TG MUTANT RAS NEOANTIGEN VACCINE

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Neoantigen Summit, Amsterdam

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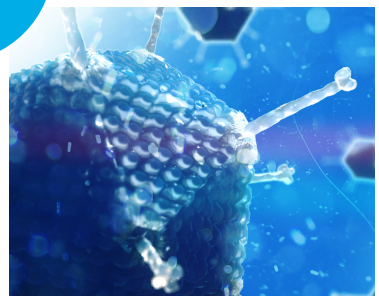
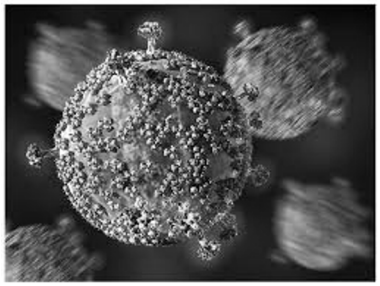
TARGOVAX IS DEVELOPING IMMUNE ACTIVATORS TO DRIVE ANTI-TUMOR T-CELL RESPONSES

Targovax focus





Immune activators

Oncolytic viruses, vaccines

Immune modulators

Checkpoint inhibitors

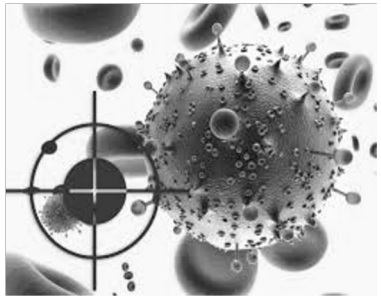
Surgery - Radio - Chemo

Cell therapy

CAR-Ts, TCRs

Targeted therapy

TKIs, PARPs, etc.



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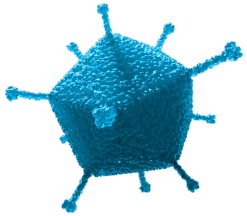
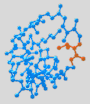
TARGOVAX HAS TWO CLINICAL STAGE IMMUNE ACTIVATOR PROGRAMS



ONCOS
Oncolytic virus

- Genetically armed **oncolytic immunotherapy**
- **Clinically validated immune activation** shown in several solid tumors
- **Clinical efficacy** in combination with both anti-PD1 and chemotherapy



TG
Neoantigen vaccine

- **Polyvalent mutant KRAS** neoantigen cancer vaccine
- Triggers **T-cell responses** to oncogenic **RAS driver mutations**
- **Survival benefit** demonstrated in Phase 1
- **Phase 2 program under planning** in several indications

Activates the immune system

Triggers patient-specific responses

No need for personalization

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A vaccine approach to target mutant RAS

2. TG vaccine clinical data
3. Next generation TG program

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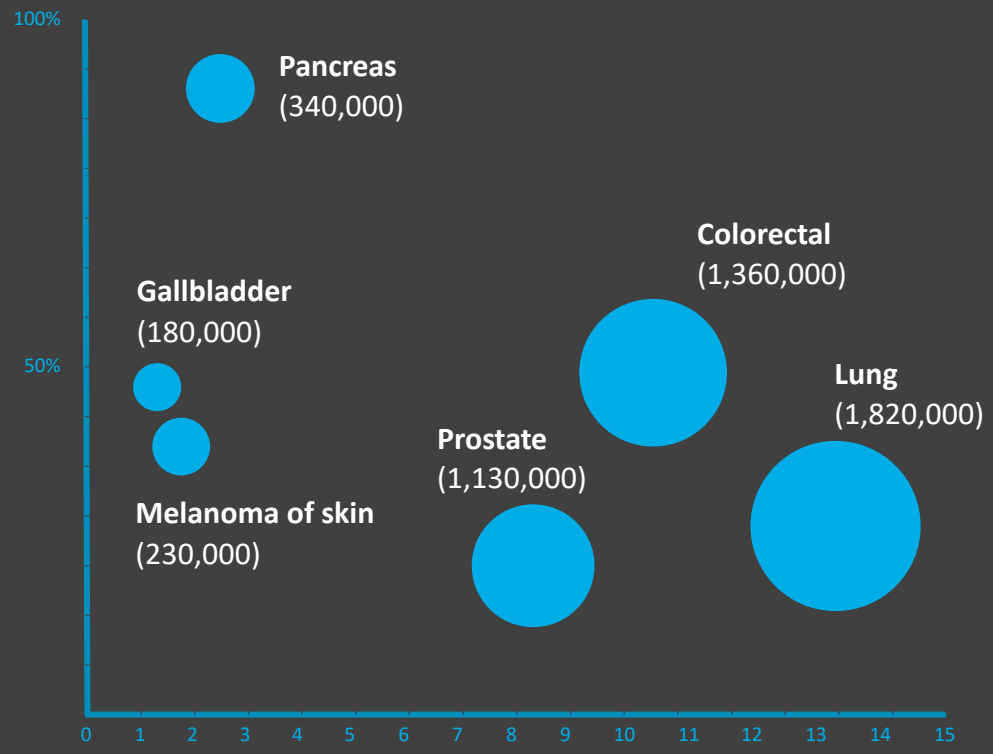
THE KRAS GENE IS MUTATED IN 25-30% OF ALL CANCERS

INCLUDING 90% OF PANCREATIC AND 40% OF COLORECTAL CANCERS

Frequency of KRAS mutations

Global cancer incidents per 10,000

(xx) = no. of cancer patients



- KRAS is the **most frequently** occurring oncogenic **driver mutation**
- KRAS is a **clinically validated shared neoantigen**
- Mutant KRAS 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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KRAS IS POTENTIALLY AN EXCELLENT TARGET FOR A SHARED NEOANTIGEN CANCER VACCINE APPROACH

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

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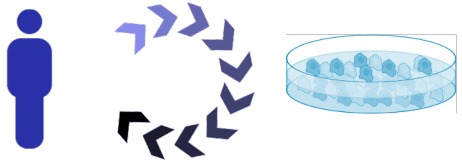
MUTANT KRAS T-CELLS CAN FORM SPONTANEOUSLY IN PATIENTS, AND RECOGNIZE AND KILL TUMOR CELLS

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

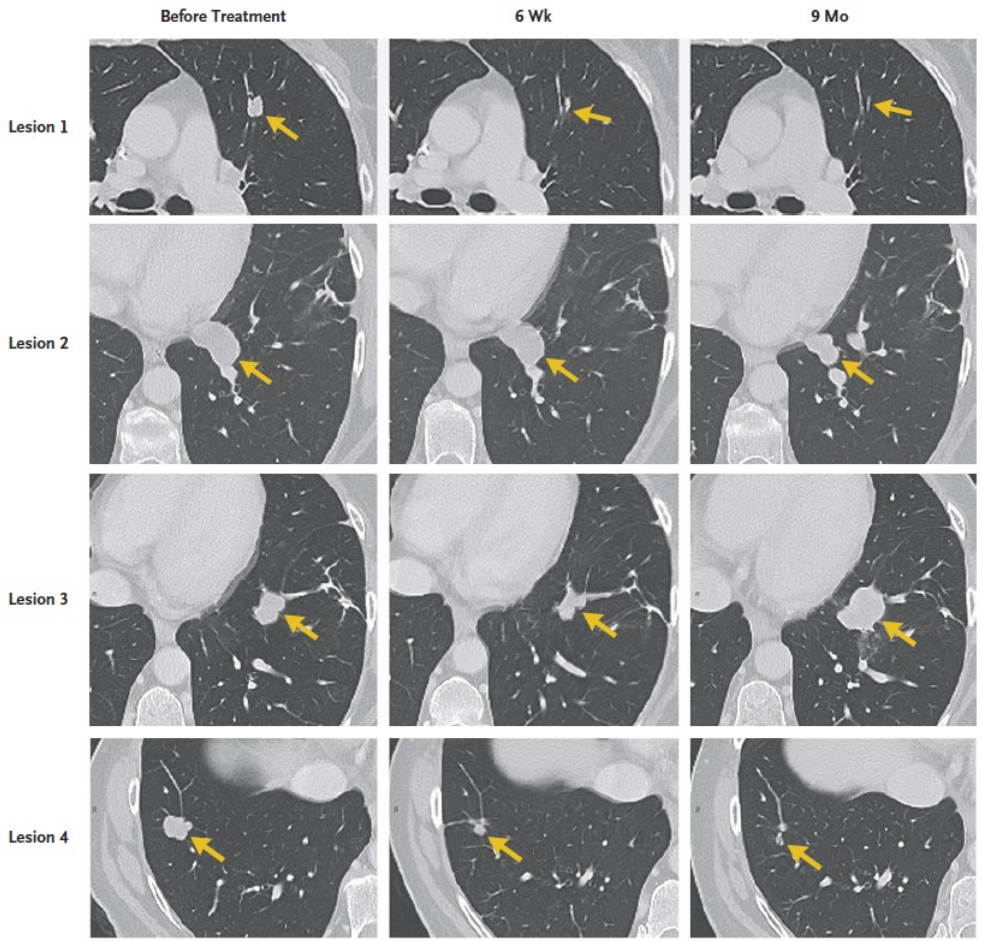


Endogenous CD8+ tumor-infiltrating lymphocytes (TIL) recognizing the **G12D RAS mutation** were **isolated from a colorectal cancer patient**

The G12D **mutRAS CD8+ T-cells** were **expanded *ex vivo*** and **transfused back** into the patient (single infusion of $1.48x10^{11}$ cells)

Key results

- **All seven lung metastases** detected in the patient **showed regression** (pictured on the 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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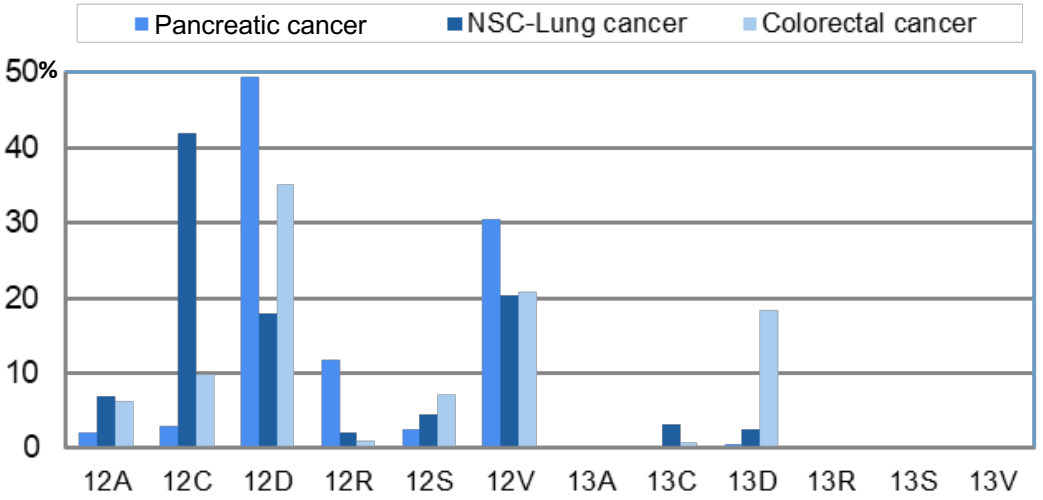
THE TG VACCINES ARE PEPTIDE COCKTAILS COVERING ~99% OF ALL KRAS CODON 12/13 MUTATIONS

Oncogenic codon 12 & 13 KRAS mutations

1 12 13
MTEYKLVVVGAGGVGKSALTIQLIQ .....

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



TG product characteristics

- **Two clinical stage products**
  - **TG01**: 7 peptides covering ~99% of KRAS 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 mutKRAS 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

3. Next generation TG program

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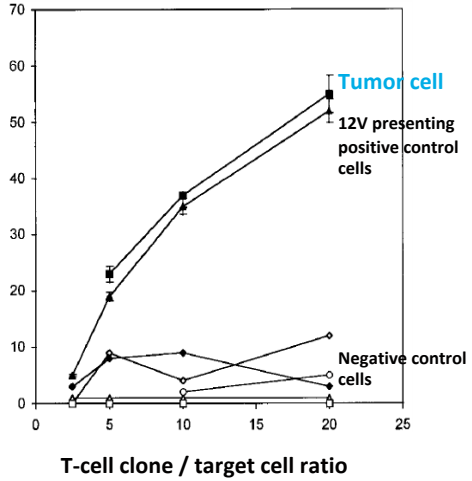
TG VACCINATION INDUCED CD4+ AND CD8+ MUTANT RAS T-CELL RESPONSES HAVE BEEN VALIDATED IN PATIENTS

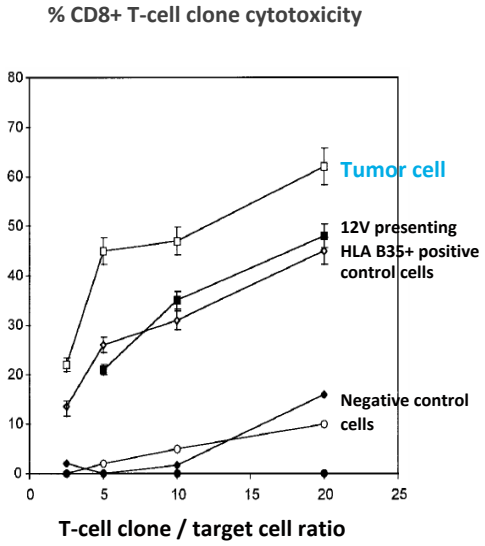
mutRAS specific CD4+ T-cells isolated from vaccinated patient

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



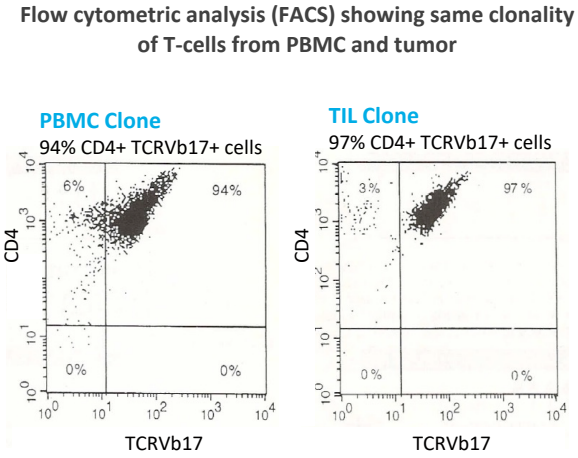
mutRAS specific CD8+ T-cells isolated from vaccinated patient

- CD8+ T-cell clone lyses cancer cells isolated from 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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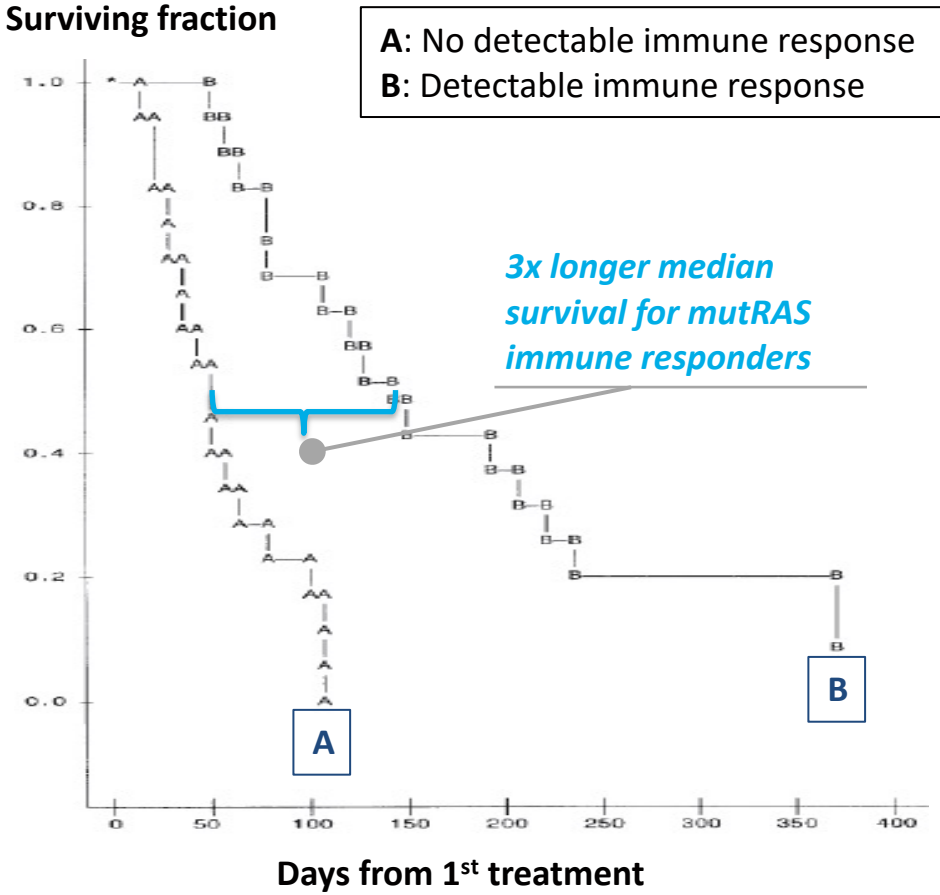
IMPROVED SURVIVAL OF ADVANCED STAGE PANCREATIC CANCER PATIENTS WITH DOCUMENTED IMMUNE RESPONSES AGAINST RAS

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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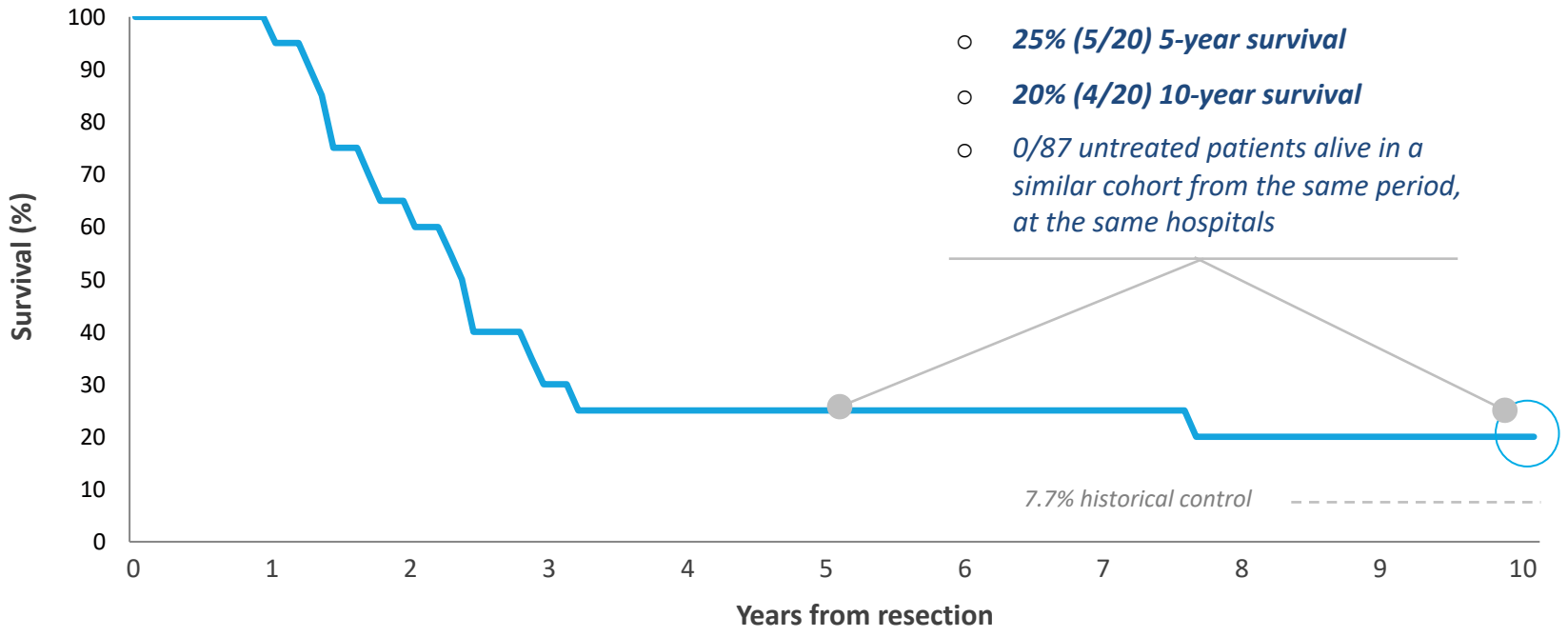
PHASE I MONOTHERAPY SURVIVAL DATA

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

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	Treatment	**TG01 / GM-CSF** (up to 2 years) **Gemcitabine** (6 cycles)
Objective	Assess **safety, mutant RAS immune response** and **clinical efficacy**	Study design	**Single arm**, open label with safety lead-in **2 cohorts with different dosing regimens**

Study cohorts

Safety cohort (n=6)
TG01 (26 vaccinations)
Gemcitabine (6 cycles)

→

First cohort (n=19)
TG01 (up to 27 vaccinations)
Gemcitabine (6 cycles)

Second cohort (n=13)
Reduced intensity regimen
TG01 (up to 15 vaccinations)
Gemcitabine (6 cycles)

4 sites in Norway and UK: Oslo University Hospital, Clatterbridge, Liverpool, Christie Manchester and QEH, Birmingham

Palmer et al. Br J Cancer, 2020

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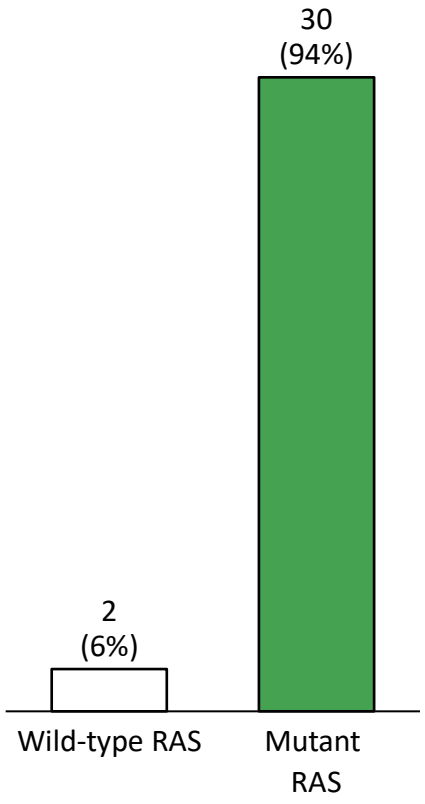
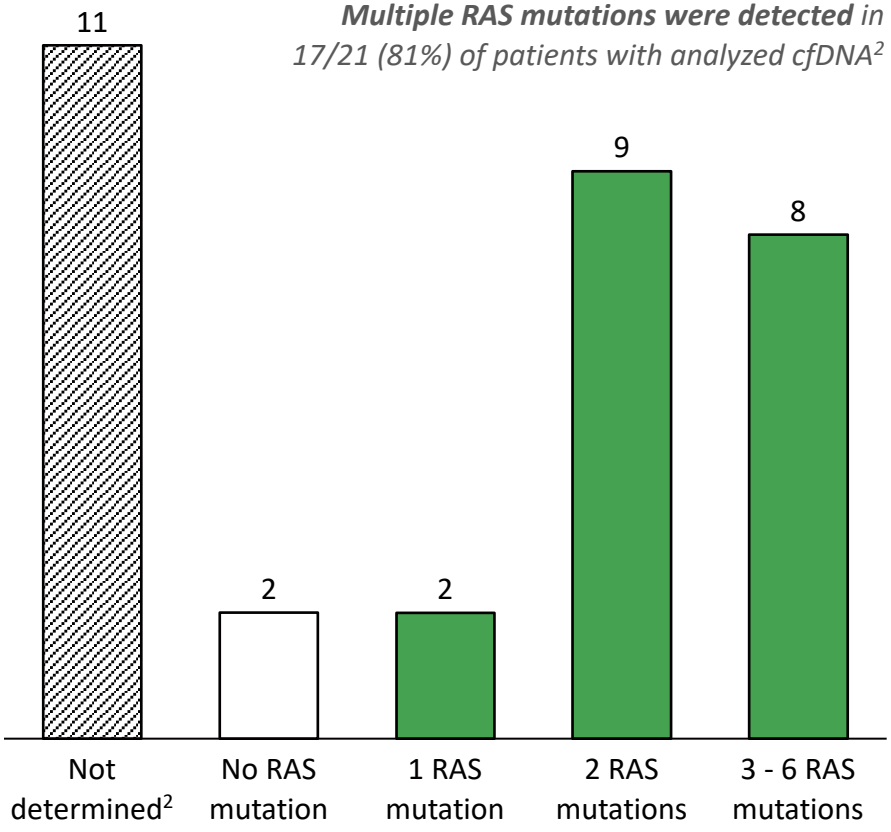
30/32 PATIENTS IN THE TRIAL WERE CONFIRMED AS MUTANT KRAS, WITH MAJORITY CARRYING MUTIPLE POINT MUTATIONS

Patient RAS status
wt/mut genetic RAS [1]



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

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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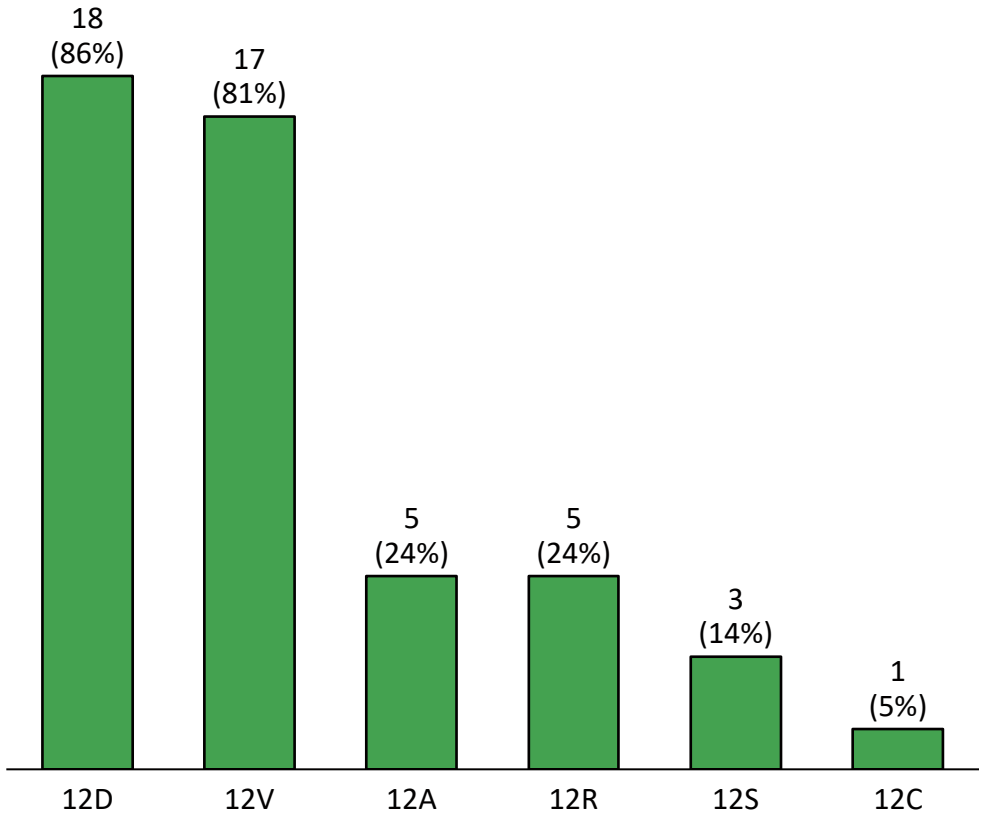
12D AND 12V WERE THE MOST FREQUENTLY OCCURRING KRAS MUTATIONS FOUND IN THE PATIENTS

Frequency of individual RAS point mutations detected in ctDNA[1]

Number of patients (%) with mutation confirmed in ctDNA for at least one time point in study (n=21)



- **12D and 12V mutations** co-existed in **17/21 (81%)** of patients
- **12C mutation** was only detected in **one patient**
- In **one patient all six assessed KRAS mutations were detected** during the course of the study
- Profiles of detectable **mutations shifted over time**, indicating **selection pressure** against particular mutKRAS variants

1 Eleven patients were not screened for individual mutations in cfDNA

Company data, unpublished

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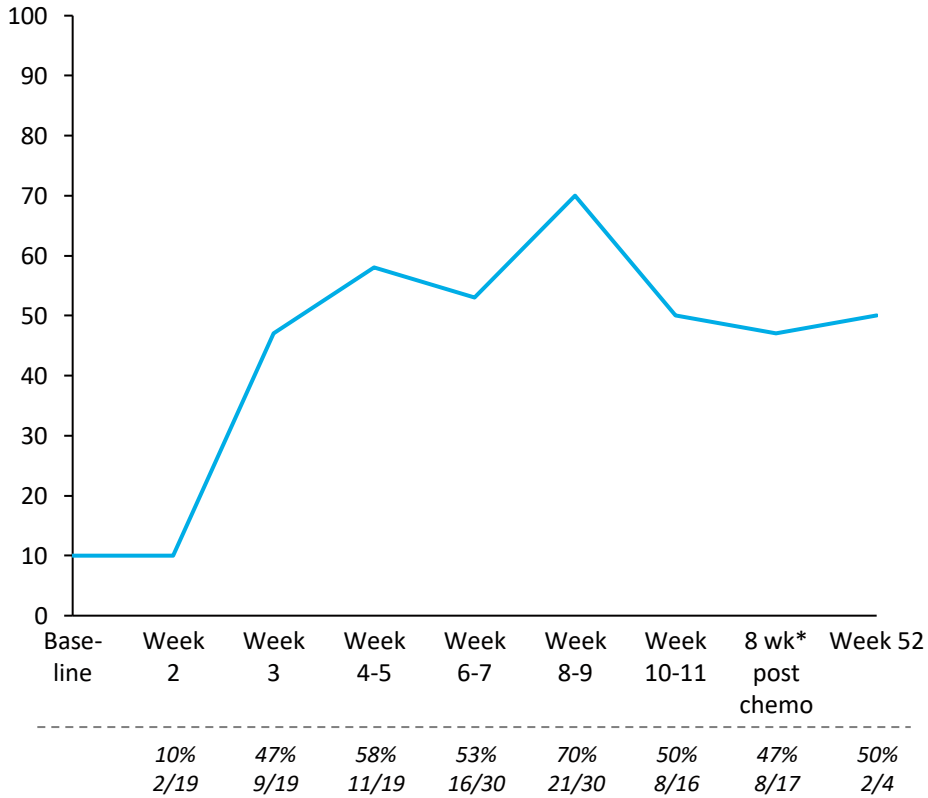
ROBUST LEVELS OF DTH AND PBMC MUTANT KRAS IMMUNE RESPONSES BUILDING UP OVER TIME

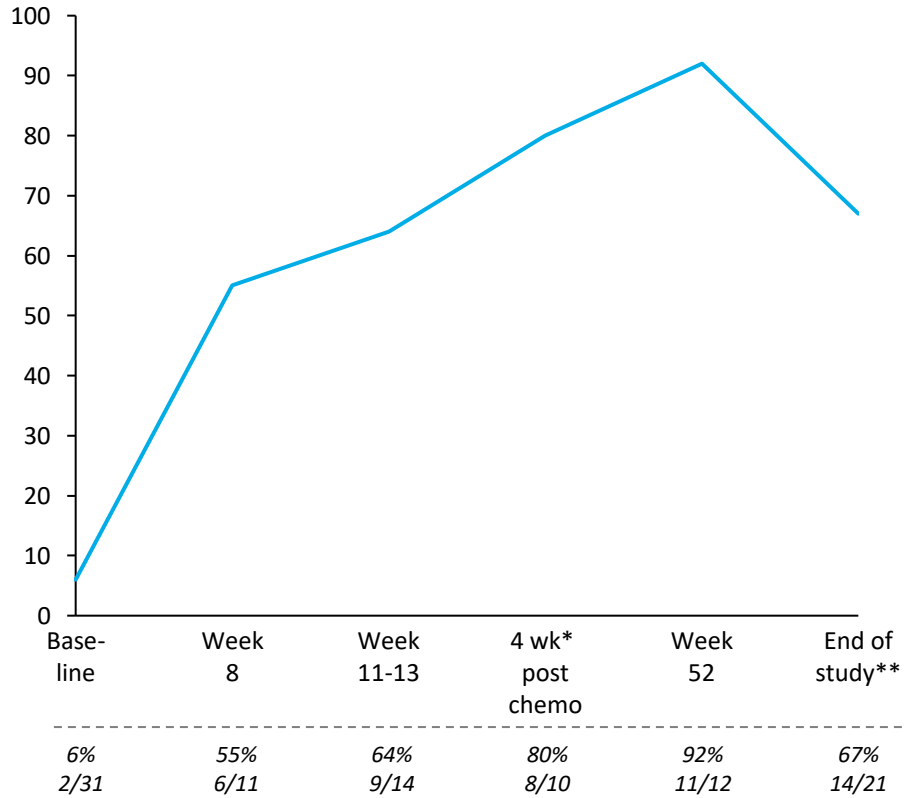
DTH responses over time

% 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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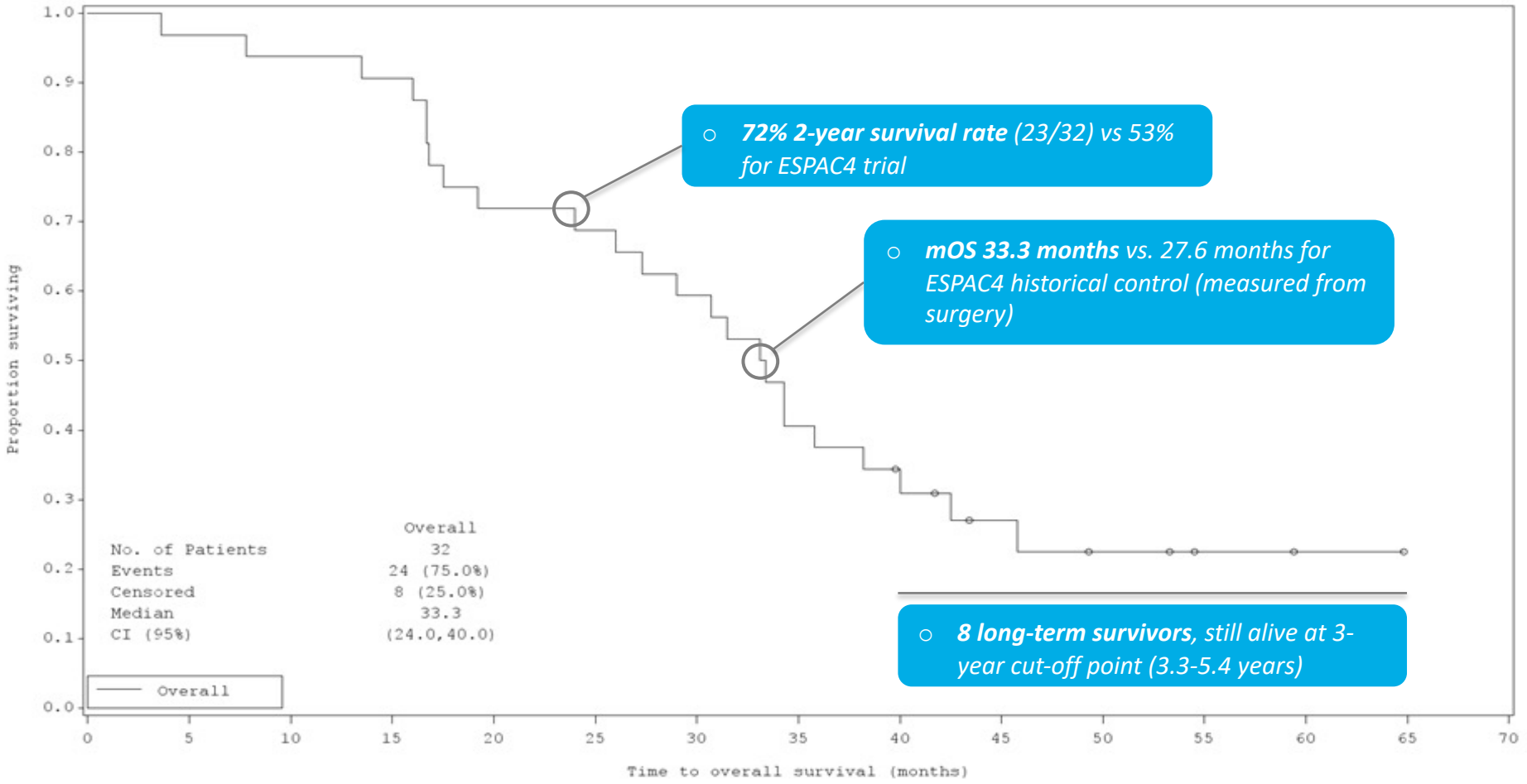
TG VACCINATION PROVIDED 6 MONTHS MEDIAN OVERALL SURVIVAL BENEFIT OVER HISTORICAL DATA



Palmer et al. Br J Cancer, 2020

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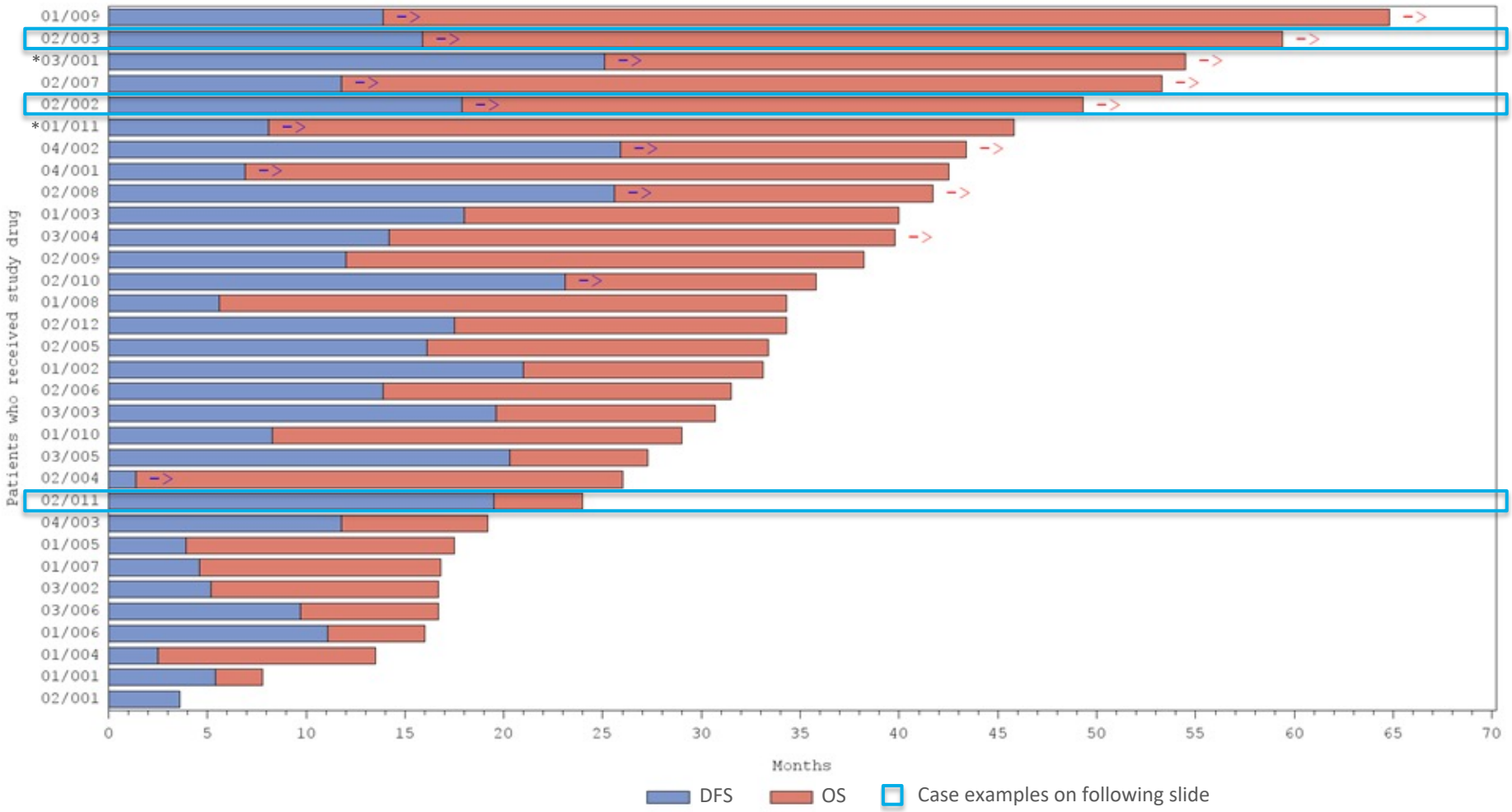
TG01 RESECTED PANCREAS TRIAL - SWIMMER PLOT SHOWING INDIVIDUAL PATIENT OUTCOMES



* RAS wild type (2/32 patients)

All measurements in months from surgery

Palmer et al. Br J Cancer, 2020

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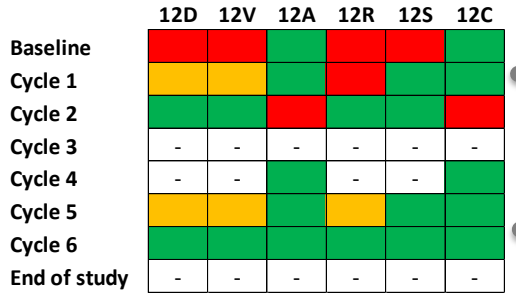
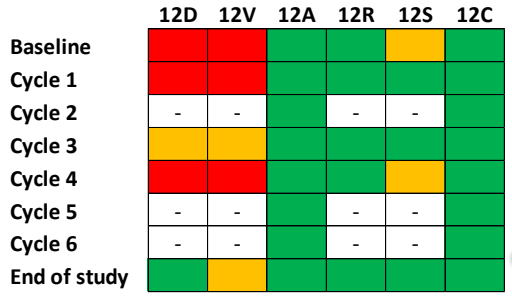
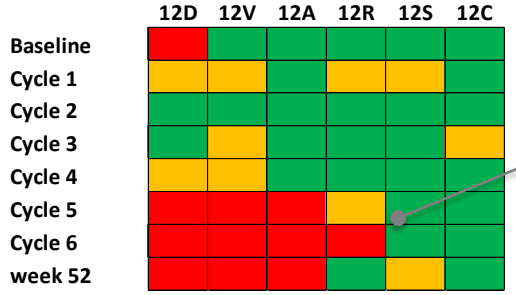
MULTIPLE KRAS MUTATIONS DETECTED IN ctDNA IN MOST PATIENTS, AND EVIDENCE OF CLONAL CLEARANCE FOLLOWING TG VACCINATION

	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 base-line, cleared by cycle 2*
- ***Multiple clones re-emerged*** *by cycle 5/6*
- ***Tumor recurred*** *at 20 months*

Unpublished company data

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Next generation TG program

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BUILDING MUTANT KRAS IMMUNOTHERAPY PROGRAM THROUGH STRATEGIC PARTNERSHIPS

Targovax mutRAS immunotherapy strategy

Polyvalent mut KRAS cancer vaccine

Clinical stage

- Enhanced versions of TG vaccines and novel combination strategies
- NOK 18m in research grant funding

Next generation mut KRAS concepts

Pre-clinical discovery

- Innovative, first-in-class mutRAS IO concepts
- Leverage ONCOS platform
- Strategic R&D partnerships

mutant KRAS immunotherapy pipeline

TG01 mutKRAS vaccine – IITs to launch in 2022 testing novel indications and IO combinations

IOVAXIS THERAPEUTICS

Option to license TG01/02 vaccines for Greater China and Singapore

VALO THERAPEUTICS

Oncolytic virus w/ mutKRAS vaccine coating - Coat ONCOS-102 with mutant RAS neoantigen PeptiCRAd peptides

OBLIQUE THERAPEUTICS

Oncolytic virus w/ mutRAS antibody payload - Express AbiProt mutant RAS targeting antibodies from ONCOS backbone

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SUMMARY – TG VACCINE FOR KRAS MUTANT CANCER

Targets all RAS mutations with one product

- **Covers 99%** of codon 12 and 13 oncogenic **KRAS mutations**
- Patients can have **multiple KRAS mutant 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 KRAS ctDNA**

Potential as genetic marker “pan-RAS” vaccine

- Mutant KRAS 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

R&D collaborations to launch next generation TG program

- **QS-21 selected as adjuvant** for Phase 2 development
- **World class academic and industry** collaboration network being established

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