TG mutant RAS neoantigen vaccine

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RAS Targeted Drug Discovery Summit

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1 Introduction

2. A vaccine approach to target mutant RAS
3. TG clinical data
4. Summary & conclusions

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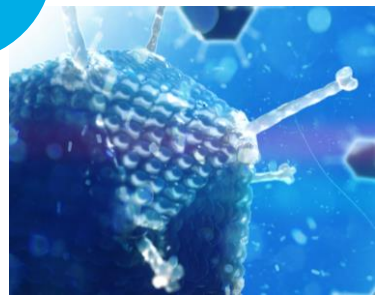
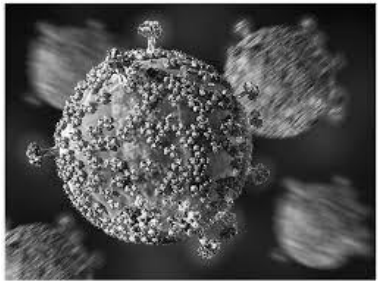
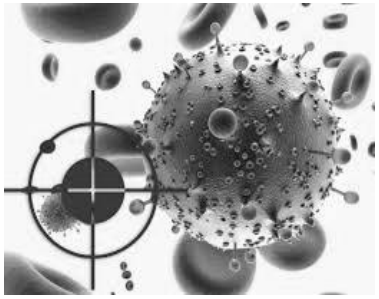
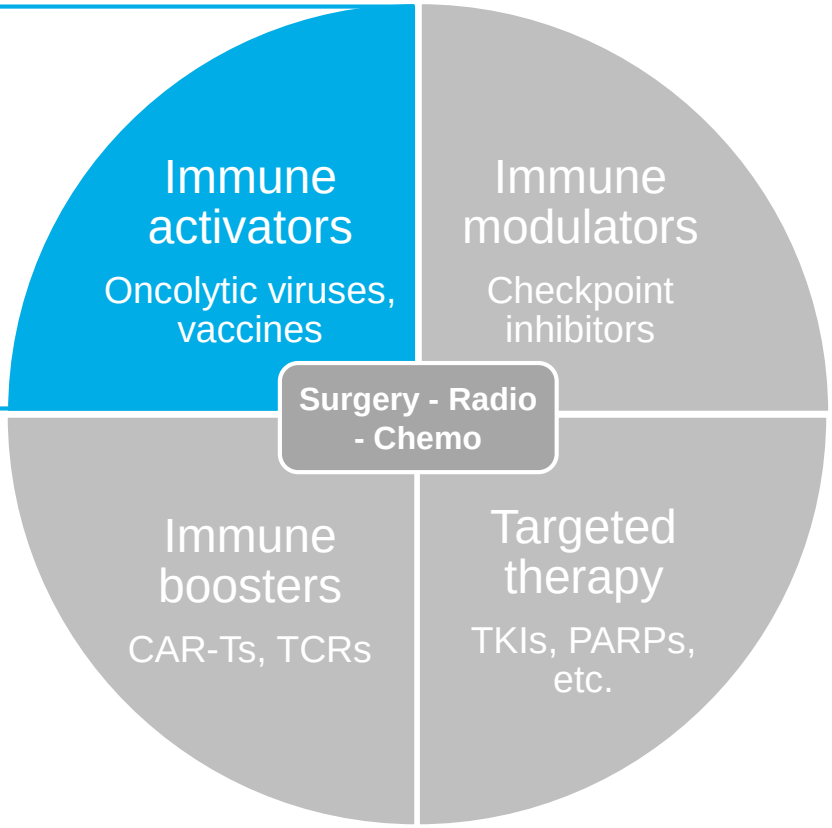
TARGOVAX AIMS TO ACTIVATE THE PATIENT'S OWN IMMUNE SYSTEM TO FIGHT CANCER

Targovax focus

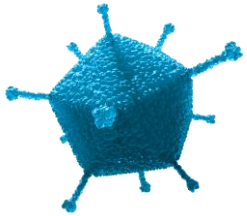






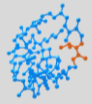


TARGOVAX HAS TWO CLINICAL STAGE IMMUNE ACTIVATOR PROGRAMS



ONCOS
Oncolytic virus

- Genetically **armed adenovirus**
- Turns cold **tumors hot**
- Induces **tumor specific T-cells**
- Single agent **phase I completed**
- **4 ongoing combination trials**



TG
Neoantigen vaccine

- **Shared mutant RAS neoantigen** therapeutic cancer vaccine
- Triggers **T-cell responses** to oncogenic **RAS driver mutations**
- 32 patient **phase I/II trial completed**

Activates the immune system

Triggers patient-specific responses

No need for individualization

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A vaccine approach to target mutant RAS

3. TG clinical data
4. Summary & conclusions

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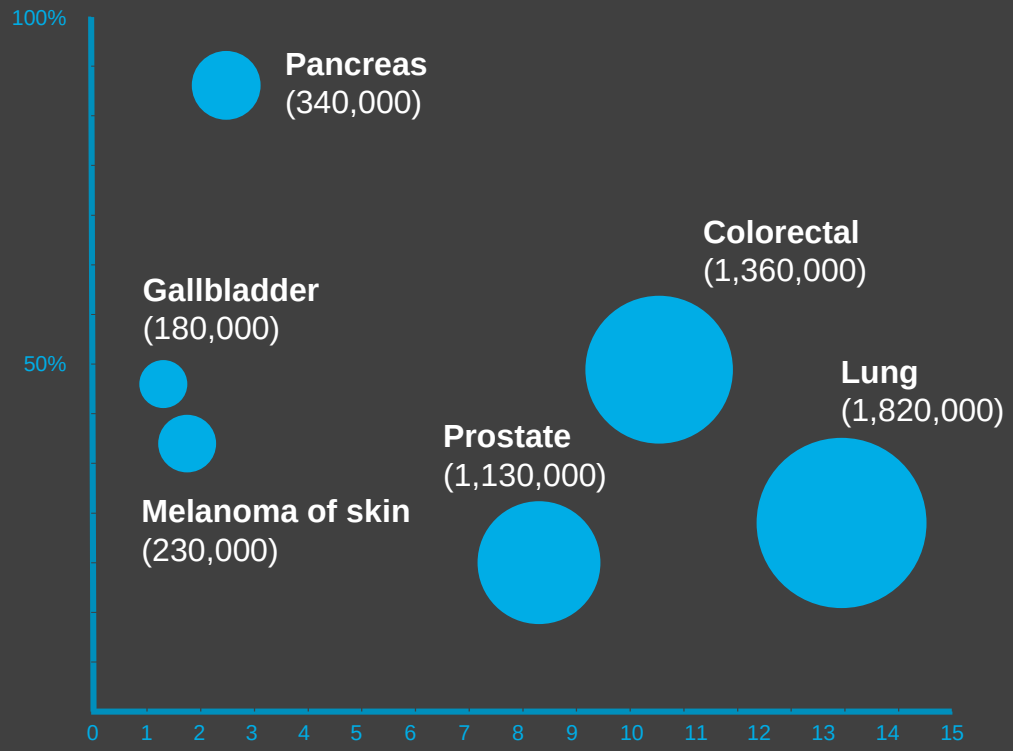
THE RAS GENE IS MUTATED IN 25-30% OF ALL CANCERS

Including 90% of pancreatic and 40% of colorectal cancers

Frequency of RAS mutations

Global cancer incidents per 10,000
(xx) = no. of cancer patients



- RAS is the **most frequently** occurring **driver mutation**
- RAS is a **clinically validated shared neoantigen**
- Mutant RAS has potential as a future **"genetic marker" indication**

Fernandez-Medarde; RAS in Cancer and Developmental Diseases; Genes & Cancer. 2011;2(3)

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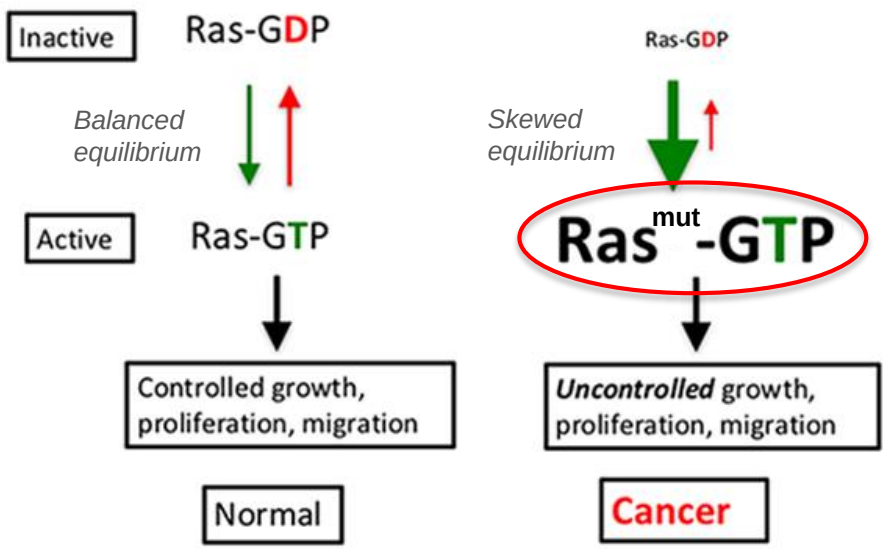
RAS “THE UNDRUGGABLE TARGET”

Oncogenic RAS mutations are key drivers behind uncontrolled cell division



Why is RAS such an elusive target?

- Very high **similarity** between **mutant and wild-type** RAS
- Multiple point **mutation variants**
- Smooth protein surface and **tight binding pocket**
- **Intracellular localization**

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RAS is potentially an excellent target for an off-the-shelf cancer vaccine approach

Neoantigen prevalence	○ RAS is the **most frequently mutated oncogene family** across all cancers ○ RAS is a **true driver mutation**, present on all sub-clones of RAS driven cancers
Neoantigen quality	○ RAS produces distinct, recognizable **surface presented neoepitopes** ○ Activated T-cells can **detect mutant RAS**
Neoantigen immunogenicity	○ RAS-specific T-cells can **occur spontaneously in patients** ○ RAS-specific T-cells are **cytotoxic** *in vitro*

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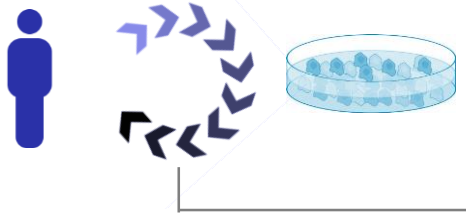
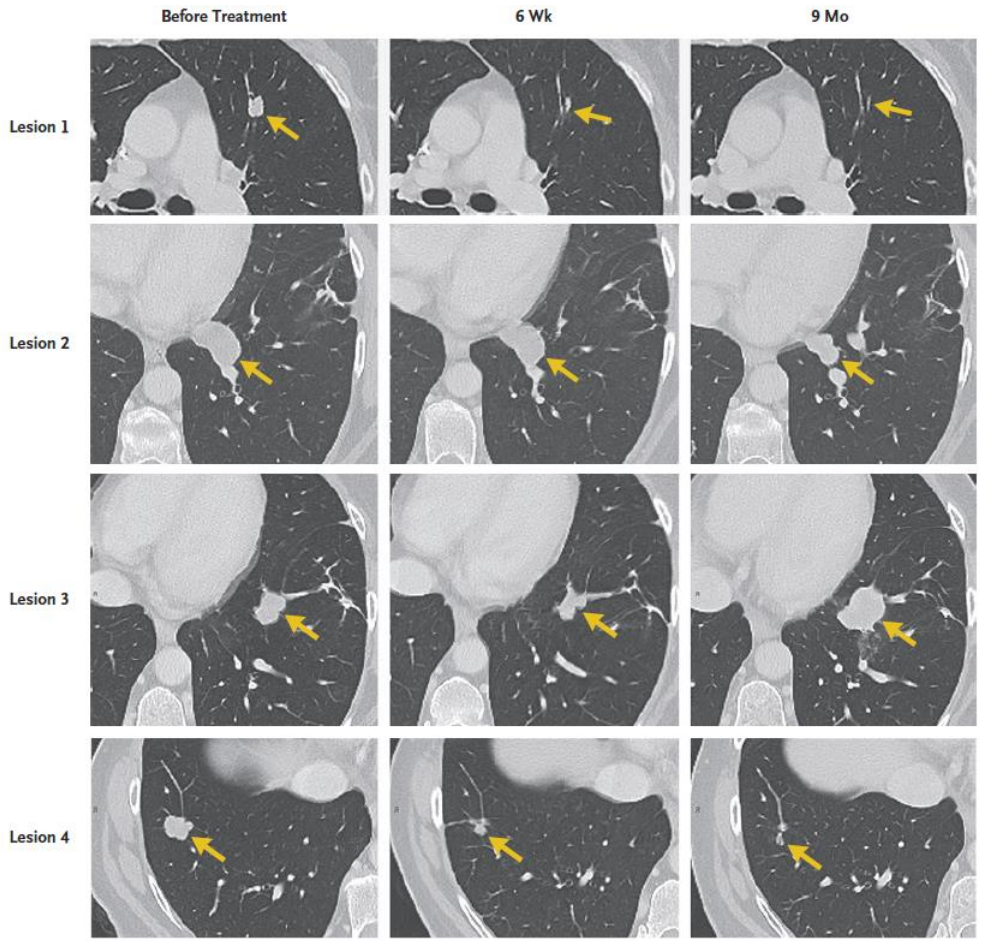
Mutant RAS T-cells can form spontaneously in patients, and recognize and destroy tumors

Rosenberg, A. et. al, (2016), New England Journal of Medicine: ***T-cell transfer therapy targeting mutant KRAS in cancer***



Endogenous CD8+ tumor-infiltrating lymphocytes (TIL) recognizing the **G12D RAS mutation** were **isolated from a colorectal cancer patient**

The G12D **mutRAS CD8+ T-cells** were **expanded *ex vivo*** and **transfused back** into the patient (single infusion of 1.48×10^{11} cells)



Key results

- The patient had **7 lung metastases** that all had **objective regressions** (pictured on right)
- One lesion (#3) progressed after 9 months of therapy, due to **loss of the HLA locus**
- **Proof-of-concept** for **spontaneous T-cell response** to mutant RAS in patients

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THE RAS DEVELOPMENT LANDSCAPE

Company	Asset/ Program	Mechanism of Action	Highest Phase
GlobeImmune	GI-4000/Tarmogen	Heat-inactivated yeast expressing target RAS mutations	Phase II (halted)
targovax	TG01 / TG02	Peptide vaccine targeting 7/8 codon 12 & 13 RAS mutations	Phase II
Silenseed	siG12D-LODER	RNAi (siRNA) targeting mutant RAS (G12D)	Phase II
AMGEN	AMG510	Small molecule inhibitor of RAS (G12C)	Phase I
MIRATI THERAPEUTICS	MRTX849	Small molecule inhibitor of RAS (G12C)	Phase I
moderna	mRNA4157	mRNA vaccine targeting 4 codon 12 RAS mutations	Phase I
GILEAD Kite	KRAS TCR	Engineered T-cell receptor targeting RAS (G12D)	Phase I
AstraZeneca	AZD4785	Antisense RNA RAS inhibitor (mutation independent)	Phase I (halted)
wellspring biosciences janssen	ARS3248	Small molecule inhibitor of RAS (G12C)	Phase I ready
SANOFI	Compound-B	Small molecule inhibitor of RAS (G12C)	Preclinical
REVOLUTION MEDICINES	NA	Small molecule inhibitor of RAS	Preclinical
COTINGA PHARMACEUTICALS	COTI219	Small molecule inhibitor of RAS	Preclinical
elicio THERAPEUTICS	ELI002	Small molecule inhibitor of RAS (G12V)	Preclinical
NEONC TECHNOLOGIES, INC.	NEO214	Small molecule inhibitor of RAS	Preclinical
Allinky BIOPHARMA	AIK4	Small molecule inhibitor of RAS	Preclinical

Small Molecule Inhibitor | *Peptide Vaccine* | *mRNA vaccine* | *Yeast Vaccine* | *CAR-T* | *RNAi*

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SOURCE: Targovax market analysis, not exhaustive

Targovax TG vaccine is a peptide cocktail designed to induce T-cell responses to RAS driver mutations

1. Activate immune system

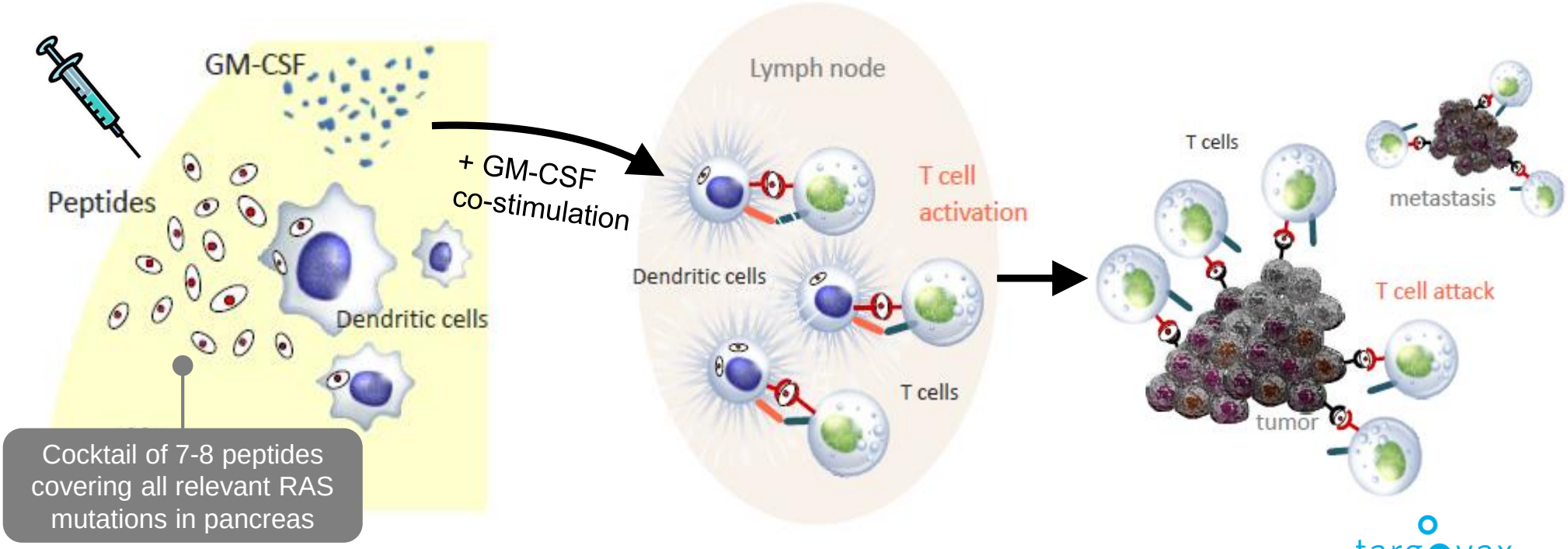
- TG peptide cocktail **injected intradermally** with GM-CSF as adjuvant

2. Induce mutRAS T-cells

- **Mutant RAS T-cells activated** by DCs in lymph nodes

3. Attack the cancer

- mutRAS T-cells identify and **destroy mutant RAS cancer cells**

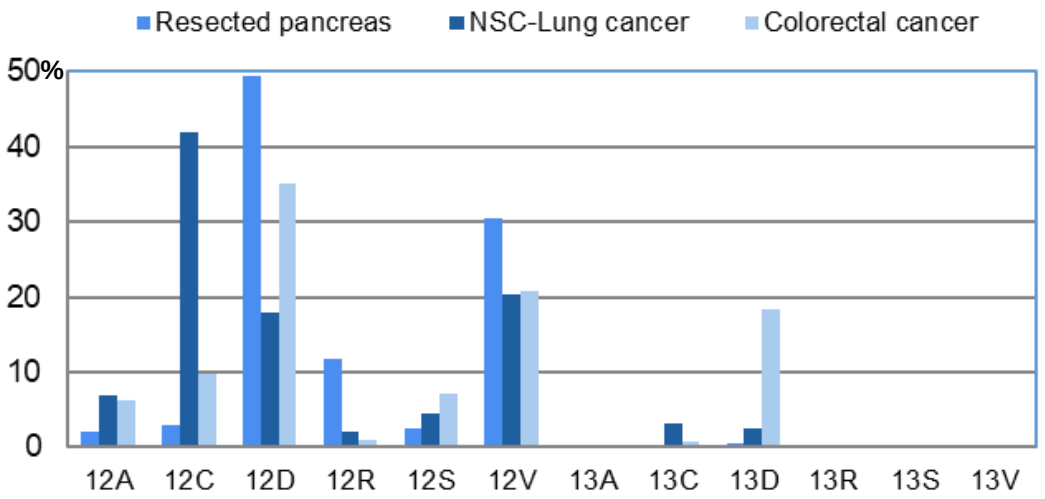


The TG peptide cocktail covers ~99% of all codon 12 and 13 RAS mutations

Oncogenic codon 12 & 13 RAS mutations

1 12 13
MTEYKLVVVGAGGVGKSALTIQLIQ ……

Wild-type RAS amino acid sequence, with mutation sites in red



TG product characteristics

- **Two clinical stage products**
  - **TG01**: 7 peptides covering ~99% of RAS mutations in pancreatic cancer
  - **TG02**: 8 peptides covering ~99% of mutations in NSCLC and CRC
- Covers **all 3 RAS family isoforms** (K, N, & H)
- **Long peptides** (17mer) generating both **CD4+ and CD8+ responses**
- **Promiscuous HLA class II binders**, covering all HLA DR, DP and DQ epitopes
- **All possible class I mutRAS epitopes covered** within sequences (after antigen processing)

Sourced from Prior et al., 2012, Cancer Res; 72(10);2457-67)

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TG Clinical data

4. Summary & conclusions

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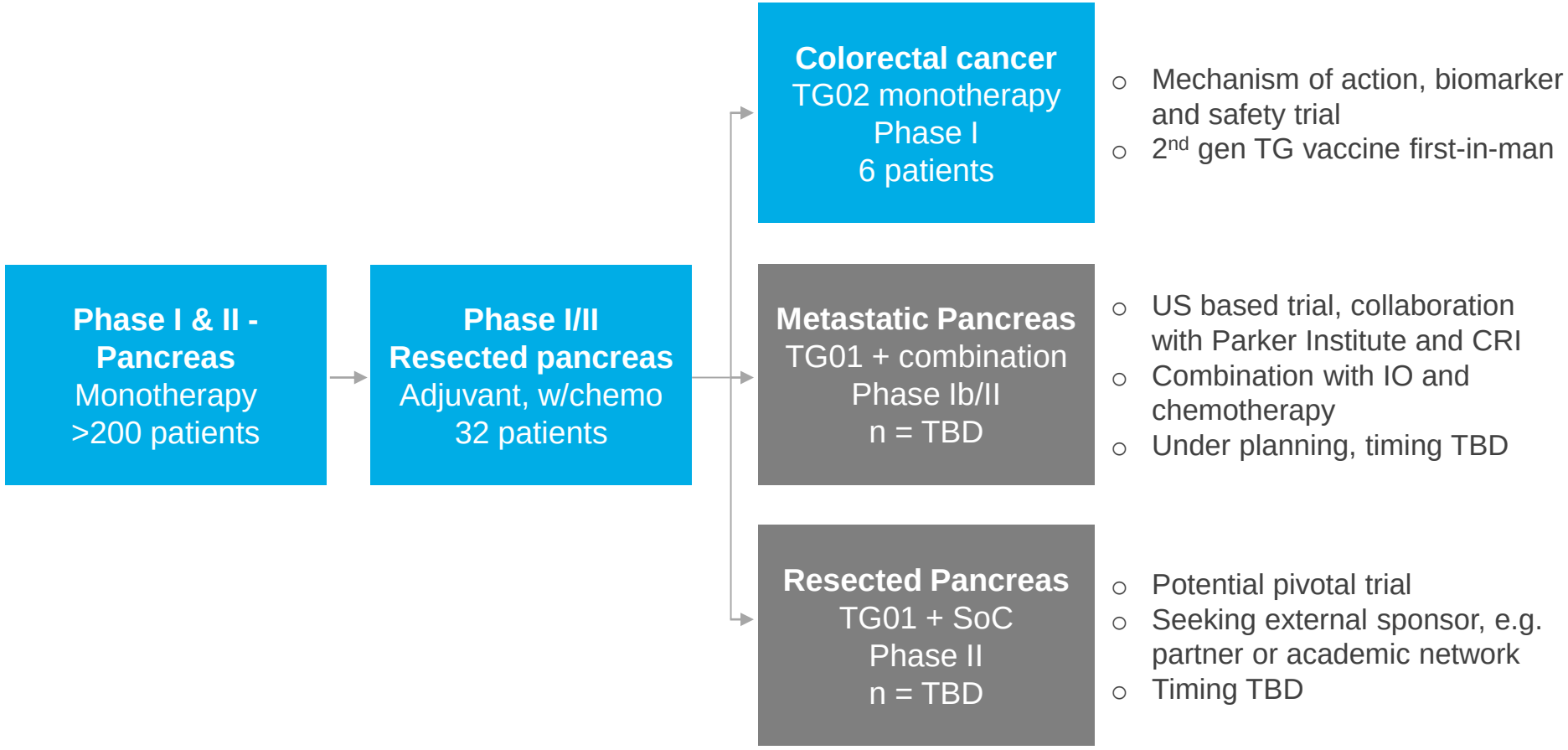
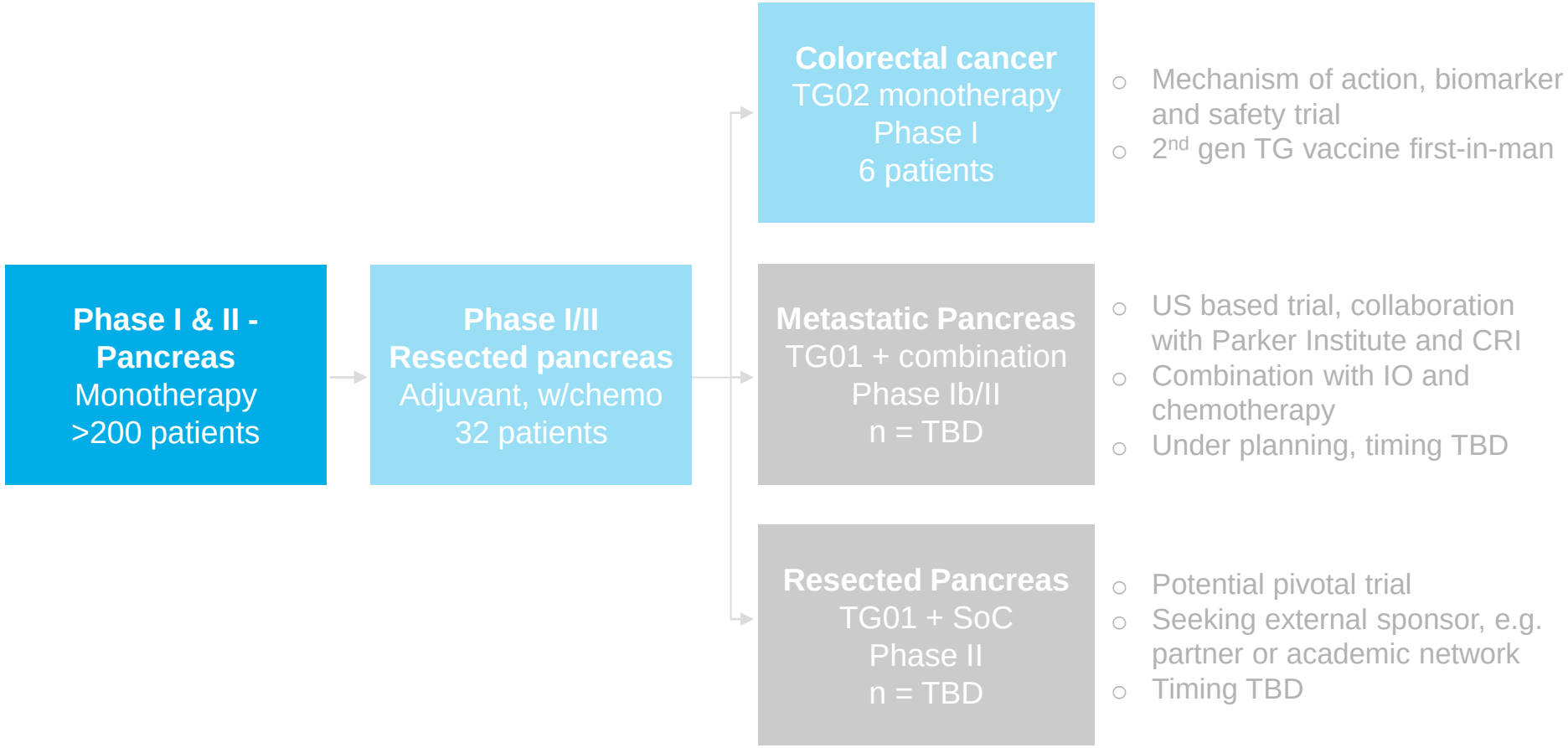
TG CLINICAL PROGRAM OVERVIEW



TG CLINICAL PROGRAM OVERVIEW



Completed trials Trials under planning

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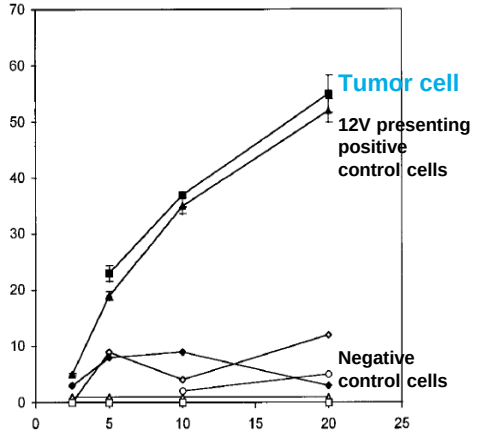
TG vaccination induced CD4+ and CD8+ mutant RAS T-cell responses has been validated in patients

mutRAS specific CD4+ T-cells isolated from vaccinated patient

- CD4+ T-cell clone lyse cancer cells isolated from the same patient (*in vitro* cytotoxicity assay)

% CD4+ T-cell clone cytotoxicity

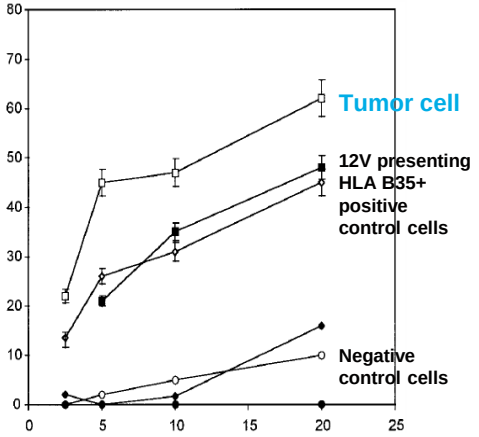


T-cell clone / target cell ratio

mutRAS specific CD8+ T-cells isolated from vaccinated patient

- CD8+ T-cell clone lyse cancer cells isolated rom the same patient (*in vitro* cytotoxicity assay)

% CD8+ T-cell clone cytotoxicity

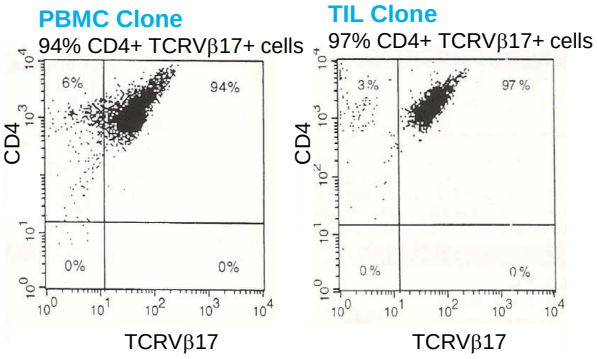


T-cell clone / target cell ratio

mutRAS specific T-cell clones identified both in blood and tumor

- T-cell clone matching the patient's mutation (G12R) was found in tumor biopsy

Flow cytometric analysis (FACS) showing same clonality of T-cells from PBMC and tumor

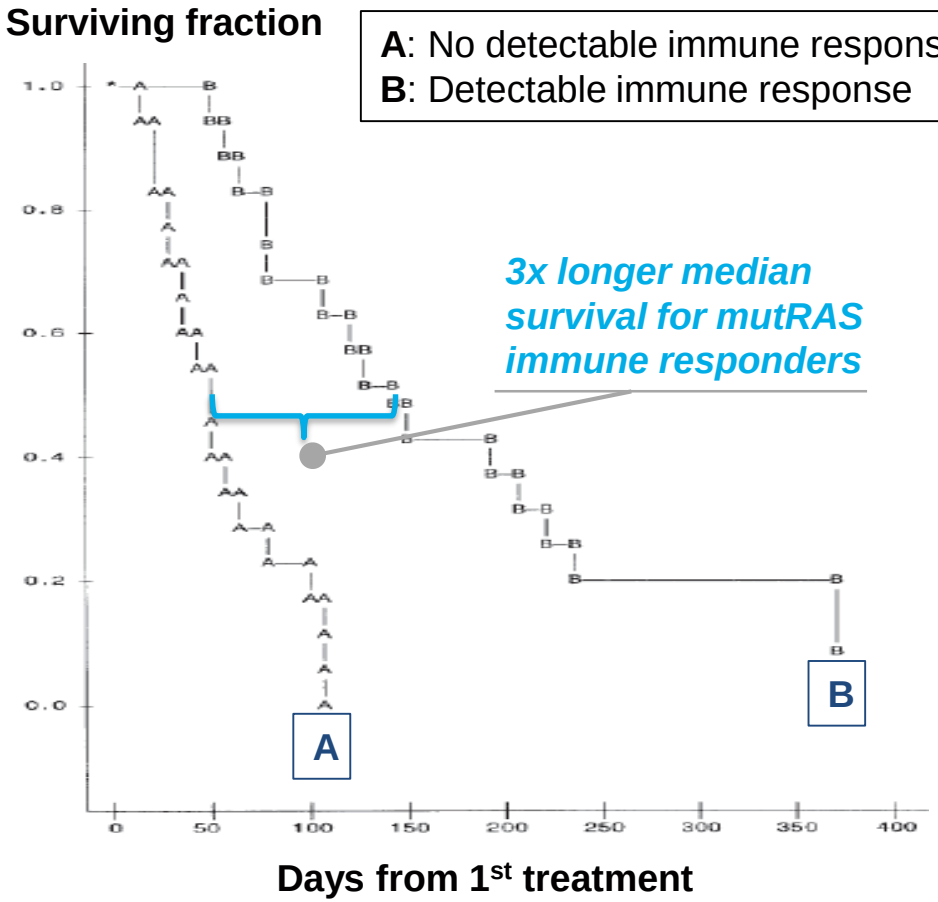


T-cells specific for other RAS mutations than 12R were found in PBMC, but not in tumor

Source: Gjertsen et al., 1997; Gjertsen et al. 2001

Improved survival for mutRAS immune responders observed in advanced pancreatic cancer patients

Clinical study in advanced pancreatic cancer (36 patients)**; Cocktail of 4 (of 7) TG01 peptides**



- **19 of 36 (52%) patients had mutRAS immune response**
  - *Immune response measured as mutRAS specific skin DTH test, and mutRAS specific T cell proliferation in blood*
- **3x longer median survival for responders**
  - *144 days for immune-responders (n=19)*
  - *48 days for non-responders (n=17)*

SOURCE: Gjertsen et al., 2001

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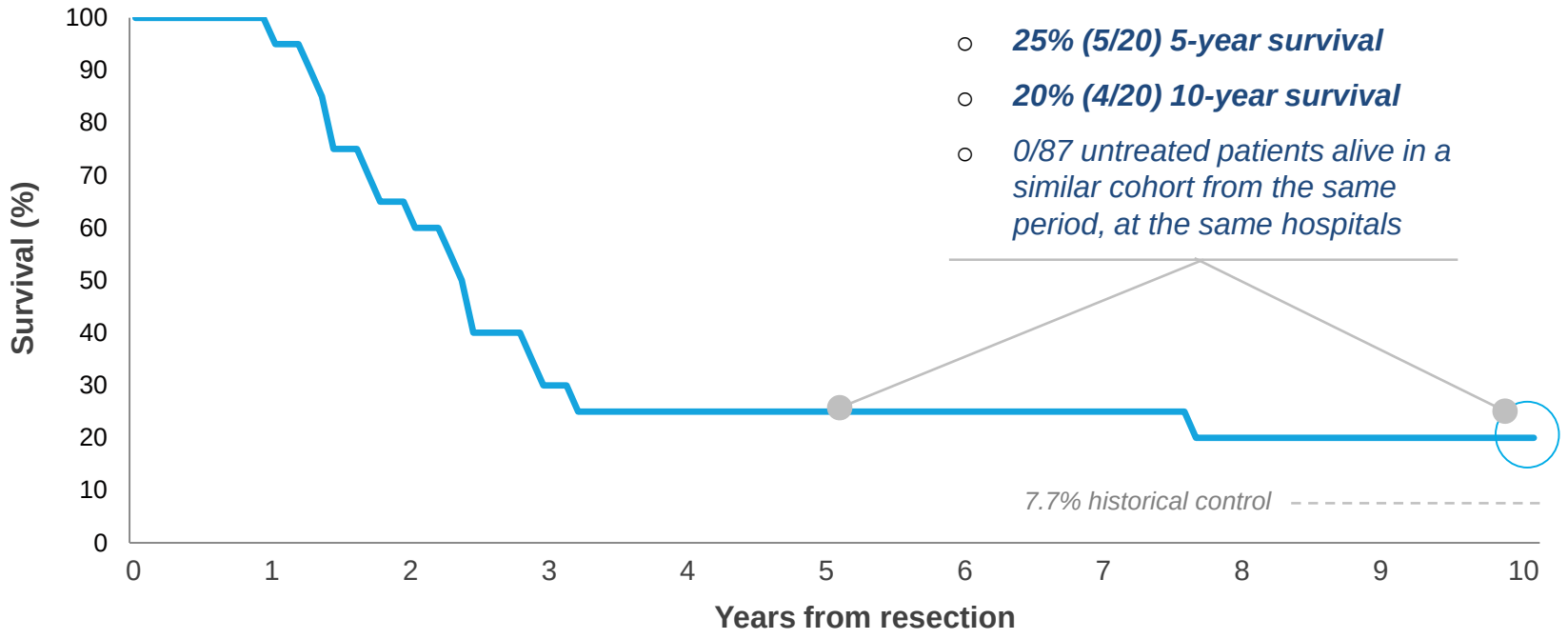
PHASE I MONOTHERAPY SURVIVAL DATA

TG vaccination showed 20% 10 year survival in resected pancreatic cancer

10 year survival in historical TG trials in resected pancreatic cancer[1]

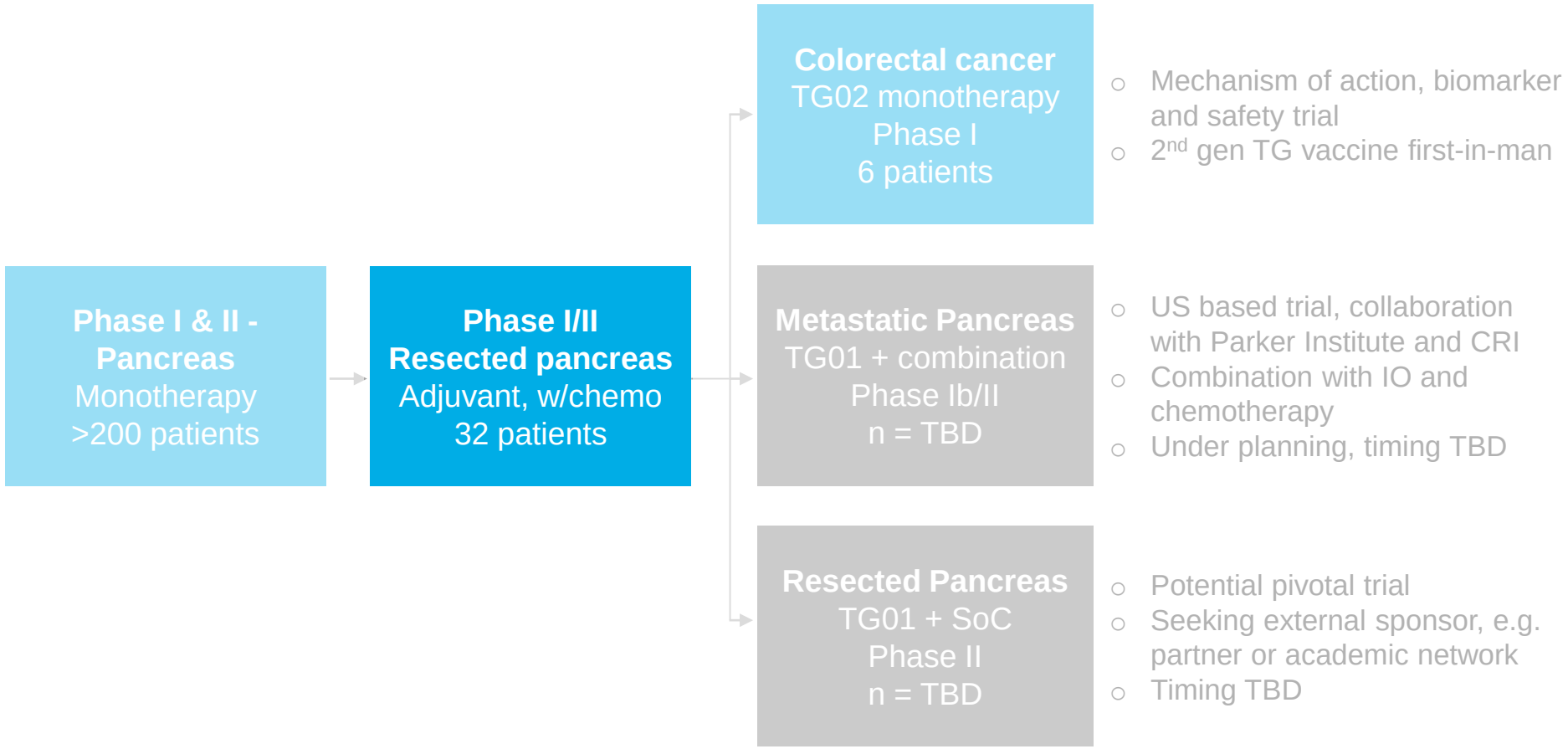
n=20, resected patients from two clinical trials, TG monotherapy



[1] Wedén et al., 2011

[2] Oettle H et al., JAMA 2013, vol 310, no 14

TG CLINICAL PROGRAM OVERVIEW



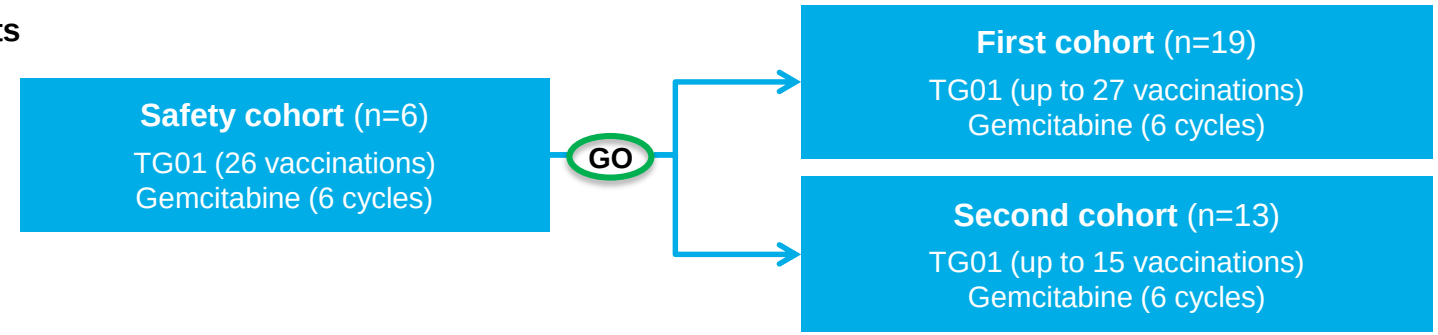
TG01 – RESECTED PANCREAS STUDY SCHEMA

Phase I/II trial combining TG01 with adjuvant gemcitabine, 32 patients

Patient population	**Resected adenocarcinoma of the pancreas** and candidates for adjuvant chemotherapy
Objective	Assess **safety, mutant RAS immune response** and **clinical efficacy**

Treatment	**TG01 / GM-CSF** (up to 2 years) **Gemcitabine** (6 cycles)
Study design	**Single arm**, open label with safety lead-in **2 cohorts with different dosing regimens**

Study cohorts



Treatment schedule

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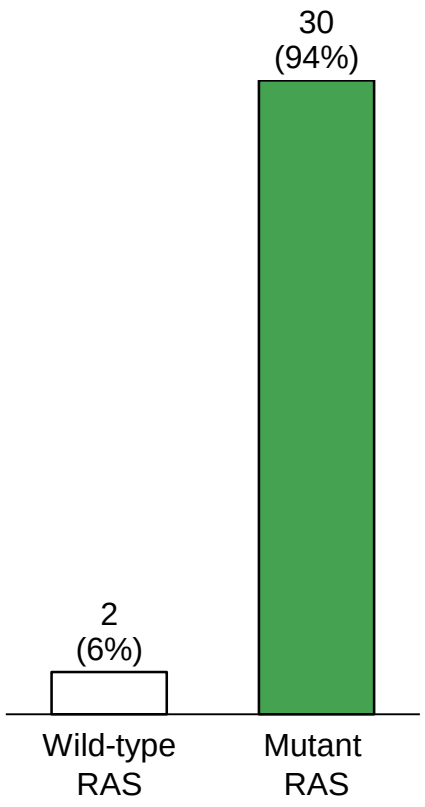
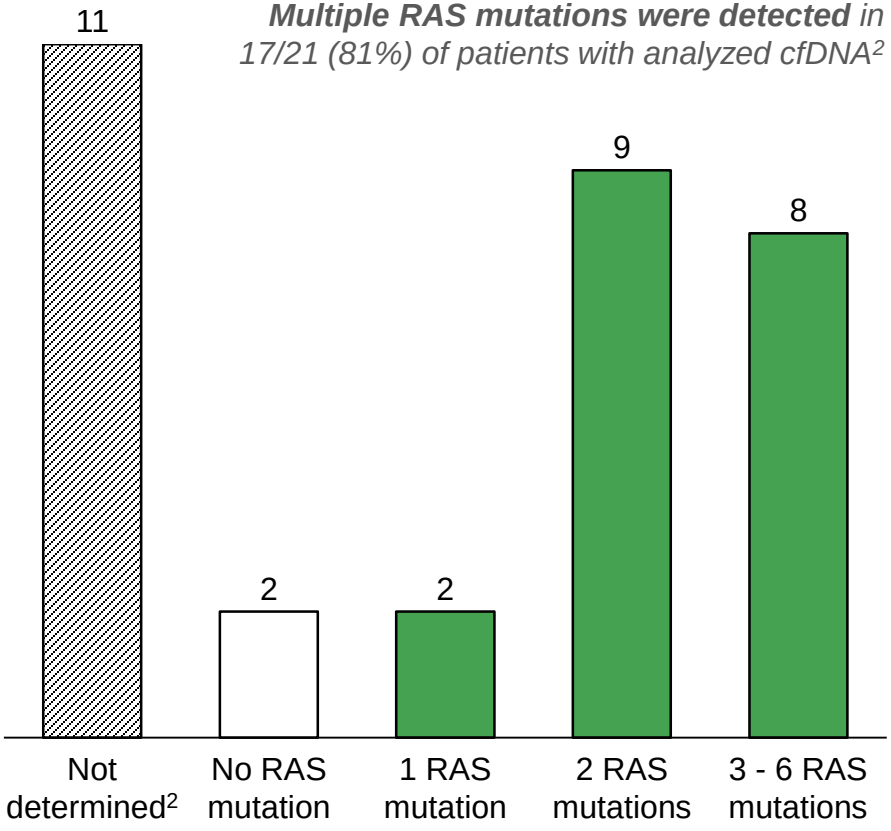
30/32 patients in the trial were confirmed as mutant RAS, with most showing presence of multiple point mutations

Patient RAS status
wt/mut genetic RAS [1]



Number of different RAS mutations detected
qPCR detection of RAS point mutations in cfDNA

Multiple RAS mutations were detected *in 17/21 (81%) of patients with analyzed cfDNA[2]*



1 RAS status determined by tumor biopsy and/or cfDNA

2 Eleven patients were not screened for individual mutations

Company data, unpublished

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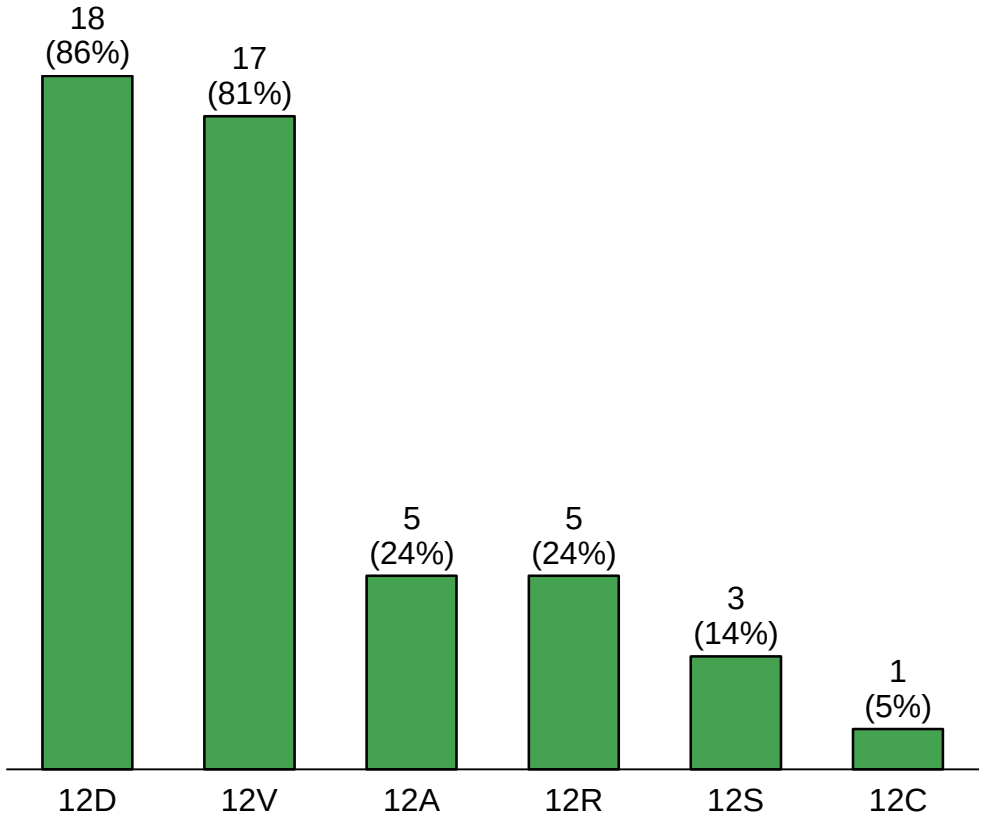
12D and 12V were the most frequently occurring RAS mutations found in the patients

Frequency of individual RAS point mutations detected in cfDNA[1]
Number of patients (%) with mutation confirmed in cfDNA for at least one time point in study (n=21)



- **12D and 12V mutations** co-occurred in **17/21 (81%)** of patients
- **12C mutation** was only detected in **one patient**
- In **one patient all six assessed RAS mutations were detected** during the course of the study
- Presence of specific **mutations shifted over time**, indicating selection pressure for specific mutant RAS clones

1 Eleven patients were not screened for individual mutations in cfDNA
Company data, unpublished

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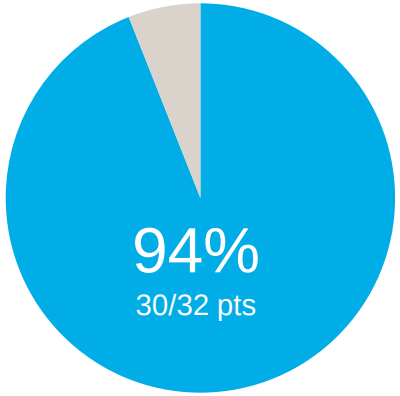
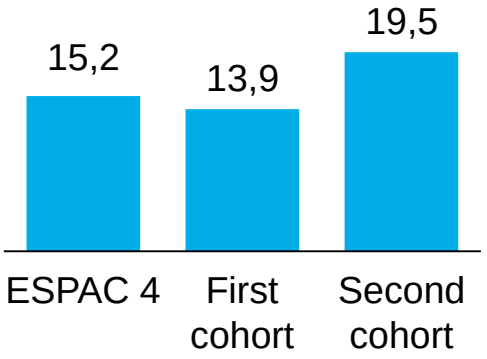
TOP-LINE DATA SUMMARY TG01 + GEMCITABINE

as adjuvant combination treatment in resected pancreatic cancer

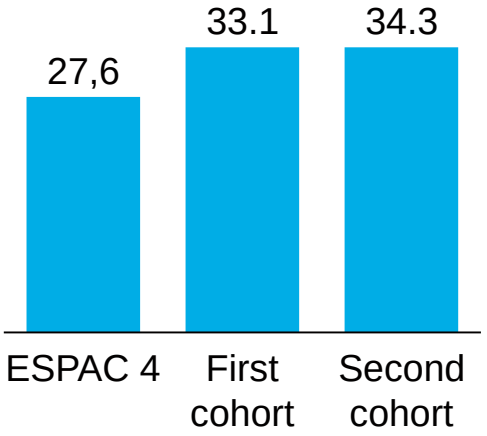
1 RAS-specific immune activation



2 Median disease free survival, months



3 Median overall survival, months



TG01 is well-tolerated - improved dosing regimen in second cohort

First cohort: 19 pts, Second cohort: 13 pts. Total 32 pts.
DFS both cohorts combined: 16.1 months
European Society for Pancreatic Cancer ESPAC4 trial data for gemcitabine monotherapy arm (2017), data adjusted to reflect time from surgery

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RAS specific immune response confirmed in 30 out of 32 patients

Parameters	1st Cohort (n=19)	2nd Cohort (n=13)	Overall (N=32)
Immune responder*	*18 (95 %)*	*12 (92 %)*	*30 (94 %)*
DTH Positive (skin hypersensitivity test)	18 (95 %)	8 (62 %)	26 (81 %)
mutRAS Specific T-cells (PBMC proliferation assay)	14 (74 %)	12 (92 %)	26 (81 %)

* Immune responder defined as positive DTH test or PBMC proliferation assay for at least one time point

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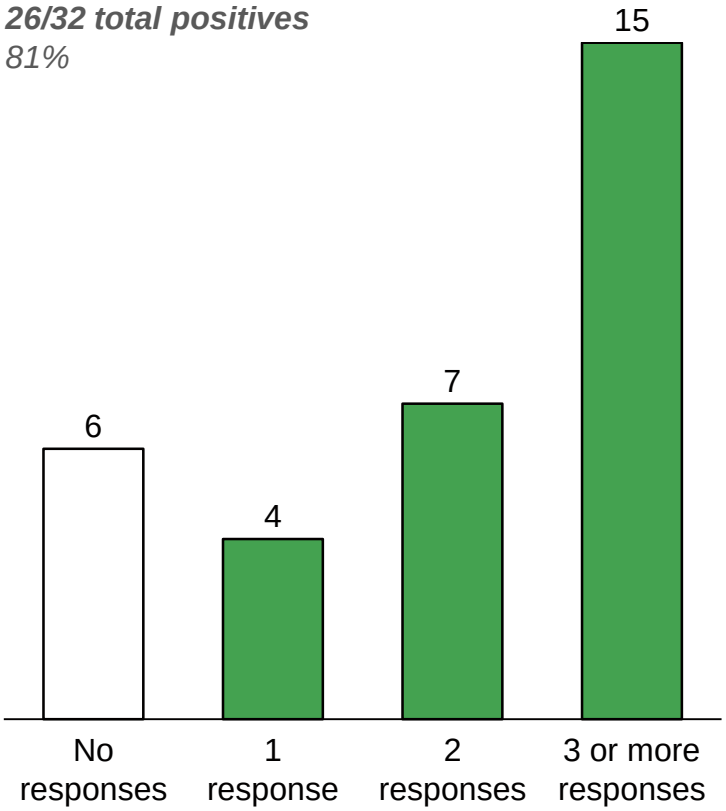
1 Robust levels of DTH and PBMC mutant RAS immune responses in study

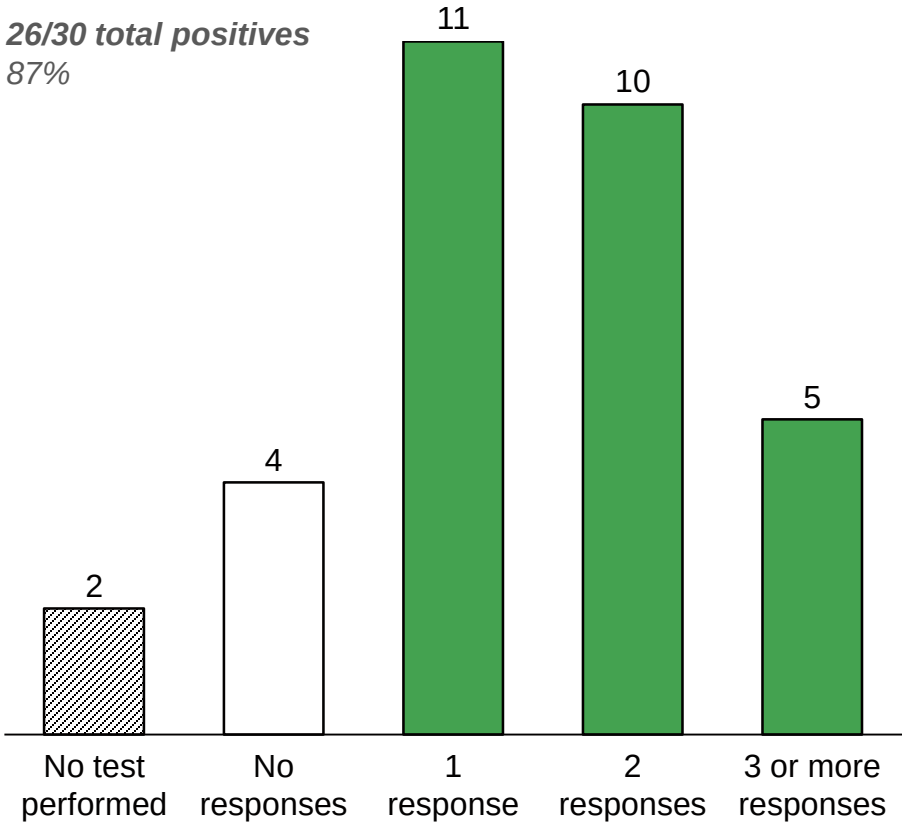
Overall positive DTH responses during study
number of patients per group

26/32 total positives
81%



Overall positive PBMC responses during study
number of patients per group

26/30 total positives
87%



Company data, unpublished

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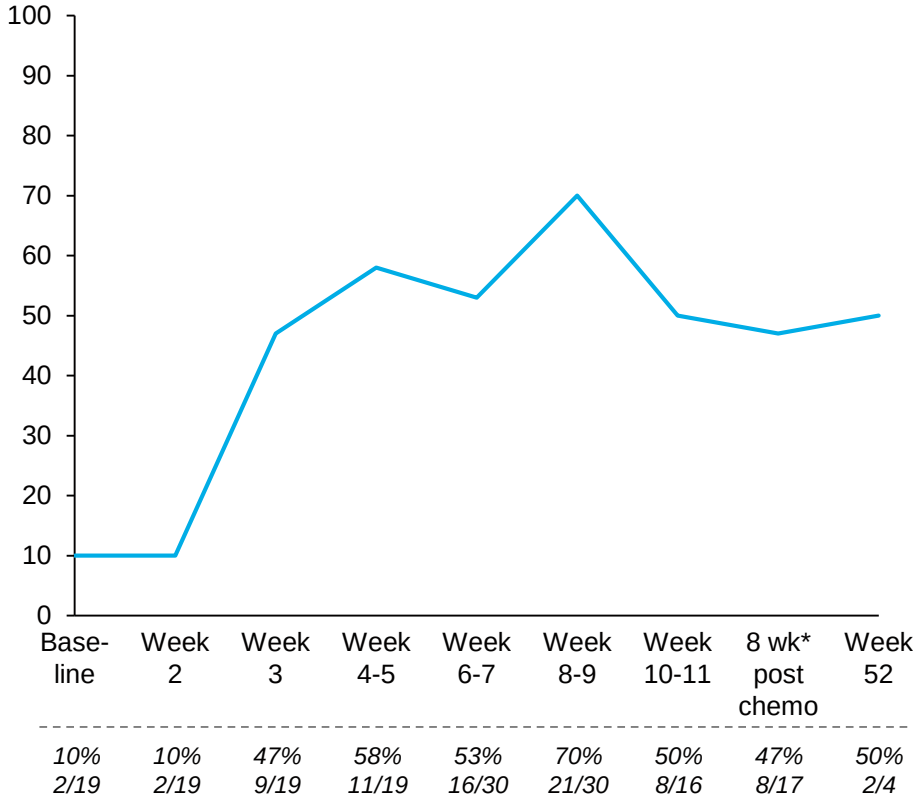
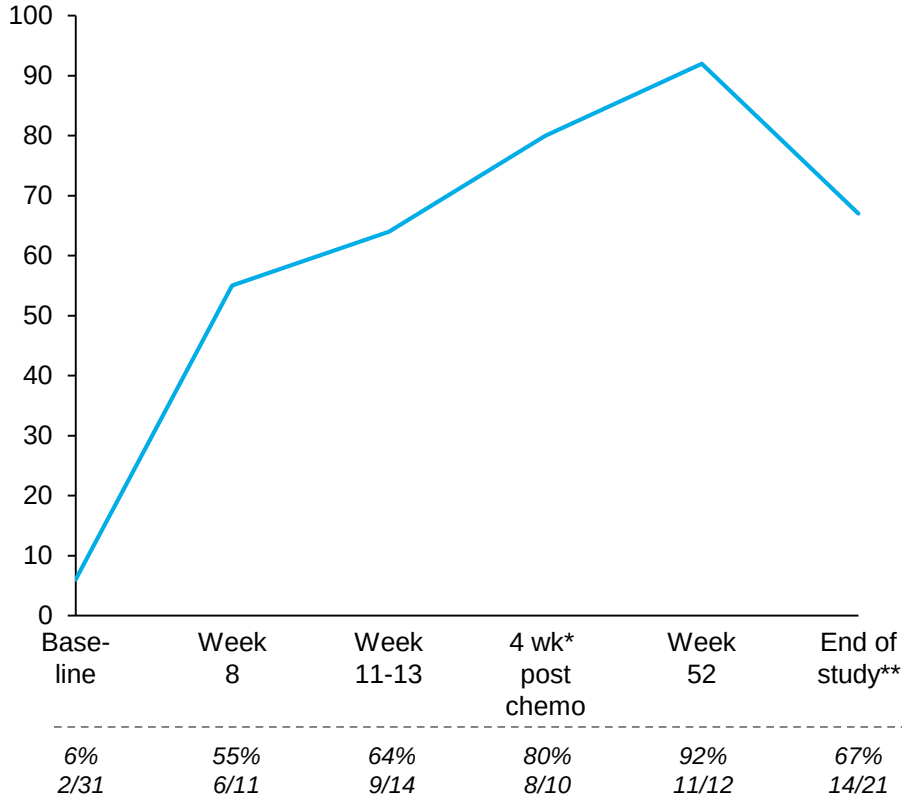
1 DTH and PBMC mutant RAS immune responses increased over time

DTH responses over time
% of analyzed patients with positive DTH at each time point



PBMC responses over time
% of analyzed patients with positive PBMC at each time point



Measured 4/8 weeks after last cycle of chemotherapy ** EoS time point varies between patients
Baseline response prior to first vaccination (week 1), not defined as positive immune response to TG
Company data, unpublished

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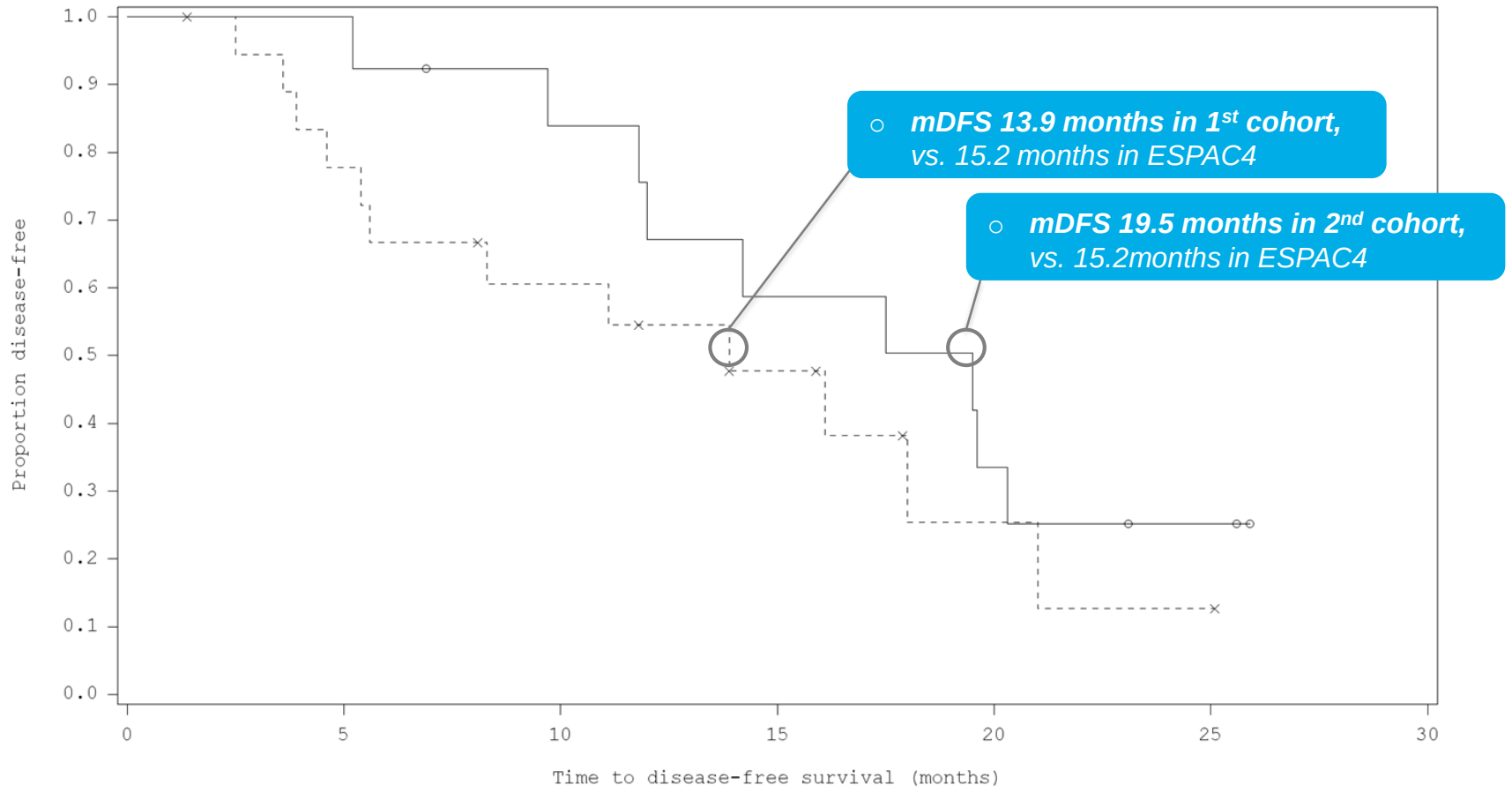
2 Disease free survival (DFS) Kaplan-Meier plot



Censored= No progression on latest scan collected

DFS was measured from surgery

Company data, unpublished

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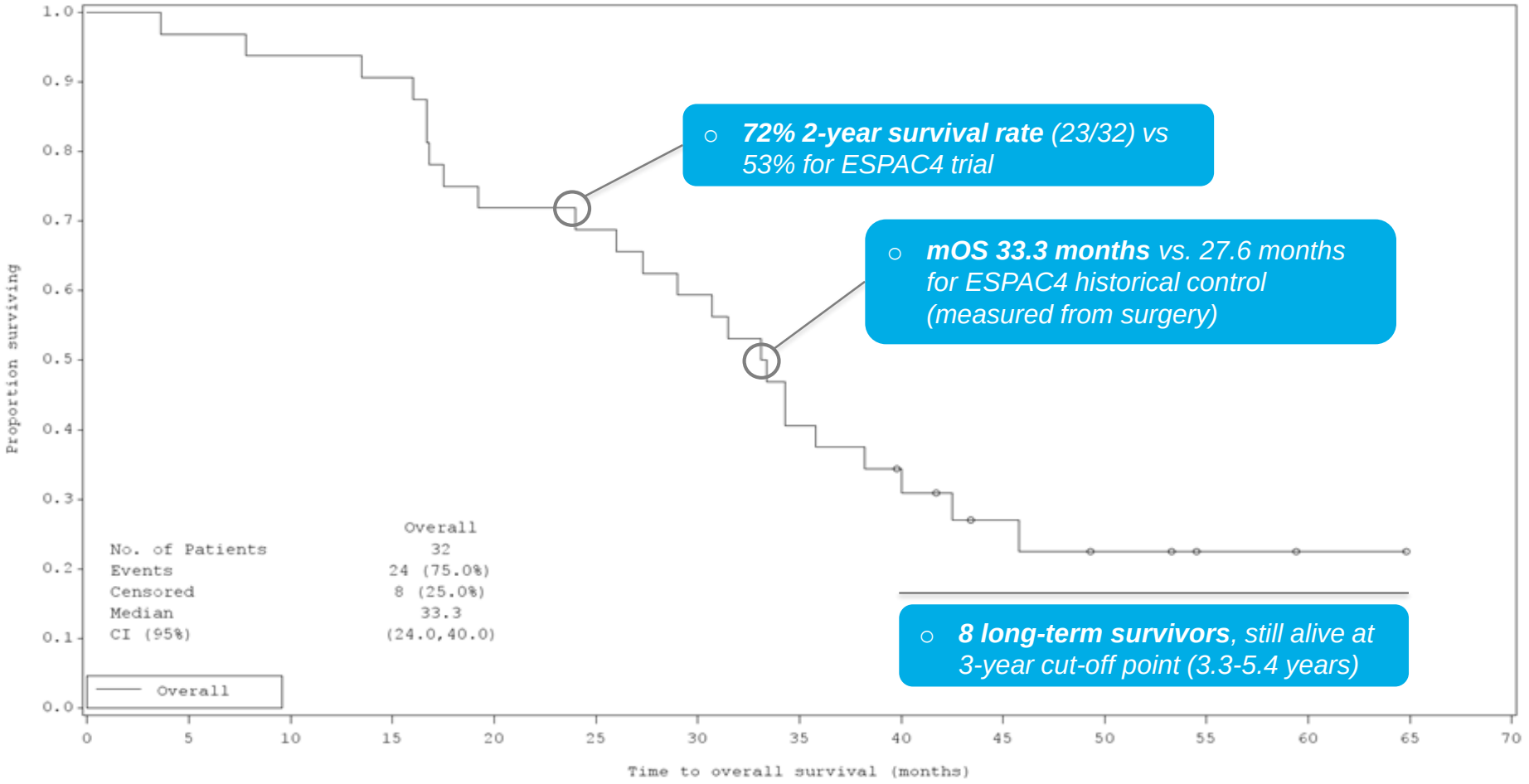
Kaplan-Meier survival plot for all 32 patients - signal of clinical benefit of TG vaccination



Company data, unpublished

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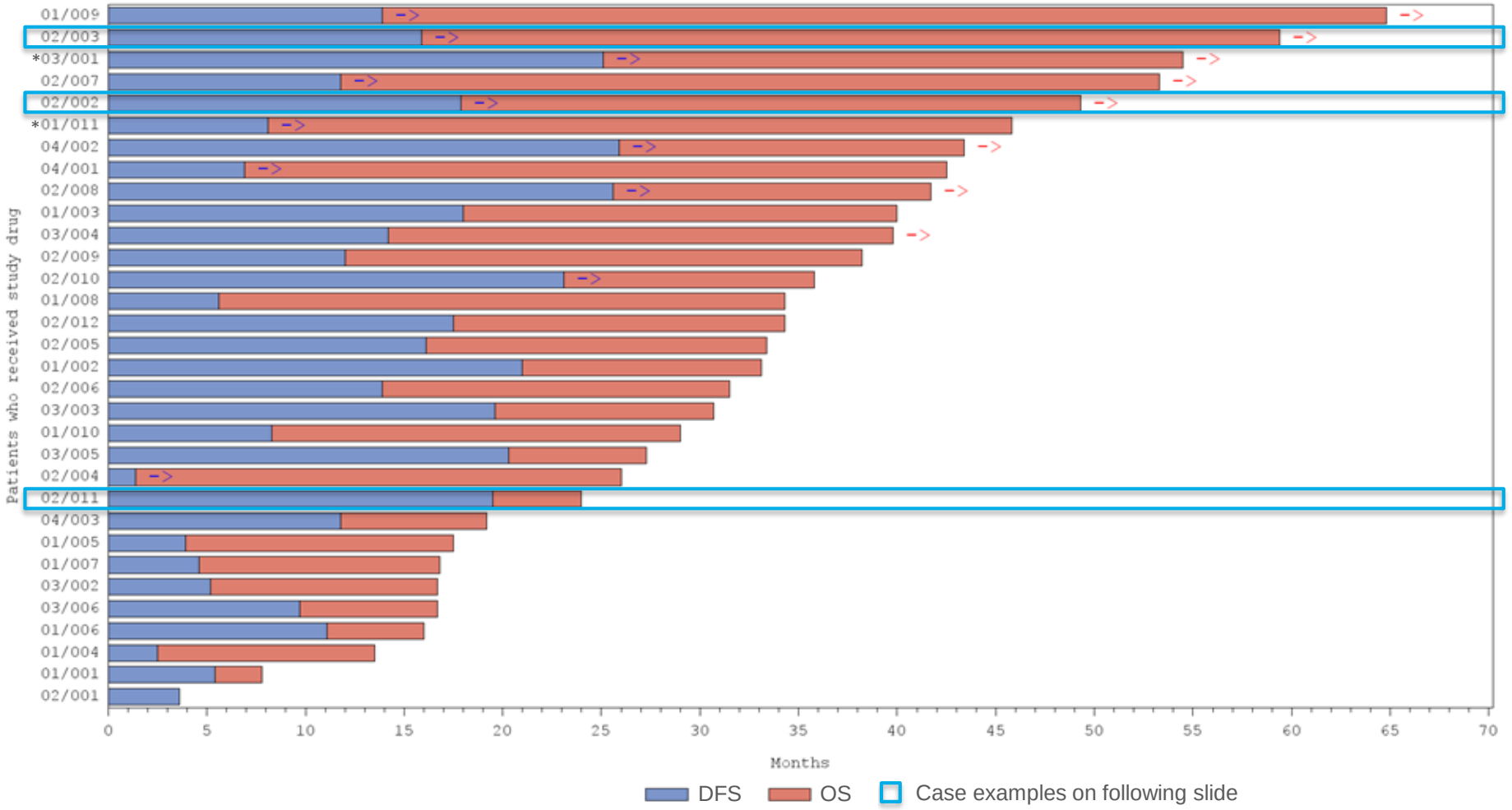
3 TG01 resected pancreas trial - swimmer plot showing individual patient outcomes



* RAS wild type (2/32 patients)

All measurements in months from surgery

Company data, unpublished

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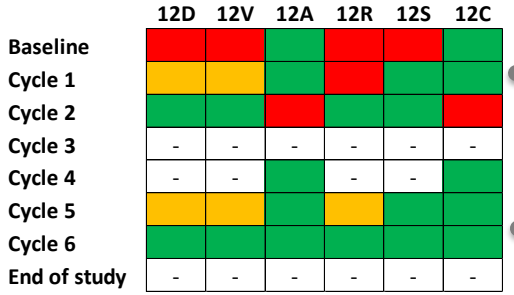
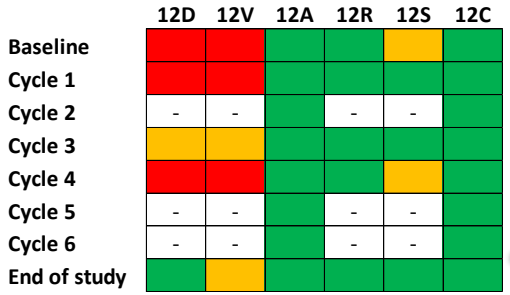
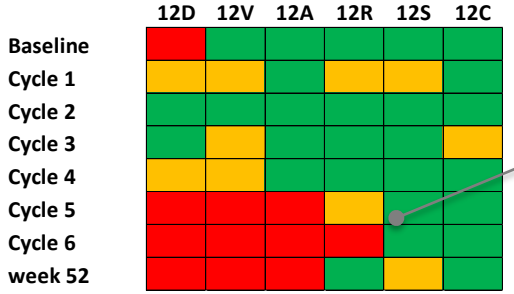
3 Multiple RAS mutations detected in cfDNA in most patients, and evidence of clonal clearance following TG vaccination

	RAS mutation	Immune response	Clinical outcome	Mutant RAS cfDNA analysis
Pt. 02-002	**6 detected** 12D 12V 12A 12R 12S 12C	**DTH:** 4/7 positive assays **PBMC:** 2/2 positive assays	**R0 resection** **No progression reported** **Patient still alive after 4 years**	
Pt. 02-003	**2 detected** 12D 12V	**DTH:** 3/6 positive assays **PBMC:** 1/1 positive assays	**R0 resection** **No progression reported** **Patient still alive after 5 years**	
Pt. 02-011	**4 detected** 12D 12V 12A 12R	**DTH:** 2/3 positive assays **PBMC:** 2/3 positive assays	**R1 resection** **Progression at 20 months** **Patient survived 24 months**	

- ***RAS mutations changed*** *over time*
- ***All mutations cleared*** *at last time point*
- ***Patient alive*** *at 4 years*

- ***Mutational load reduced*** *(only one possible mutant left at EoS)*
- ***Patient alive*** *at 5 years*

- ***One mutation*** *at baseline, cleared by cycle 2*
- ***Multiple clones re-emerged*** *by cycle 5/6*
- ***Tumor recurred*** *at 20 months*

Preliminary data, unpublished

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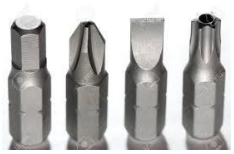
4

Summary & conclusions

SUMMARY – TG MUTANT RAS VACCINE

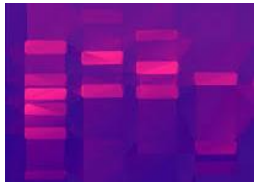


Targets all RAS mutations with one product

- **Covers 99%** of codon 12 and 13 oncogenic **RAS mutations**
- Patients frequently have **multiple RAS mutation clones** present

Promising immune response and efficacy data

- **Signal of survival benefit** in resected pancreatic cancer
- Mutant RAS **T-cell responses in >90%** of vaccinated patients
- **Clearance of mutant RAS clones** in cfDNA



Potential as genetic marker “pan-RAS” vaccine

- Mutant RAS found in **25-30% of all solid tumors**
- First examples of **genetic marker approvals** already given by **FDA**
- **Excellent tolerability**, with broad potential for IO and chemo combinations

Available for partnering

- **Combination trials, novel adjuvants** and delivery strategies
- Global or regional **licensing, asset unencumbered**

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ACTIVATING THE PATIENT`S IMMUNE SYSTEM

to fight cancer

Oncolytic virus

Strong single agent data

Re-activation of anti-PD1 resistant tumors

Rich news flow 2019-2020

Mutant RAS vaccine

Robust immune activation

Signal of clinical benefit

Available for partnering and collaborations

Innovative pipeline

Next generation viruses in pre-clinical testing

Novel RAS targeting concepts