TG mutant RAS neoantigen vaccine

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RAS Targeted Drug Discovery Europe

Vienna, 27 February 2020

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Introduction

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

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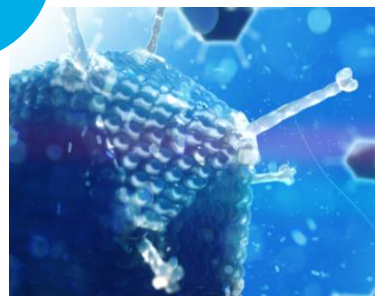
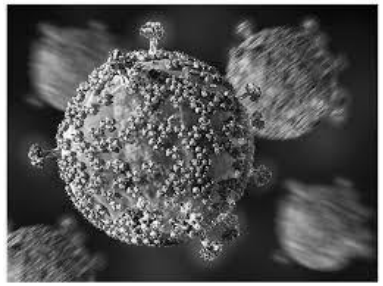
TARGOVAX AIMS TO ACTIVATE THE PATIENT'S OWN IMMUNE SYSTEM TO FIGHT CANCER

Targovax focus





Immune activators

Oncolytic viruses

Immune modulators

Checkpoint inhibitors

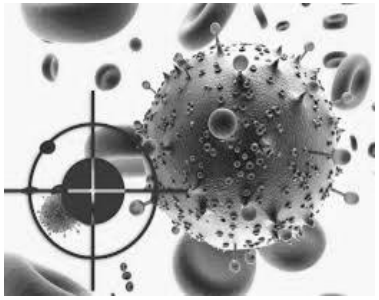
Surgery - Radio - Chemo

Immune boosters

CAR-Ts, TCRs

Targeted therapy

TKIs, PARPs, etc.



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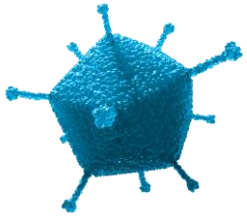
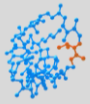
TARGOVAX HAS TWO CLINICAL STAGE IMMUNE ACTIVATOR PROGRAMS



ONCOS
Oncolytic virus

- Genetically **armed adenovirus**
- Turns cold **tumors hot**
- 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 vaccine clinical data
4. Summary & conclusions

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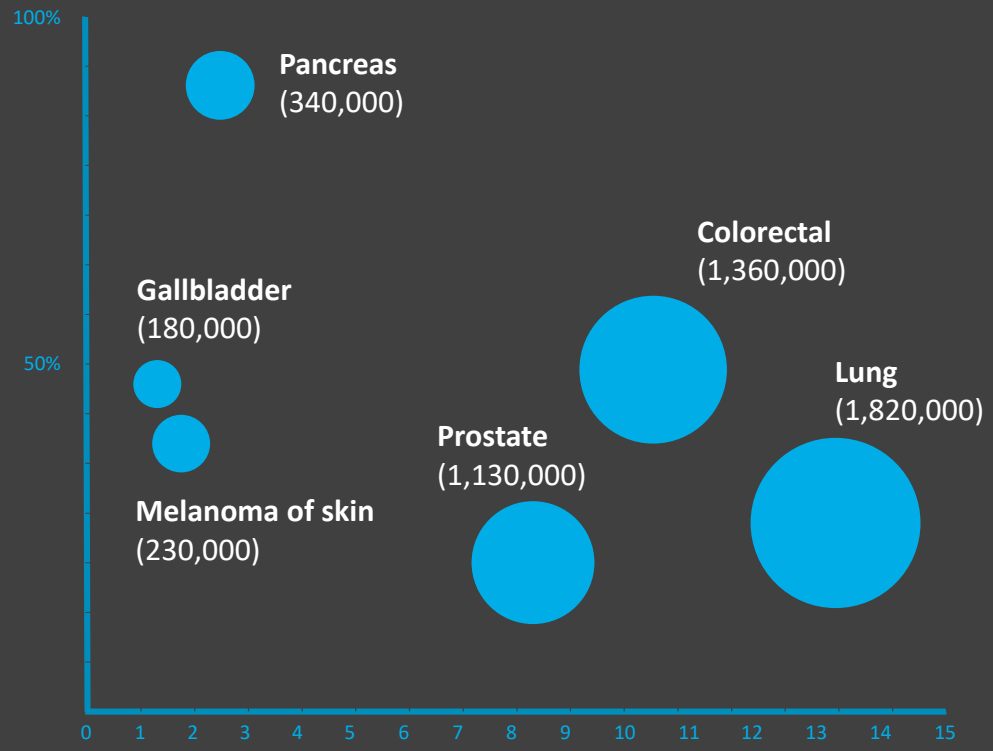
THE RAS GENE IS MUTATED IN 25-30% OF ALL CANCERS

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 IS POTENTIALLY AN EXCELLENT TARGET FOR A SHARED NEOANTIGEN CANCER VACCINE APPROACH

Clinically validated IO target	○ **Endogenous mutant RAS T-cell responses** have been observed clinically ○ RAS-specific T-cells can **eradicate tumors in patients**
One-size-fits all	○ **Limited set** of well-characterized oncogenic **RAS driver mutations** ○ Poly-valent vaccines can **deal with all RAS mutations in one product**
Off-the-shelf product	○ RAS is the **most frequently mutated oncogene** across all cancers ○ **No need for individualization**

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MUTANT RAS T-CELLS CAN FORM SPONTANEOUSLY IN PATIENTS, AND RECOGNIZE AND KILL TUMOR CELLS

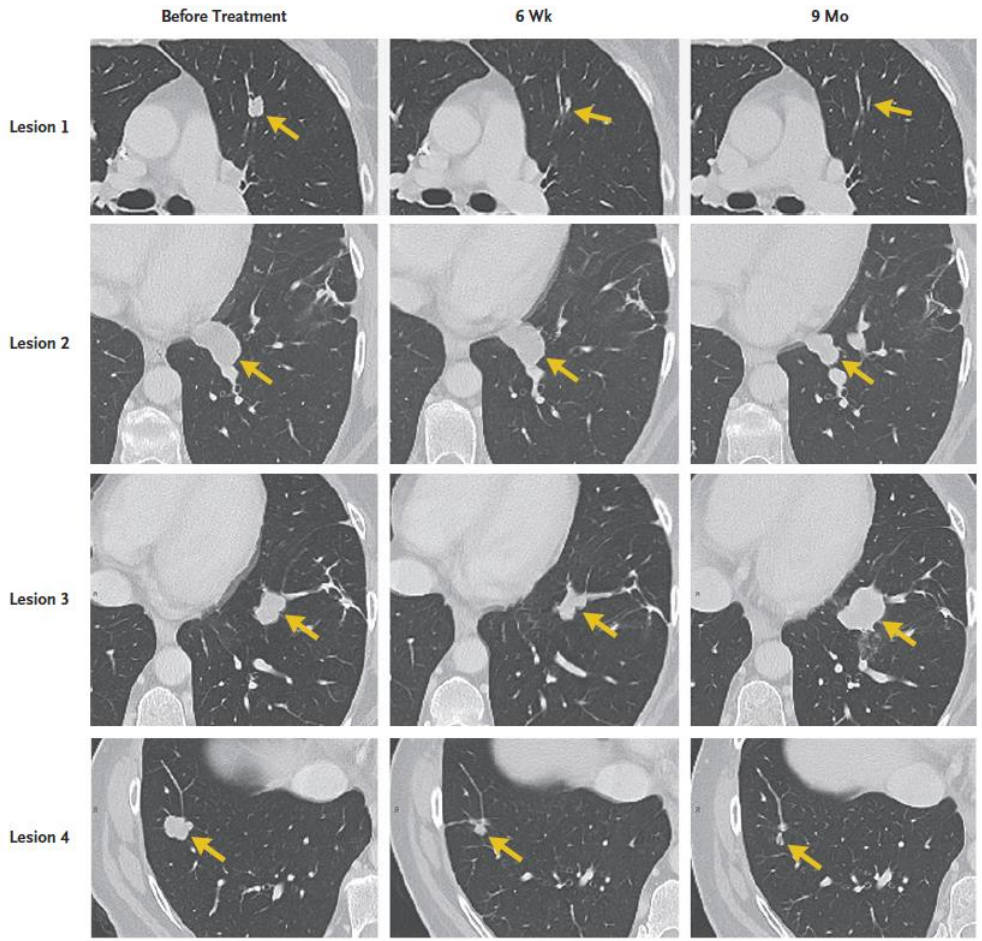
Rosenberg, A. et. al, (2016), New England Journal of Medicine: ***T-cell transfer therapy targeting mutant KRAS in cancer***

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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TARGOVAX TG VACCINE IS A PEPTIDE COCKTAIL DESIGNED TO INDUCE T-CELL RESPONSES TO RAS DRIVER MUTATIONS

1. Activate immune system

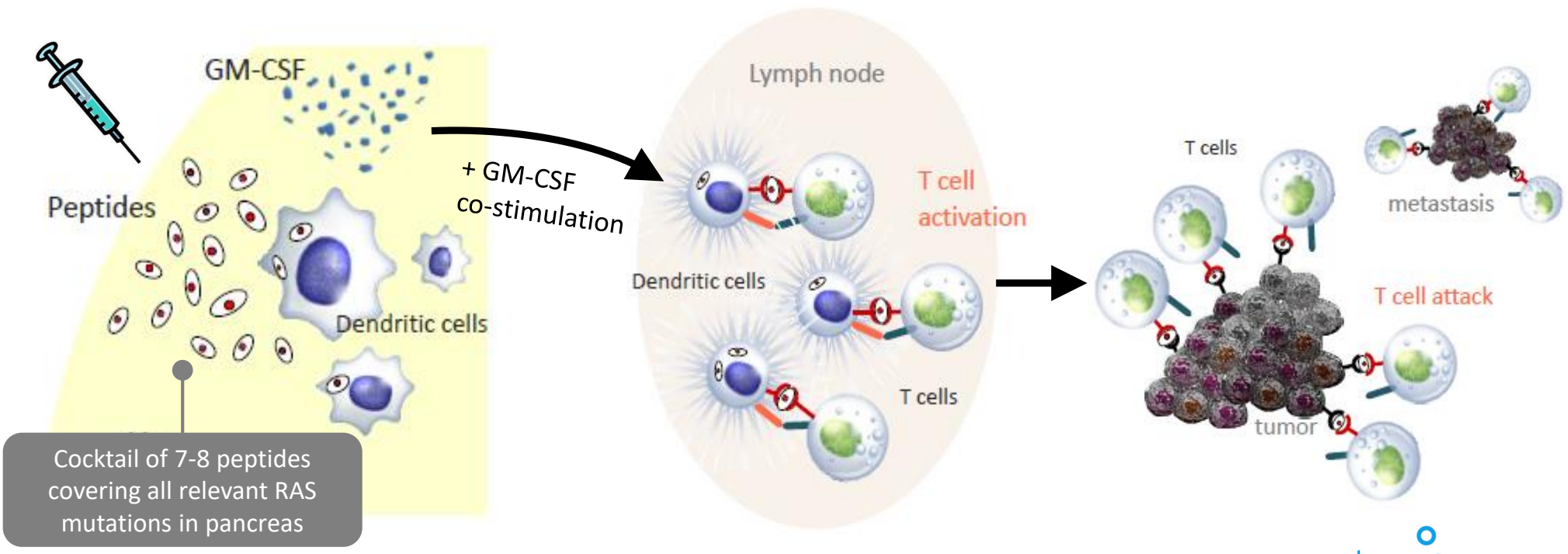
- TG peptide cocktail **injected intradermally** with GM-CSF as adjuvant

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**

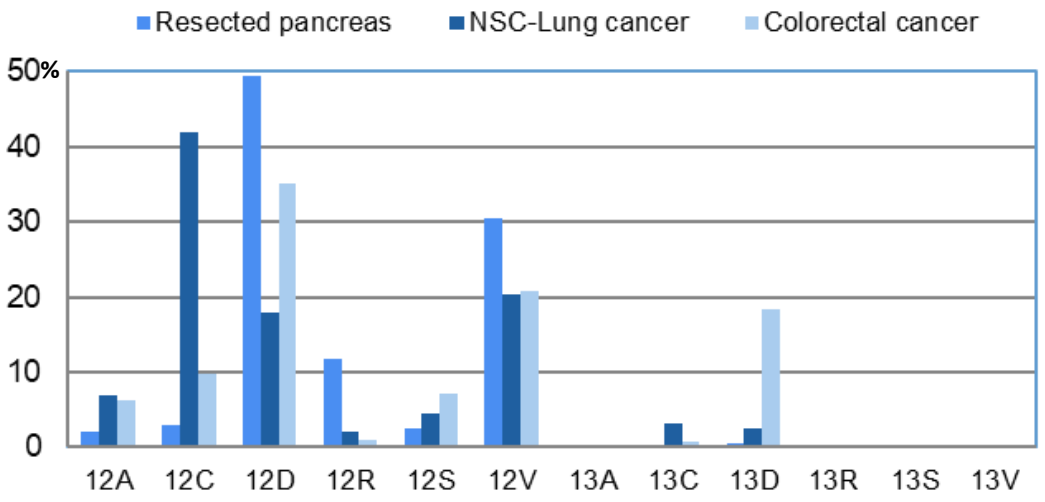


THE TG PEPTIDE COCKTAIL COVERS ~99% OF ALL CODON 12 AND 13 RAS MUTATIONS

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 vaccine clinical data

4. Summary & conclusions

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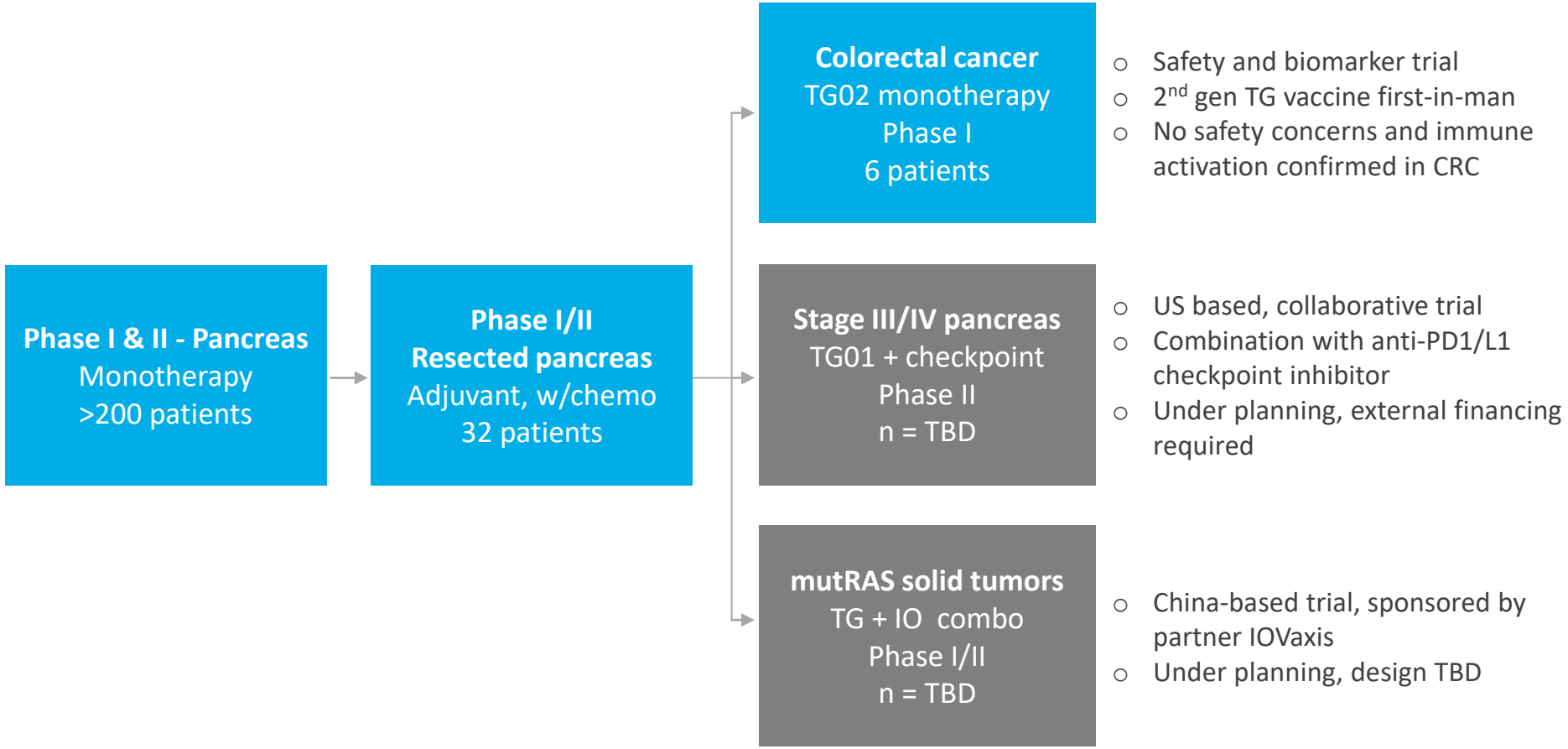
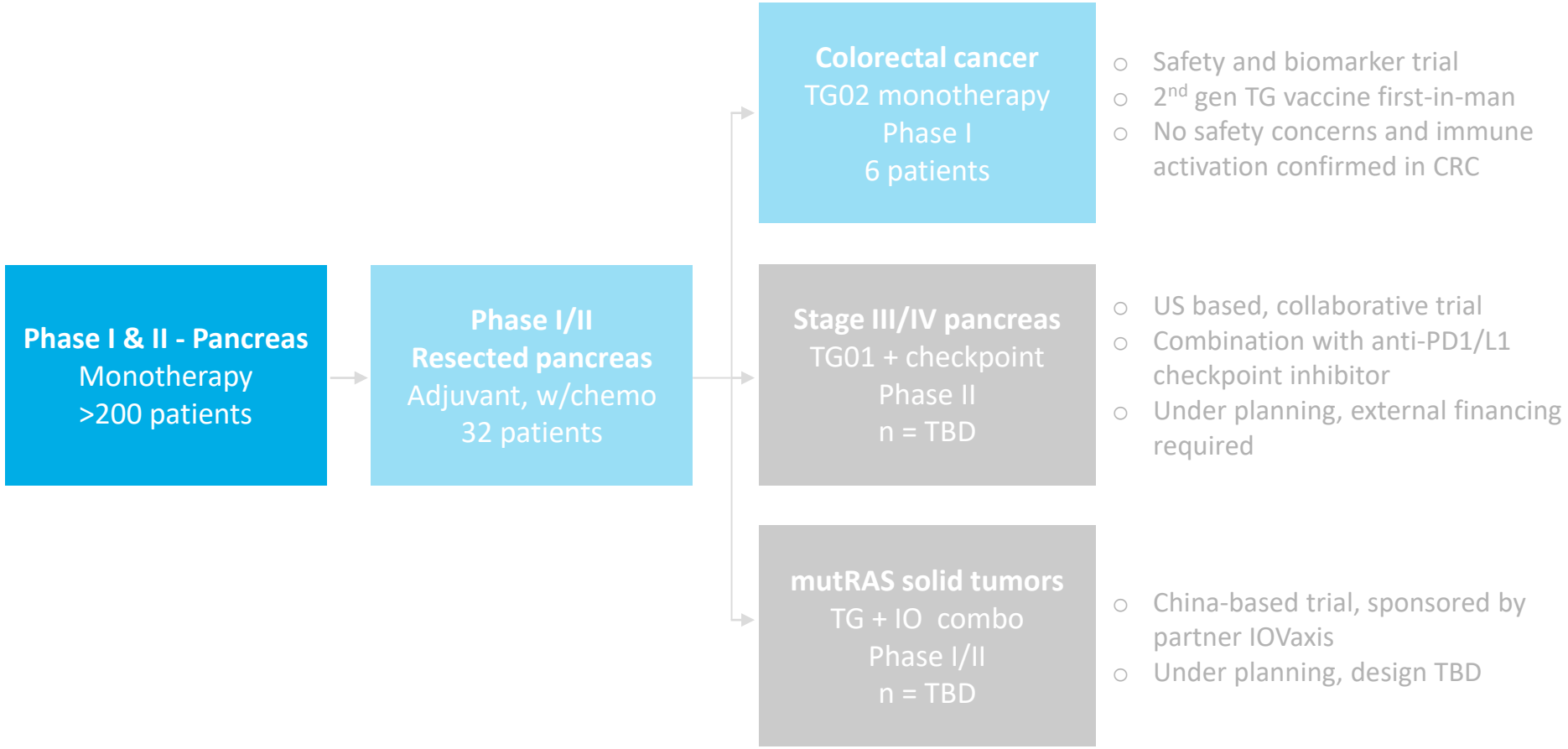
TG CLINICAL PROGRAM OVERVIEW



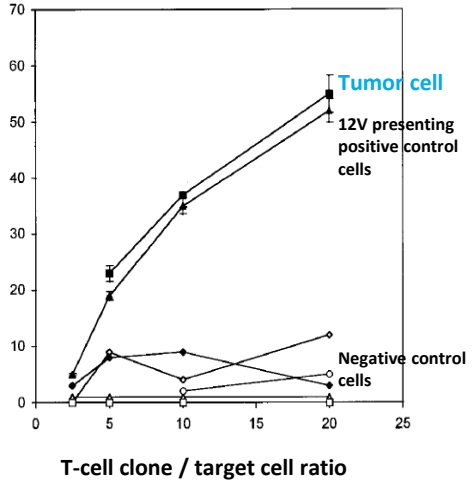
TG CLINICAL PROGRAM OVERVIEW



TG VACCINATION INDUCED CD4+ AND CD8+ MUTANT RAS T-CELL RESPONSES HAS BEEN VALIDATED IN PATIENTS

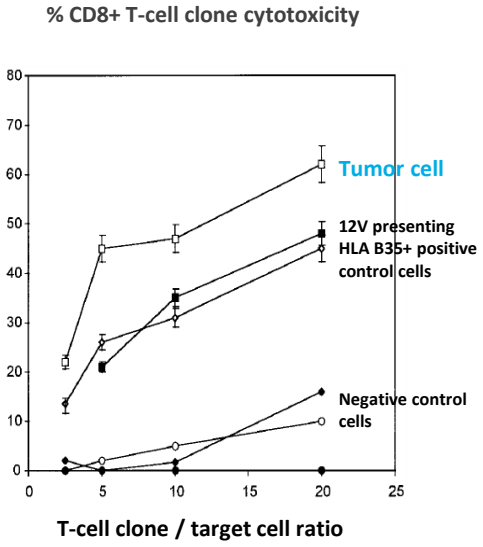
mutRAS specific CD4+ T-cells isolated from vaccinated patient

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



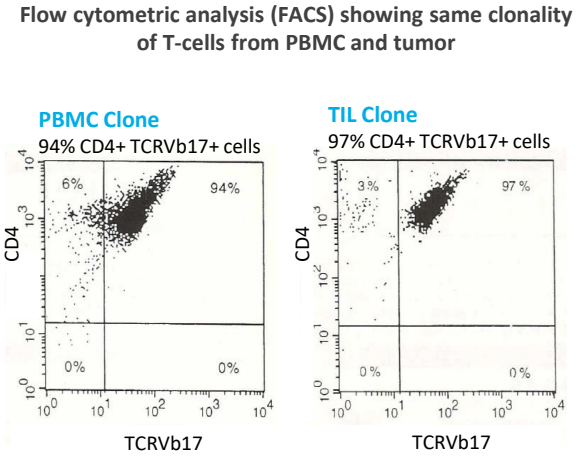
mutRAS specific CD8+ T-cells isolated from vaccinated patient

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



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



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

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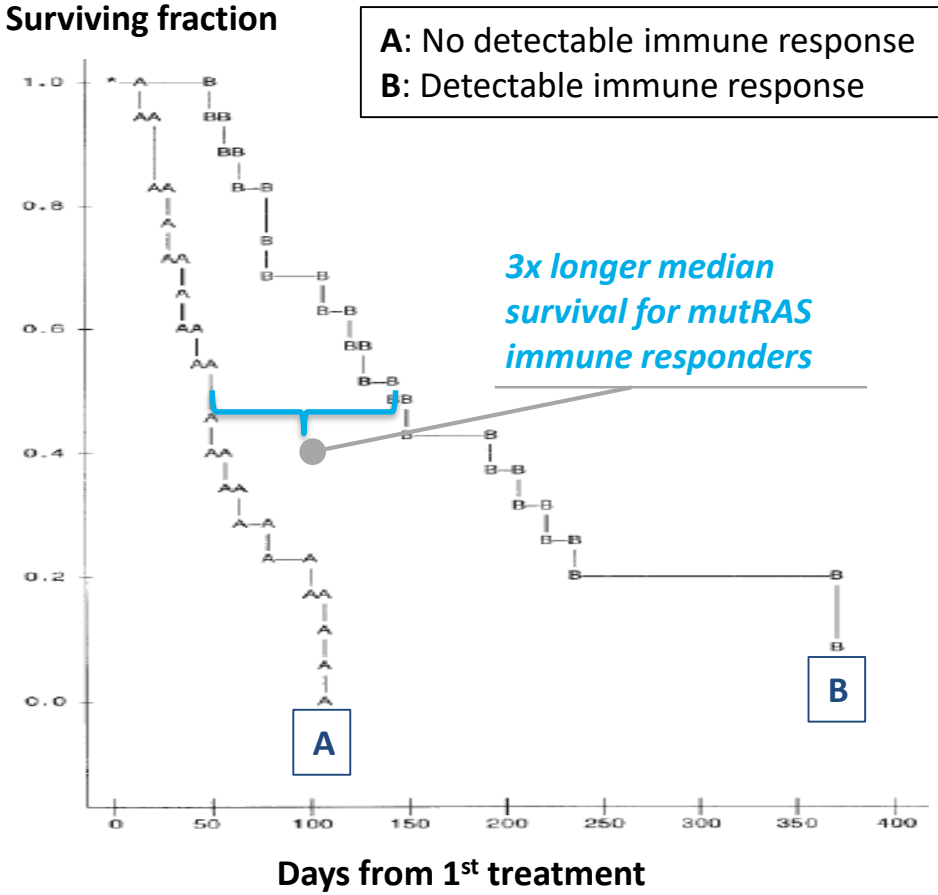
IMPROVED SURVIVAL FOR MUTRAS IMMUNE RESPONDERS OBSERVED IN ADVANCED PANCREATIC CANCER PATIENTS

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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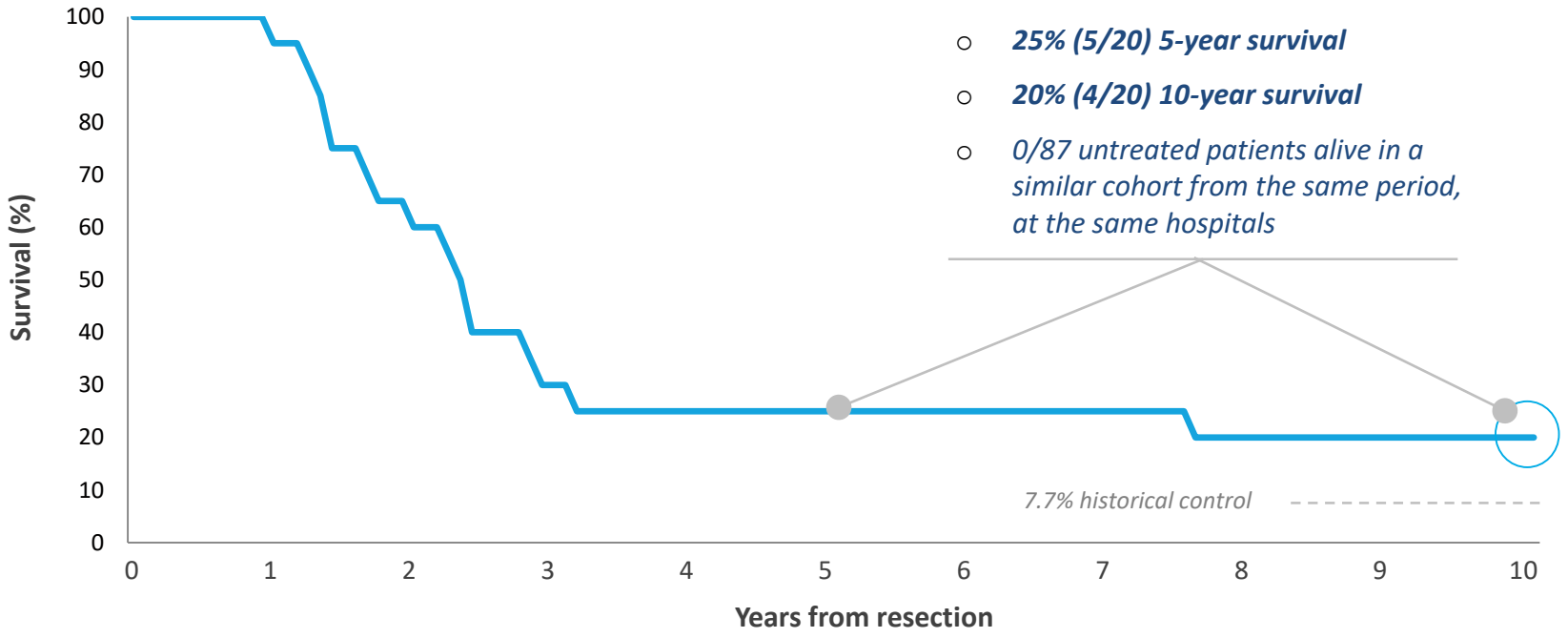
PHASE I MONOTHERAPY SURVIVAL DATA

TG VACCINATION SHOWED 20% 10 YEAR SURVIVAL IN RESECTED PANCREATIC CANCER

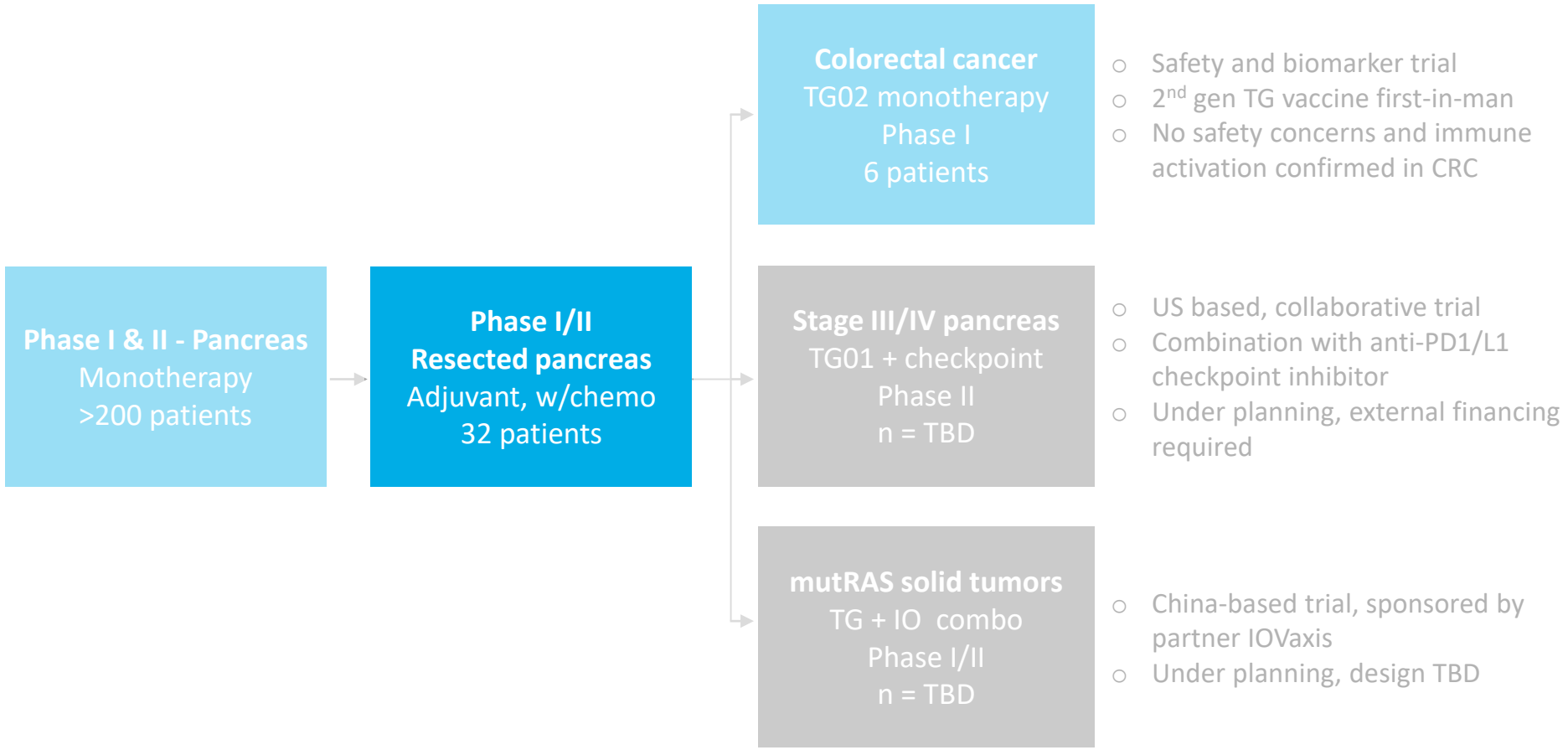
10 year survival in historical TG trials in resected pancreatic cancer[1]

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



Completed trials Trials under planning

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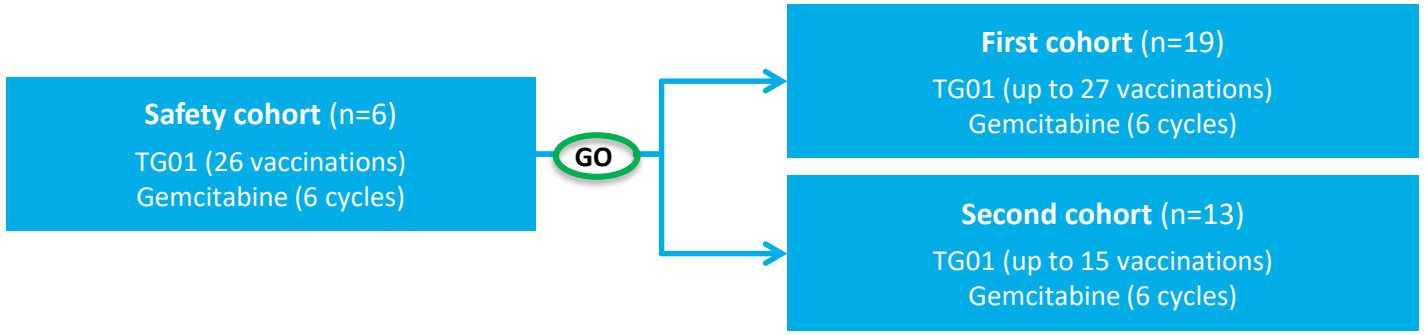
TG01 – RESECTED PANCREAS STUDY SCHEMA

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



Palmer et al. Br J Cancer, 2020

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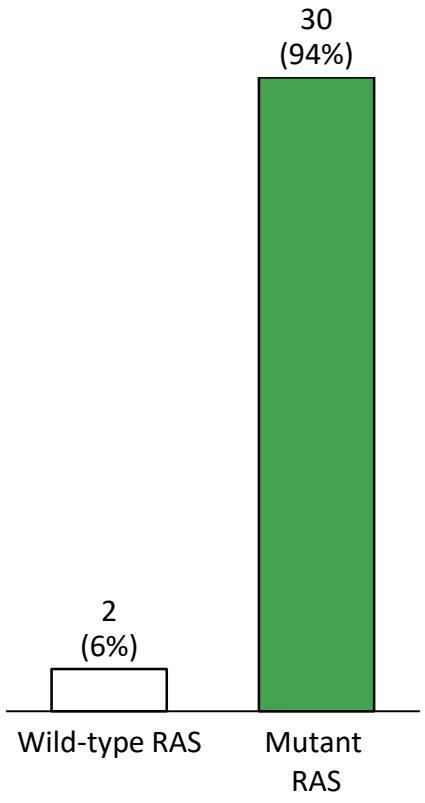
TG01 RESECTED PANCREATIC CANCER PHASE I/II TRIAL DESIGN AND DOSING COHORTS

	Number of vaccinations	Gemcitabine regimen	Vaccinations during phase			Completion rate
			Induction	Treatment	Maintenance	
First cohort 19 patients *full regimen*	**Up to 27**	**6 cycles** starting by wk12 post surgery	✓ **6** 3 wks	✓ **12** Bi-weekly	✓ **up to 9** up to 2 yrs	**18 vaccinations on average** 1/19pts completed, 18 withdrawn before 2 years
Second cohort 13 patients *optimized regimen*	**Up to 15**	**6 cycles** starting by wk12 post surgery	✓ **5** 5 wks	✖ - 	✓ **up to 10** up to 2 yrs	**12 vaccinations on average** 3/13pts completed, 10 withdrawn before 2 years

Treatment schedule

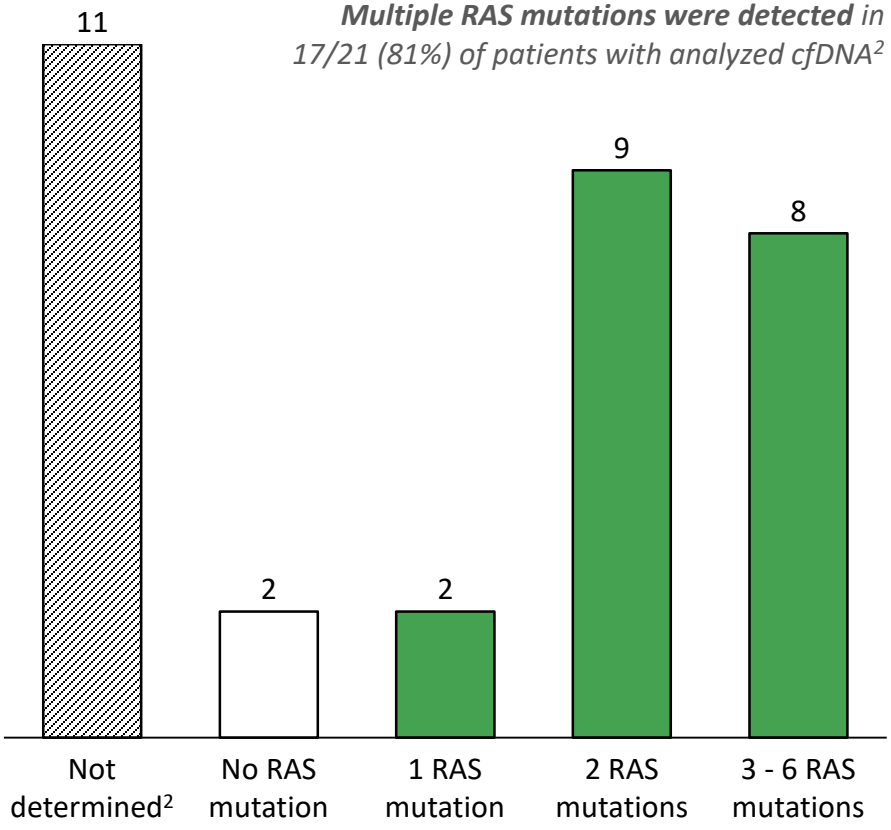
30/32 PATIENTS IN THE TRIAL WERE CONFIRMED AS MUTANT RAS, WITH MOST SHOWING PRESENCE OF MUTIPLE POINT MUTATIONS

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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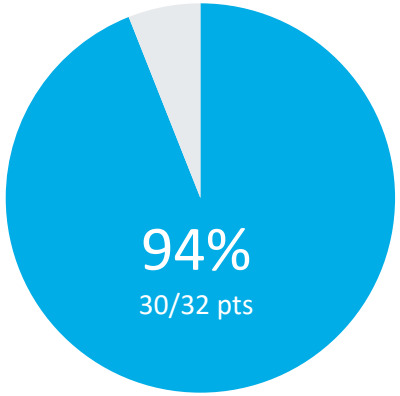
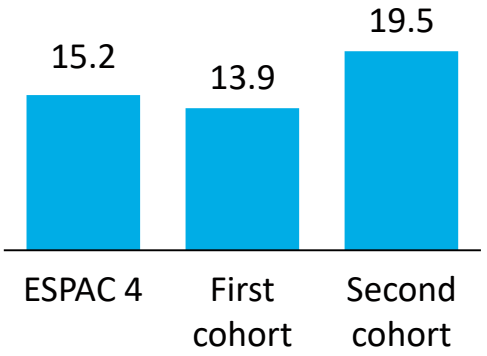
TOP-LINE DATA SUMMARY TG01 + GEMCITABINE

AS ADJUVANT COMBINATION TREATMENT IN RESECTED PANCREATIC CANCER

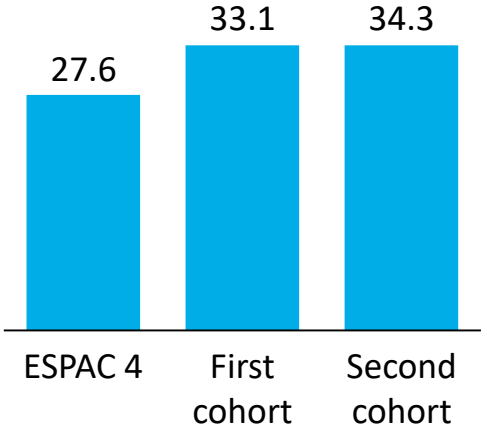
1 RAS-specific immune activation



2 Median disease free survival (mPFS), months



3 Median overall survival (mOS), months



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

Palmer et al. Br J Cancer, 2020
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

Palmer et al. Br J Cancer, 2020

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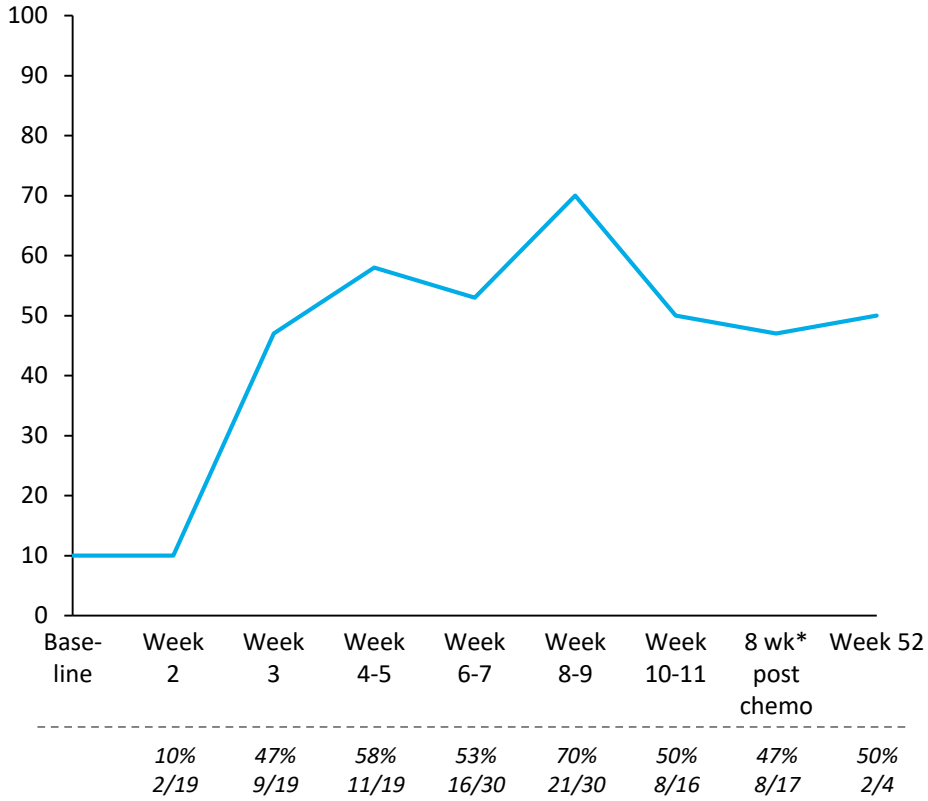
1 ROBUST LEVELS OF DTH AND PBMC MUTANT RAS IMMUNE RESPONSES BUILDING UP OVER TIME

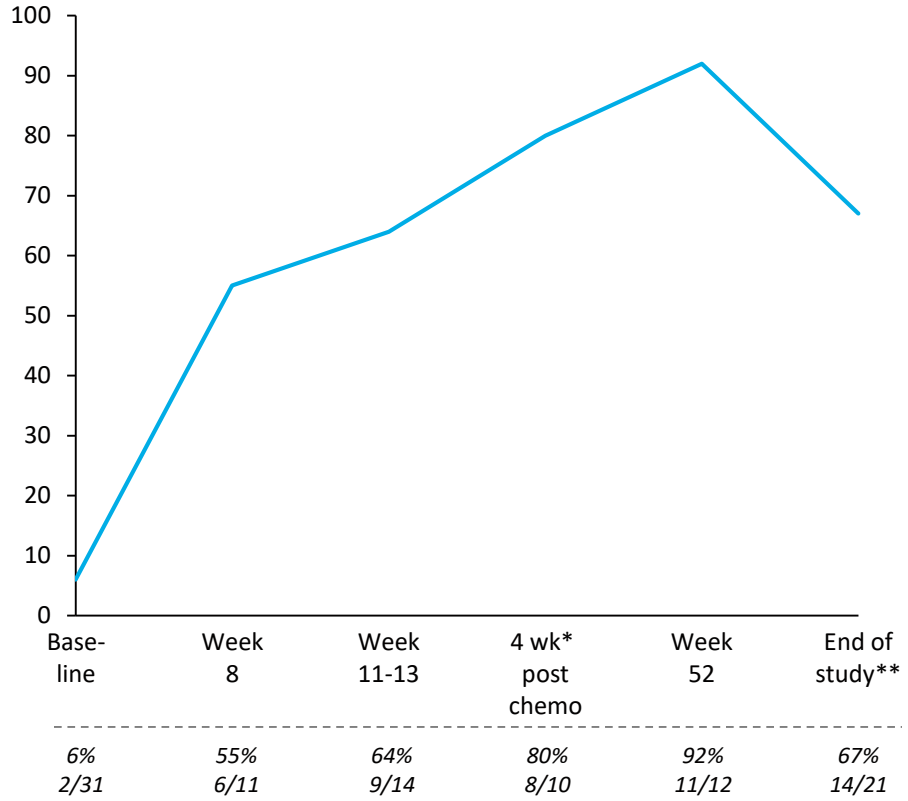
DTH responses over time

% 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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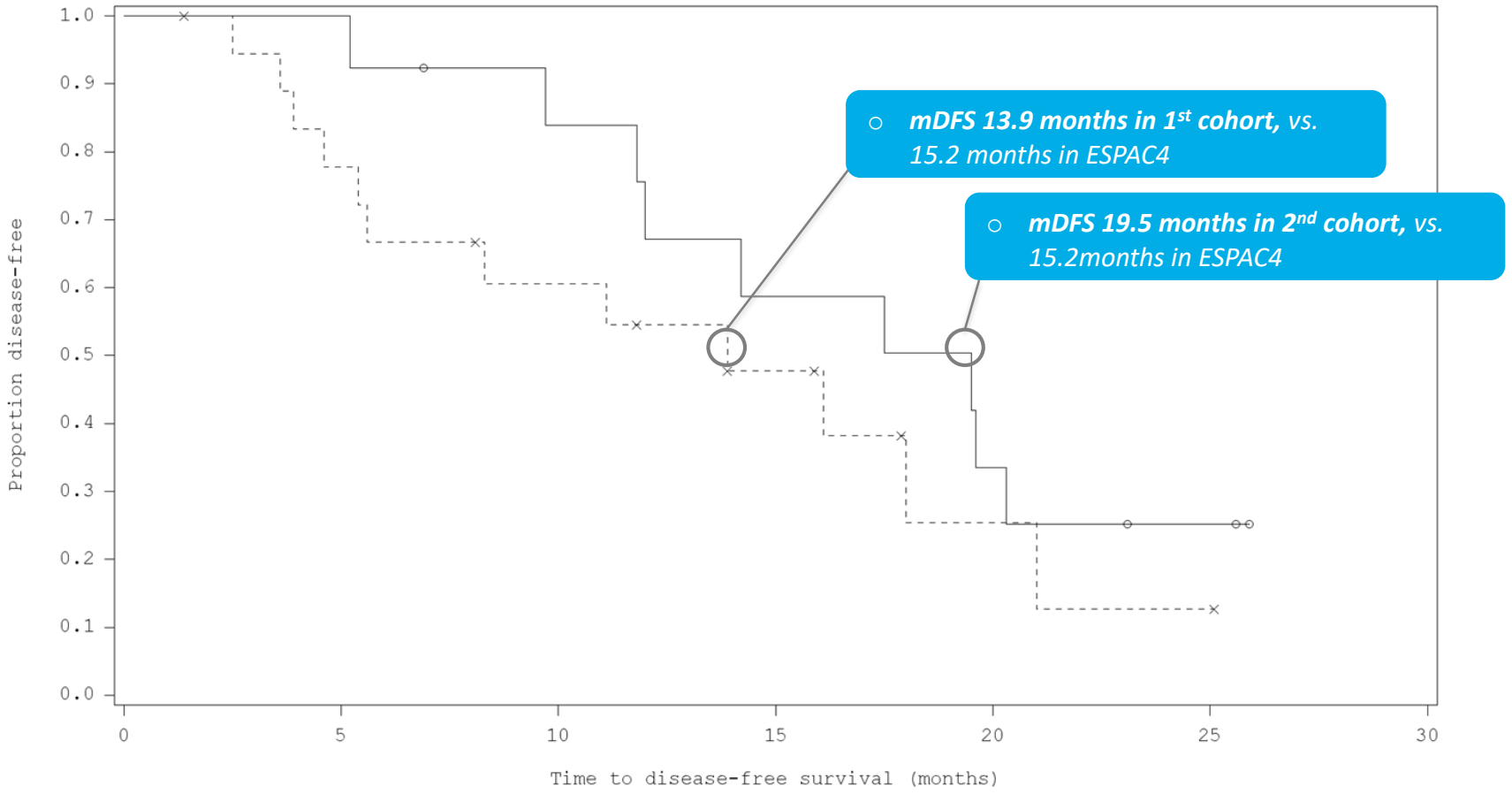
2 DISEASE FREE SURVIVAL (DFS) KAPLAN-MEIER PLOT



Censored= No progression on latest scan collected

DFS was measured from surgery

Palmer et al. Br J Cancer, 2020

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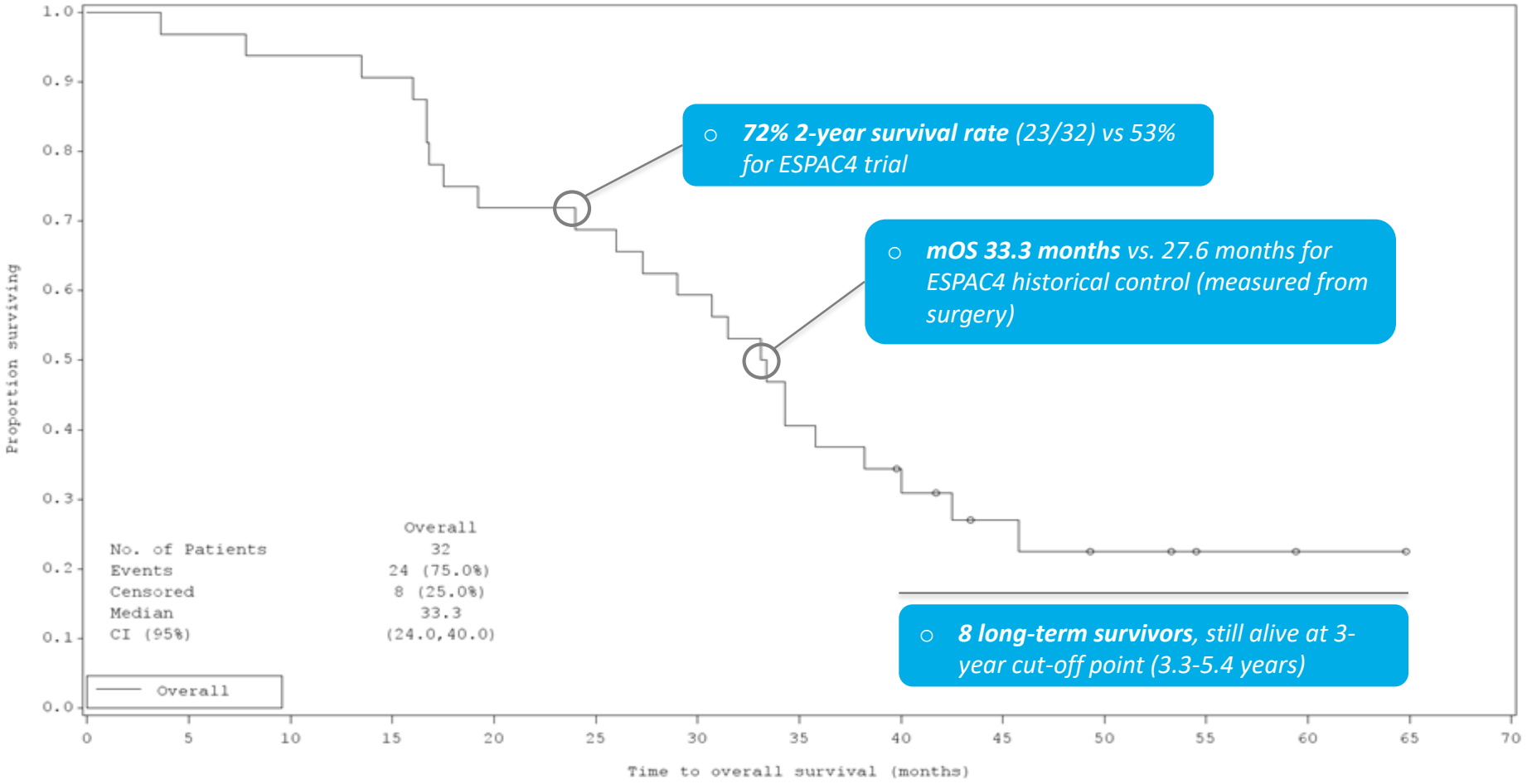
3 KAPLAN-MEIER SURVIVAL PLOT FOR ALL 32 PATIENTS - SIGNAL OF CLINICAL BENEFIT OF TG VACCINATION



Palmer et al. Br J Cancer, 2020

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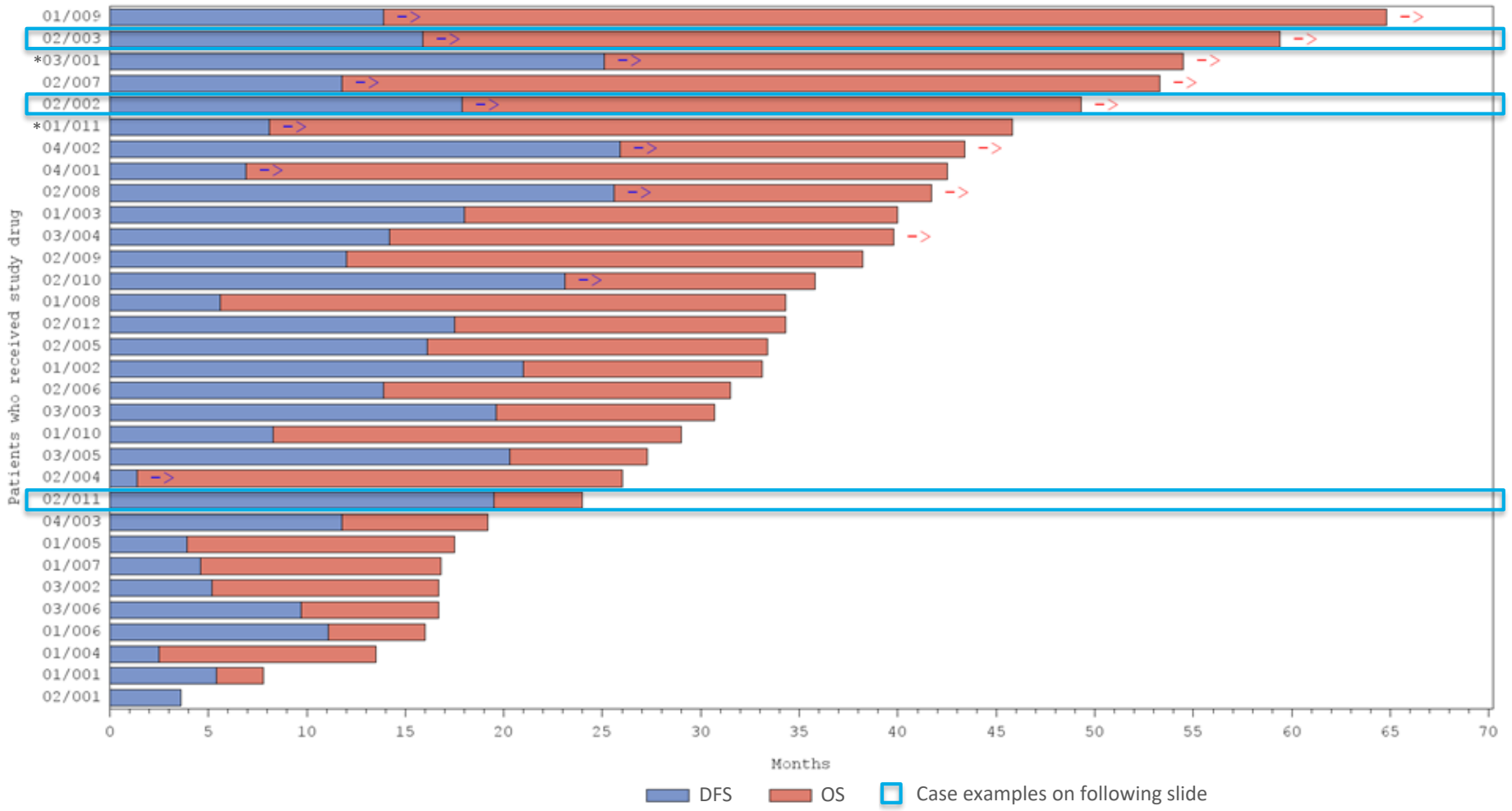
TG01 RESECTED PANCREAS TRIAL - SWIMMER PLOT SHOWING INDIVIDUAL PATIENT OUTCOMES



* RAS wild type (2/32 patients)

All measurements in months from surgery

Palmer et al. Br J Cancer, 2020

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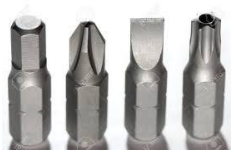
4

Summary & conclusions

SUMMARY – TG MUTANT RAS VACCINE

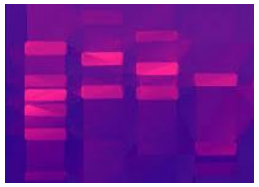


Targets all RAS mutations with one product

- **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
- **Available for partnering**, IOVaxis Therapeutics has option to China rights

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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