C1D4: positive	IHC cancelled, biobanking only
	C1D4: positive	C1D4: positive	C1D4: negative	C1D4: positive	IHC cancelled, biobanking only

Leeds, UK, analysis of TG6002 tumor DNA

Positive in:
- $1x10^6$ pfu; 0/4 patients
- $1x10^7$ pfu; 1/3 patients
- $1x10^8$ pfu; 2/3 patients

In which GI cancers could OV make an impact?

Colorectal cancer:

- 5FU sensitive
- dMMR Vs pMMR
- Neoadjuvant therapy pre resection of CRLM

Hepatocellular carcinoma:

- Immune sensitive cancer
- No current neoadjuvant or adjuvant therapy
- No standard second line therapy
- Could add OV to first line therapy

Cholangiocarcinoma:

- No current neoadjuvant therapy
- No standard second line therapy
- Could add OV to first line therapy

New Invir.IO™ Candidate: an IL-12 Construct

invir io

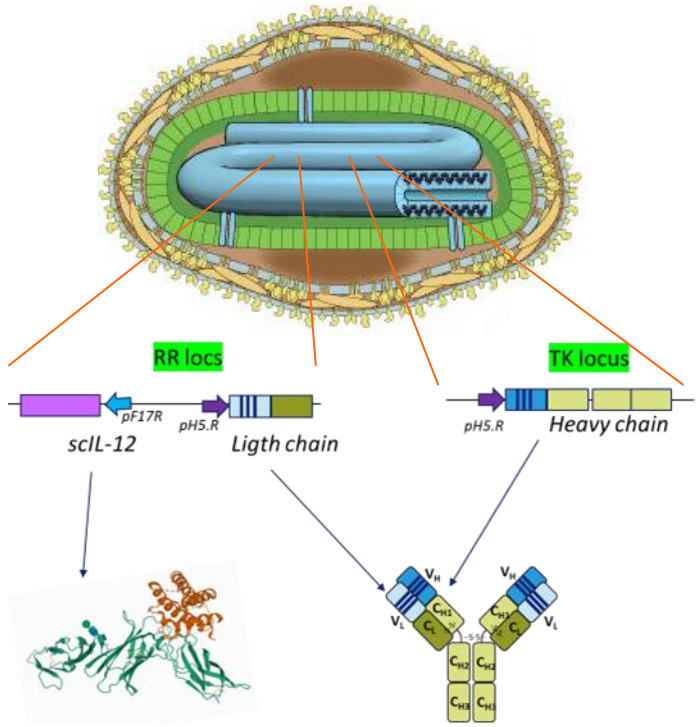
ÉRIC QUÉMÉNEUR, PharmD, PhD
Chief Scientific Officer
Executive VP
Transgene

transgene

VV-IL12-X : A Potent Invir.IO™ Product to Target Immune-Resistant Tumors

Product description

VACV$_{COP}$(Δ*J2R*,Δ*I4L*,**Δ*M2L*,*A56Rmut***)



Based on **3 TG patents families**

Target product profile

- **Immuno-suppressed solid tumors where immune remodeling of the TME can be beneficial** (e.g. poorly T-cell infiltered tumor, exhausted resident CD8+ T cells, low abundance of APCs or NK cells, etc.); e.g. NSCLC-2L
- **IV administration** to target deep lesions, and metastatic stage disease
- Tumor targeted IL-12 therapy, to reach high intratumoral concentration (up to 10 µg/kg), and prevent high systemic exposure (below 0.5 µg/kg, or below serum Cmax at 100ng/mL)
- Possible combination with approved CPI, and/or CT
- Synergic arming with Mab (yet undisclosed), directly acting on the balance between effector or helper cells, and immunosuppressive cells

IL-12, a “Must-Have”?

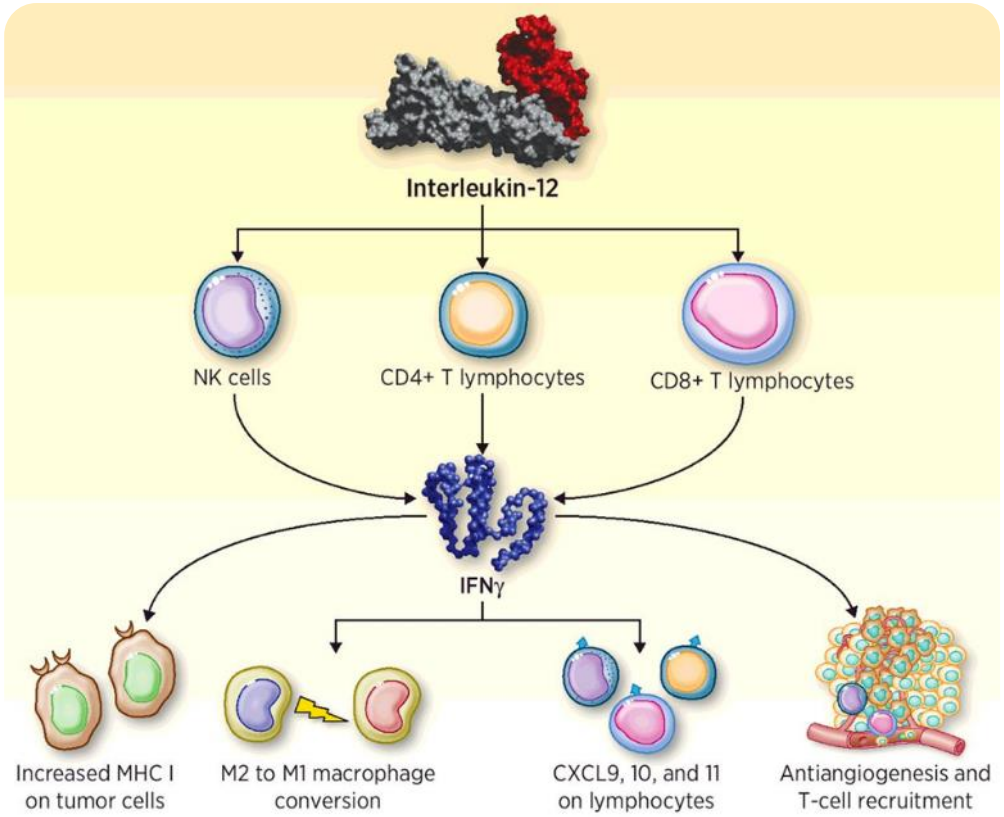
IL-12 is a POTENT PRO-INFLAMMATORY TYPE 1 CYTOKINE that is able to engage multiple effector mechanisms, and to reverse tumor-induced immunosuppression

IL-12 is master regulator of both innate and adaptive anti-tumor immune responses, which **directly** :

- **stimulates growth and cytotoxic activity of NK cells and T cells** (both CD4+ and CD8+)
- **induces differentiation of CD4+ T cells towards Th1 phenotype**

and **indirectly** acts on :

- **tumor cells immunogenicity**, via upregulation of both MHC-I and MHC-II molecules
- **macrophages**, skewing from M2 to M1 phenotypes
- **lymphocytes**, via the chemokine signaling pathway (paracrine axis)
- **endothelial cells**, inhibition of tumor angiogenesis and increased porosity to T cell homing



Berraondo et al. Clin Cancer Res (2018) 24 (12): 2716–2718.

IL-12, Strong Justification for Intratumoral Delivery

- Despite encouraging success in preclinical **studies, the early stages of IL-12 clinical trials did not meet expectations**, mostly because of its very high toxicity when administered in the intravenous route
- **The maximal tolerated dose** is generally considered at **0.5 µg/kg/day**, with a narrow therapeutic window
- Beside the interest of localized IL-12 therapy for safety, **local delivery** is also justified by many biological reasons :
  - Activation, and differentiation of tumor-specific T cell clones, over general expansion of the total lymphocyte population
  - Reversion of immuno-suppressive mechanisms (anergy, TAMs, MDSCs, Tregs) require rather large concentrations of IL12
  - The chemokine signaling axis requires marked concentration gradient

Nguyen et al. (2020) Frontiers Immunol. 11, 575597

A Strong Competition Which Reveals the Consensus on IL-12

Current IL-12 delivery strategies and results in monotherapy

Our ambition is to become the first OV in the intravenous route

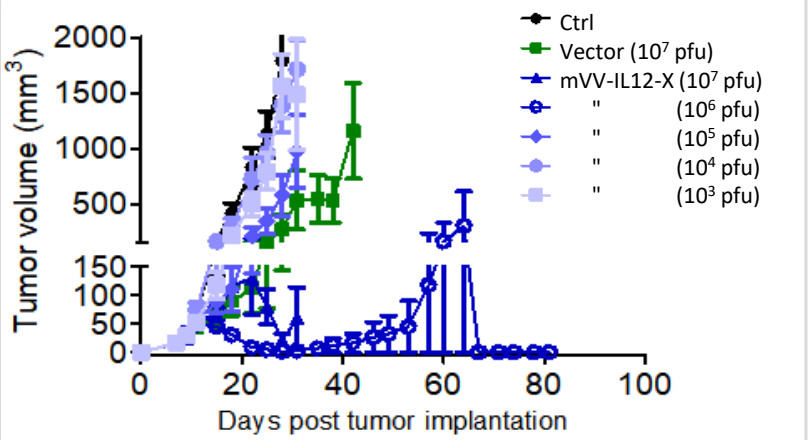
Product name	TAVO	GEN-1	NHS-IL12	DF6002	Ad-RTS-IL12	MEDI-9253	MEDI-1191	SAR441000
Sponsor	Oncosec	Celsion	Merck KG	BMS/Dragonfly	Ziopharm	AZ	AZ/Moderna	Sanofi/ BioNTech
Technology	plasmid	plasmid	Fusion protein	Fusion protein	Adeno	NDV	mRNA	mRNA
ROA	IT	IP	SC	SC	IT	IV	IT	IT
Clinical start	2004	2008	2011	2020	2012	2020	2019	2019
Status	Phase II	Phase I / II	Phase II	phase I	phase II	phase I	phase I	phase I
Tumor types	Melanoma, Merkel	OvCa, GBM	Kaposi, CRC	Solid tumors	GBM	Solid tumors	Solid tumors	Melanoma CSCC, HNSCC
Efficacy as single agent	10-30% ORR in Melanoma 25% in Merkel	0 % (n=22)	0 % (n = 59)	NA	NA	NA	NA	NA
Combination	pembrolizumab	NACT	?	nivolumab	veledimex	durvalumab	durvalumab	cemiplimab
Efficacy in combination	41% ORR 36% CR	?	?	?	?	?	?	?

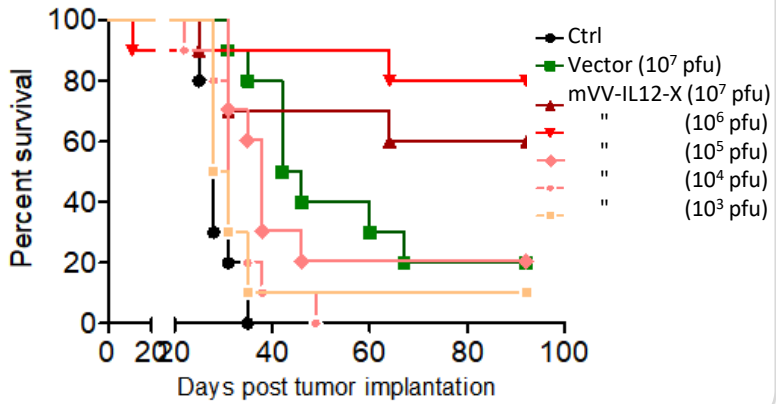
Product name	RIVAL-01	ONCR-177	ASP9801	M-032 NSC-733972	Ad5yCD/ mutTKSR39rep-ADP	MVR-T3011	VG-161
Sponsor	Turnstone / Takeda	Oncorus	Astellas	Aettis	Henry Ford Health System	Immvira	Virogin Biotech
Vector	VV	HSV	VV	HSV	AdV	HSV	HSV
Payloads	IL-12, Flt3L, aCTLA4	IL-12, Flt3L CCL4, aPD1, aCTLA4	IL-12, IL-7	IL-12	IL12, yCD	IL-12, aPDL1	IL12, IL15-IL15RA, PD1p
ROA	IT, then IV	IT	IT	IT	IT	IT	IT
Clinical start	DEC2020	APR 2020	2019	2014	2017	2020	2020
Status	Phase I/IIa	Phase I	Phase I	Phase I	Phase I	Phase I	Phase I
Tumor types	Mel., TNBC, MSS-CRC	Mel., Breast, HNSCC	Solid tumors	GBM	PAC	Cut. or SC mets of solid tumors	HCC
Combination with	pembro	pembro	pembro		5FC, CT		

transgene

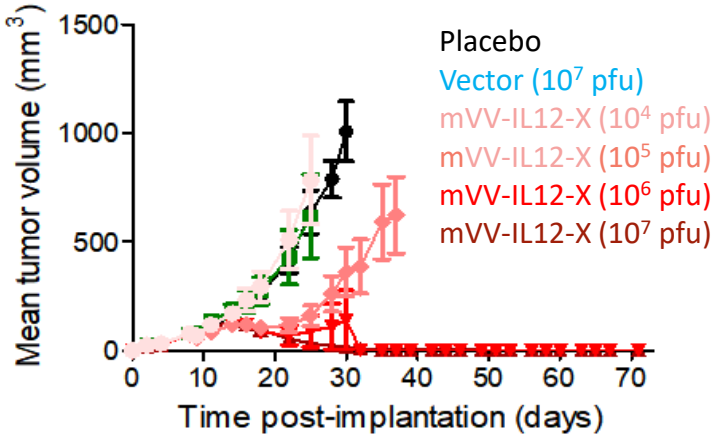
Preclinical Antitumoral Activity in Immunocompetent Models

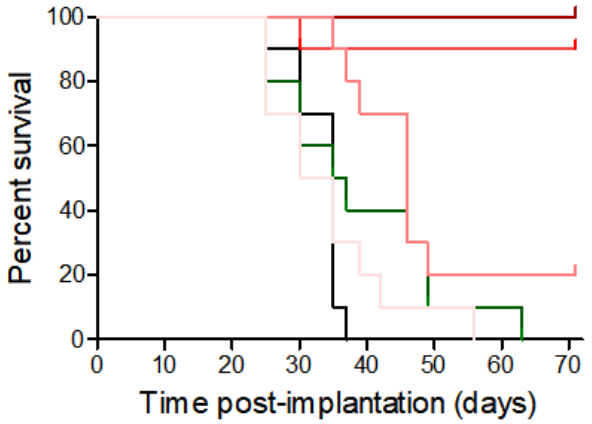
CT26 (colon carcinoma) in C57BL/6 **(Th1 immune bias)**, reference model in our invir.IO™ program



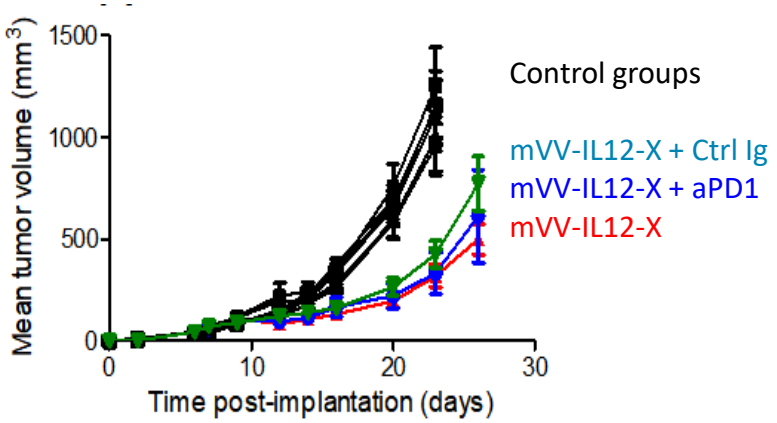


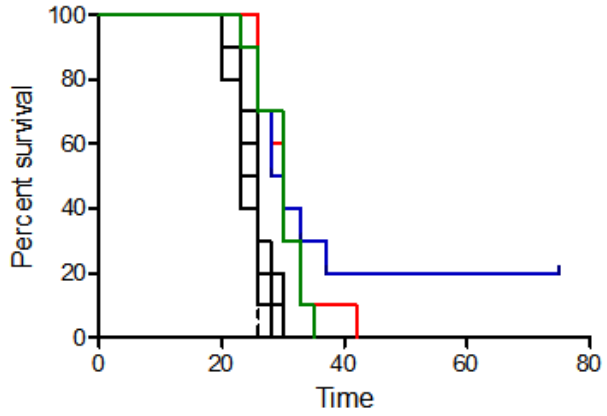
EMT6 (mammary carcinoma) in Balb/c (Th2 bias) an immuno-sensitive model





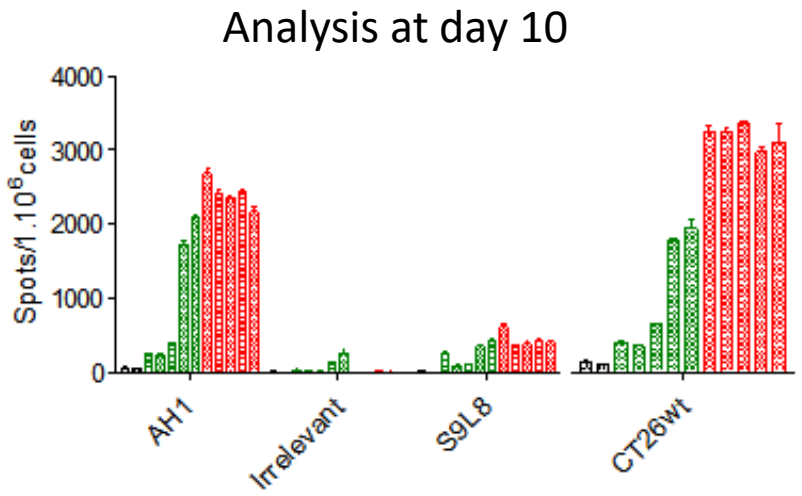
LLC1 (Lewis lung carcinoma) on C57BL/6, a resistant model to single agent immunotherapy generally used for drug combination





Induction of a Specific Antitumoral Immune Response

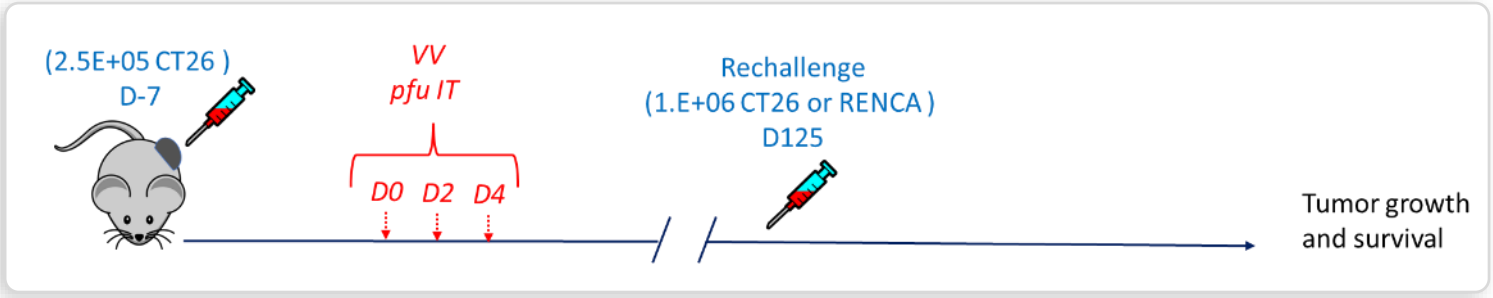
Elispot analysis of circulating T cell specificities after VV-IL12-X treatment in the CT26 model

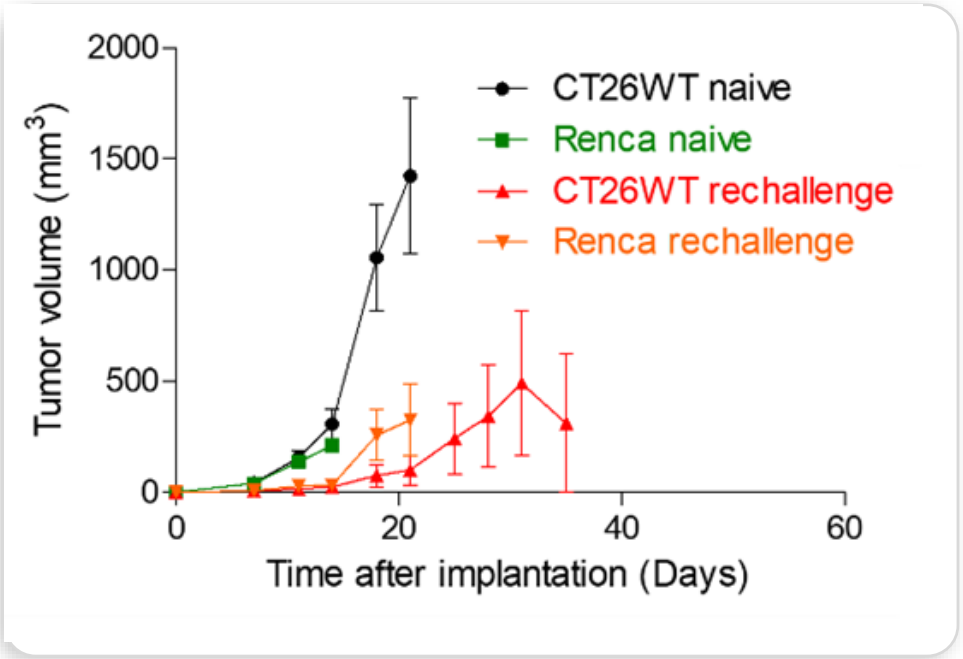


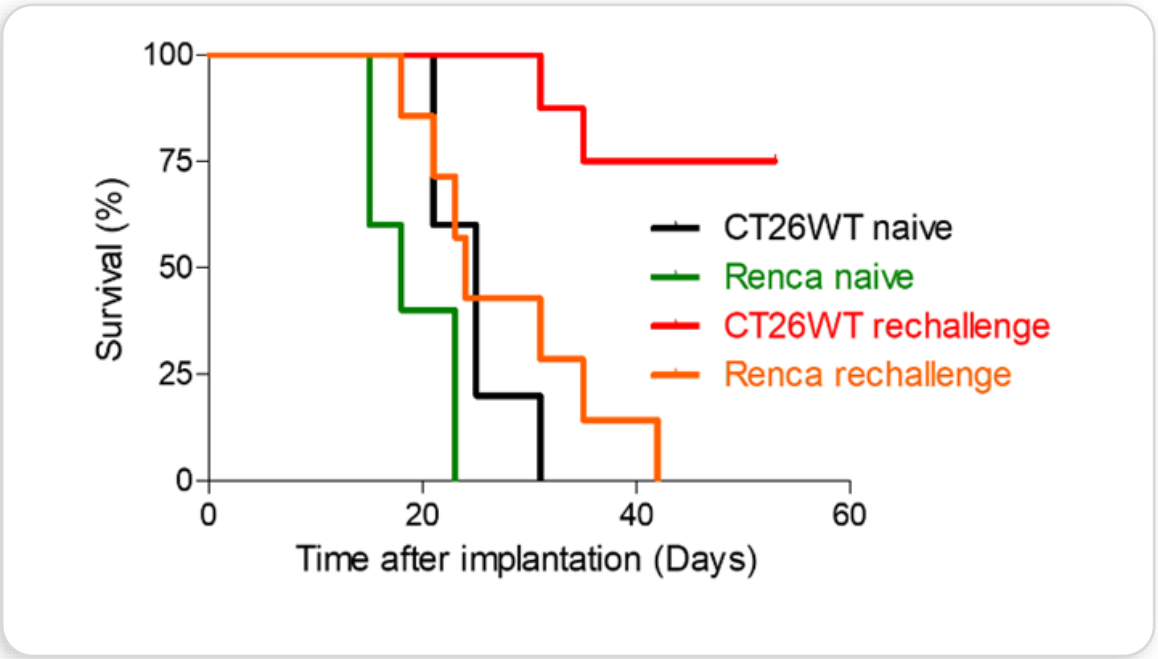
Stimulation Agent
AH1 : MHC-I CT26-specific peptide
S9L8 : VACV-specific peptide
CT26wt : CT26 protein lysate

Memory Cells are Engaged in the Specific Antitumoral Immune Response

Rechallenge experiments in the CT26 model

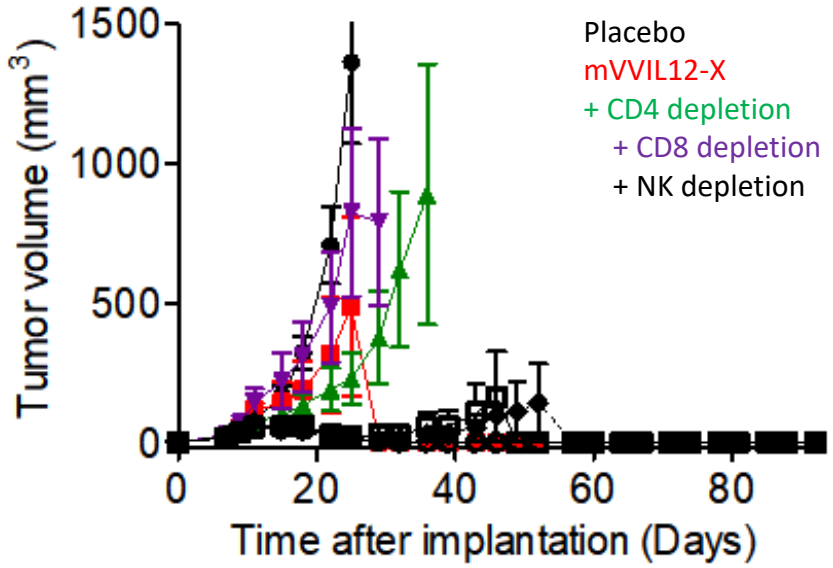


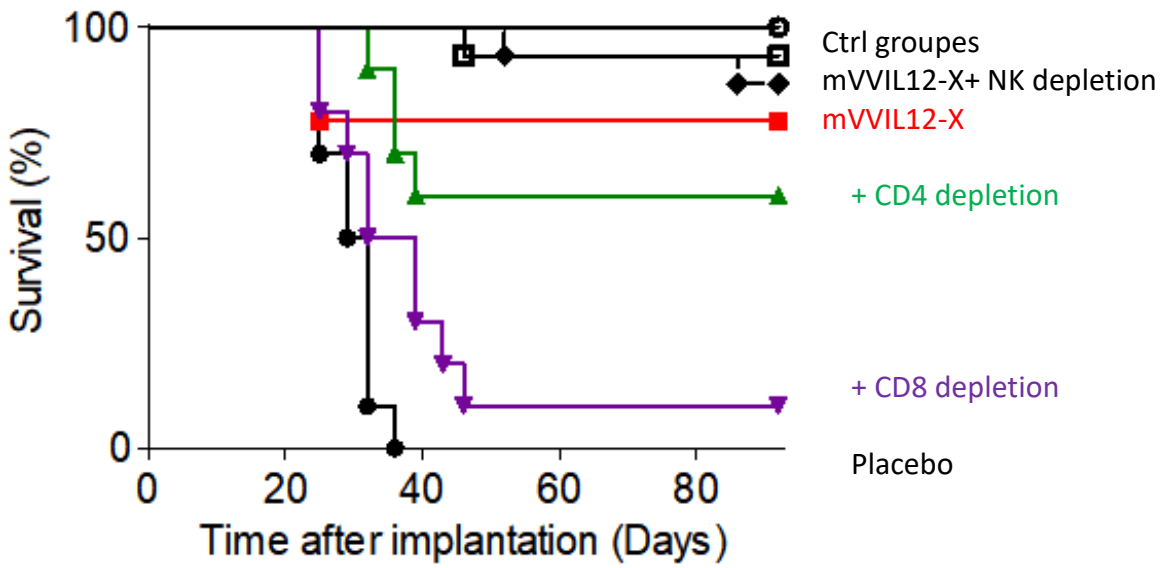




Key Role of CD8+ T Cells

Specific CD4, CD8 or NK depletion experiments in the CT26 model





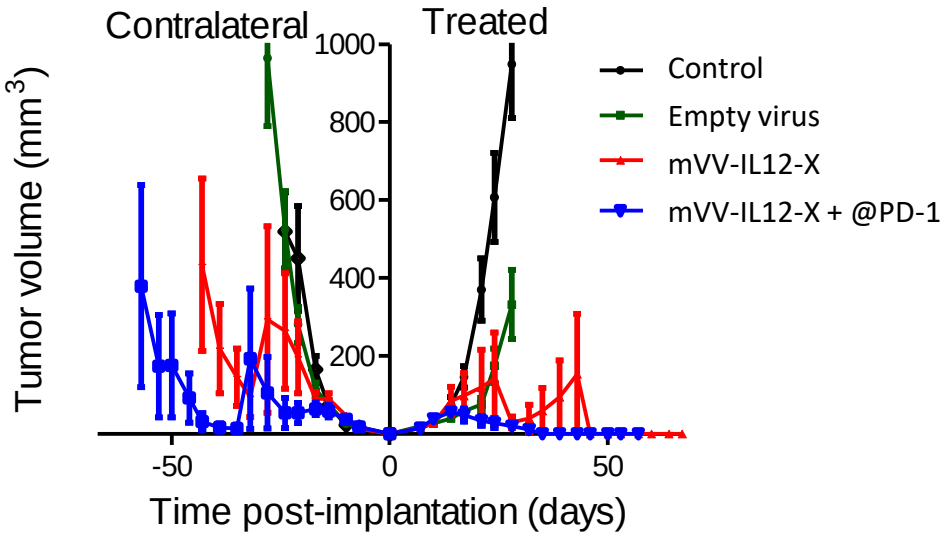
- **CD8+ T** cells are essential for the anti-tumor activity of **mVV-IL12-X**
- **CD4+ T** cells are much less contributive to the **mechanism**
- **NK** cells look also important but transient effect

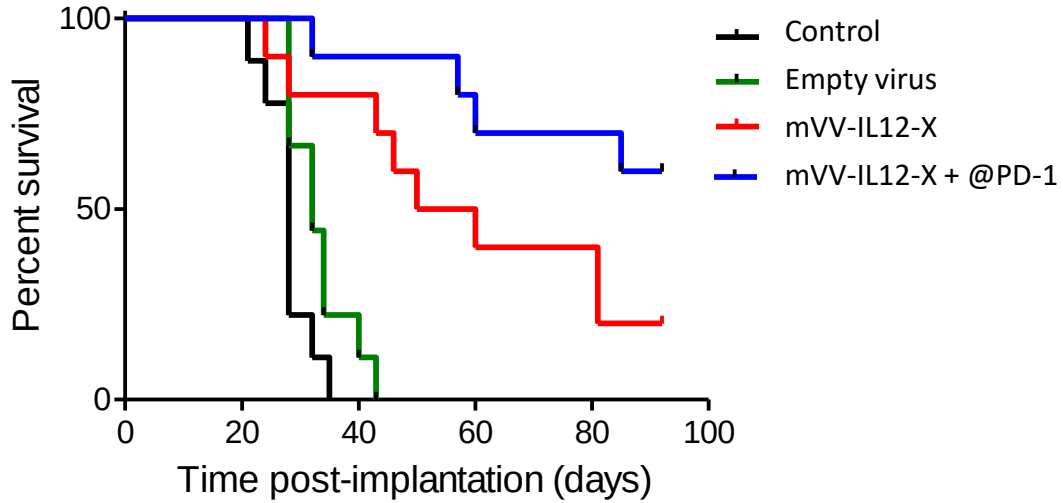
Local Immune Response Translates into Systemic Effect

Abscopal response in the CT26 model

CT26

← i.t. injection
of mVV-IL12-X ± anti-PD1



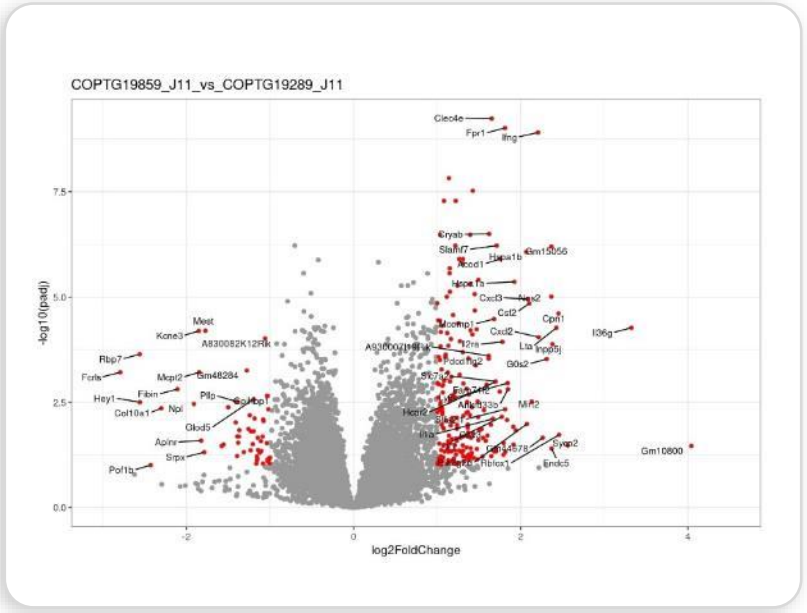


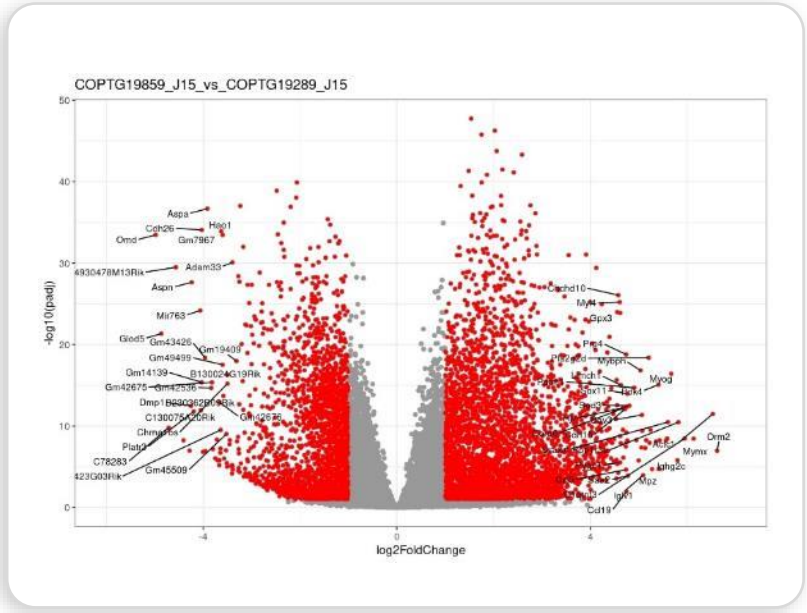
Very Large Involvement of Multiple Pathways in Anti-Tumor Response (1/2)

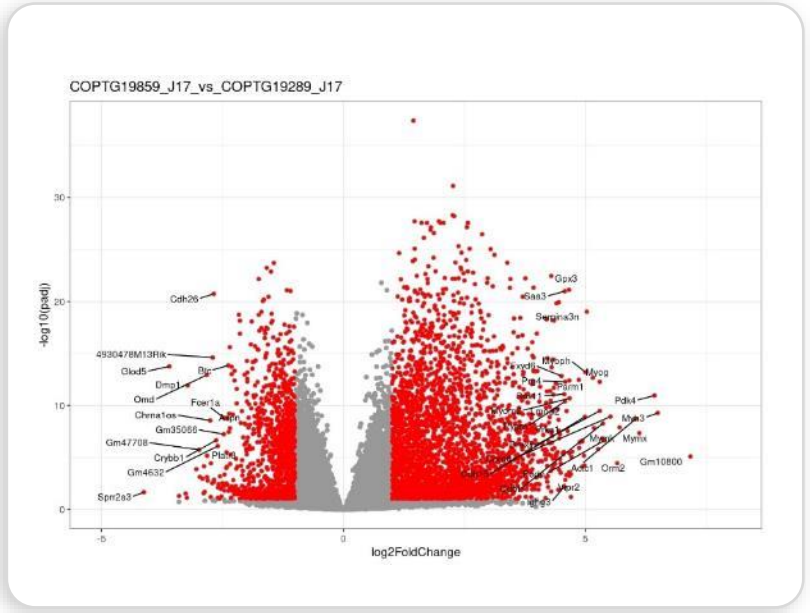
Differential transcriptomic analysis (3' RNASEQ), CT26 model, early time points (D11, 15, 17)

"Empty" vector VS mVV-IL12-X

Day 11 — Day 15 — Day 17



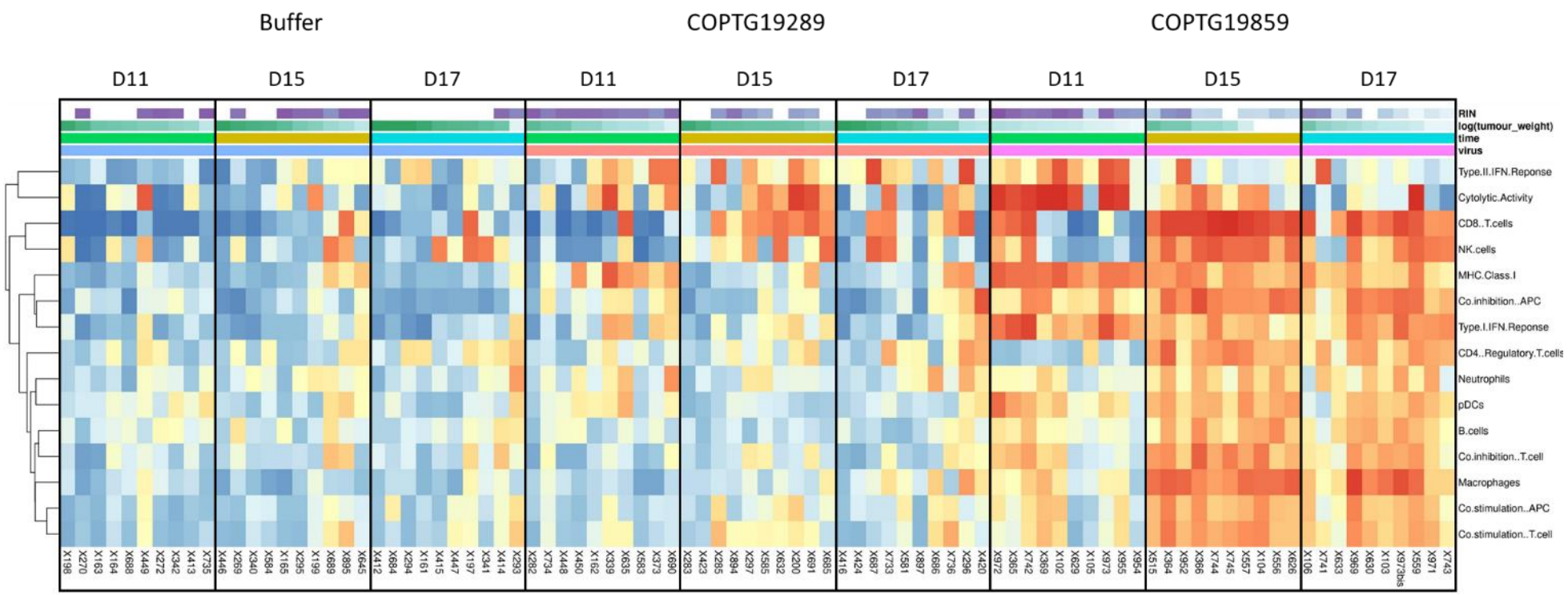




Treatment by **mVV-IL12-X** induced much more transcriptional changes than the vector

Very Large Involvement of Multiple Pathways in Anti-Tumor Response (2/2)

Differential transcriptomic analysis (3' RNASEQ), CT26 model, early time points (D11, 15, 17)



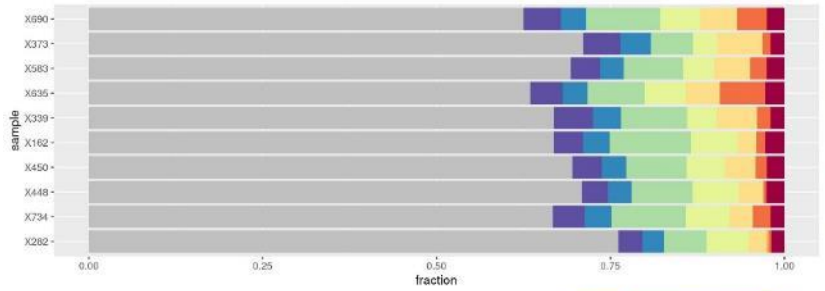
Treatment by **mVV-IL12-X** induced the upregulation of several innate and adaptive immune pathways

Deconvolution of Immune Cell Subtypes Using Expression Signature

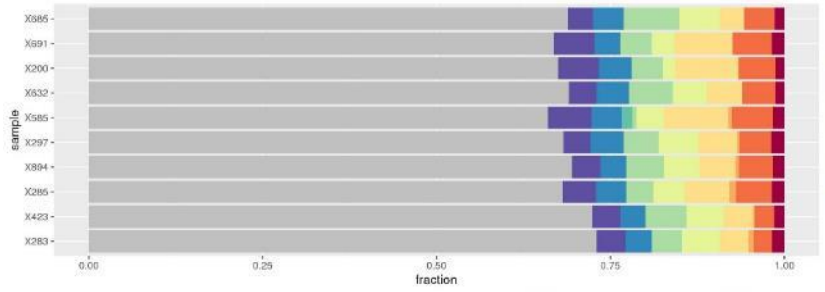
TIMER 2.0 - Quantiseq

Empty vector

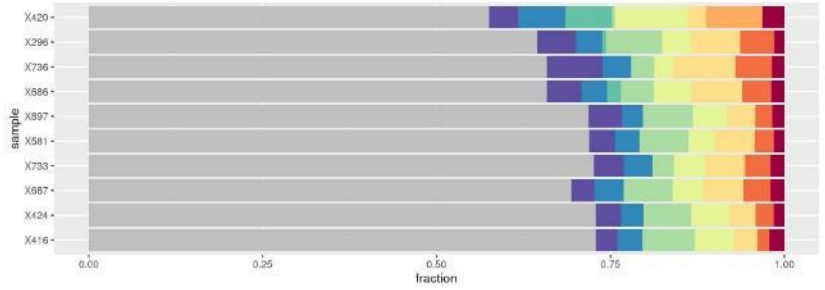
D11



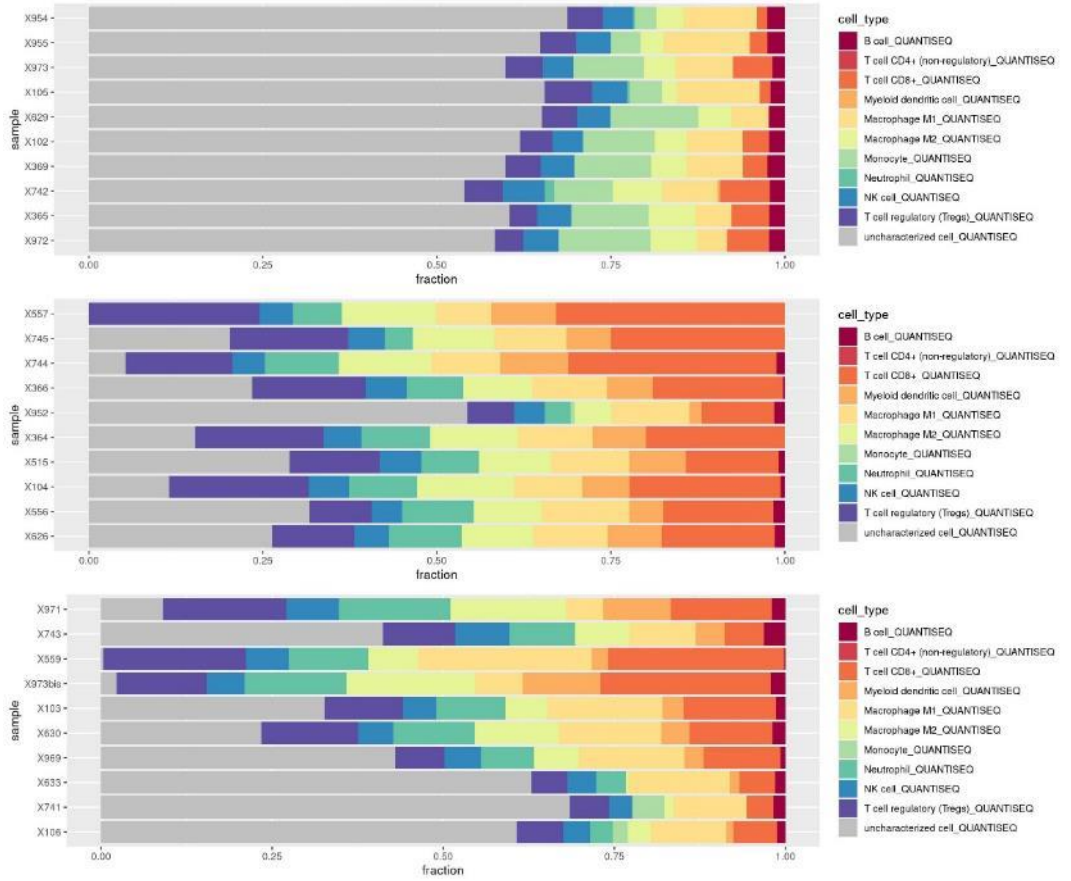
D15



D17



mVV-IL12-X



Treatment by **mVV-IL12-X** induced **tumor infiltration** by CD8, neutrophils, DC and Treg

Summary and Next Steps

- **VV-IL12-X is a novel candidate product which incorporates all lessons learned from our experience with oncolytic virotherapy in the IV** : improved vector (DM2L), potent payloads, stronger promoter for rec. MAb, improved GMP manufacturing process
- **Tumor-specific delivery of IL-12** into the tumor via oncolytic vector is associated with strong antitumoral activity in syngenic models
- The **pleiotropic mode of action** of VV-IL12-X engages a large set of immune mechanisms*, as the result of synergistic effects between VVCOP vector itself, IL-12, and recombinant Mab
  * induction of immune CD8+ memory cells, tumor-specific T cell response higher than vector-specific T cells, upregulation of both innate and adaptive immune pathways, immune infiltration, etc.
- **Very good tolerance** of the novel vector (DRF studies IV in NHP available, pivotal tox study in progress) would allow high dose regimen in the IV route, in combination with anti-PD1, to target very challenging solid tumors with high medical need
- Lung cancer identified as indication of choice
- **Ready to move into clinical development** also from a CMC standpoint

invir io a Versatile Platform Enabling Multiple Collaborations with Potential Future Value

STEVEN BLOOM
Chief Business Officer
Transgene

Invir.IO™ Oncolytic Viruses Are Designed to Address Most Cancer Indications

Competitive Advantage of the Patented Backbone $VV_{cop}TK^{-}RR^{-}$ from Invir.IO™ Platform

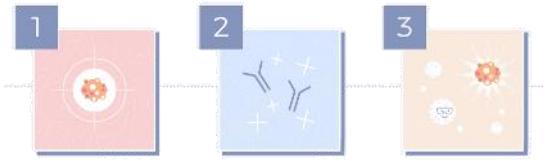
Safety and Selectivity

Patented $TK^{-}RR^{-}$ deletion for enhanced tumor selectivity

Broad spectrum infectivity
Can infect all types of tumor cells

No nucleus integration

Tumor eradication including metastases



Multiple modes of action

Highly infective capabilities and **strong lytic effect**

Good immunological balance (Th1 vs Th2, anti-tumor vs anti-viral responses, etc.)

Broad applicability

Large capacity (up to 25kb)

Several payloads can be encoded in one multi-armed OV

Immune and TME modulators (incl. full length Ab), immune booster, prodrug activators, …

Can address all solid tumors

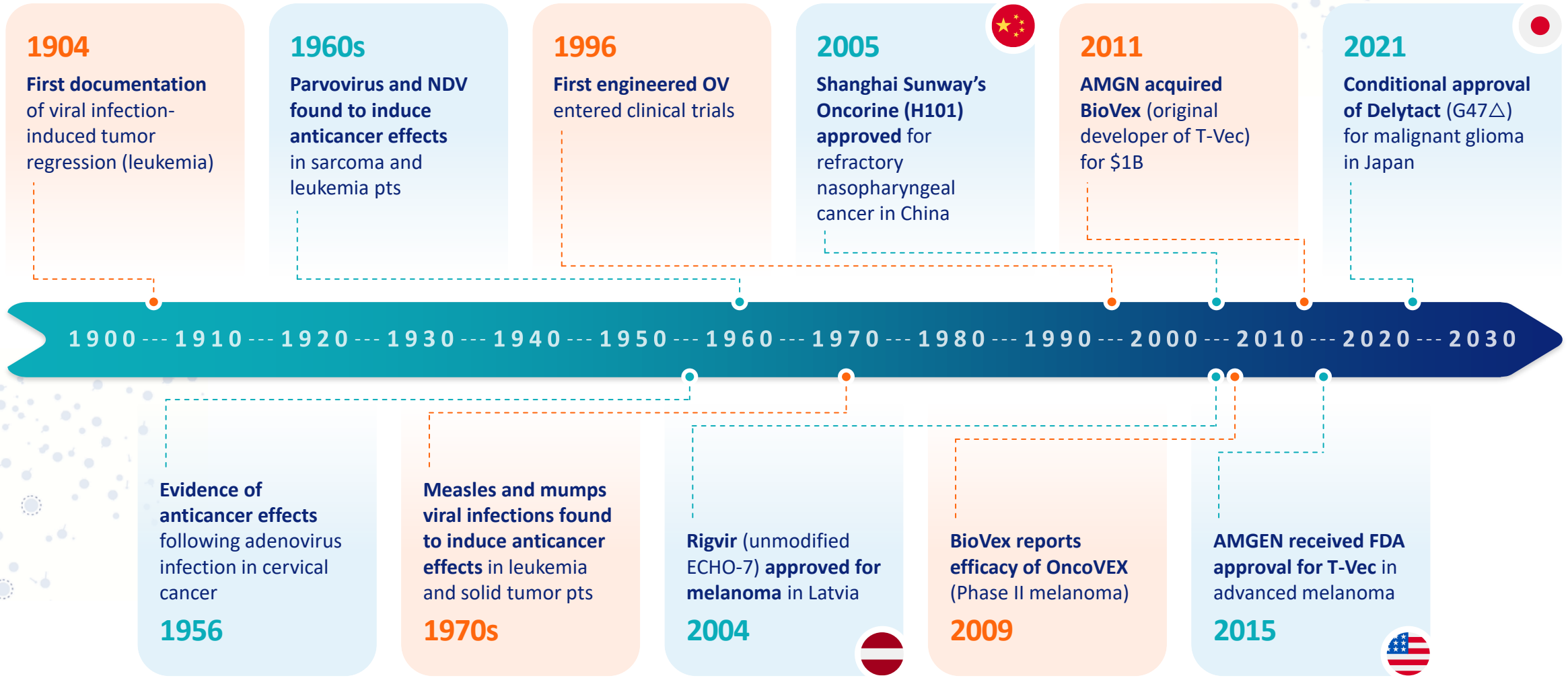
Demonstrated PoC of IV administration

Strong back record of clinical use

Well established process for GMP manufacturing

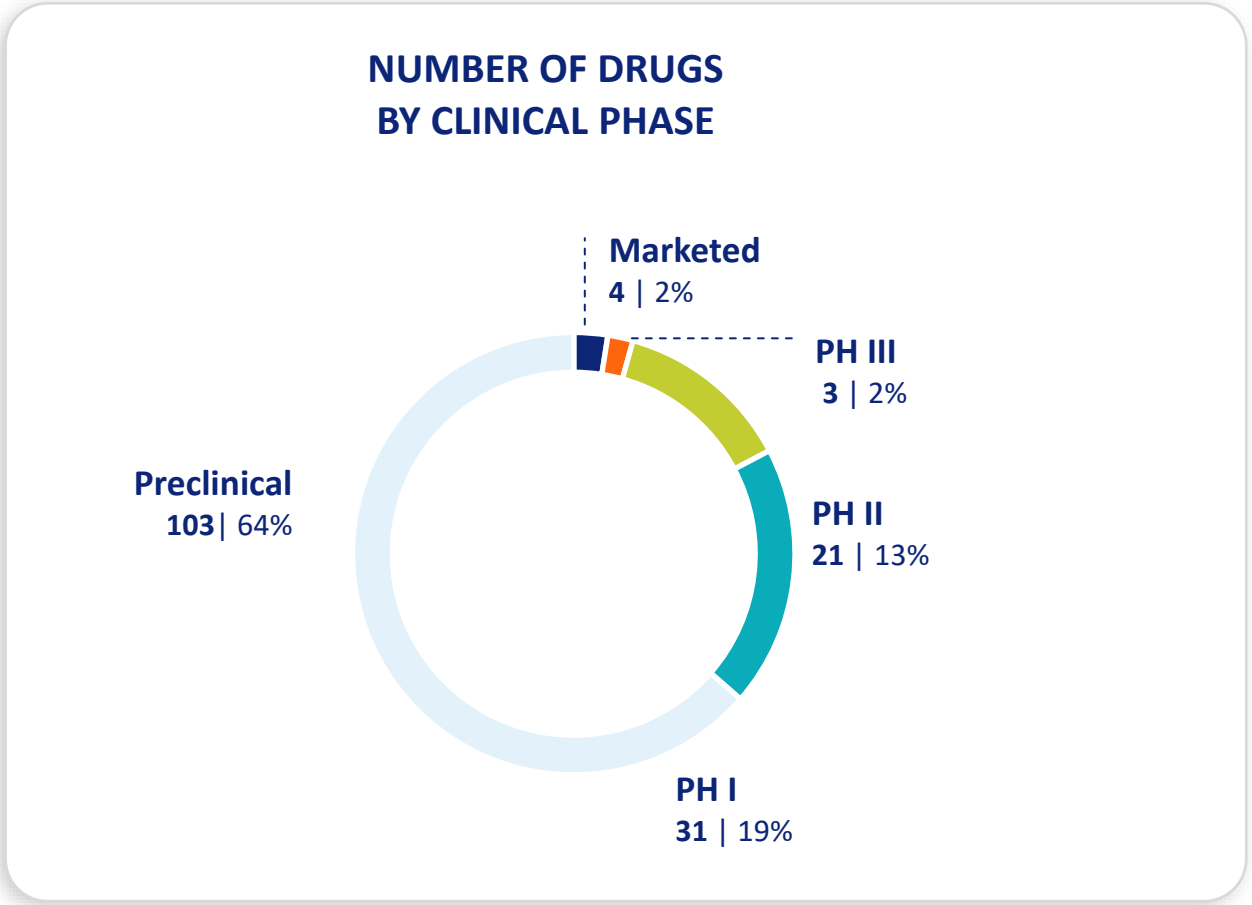
Oncolytic Virus Technology Evolution

Key events in oncolytic virus drug development



Source: Piper Sandler Research

Oncolytic Virus Development is an Active Space



Source: Pharmaprojects, June 2022

2022 Oncolytic Virus (OV) Landscape

Market Leadership Race – IV route of administration is the big prize

OV's are being developed for approximately 40 different types of cancer - mainly solid tumors

112 OV programs are in clinical development (IV and IT) - Only 25 IV trials in the clinic; all < Ph2

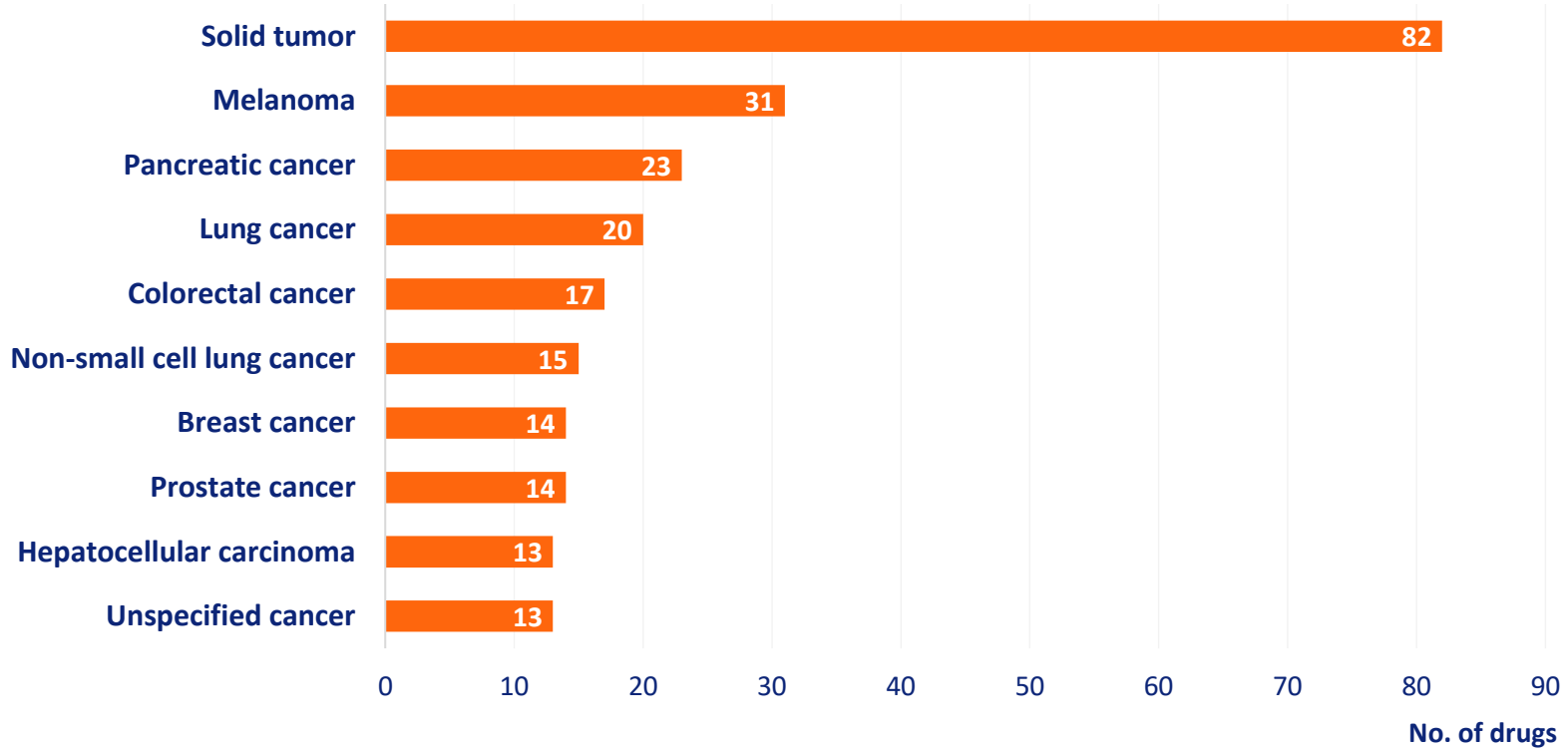
IV administration of an OV creates many potential solid tumor pathways to approval - higher cancer incidence rates represent a larger market opportunity

Combination strategies with CPI's could improve OV activity profiles **and attract** big pharma partnering opportunities

Oncolytic Virus (OV) Development

Target Indications

Drugs by indication



More than a half of OV's are developed in solid tumors

Source: GlobalData

Oncolytic Virus Development – Leading Encoded Genes by Cancer Type

Top Encoded Genes In Oncolytic Virus Therapies

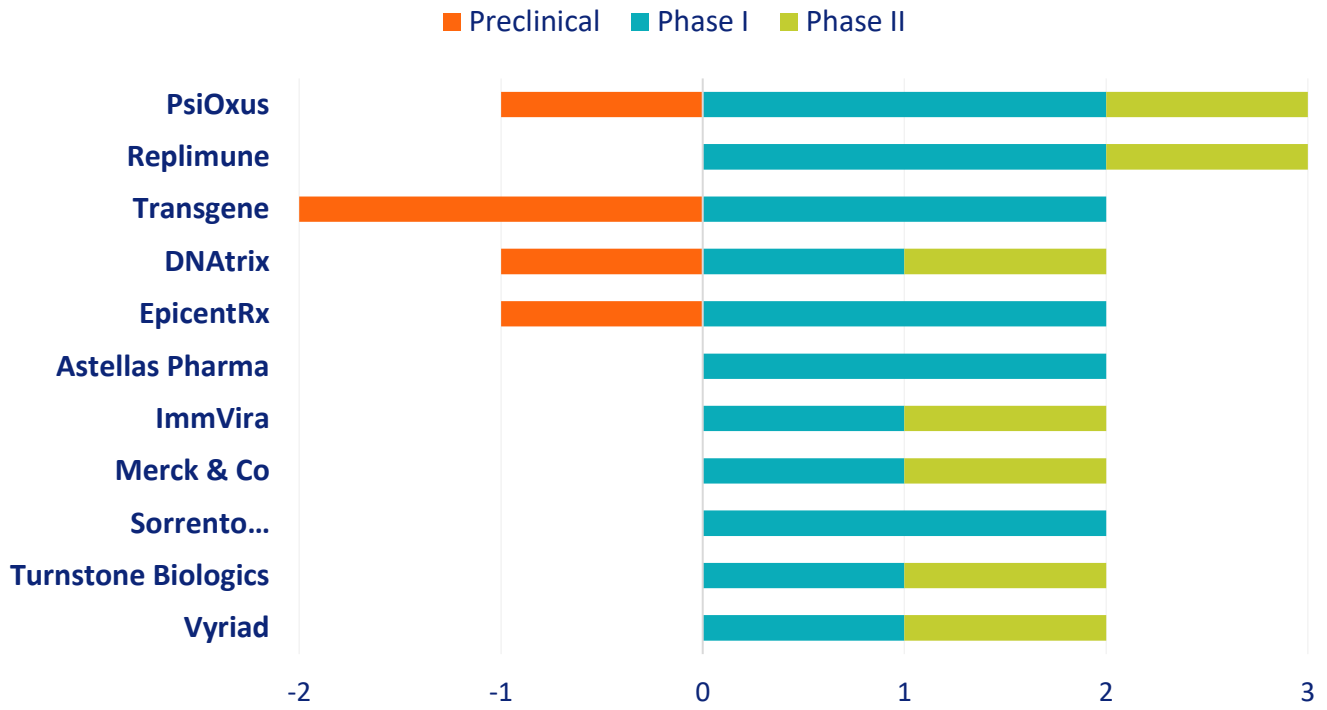
Cancer Type	Top Encoded Genes
Bladder	GM-CSF, mTOR, STAT
Brain	IL13, PVR, thymidylate synthetase
Breast	GM-CSF, CTLA-4, PVR, FLT3L
Colorectal	GM-CSF, CTLA-4, PD1, PVR
Head and Neck	GM-CSF, CTLA-4, STAT, mTOR
Liver	GM-CSF, TNF4
NSCLC	IFN-beta
Melanoma	GM-CSF, CTLA-4, IL2, PD1, PVR, TNF
Ovarian	IL2, TNF
Pancreatic	mTOR, STAT

Source: Pharmaprojects, June 2022

Oncolytic Virus Development Landscape

Company Portfolio Leadership

Top competitors in the oncolytic virus space



Source : Bonello. " A Promising Future For Oncolytic Viruses As Cancer Immunotherapies", Pharmaprojects, June 2022

Transgene Invir.IO™ Collaboration Strategy

Assisting Companies Throughout the LCM Planning Process

Novel OV constructs
(AZ and BioInvent Partnerships)

Synergize mechanisms
with IO programs

Salvage "pharma partner" de-prioritized programs
- Toxicity signal
- Optimize tumor targeting potential

Life cycle management
(LCM) planning

Transgene invir.IO™ Value Proposition

Great Science, Growing Pipeline, Focused Business Plan

Transgene aspires to be a world leader in innovative cancer therapies - Hedi Ben-Brahim, CEO - 7/9/22

Transgene will continue to grow the invir.IO™ platform of programs focused on IV and IT ROA's - become the market leader in the IV delivery space

Transgene is a partner of choice for biopharma companies looking to vectorize key target payloads

Transgene is committed to continuous improvement of its OV backbone technology

Q & A

transgene

3

Business, Scientific and Medical Perspectives

Agenda

BUSINESS, SCIENTIFIC, AND MEDICAL PERSPECTIVE

TIME	TOPIC	SPEAKER
5:25 pm – 5:45 pm	Opportunities in the immuno-oncology field	*Pedro Romero*
5:45 pm – 5:55 pm	Closing remarks	*Hedi Ben Brahim*

Opportunities in the immuno-oncology field

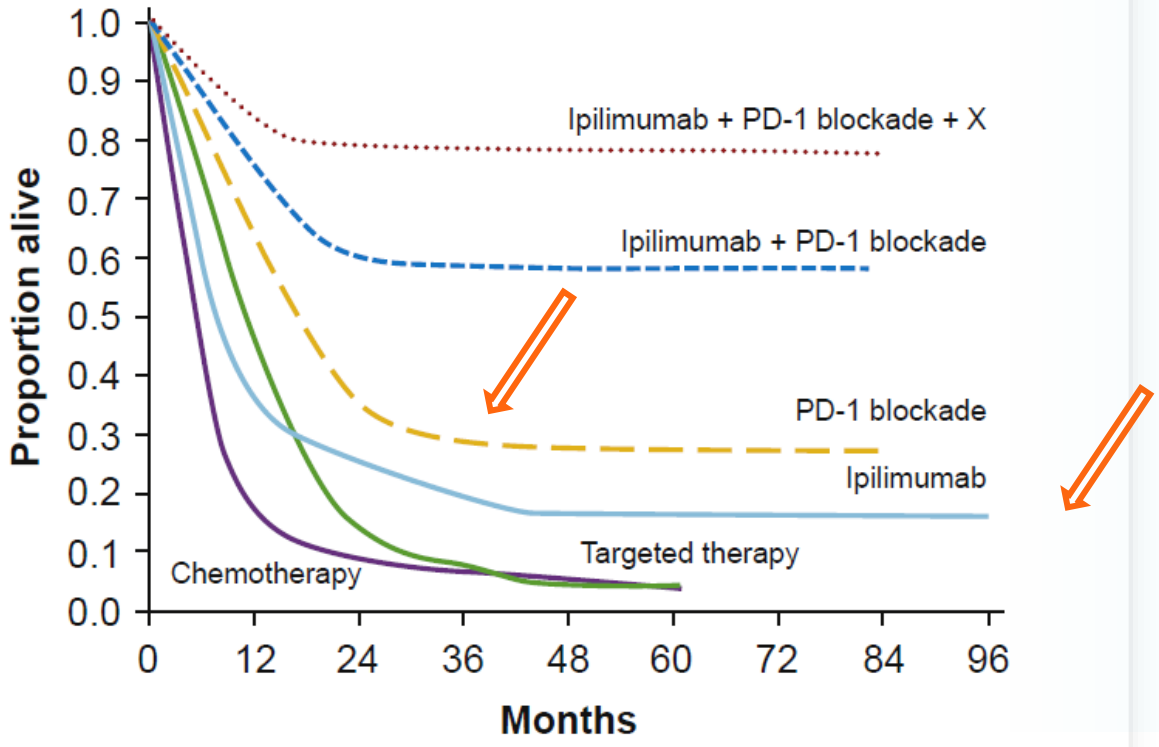
LUDWIG CANCER RESEARCH

Journal for ImmunoTherapy of Cancer

PEDRO ROMERO, MD, PhD
Chief Editor of the JITC
Deputy scientific managing director of the Lausanne Branch of the Ludwig Institute for Cancer Research

transgene

A Model Illustrating The Potential Impact of Single Agent and Combination Cancer Immunotherapies on Survival



~70%

Therapeutic vaccines

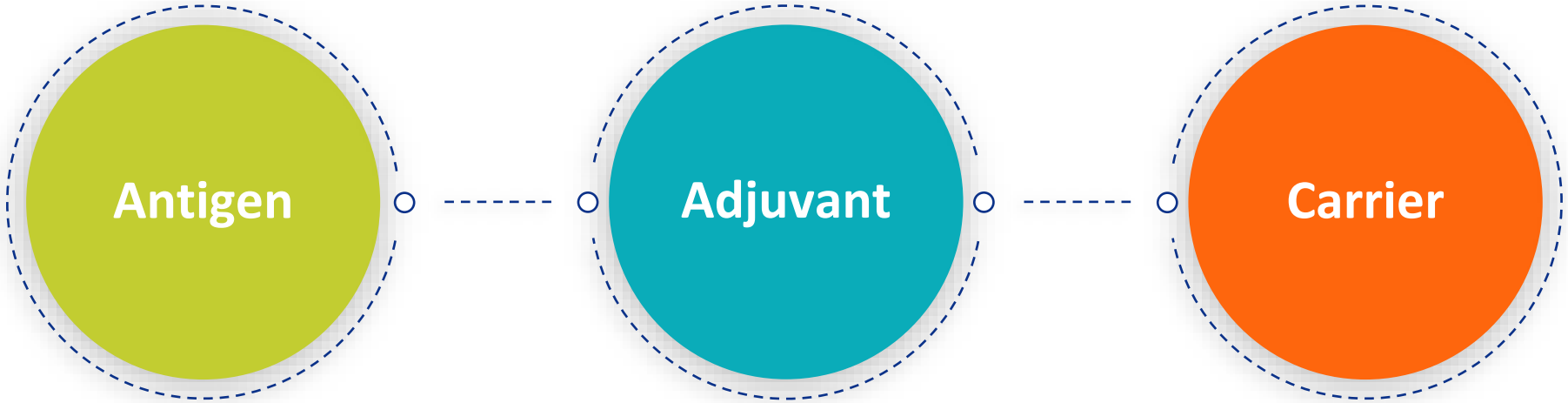
HOT TUMORS

Emens L et al. Eur J Cancer 2017

The Goals for Cancer Vaccines

- Elicit (de novo) tumor antigen specific T cell responses
- High levels of tumor reactive CD8 T cells
- **Recruit the highest TCR affinity/avidity clonotypes**
- Achieve tumor infiltration and a type I polarity
- **Long lived memory T cell immunity**

Molecularly Defined Vaccines



Cancer Vaccines Based on CTL-Defined Tumor Antigens

1. **Shared, tumor specific antigens**
(e.g: MAGE-A3, NY-ESO-1)

2. **Differentiation antigens**
(e.g: gp100, PSA, CEA)

3. **Overexpressed antigens**
(e.g: HER-2/neu, WT-1)

4. **Mutated, unique antigens**
(e.g: MUM-1, idiotypes)

5. **Virus encoded antigens**
(e.g: HPV-16 E6/E7, HBV, HCV)

~300 T cell defined tumor antigens, short peptides

http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm

Intense Early Clinical Trial Testing, Even Phase III and One Approval in Cancer Vaccines

Prostate:
Provenge (PSMA), GVAX, Prostvac (PSA)

Renal Cell Carcinoma:
IMA 109 (eluted peptides), G250

Lung cancer:
MAGRIT (MAGE-A3), Tecemotide (MUC-1)

Breast cancer:
WT-1 in neoadjuvant in TNBC; dHER2/AS15 in adjuvant HER2+ BC

Glioblastoma:
EGFTvIII (30% gliomas), IMA 950 (eluted peptides)

Melanoma:
DERMA (MAGE-A3), peptides, rt vectors, DCs

Lymphomas:
Idiotypes

LETTER

https://doi.org/10.1038/s41586-018-0810-y

Actively personalized vaccination trial for newly diagnosed glioblastoma

Norbert Hilf[1,26], Sabrina Kuttruff-Coqui[1,26], Katrin Frenzel[2], Valesca Bukur[2], Stefan Stevanović[3,4], Cécile Gouttefangeas[3,4,5], Michael Platten[6,7,8], Ghazaleh Tabatabai[3,4,9], Valerie Dutoit[10], Sjoerd H. van der Burg[5,11], Per thor Straten[5,12,13], Francisco Martínez-Ricarte[14], Berta Ponsati[15], Hideho Okada[16,17], Ulrik Lassen[18], Arie Admon[19], Christian H. Ottensmeier[20], Alexander Ulges[1], Sebastian Kreiter[2,5], Andreas von Deimling[6,7], Marco Skardelly[9], Denis Migliorini[10], Judith R. Kroep[11], Manja Idorn[12,13], Jordi Rodon[14,22], Jordi Piró[15], Hans S. Poulsen[18], Bracha Shraibman[19], Katy McCann[20], Regina Mendrzyk[1], Martin Löwer[2], Monika Stieglbauer[3,5], Cedrik M. Britten[2,5,23], David Capper[6,7,24], Marij J. P. Welters[5,11], Juan Sahuquillo[14], Katharina Kiesel[1], Evelyna Derhovanessian[2], Elisa Rusch[3,5], Lukas Bunse[6,7], Colette Song[1], Sandra Heesch[2], Claudia Wagner[1], Alexandra Kemmer-Brück[2], Jörg Ludwig[1], John C. Castle[2,25], Oliver Schoor[1], Arbel D. Tadmor[21], Edward Green[7,8], Jens Fritsche[1], Miriam Meyer[1], Nina Pawlowski[1], Sonja Dorner[1], Franziska Hoffgaard[1], Bernhard Rössler[1], Dominik Maurer[1], Toni Weinschenk[1], Carsten Reinhardt[1], Christoph Huber[2], Hans-Georg Rammensee[3,4], Harpreet Singh-Jasuja[1], Ugur Sahin[2], Pierre-Yves Dietrich[10] & Wolfgang Wick[6,7]*

Reasons for Cancer Vaccines' Modest Clinical Impact

Tolerant T cell repertoire to self antigen, hence the value of neoantigens and viral antigens

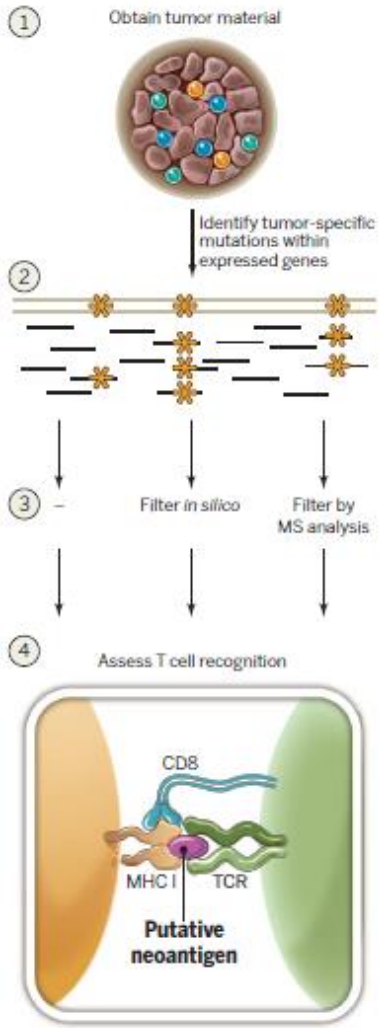
Monovalent antigen vaccines which lead to immune selection and tumor escape

Delivery methods of the vaccine remain suboptimal

Immune suppressive microenvironment

Romero et al. Sci Trans Med 2016

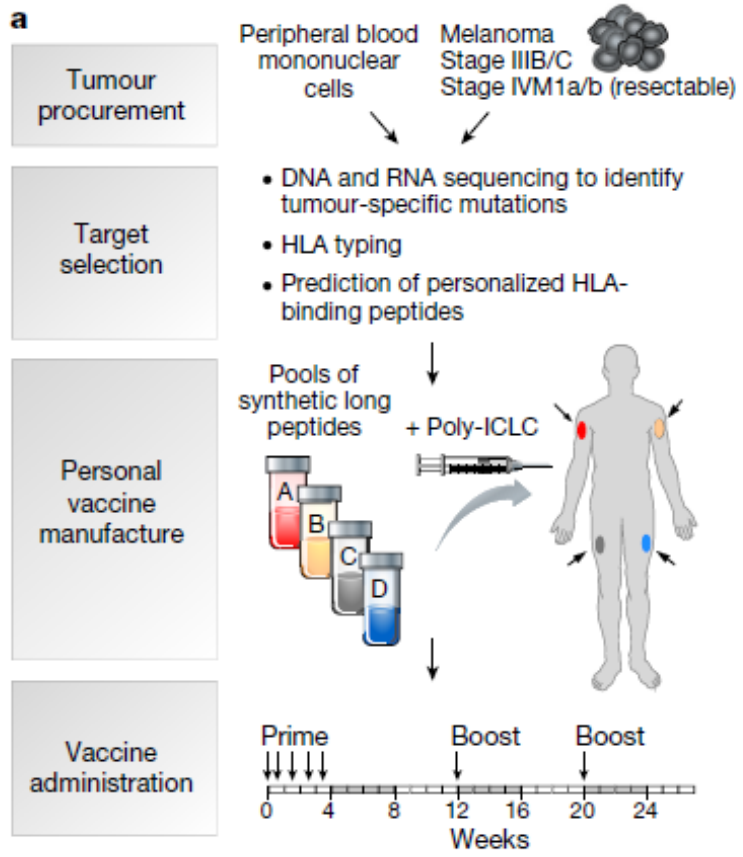
A New Generation of Tumor Specific Antigens: the « Neoantigens »



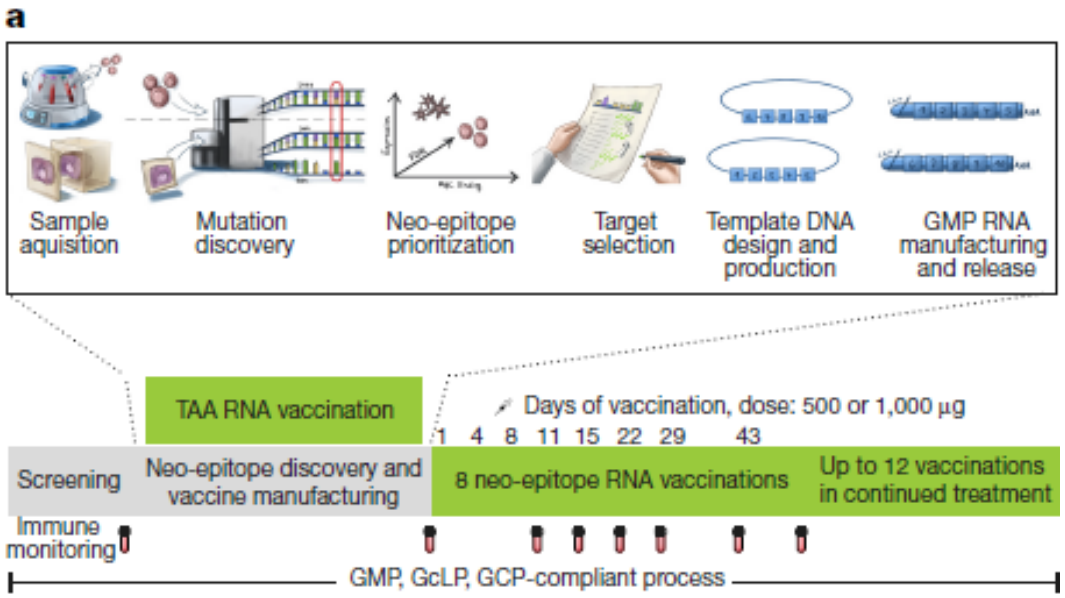
Schumacher & Schreiber, Science 2015

- **Somatic mutations**
- **No central tolerance**
- **Highly individual**

Neoantigen-based Anti-Cancer Vaccine



Ott PA et al. Nature 2017



Sahin U et al. Nature 2017

Cell

Article

A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer

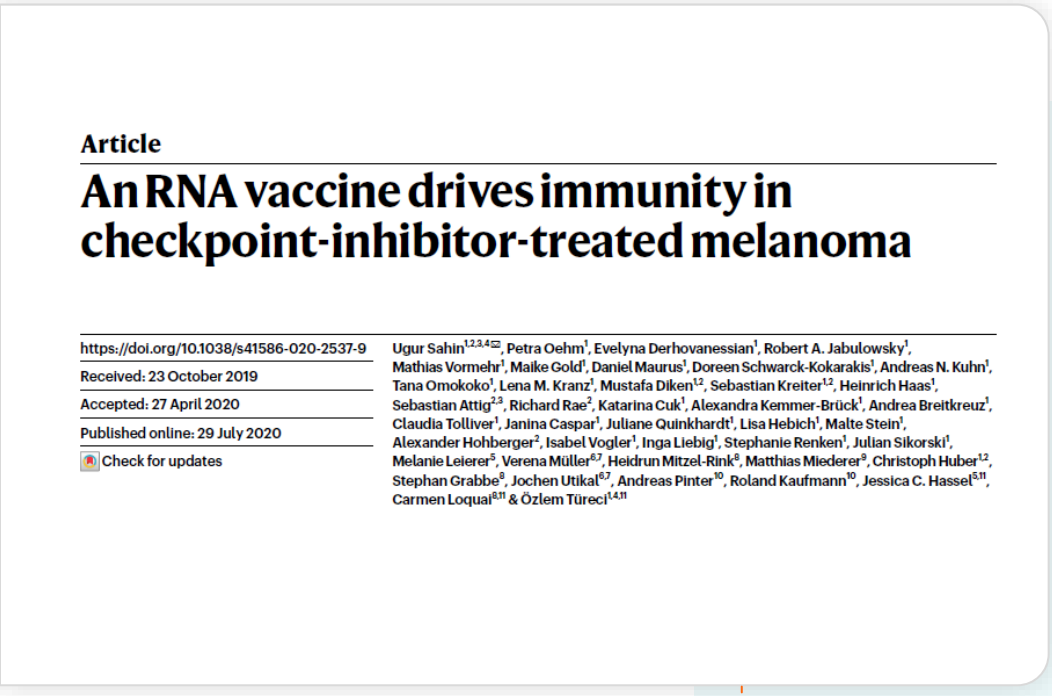
- The **personalized neoantigen vaccine** Neo-PV-01 plus nivolumab is feasible and safe
- NEO-PV-01 plus nivolumab **stimulates durable neoantigen specific T cell** reactivity
- NEO-PV-01**-specific T cells have cytotoxic potential and can traffic to the tumor**
- NEO-PV-01 induces **epitope spreading** consistent with vaccine-mediated tumor cytotoxicity

transgene

Ott P et al. Cell 2020

Melanoma FixVac (BNT111), an Intravenously Administered Liposomal RNA (RNA-LPX) Vaccine

(Lipo-MERIT trial, ClinicalTrials.gov identifier NCT02410733)



Article

An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma

https://doi.org/10.1038/s41586-020-2537-9
Received: 23 October 2019
Accepted: 27 April 2020
Published online: 29 July 2020
Check for updates

Ugur Sahin[1,2,3,4✉], Petra Oehm[1], Evelyna Derhovanessian[1], Robert A. Jabulowsky[1], Mathias Vormehr[1], Maike Gold[1], Daniel Maurus[1], Doreen Schwarck-Kokarakis[1], Andreas N. Kuhn[1], Tana Omokoko[1], Lena M. Kranz[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Heinrich Haas[1], Sebastian Attig[2,3], Richard Rae[2], Katarina Cuk[1], Alexandra Kemmer-Brück[1], Andrea Breitkreuz[1], Claudia Tolliver[1], Janina Caspar[1], Juliane Quinkhardt[1], Lisa Hebich[1], Malte Stein[1], Alexander Hohberger[2], Isabel Vogler[1], Inga Liebig[1], Stephanie Renken[1], Julian Sikorski[1], Melanie Leierer[5], Verena Müller[6,7], Heidrun Mitzel-Rink[6], Matthias Miederer[9], Christoph Huber[1,2], Stephan Grabbe[8], Jochen Utikal[6,7], Andreas Pinter[10], Roland Kaufmann[10], Jessica C. Hassel[5,11], Carmen Loquai[8,11] & Özlem Türeci[1,4,11]

Sahin U et al. Nature 2020

- **Alone or in combination** with blockade of the checkpoint inhibitor PD1, mediates **durable objective responses in checkpoint-inhibitor (CPI)-experienced patients** with unresectable melanoma.
- **Clinical responses** are accompanied by the **induction of strong CD4+ and CD8+ T cell immunity** against the vaccine antigens.
- The antigen-specific cytotoxic T-cell responses in some responders **reach magnitudes typically reported for adoptive T-cell therapy**, and are durable.
- **RNA-LPX vaccination is a potent immunotherapy in patients with CPI-experienced melanoma**, and suggest the **general utility of non-mutant shared tumour antigens as targets** for cancer vaccination.

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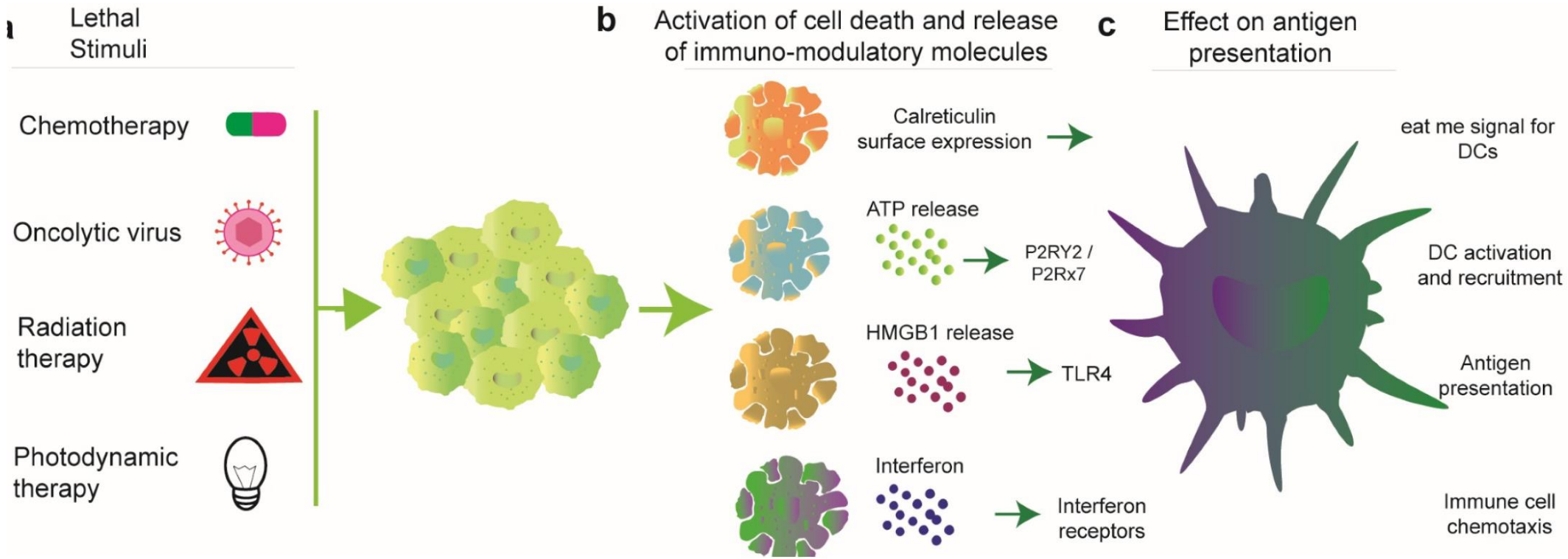
Immunogenic Tumor Cell Death

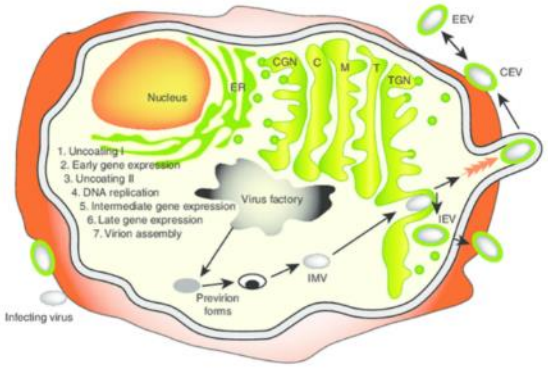


Workenhe ST et al, Oncoimmunol 2021

Vaccinia Virus Life Cycle

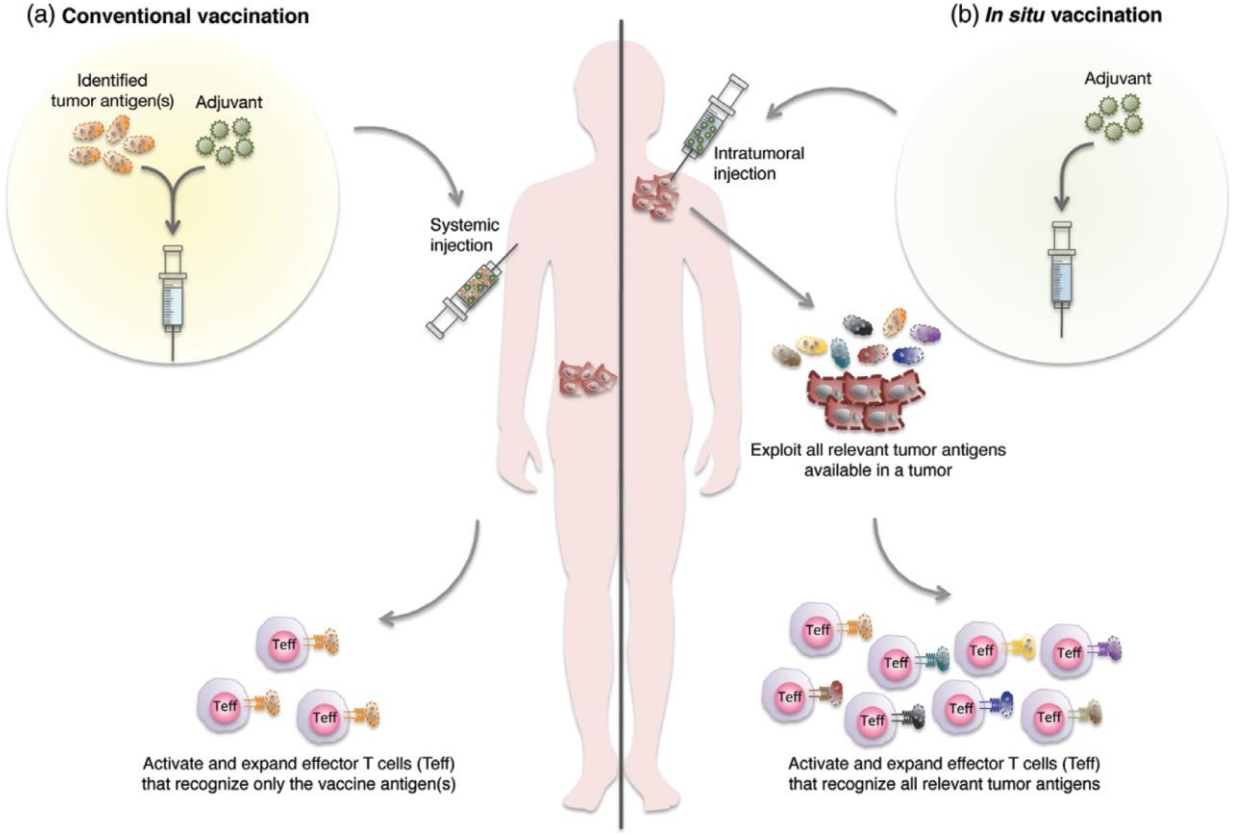
Virus	W	Herpes simplex virus (HSV)	Coxsackievirus A21, B3 (CVA21 and CVB3)
Genome	dsDNA (~ 180-Kb, 200 genes)	dsDNA (~ 152-kb, 80 genes)	(+) ssRNA (~ 7.4-Kb, one polyprotein)
Capacity of inserted DNA	25–40 Kb	30–40 Kb	300 bases for stable recombinant
Tumor selectivity (once inside the cells)	Pexa-Vec selectively replicates in and destroys cancer cells driven by genetic pathways commonly activated in cancers.	T-VEC: two mutations make up cancer selectivity with activated Ras and high endogenous ribonucleotide reductase	Aberrant signaling pathways within tumor cells On cell surface: CVA21: ICAM-1 dependent. CVB3: CAR dependent
Life cycle	Cytoplasm (no risk of integration)	Nucleus (more risk of integration)	Cytoplasm
Mechanisms of cell death	Apoptosis and necroptosis (ICD)[a]	Apoptosis, necrosis, and pyroptosis (ICD)	Immunogenic apoptosis, autophagy (ICD)
Immunogenicity	High	High	High
Transgene expression	High	High	High
Clinical trial stage	Phase III for liver cancer	T-VEC approved for melanoma	Phase II study in advanced melanoma (CVA21)

[a]*ICD* immunogenic cell death

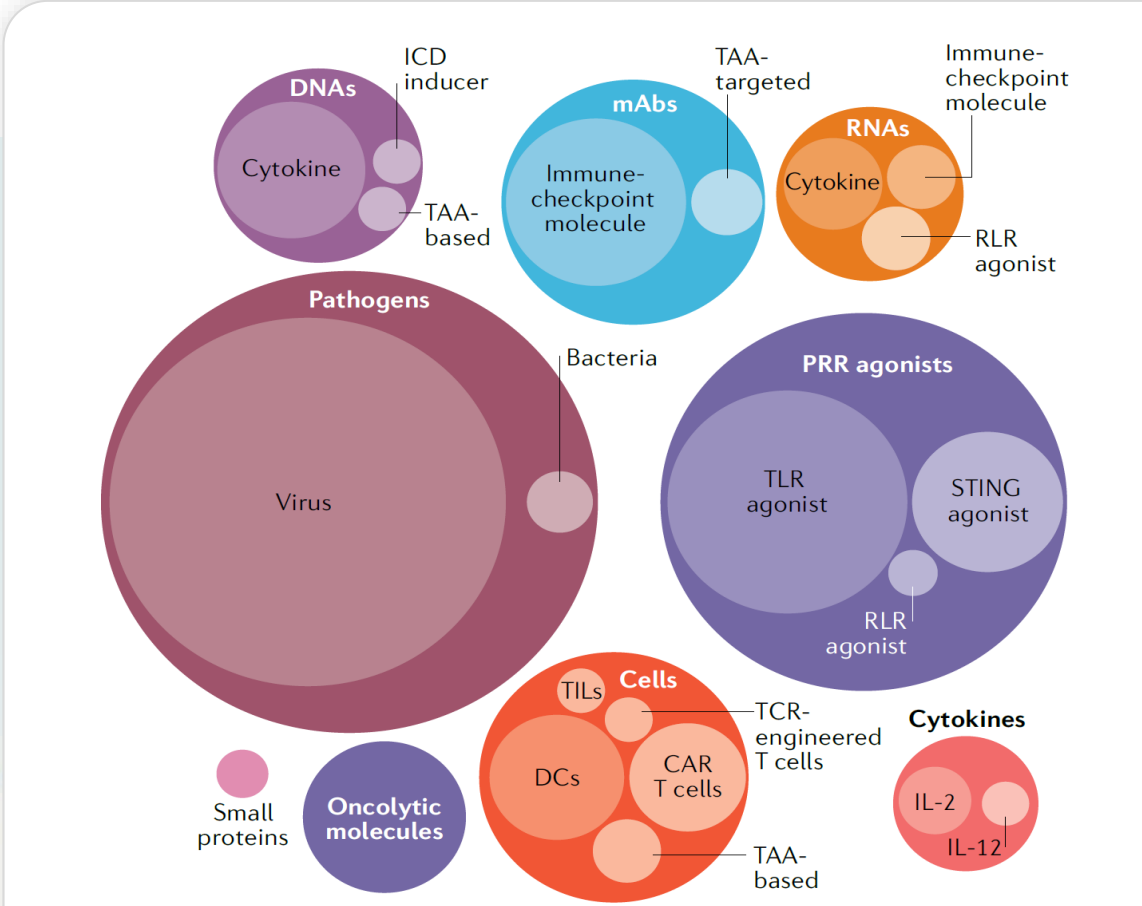


Guo et al, J Immunother Cancer 2019

Conventional Versus In Situ/In Vivo Vaccination

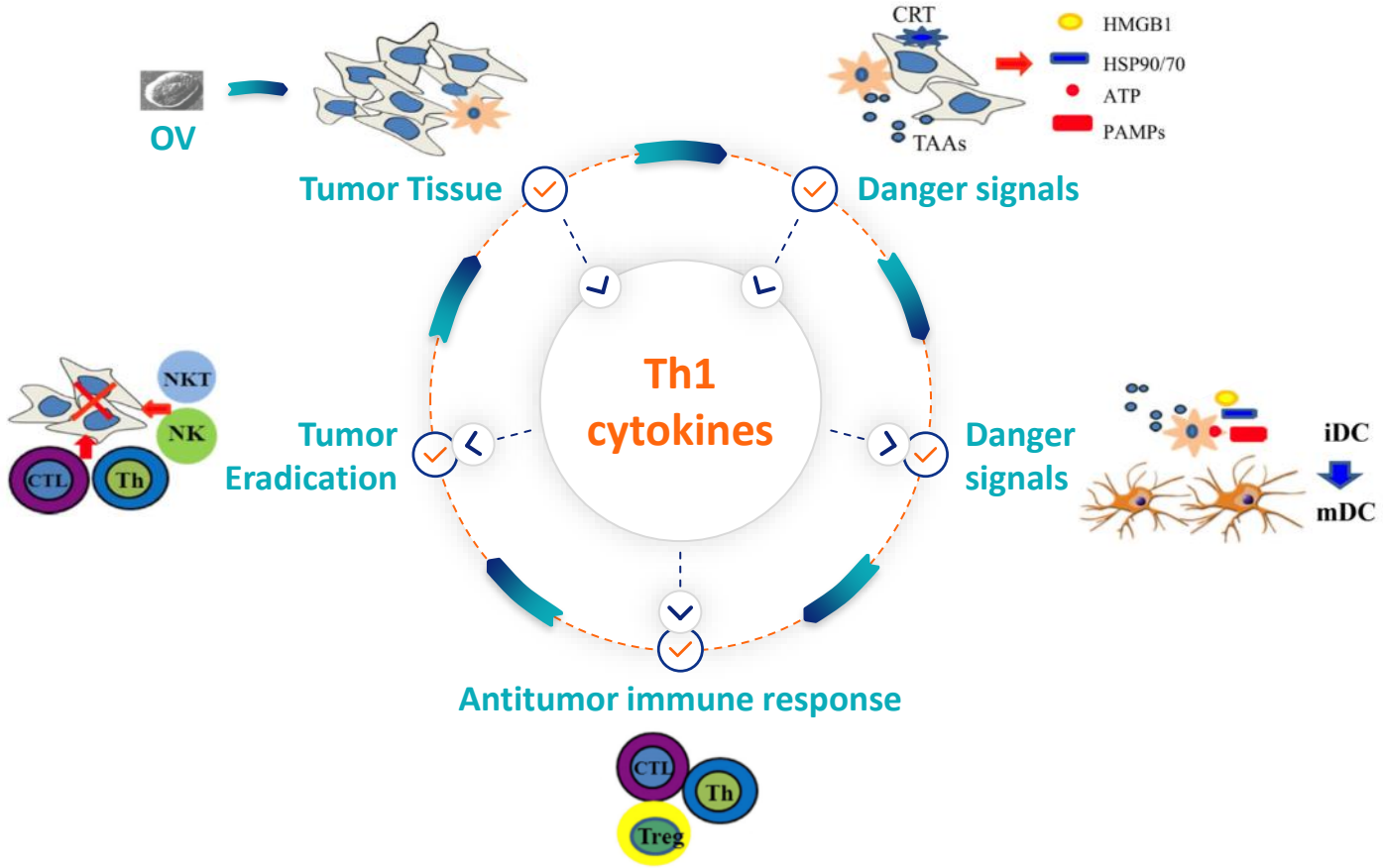


Sheen MR & Fiering S, WIREs Nanomed Nanobiotechnol 2019



Melero I et al, Nat Rev Clin Oncol 2021

Oncolytic Virus-Mediated in Situ Vaccination

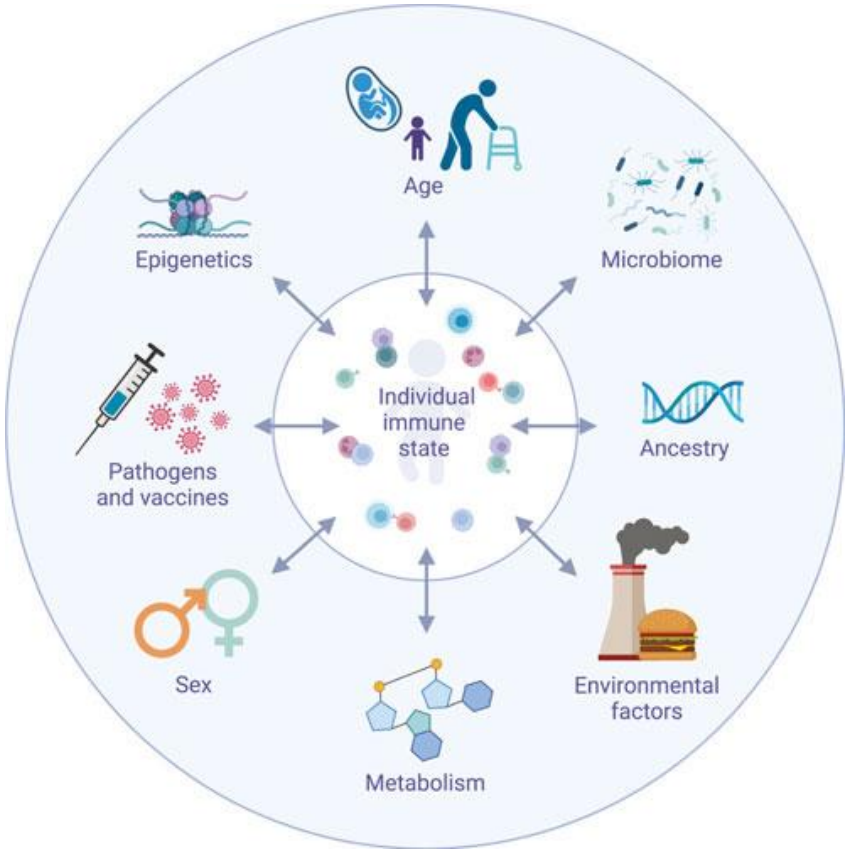


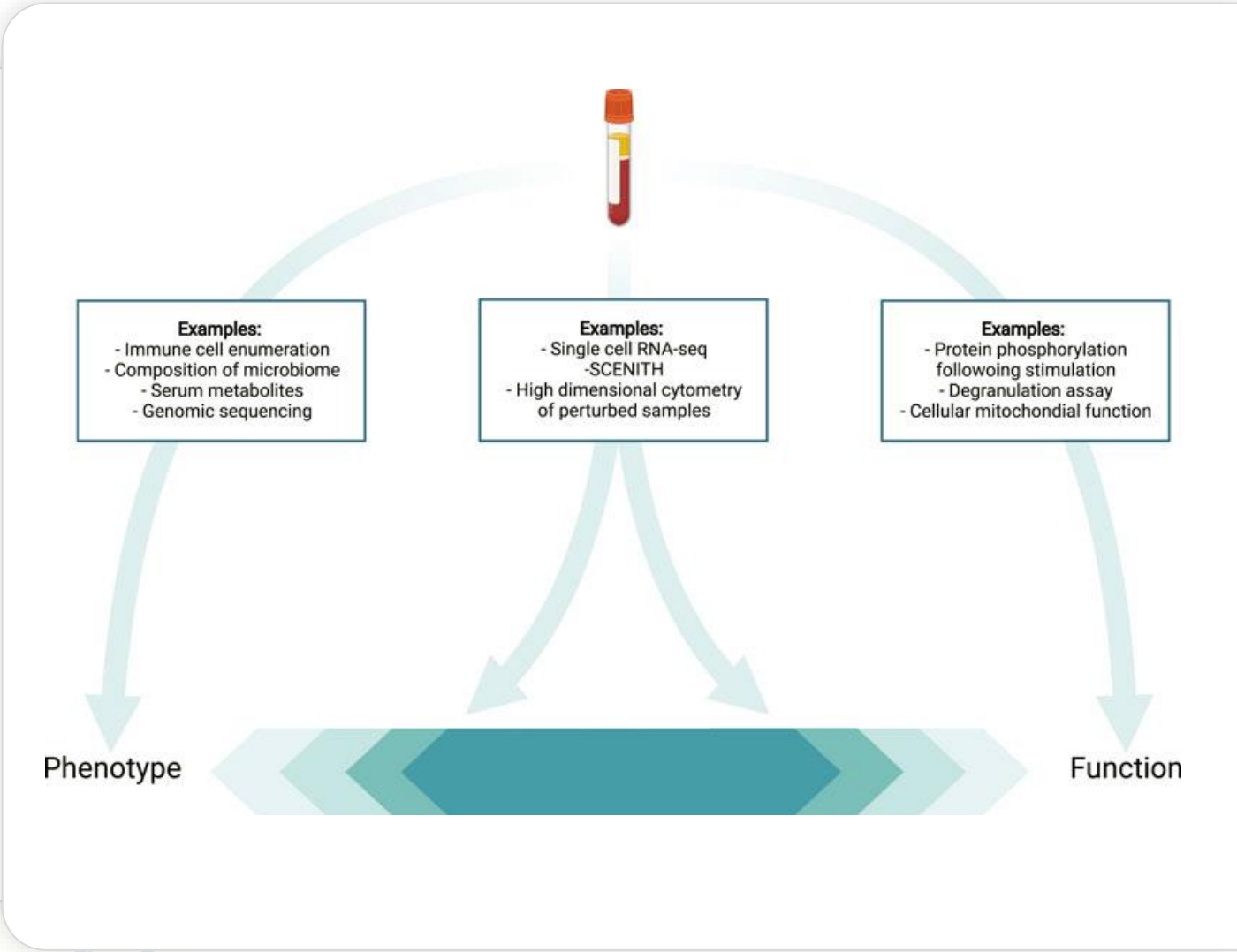
An OV selectively replicates in tumor or/and stromal cells. This leads to induction of ICD, presenting both "find me" (extracellular HMGB1 and ATP) and "eat me" signals on the cell surface (such as ecto-CRT) to phagocytes

Apoptotic bodies and cellular fragments released via ICD are engulfed by APCs, and TAAs are processed into peptides that are presented in MHC class I/II complexes in concert with costimulatory molecules to naive CD8+ and CD4+ T cells, respectively. Such activated T cells may then expand and undergo polarized differentiation predictable on additional immune-stimulatory molecules expressed by recombinant OV

Guo et al, J Immunother Cancer 2019

Immune Fitness, Aging and Immune Senescence





Mauracher AA & Henrickson, Front Systems Biol 2022

Closing Remarks

HEDI BEN BRAHIM
Chief Executive Officer
Transgene

All our Candidates and Platforms Progressed in 2022

TG4001

- Initiate trial in the US
- Include the required number of patients
- On tracks to deliver IA readout in Q4 2022

myvac

TG4050

- Generate and present new positive data at major congresses
- Inclusions completed in the two Phase I trials

invirio

- Deliver clinical data confirming the feasibility of the IV route
- Expand the potential of our technologies through partnerships (AZ, BioInvent, PersonGen, …)
- Select best candidates – VV-IL12-X to enter into clinical development in the IV route
- Continue research effort to further optimize viral backbone

TG6002

- Complete inclusions in the two trials
- Present new Phase I data

BT-001

- Sign clinical collaboration agreement with MSD for the supply of pembrolizumab
- Deliver first Phase I data in monotherapy

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				**Interim analysis Q4 2022**
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	IL-12-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*

Thanks for your attention