CLINICAL ACTIVITY DEMONSTRATED FOR POLYVALENT MUTANT KRAS CANCER VACCINE

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4th RAS Targeted Drug Development summit

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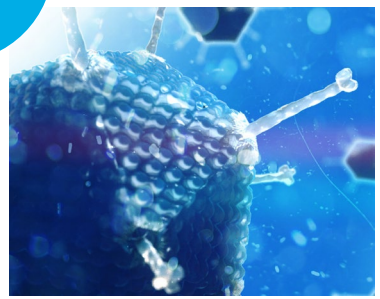
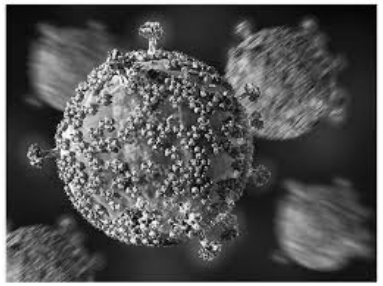
TARGOVAX IS DEVELOPING IMMUNE ACTIVATORS TO DRIVE ANTI-TUMOR T-CELL RESPONSES

Targovax focus





Immune activators

Oncolytic viruses, vaccines

Immune modulators

Checkpoint inhibitors

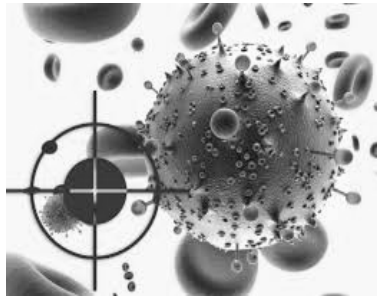
Surgery - Radio - Chemo

Cell therapy

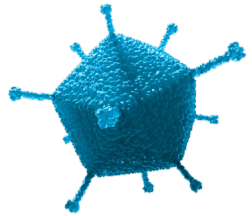
CAR-Ts, TCRs

Targeted therapy

TKIs, PARPs, etc.

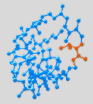


TARGOVAX HAS TWO CLINICAL STAGE IMMUNE ACTIVATOR PROGRAMS



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

1

A vaccine approach to target mutant RAS

2. TG vaccine clinical data
3. Further development plans
4. Dosing/scheduling strategy to enhance immune response

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

Clinically validated

- **Endogenous mutant KRAS T-cell responses** have been observed clinically
- KRAS-specific T-cells have been shown to **eradicate tumors in patients**

One-size-fits all

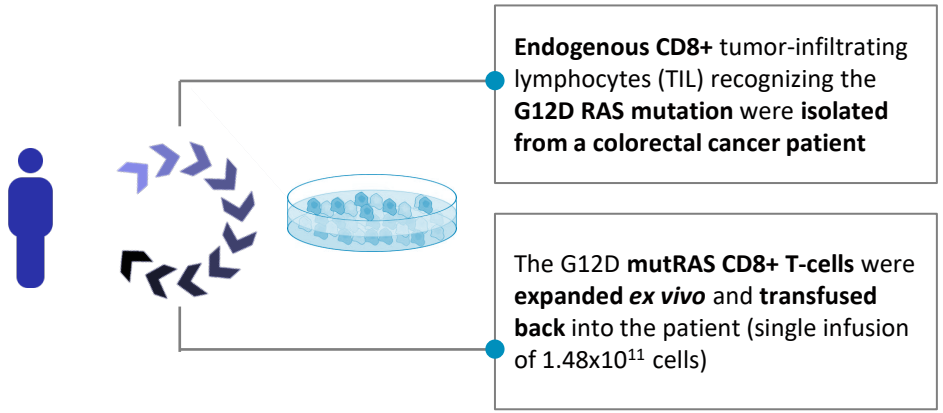
- **Limited set** of well-characterized oncogenic K**RAS driver mutations**
- Polyvalent vaccines can **deal with the main KRAS mutations in one product**

Off-the-shelf product

- KRAS is the **most frequently occuring public neoantigen** across all cancers
- **No need for personalization**

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***

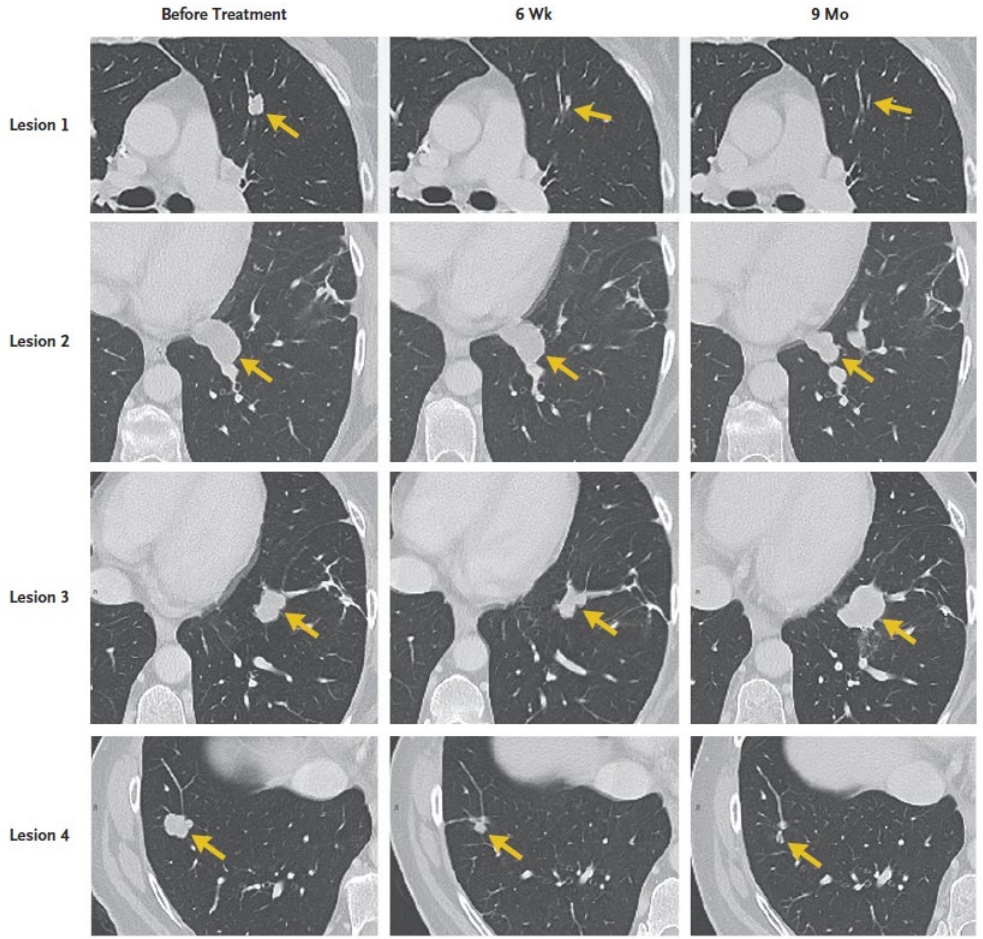


Endogenous CD8+ tumor-infiltrating lymphocytes (TIL) recognizing the **G12D RAS mutation** were **isolated from a colorectal cancer patient**

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

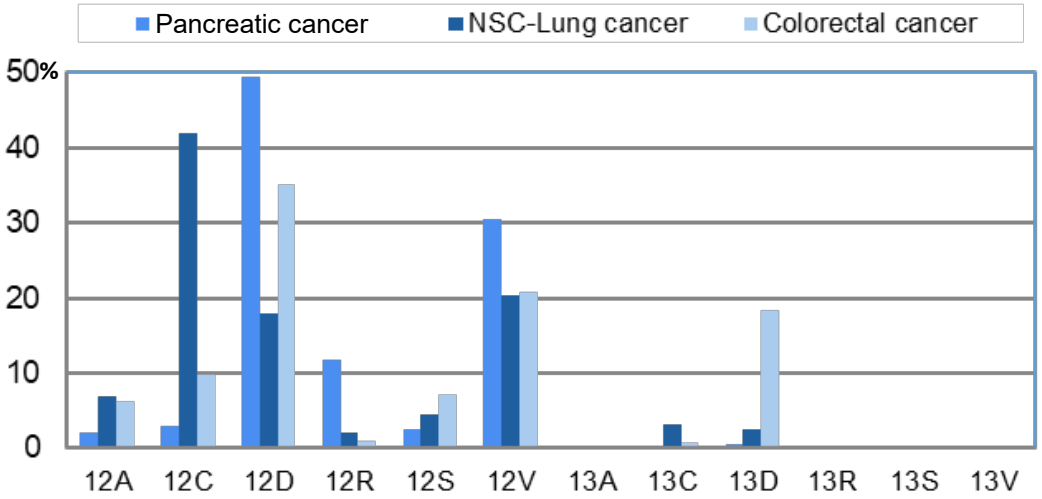


TG01 IS A PEPTIDE COCKTAIL COVERING THE MAIN ONCOGENIC RAS CODON 12/13 MUTATIONS

Oncogenic codon 12 & 13 KRAS mutations

1 12 13
MTEYKLVVVGAGGVGKSALTIQLIQ ……

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



TG product characteristics

- **Clinical stage product TG01:**
  - 7 peptides covering the most common RAS codon 12/13 oncogenic mutations
  - 99% coverage in RAS-mutant PDAC
- Covers **all 3 RAS family isoforms** (K, N, & H)
- **Long peptides** (17mer) eliciting both **CD4+ and CD8+ responses**
- **Promiscuous HLA class II binders**, covering all HLA DR, DP and DQ epitopes
- **All possible class I mutRAS epitopes nested** within sequences (after processing)
- **Adjuvanted by QS-21/Stimulon**

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

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TG vaccine clinical data

3. Dosing/scheduling strategy to enhance immune response
4. Further development plans

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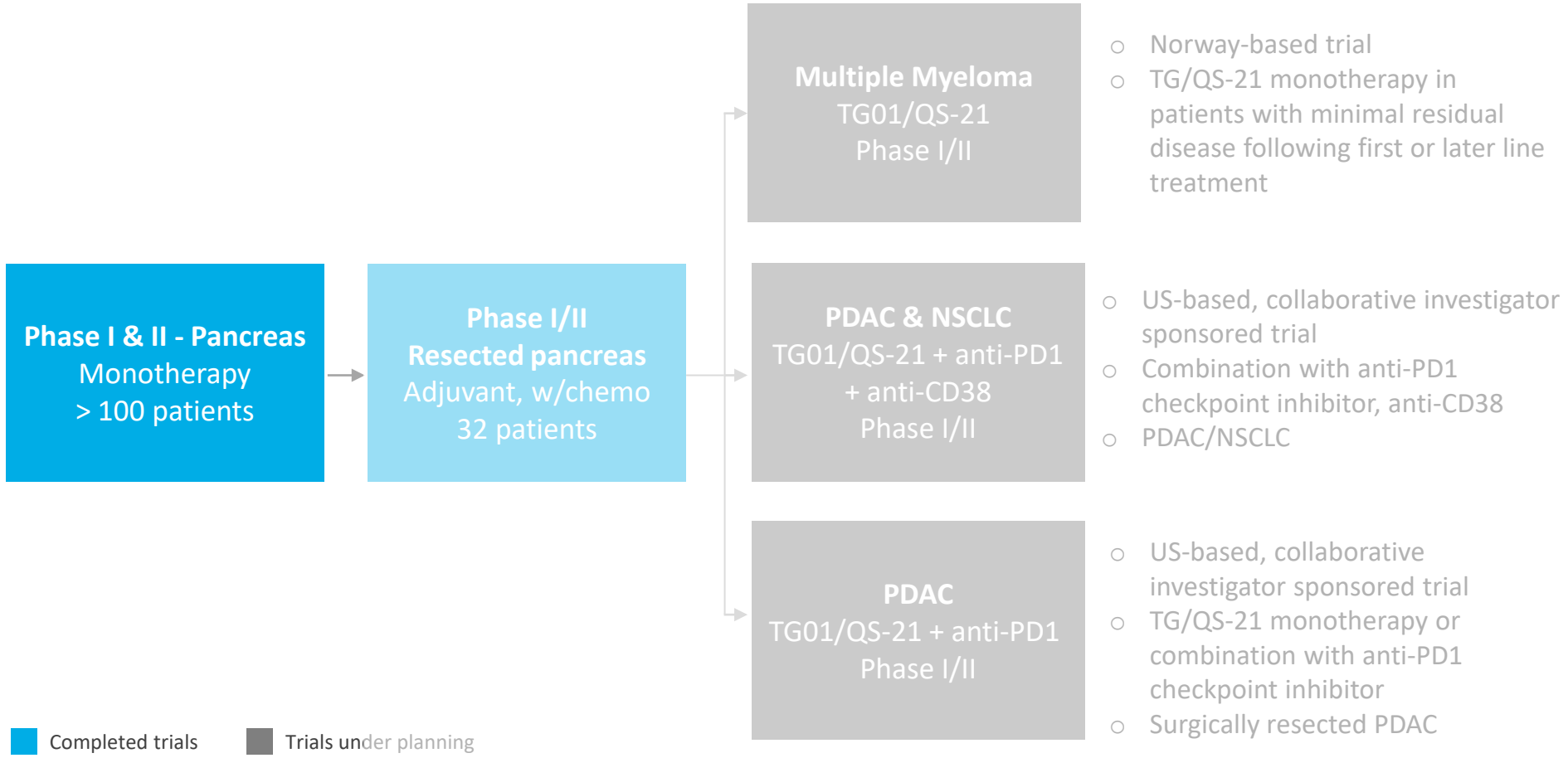
TG KRAS VACCINE CLINICAL PROGRAM OVERVIEW

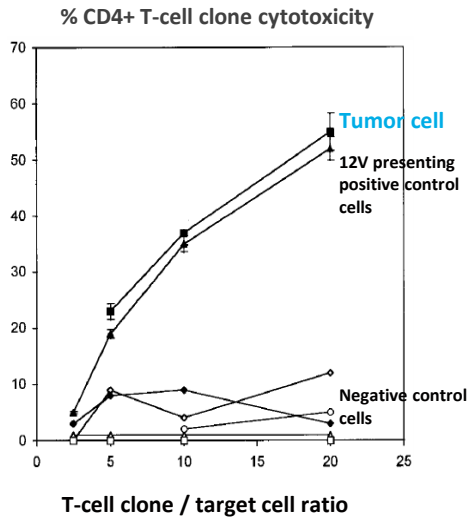


PDAC= pancreatic ductal adenocarcinoma
NSCLC= non-small cell lung cancer

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

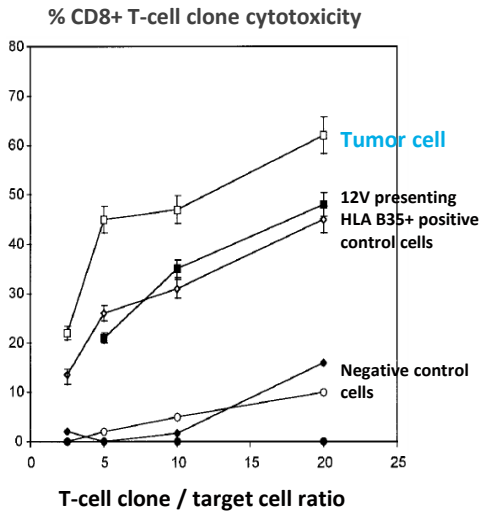
mutRAS specific CD4+ T-cells isolated from vaccinated patient

- 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

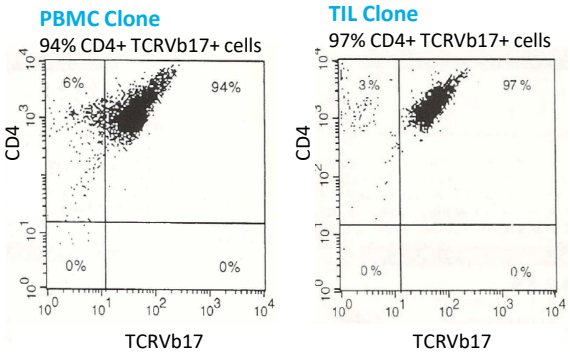
- CD8+ T-cell clone lyses cancer cells isolated from the same patient (*in vitro* cytotoxicity assay)



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

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

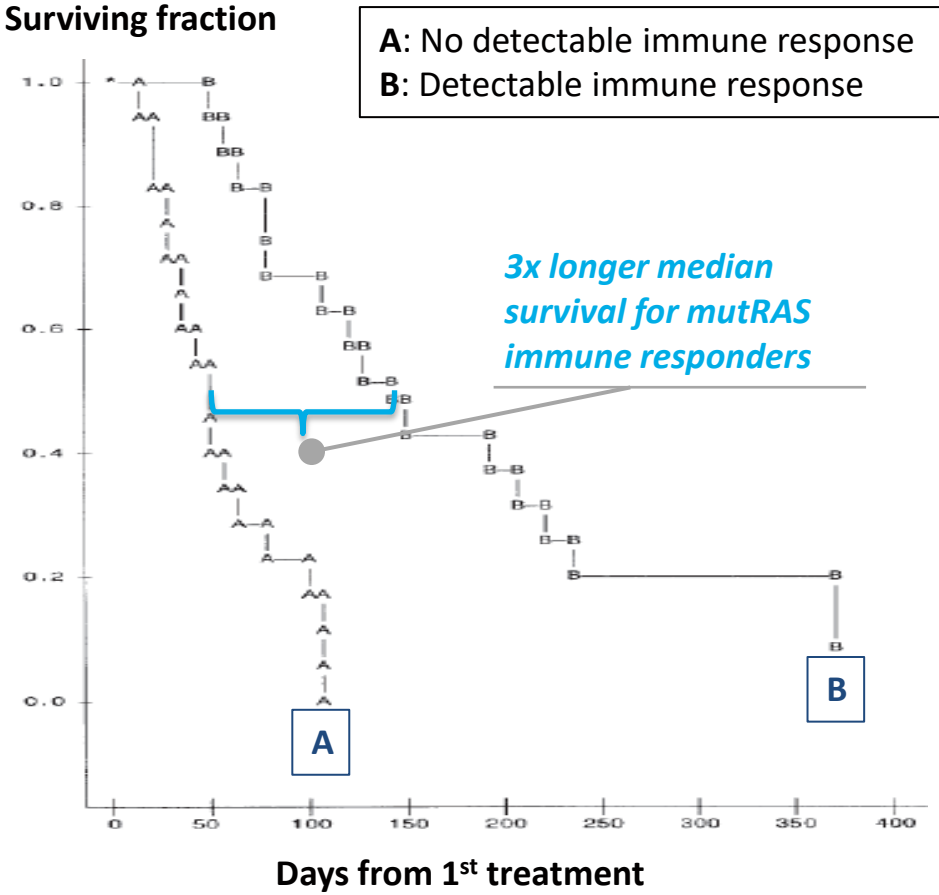


T-cells specific for other RAS mutations than 12R were found in PBMC, but not in tumor

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

IMPROVED SURVIVAL OF ADVANCED STAGE PANCREATIC CANCER PATIENTS WITH DOCUMENTED MUTANT RAS IMMUNE RESPONSES

Clinical study in advanced pancreatic cancer (n=36 patients)



- **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)*

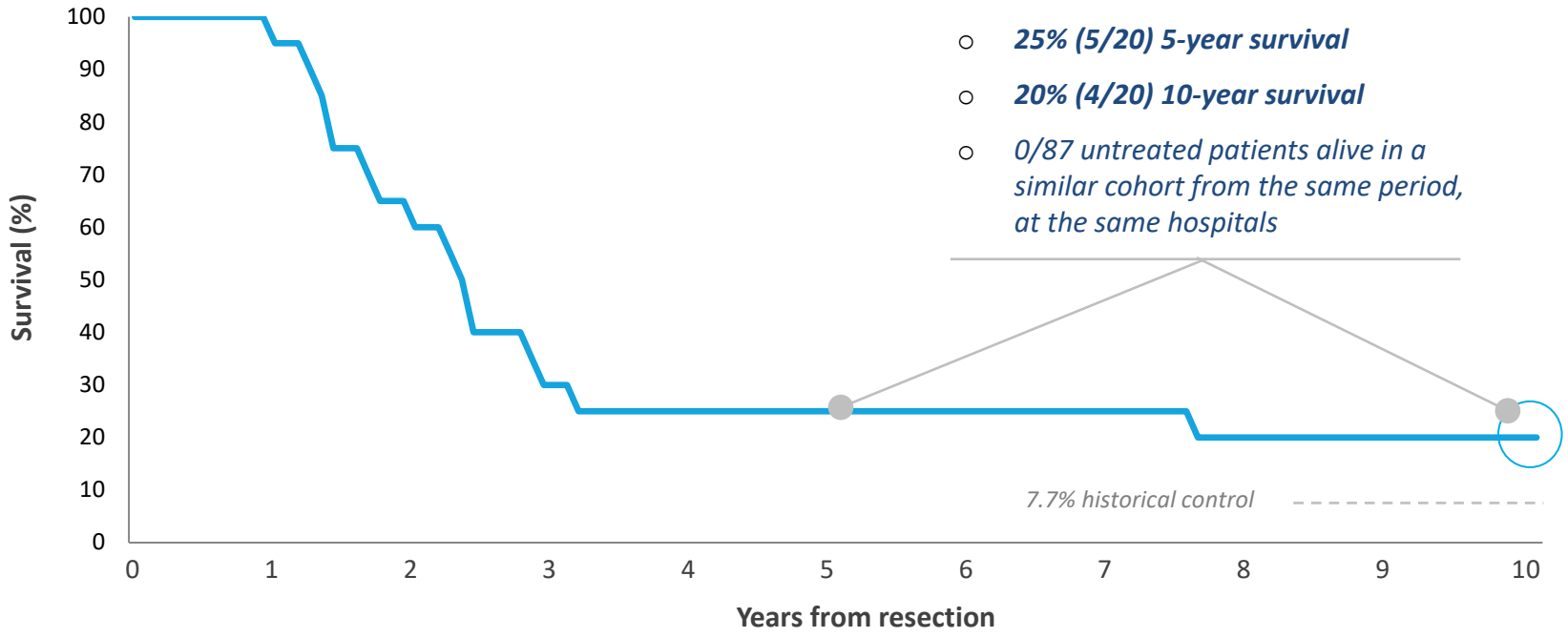
SOURCE: Gjertsen et al., 2001

TG01 PHASE 1 MONOTHERAPY SURVIVAL DATA

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

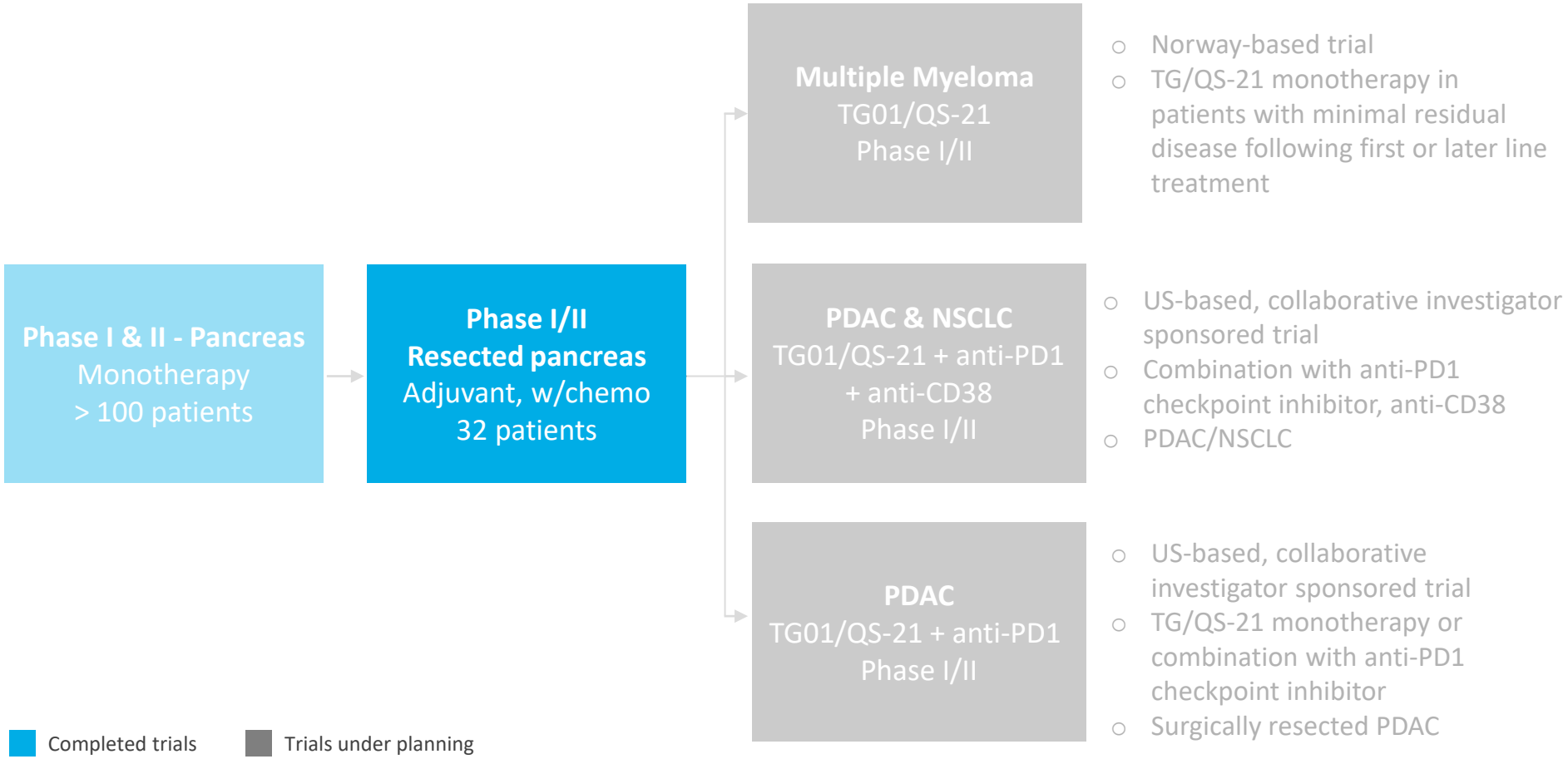
10 year survival in historical TG trials in resected pancreatic cancer[1]

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



Source: [1] Wedén et al., 2011, [2] Oettle H et al., JAMA 2013, vol 310, no 14

TG KRAS VACCINE CLINICAL PROGRAM OVERVIEW



PDAC= pancreatic ductal adenocarcinoma
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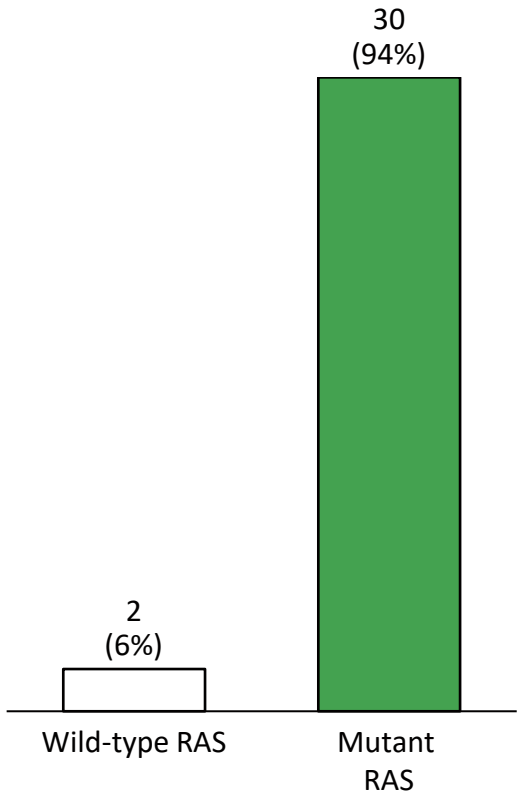
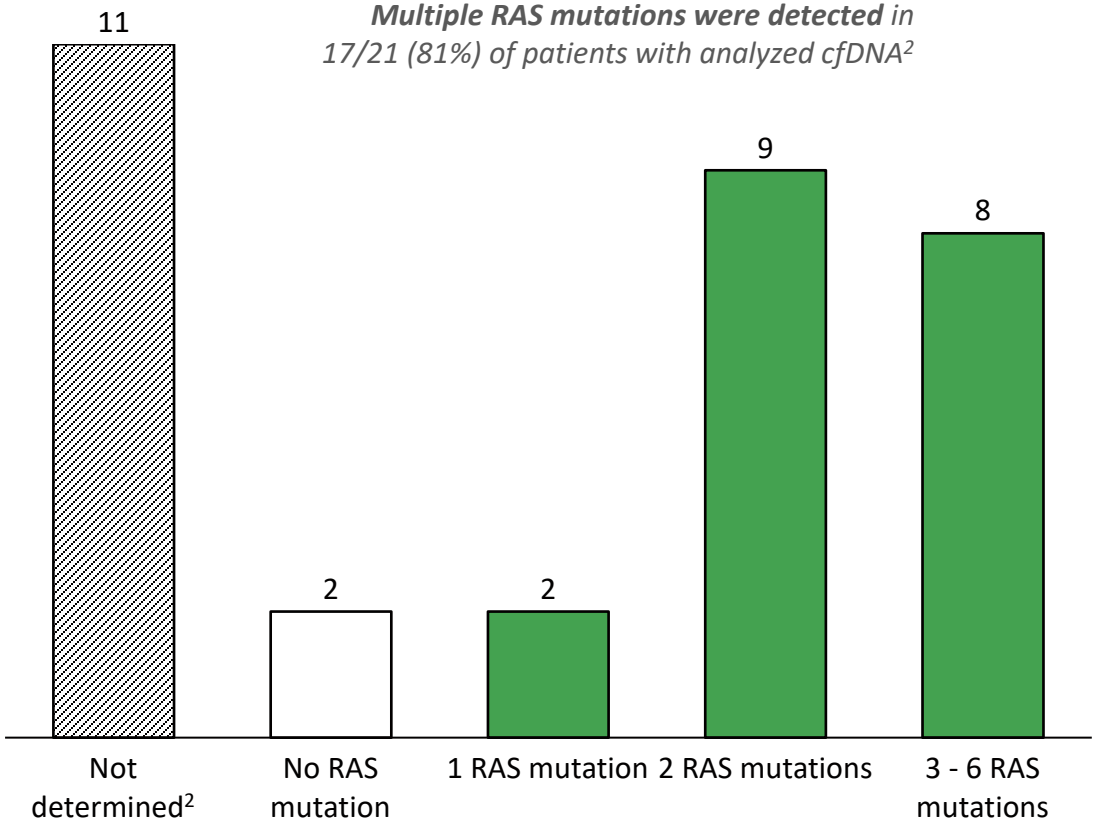
30/32 PATIENTS IN THE TRIAL WERE CONFIRMED AS MUTANT KRAS, WITH MAJORITY CARRYING MUTIPLE POINT MUTATIONS

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

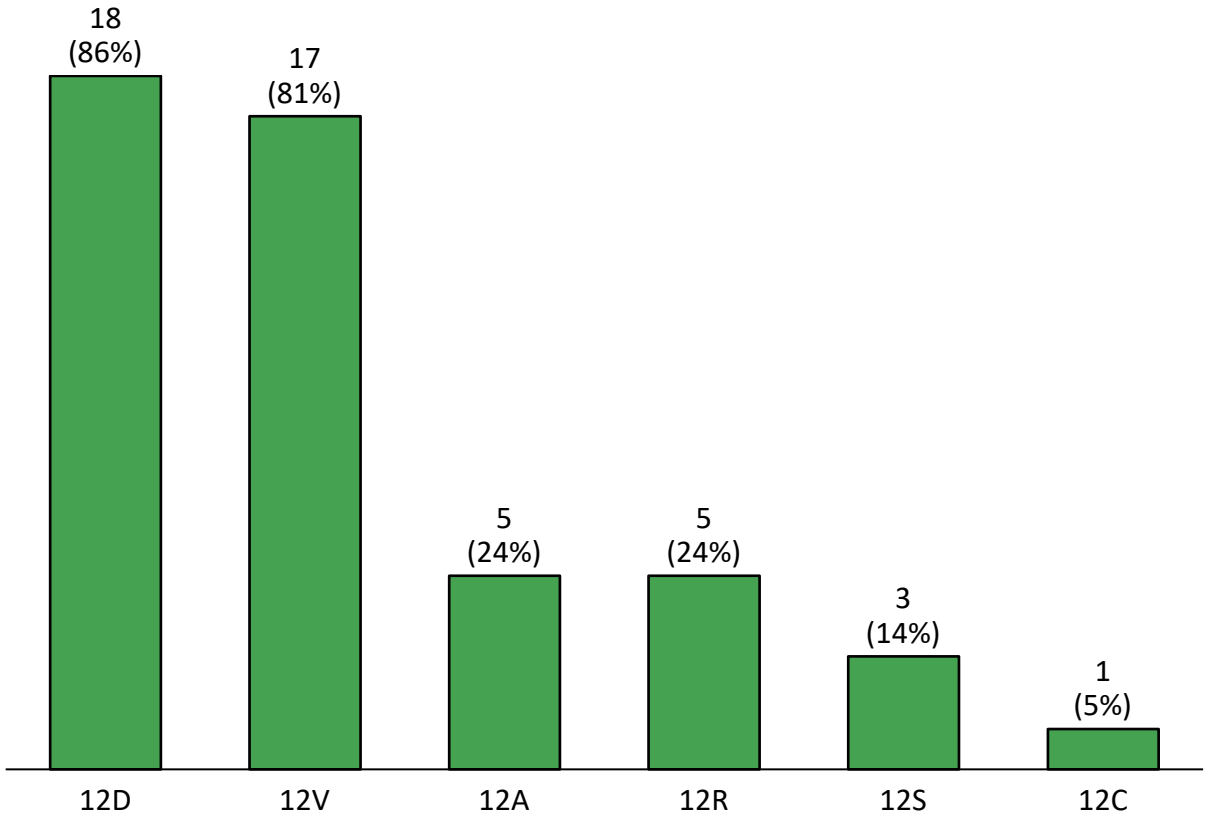
2 Eleven patients were not screened for individual mutations

Source: Targovax data on file, unpublished

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)



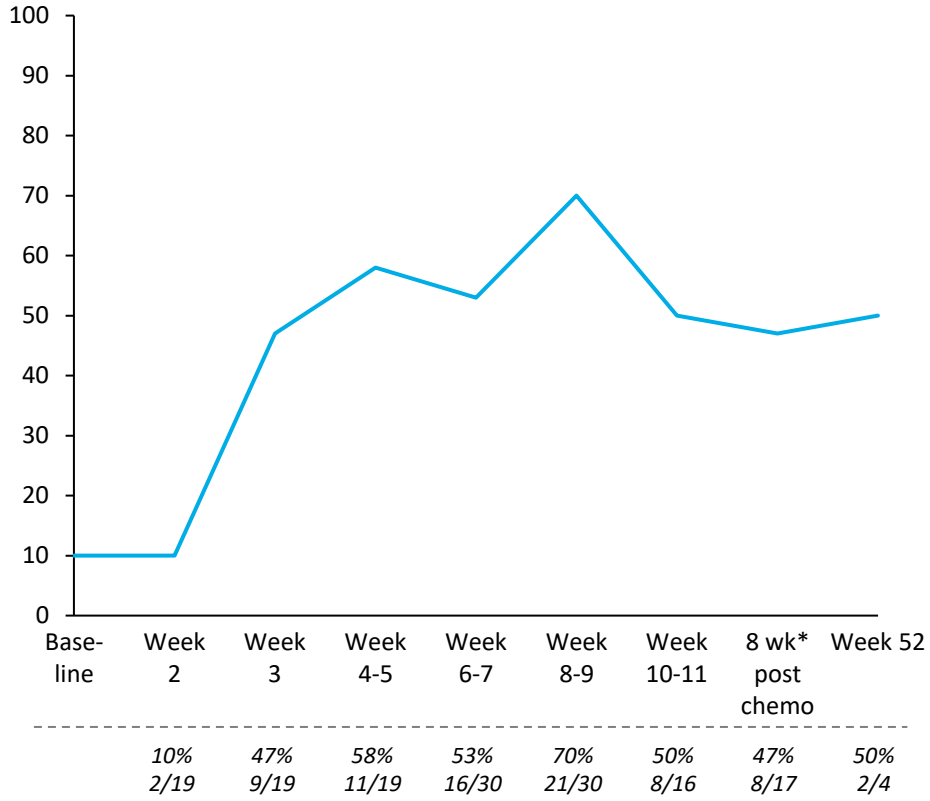
- **12D and 12V mutations** co-existed in **17/21 (81%)** of patients
- **12C mutation** was only detected in **one patient**
- In **one patient all six assessed KRAS mutations were detected** during the course of the study
- Profiles of detectable **mutations shifted over time**, indicating **selection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

1 Eleven patients were not screened for individual mutations in cfDNA

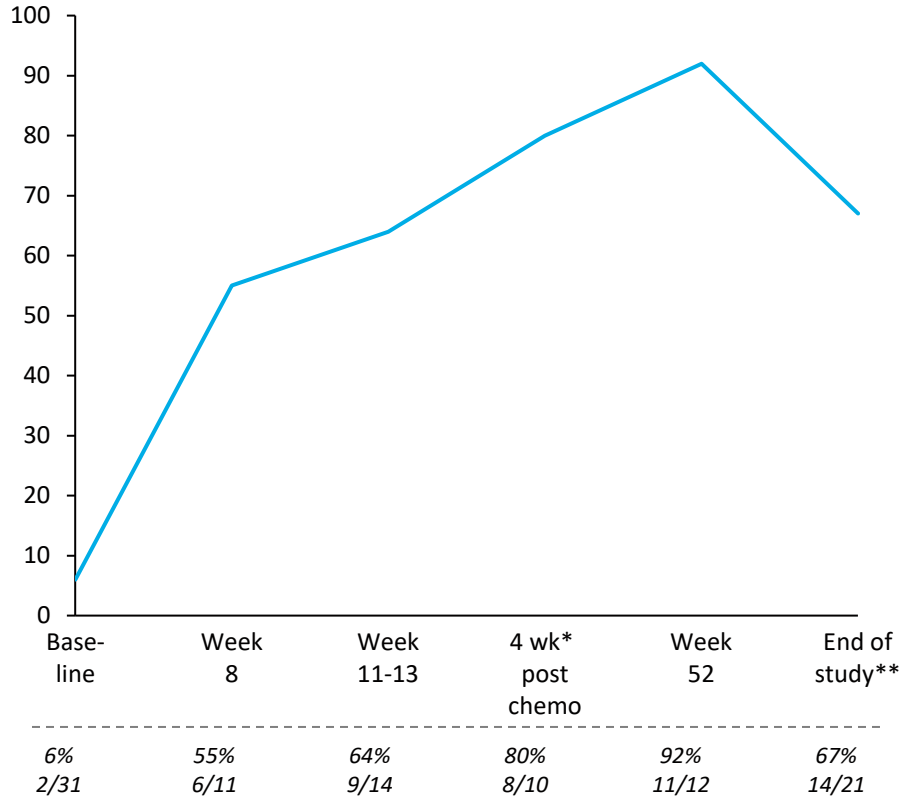
Source: Targovax data on file, unpublished

MUTANT RAS IMMUNE RESPONSES WERE GENERATED IN 30/32 PATIENTS AND STRENGTHENED OVER TIME

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



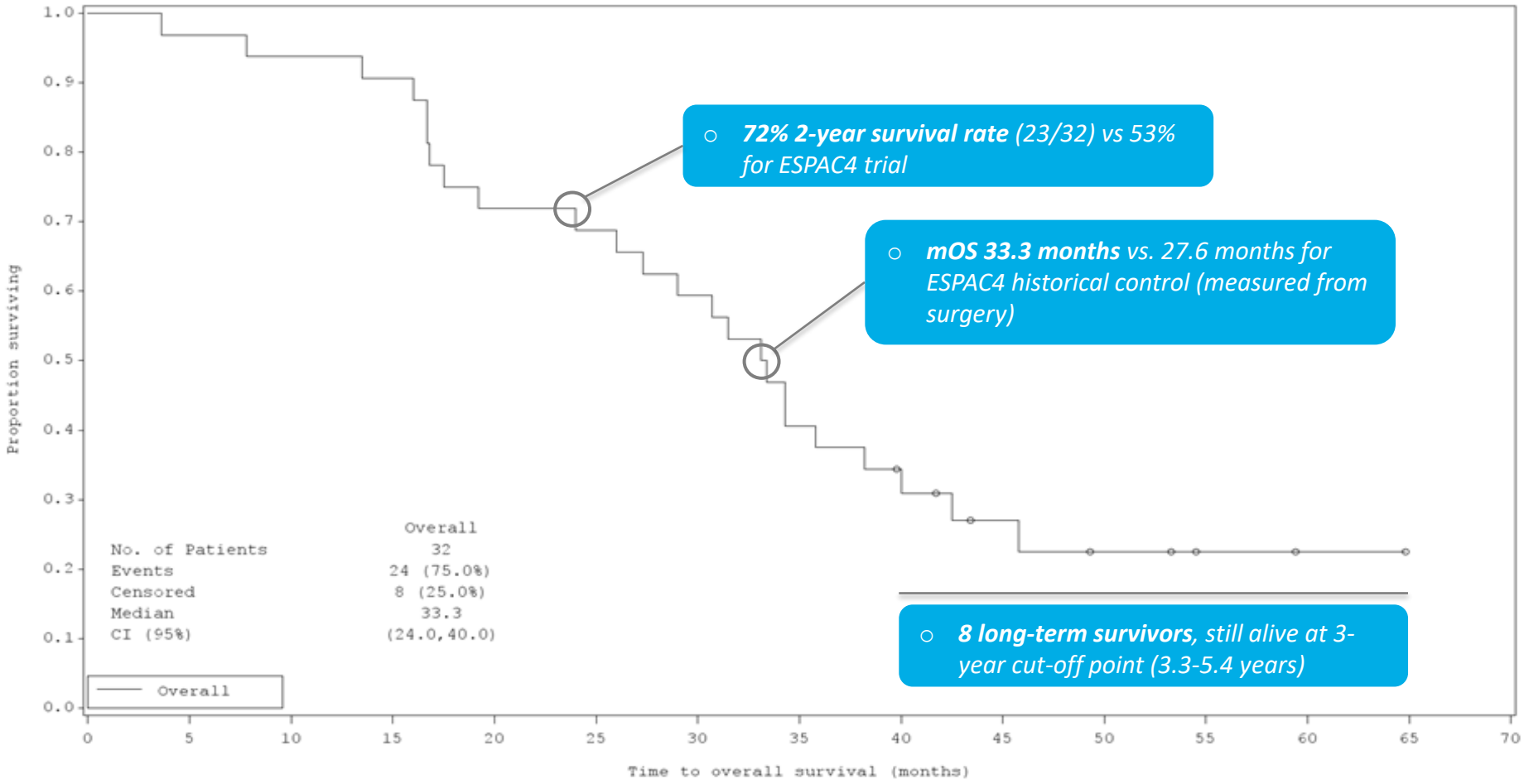
PBMC responses over time
% of analyzed patients with positive PBMC at each time point



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

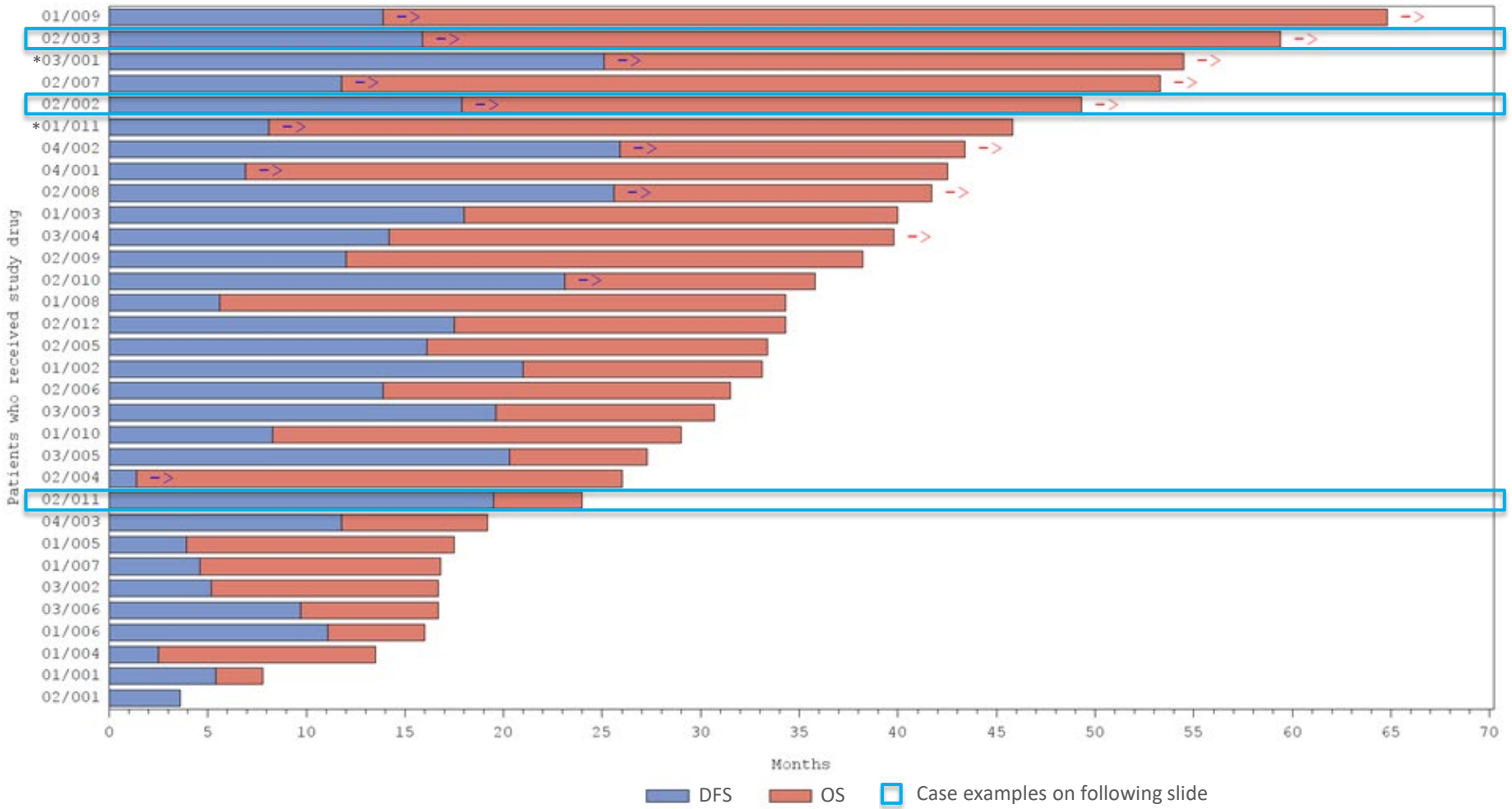
Source: Targovax data on file, unpublished

SURVIVAL AFTER TG VACCINATION COMPARED WELL TO HISTORIC CONTROL WITH GEMCITABINE ALONE



Source: Palmer et al. Br J Cancer, 2020, Neoptolomus et al, Lancet 2017

TG01 RESECTED PANCREAS TRIAL - SWIMMER PLOT SHOWING INDIVIDUAL PATIENT OUTCOMES

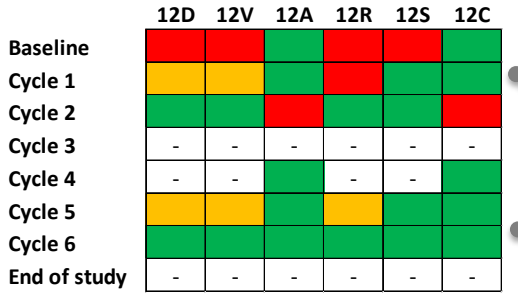
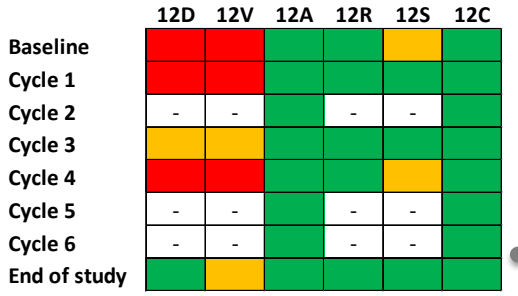
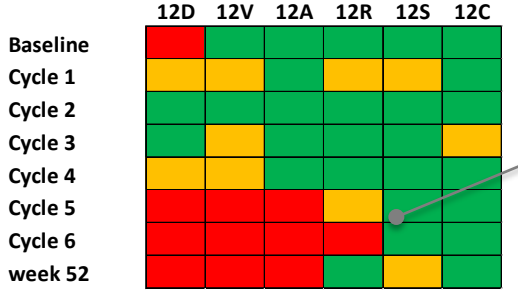


* RAS wild type (2/32 patients)

All measurements in months from surgery

Source: Palmer et al. Br J Cancer, 2020

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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Further development plans

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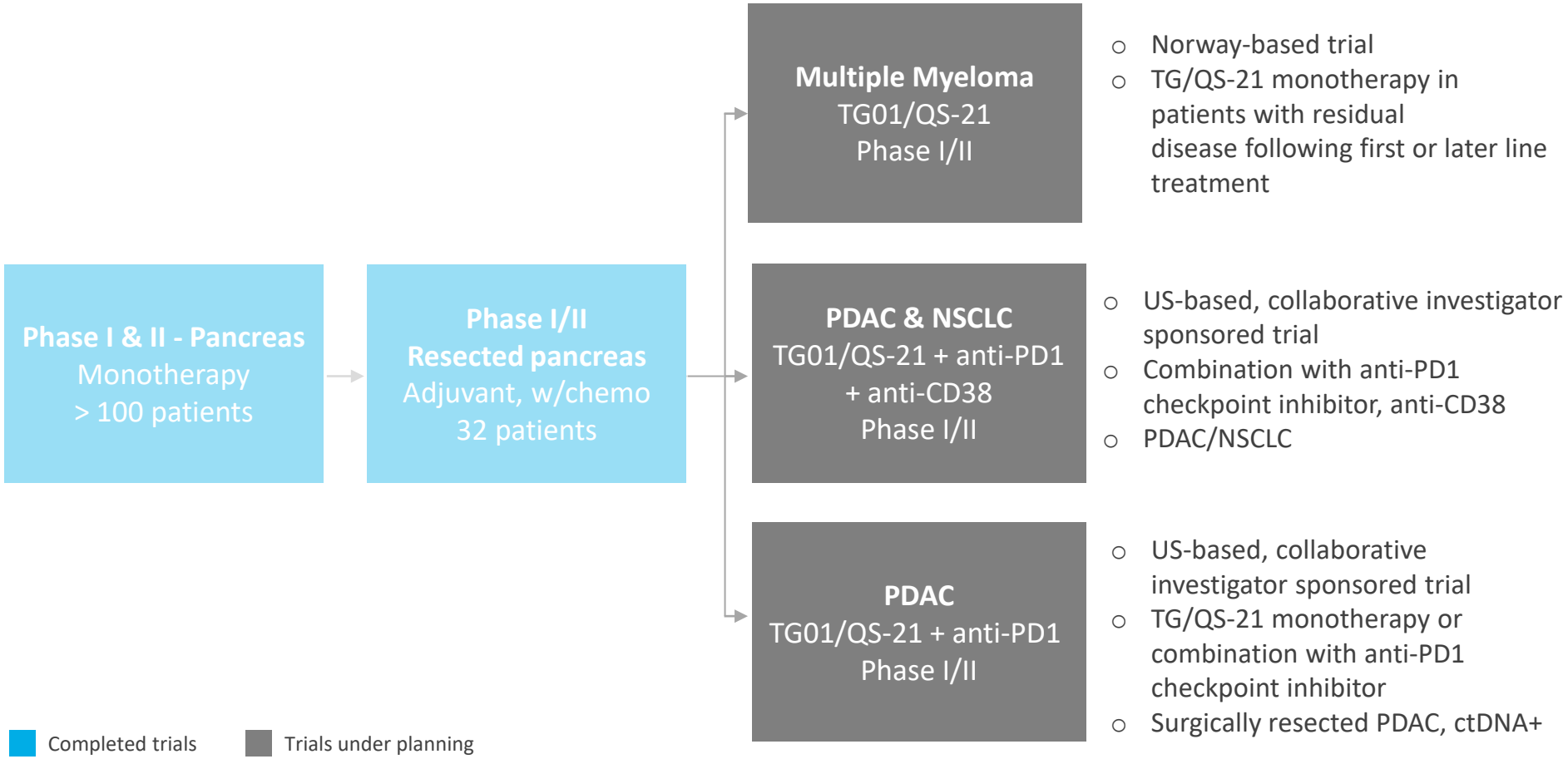
NEXT STEPS IN TG-01 KRAS VACCINE CLINICAL PROGRAM



PDAC= pancreatic ductal adenocarcinoma
NSCLC= non-small cell lung cancer

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SECOND GENERATION TG VACCINE AND COMBINATION TREATMENTS MUST BE DEVELOPED TO FURTHER IMPROVE EFFICACY

First generation TG vaccine

Promising survival data

- Clear benefit both as monotherapy and combinations

Solid immune responses

- >90% of patients achieved mutRAS immune response from the vaccination

However, several factors complicates usage

- *Intra-dermal injection is painful and technically challenging*
- *Two separate injections, higher risk of error*
- *Many injections required to build strong mutRAS immune response*
- *Vaccine does not deal with the tumor´s main anti-immunity defense mechanisms*

Second generation TG vaccine

Building on experience, and taking advantage of advances in immunotherapy:

New adjuvant – QS21 from Agenus

- Faster and more robust immune response
- S.c. injection – simpler usage and less painful for the patient
- Co-formulation, one injection only
- FDA approved, used in commercial vaccines

Immunotherapy combination – Agenus / other

- Combination with PD1 checkpoint inhibitor, which blocks the tumors first line defense against the immune system
- Combination with anti-CD38
- Possible to treat more advanced disease

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Dosing/scheduling strategy to enhance immune response

4. Further development plans

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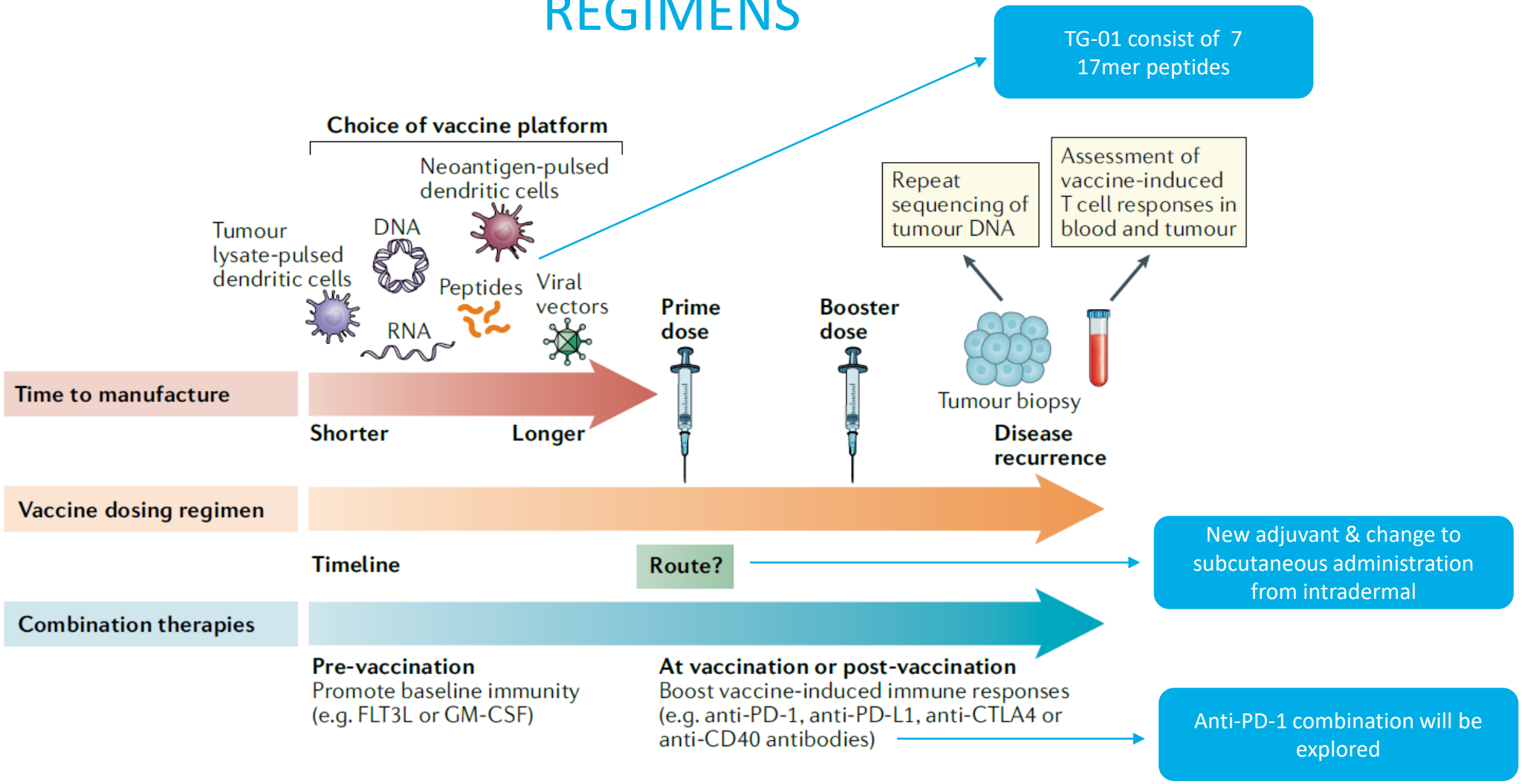
CONSIDERATIONS RELATING TO THERAPEUTIC NEOANTIGEN VACCINE REGIMENS

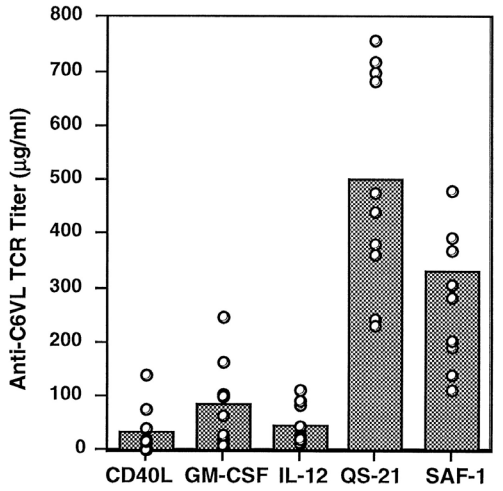


Source: Nature Reviews Clinical Oncology 2021 Blass E , Ott P

SECOND GENERATION TG VACCINE WITH QS-21/STIMULON ADJUVANT IS EXPECTED TO FURTHER IMPROVE EFFICACY

New adjuvant selected for the TG vaccines: QS-21 Stimulon™

- **QS-21** is a purified **natural saponin** derived from the soap bark tree *Quillaja Saponaria*
- **FDA approved** as a component of the ***Shingrix*** shingles vaccine. Also part of ***Mosquirix*** malaria vaccines
- **Clinically validated** to induce highly potent **antibody and T-cell responses**
- Demonstrated superiority of QS-21 vs GM-CSF in several studies
- Used as adjuvant for all Agenus neoantigen peptide cancer vaccines



Direct comparison of QS-21 to GM-CSF

- In a murine T-cell tumor model: Demonstrates 5-10 fold increase in Ab titers
- In a clinical study comparing QS-21 sc vs GM-CSF ID: QS-21 drives more potent and earlier CD8+ T-cell response when measured by ELISPOT
- Supports an **improved immunostimulatory effect**

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DOSING STRATEGY TO MAXIMISE IMMUNE RESPONSE AND DRIVE PATIENT ACCEPTABILITY

Dose

- TG01 contains 7 peptides each 17 mer
- 100 ug/peptide for a total of 700 ug/dose
- Higher dose does not increase immunisation rates

Schedule

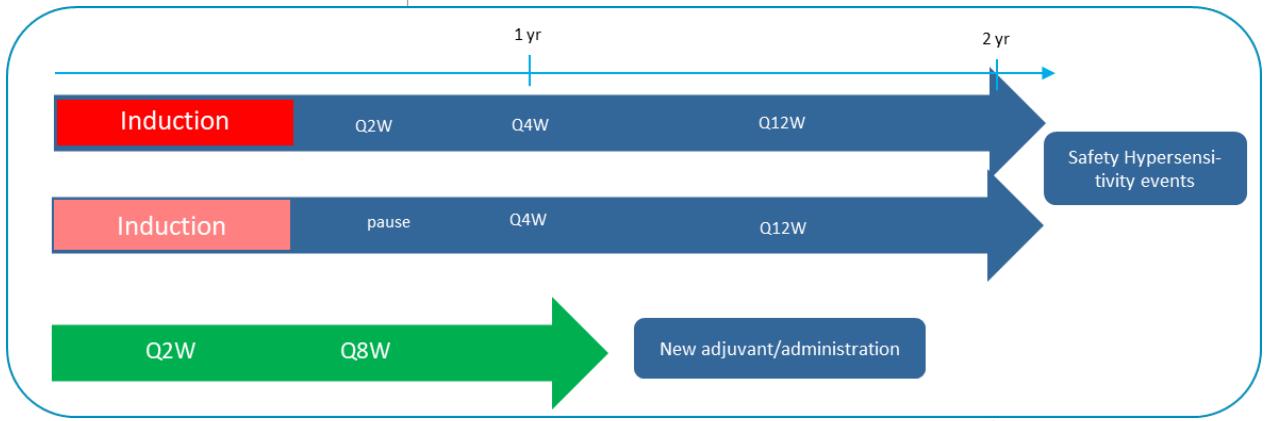
- Prior schedules explored up to 2 years dosing
- Safety driven decision to reduce number of adminstrations
- QS-21/Stimulon™ adjuvant has less dose-intense scheduling

Administration

- QS-21/Stimulon™ has extensive safety database to support administration/dose
- QS-21 has mainly been used subcutaneously
- Subcutaneous administration is clinically simpler to perform and less painful for patients.
- Can be mixed pre-injection, one injection only

Intradermal RAS-oncogene peptide immunotherapy in CRC patients. 2 different dose levels with/without GM-CSF (n=35)

	Dose Peptide/GM-CSF	T-cell response	DTH	Immune response (DTH/T-cell response)
A (n=14)	0.68 mg/ 40 ug	7/14	11/14	79%
B (n=11)	2.72 mg/ 160 ug	3/11	7/11	64%
C (n=10)	0.68 mg/0	2/10	0/10	20% (60%)



Source: MK Gjertsen et al ASCO 2001, Abs 1021, DH Palmer et al, Br J Cancer 2020

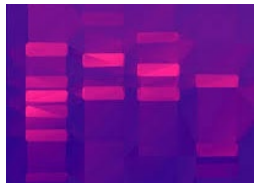
SUMMARY – TG VACCINE FOR KRAS MUTANT CANCER

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
- **Academic and industry** collaboration network established