TG mutant RAS neoantigen vaccine

NeoAntigen Summit

Amsterdam 25 April 2019

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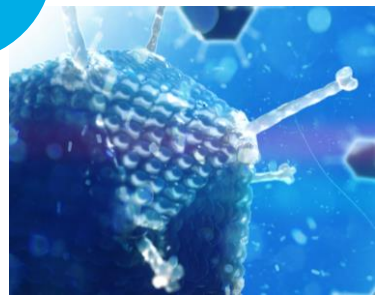
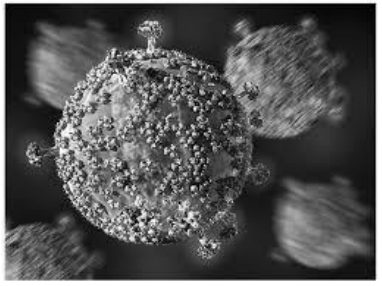
1 Introduction

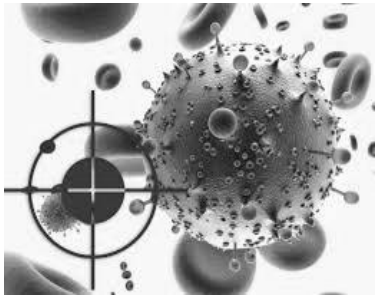
2. A vaccine approach to target mutant RAS
3. TG mutant RAS neoantigen vaccine
4. TG RAS vaccine clinical program

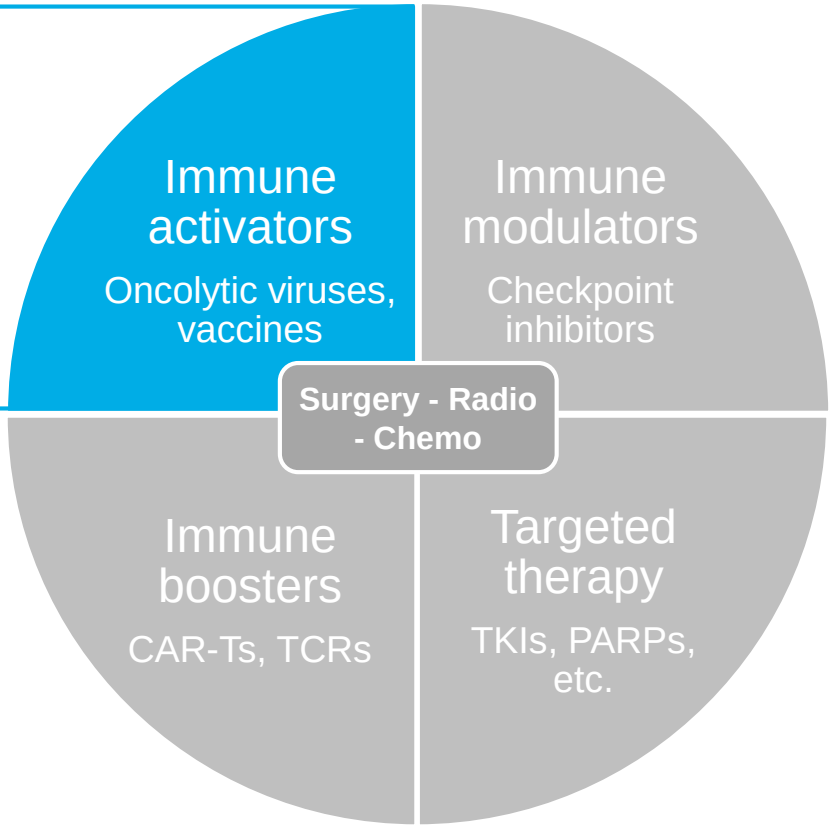
TARGOVAX AIMS TO ACTIVATE THE PATIENT'S OWN IMMUNE SYSTEM TO FIGHT CANCER

Targovax focus

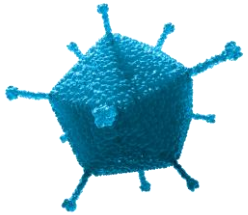






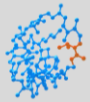


TARGOVAX HAS TWO CLINICAL STAGE IMMUNE ACTIVATOR PROGRAMS



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 response** 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 mutant RAS neoantigen vaccine
4. TG RAS vaccine clinical program

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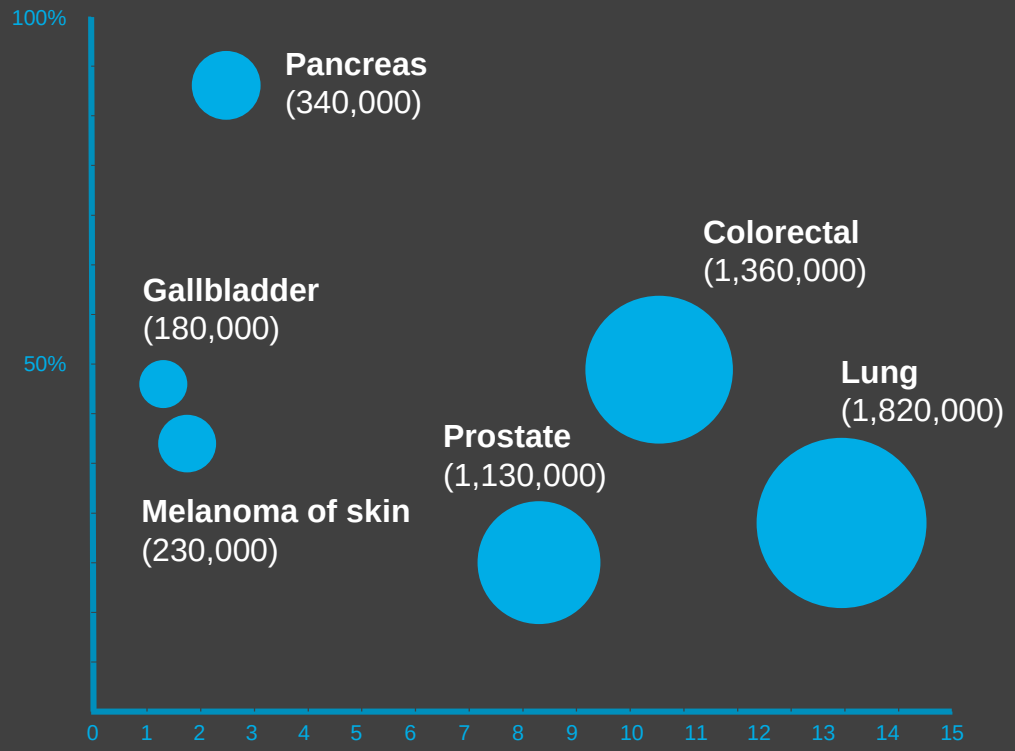
THE RAS GENE IS MUTATED IN 20-30% OF ALL CANCERS

Including 90% of pancreatic and 40% of colorectal cancers

Frequency of RAS mutations

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



- **Oncogenic RAS** point mutations result in **uncontrolled cell division**
- **There are no approved therapies** targeting mutant RAS
- Targovax' TG program is a **unique vaccine approach for mutant RAS cancers**

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

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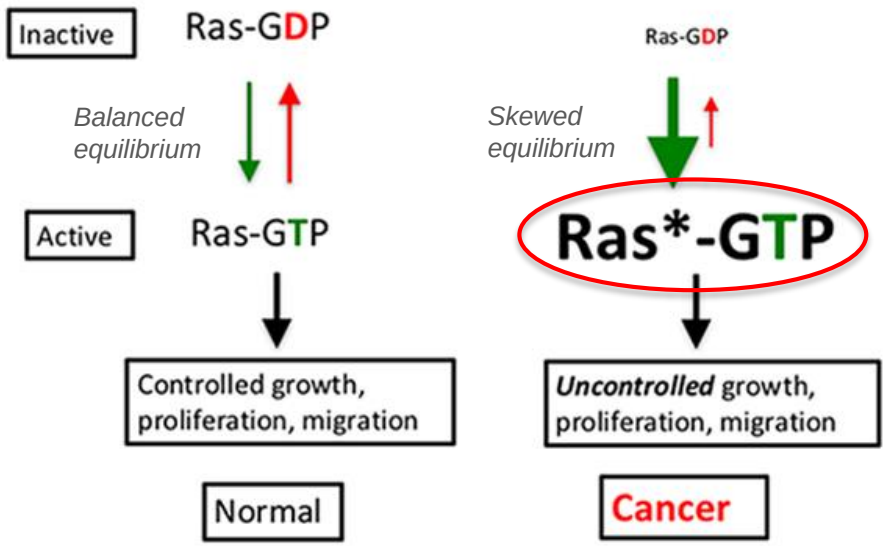
RAS “THE UNDRUGGABLE TARGET”

To date, small molecule approaches against RAS have all failed

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,** leading to **single amino acid substitutions**
- Smooth protein surface and **tight binding pocket**
- **Intracellular localization**

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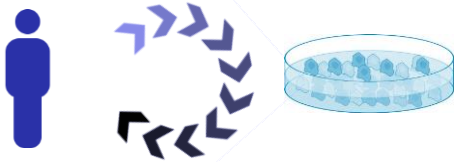
Mutant RAS T-cells can form spontaneously in patients, and recognize and destroy tumors

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

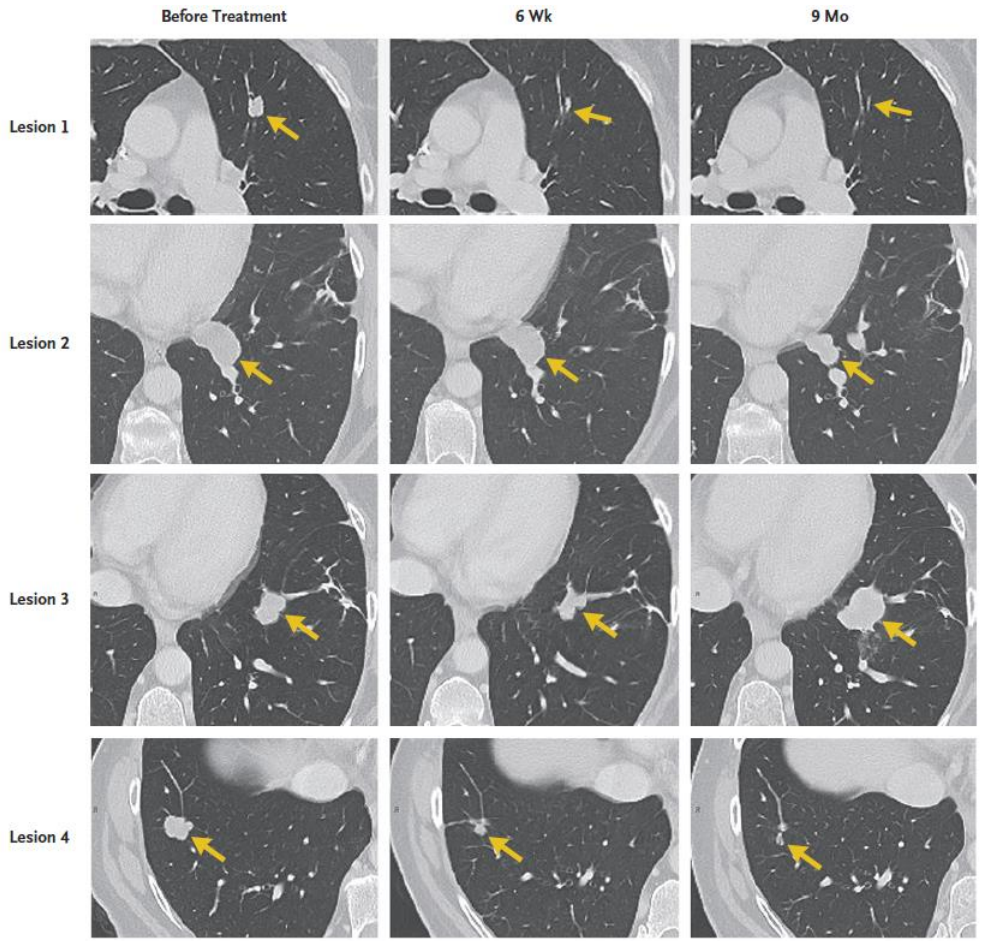


Endogenous CD8+ tumor-infiltrating lymphocytes (TIL) recognizing the **G12D RAS mutation** were **isolated from a colorectal cancer patient**

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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Peptide vaccination is a promising modality to target mutant RAS cancers[1]

	Peptide-Based Vaccines	Small Molecule Inhibitors	mRNA	Antibodies	Whole Cell-Based Vaccines	RNAi	CAR-TCR
mutRAS epitope accessibility	✓	✗	✓	✗	✓	✓	✓
RAS mutation coverage	✓	✗	✓	✗	✓	✓	✗
High mutant RAS specificity	✓	✗	✓	✓	✓	✓	✓
Off-the-shelf	✓	✓	✓	✓	✓	✓	✗
Efficient delivery / administration	✓	✓	✓	✓	✓	✗	✓
Potential durative response	✓	✗	✓	✗	✓	✗	✗
Simple CMC	✓	✓	✗	✓	✗	✓	✗
Independent of cell translation	✓	✓	✗	✓	✓	✓	✓
Tissue type unrestricted	✓	✓	✓	✓	✗	✓	✗

1 Generalized x/v analysis, there may be exceptions

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THE RAS DEVELOPMENT LANDSCAPE

Targovax has a differentiated and clinically advanced approach to target RAS

Company	Asset/ Program	Mechanism of Action	Highest Phase
GlobeImmune	GI-4000/Tarmogen	Heat-inactivated yeast expressing target RAS mutations	Phase II (halted)
targovax	TG01/02	Peptide cancer vaccine targeting RAS mutations	Phase II
Silenseed	siG12D-LODER	RNAi targeting mutant KRAS	Phase II
GILEAD	KRAS TCR	Anti-KRAS G12D Engineered T-cell Receptor	Phase I/Ib
MIRATI THERAPEUTICS	RAS targeted program	Small molecule inhibitors of KRAS (G12C)	Phase I/Ib
AstraZeneca	AZD4785	Antisense oligonucleotide (ASO) KRAS inhibitor	Phase I
moderna	mRNA-4157	mRNA KRAS cancer vaccine	Phase I
AMGEN	AMG510	Small molecule inhibitor of KRAS (G12C)	Phase I
Allinky BIOPHARMA	AIK-4	Small molecule inhibitor of RAS	Preclinical
COTINGA PHARMACEUTICALS	COTI-219	Small molecule inhibitor of KRAS	Preclinical
ADT PHARMACEUTICALS	DC070 547	Small molecule inhibitor of RAS	Preclinical
NEONC TECHNOLOGIES, INC	NEO-214	Small molecule inhibitors of RAS	Preclinical
NantBioscience	KRAS	Small molecule inhibitors of mutant KRAS	Preclinical
Warp Drive Bio	KRAS	Small molecule inhibitors of mutant KRAS	Preclinical
SANOFI	KRAS-G12C	Small molecule inhibitors of mutant KRAS (G12C)	Discovery

Peptide Based Vaccine | *Yeast Based Vaccine* | *siRNA* | *mRNA based vaccine* | *Small Molecule Inhibitor* | *CAR-T*

3

TG mutant RAS neoantigen vaccine

4. TG RAS vaccine clinical program

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

1. Activate immune system

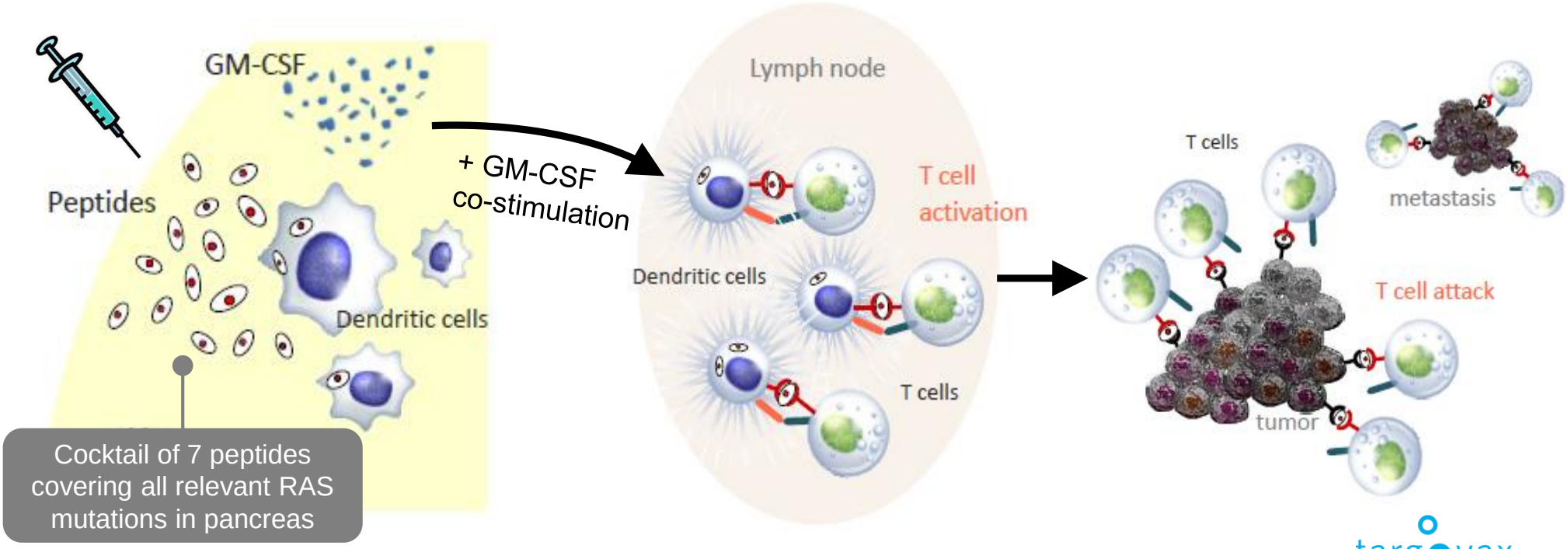
- TG peptide cocktail **injected intradermally** with GM-CSF as adjuvant

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**

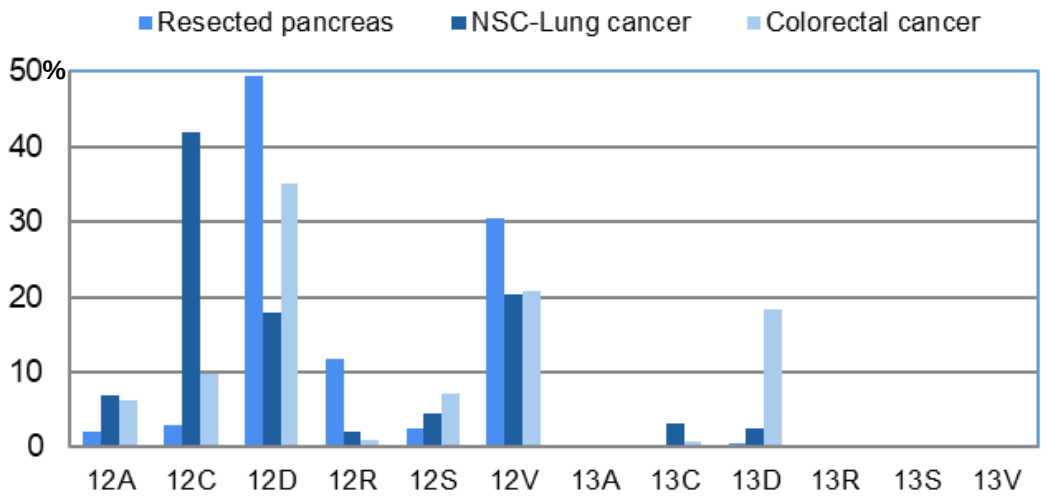


The TG peptide cocktail covers ~99% of all codon 12 and 13 RAS mutations

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 - TG01/02**
  - **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), stimulate HLA **class II and class I** (after antigen processing) **restricted T-cell responses**
- **Promiscuous HLA class II epitopes**, hence no need for tissue typing
- **CD4+ and CD8+ T-cell responses** demonstrated clinically

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

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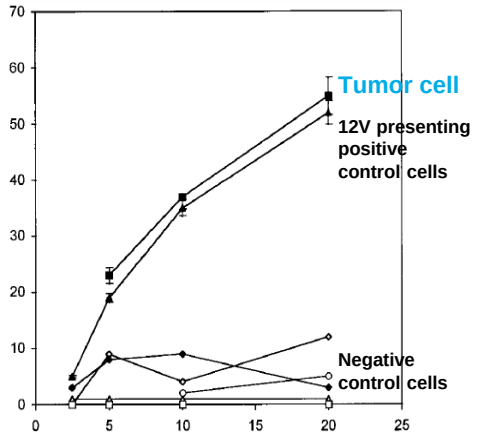
TG vaccination induced CD4+ and CD8+ mutant RAS T-cell responses has been validated in patients

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

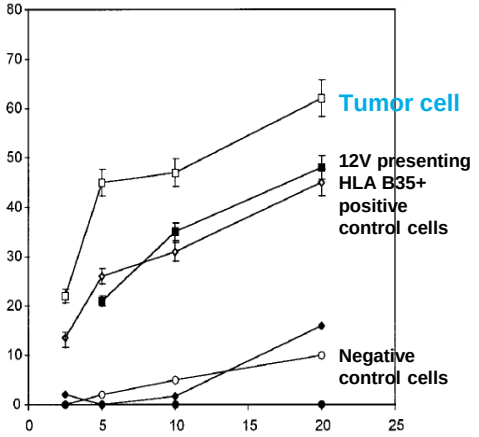


T-cell clone / target cell ratio

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

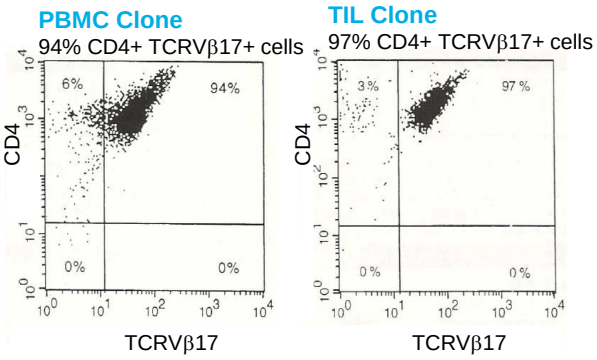


T-cell clone / target cell ratio

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

- Only 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

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TG RAS vaccine clinical program

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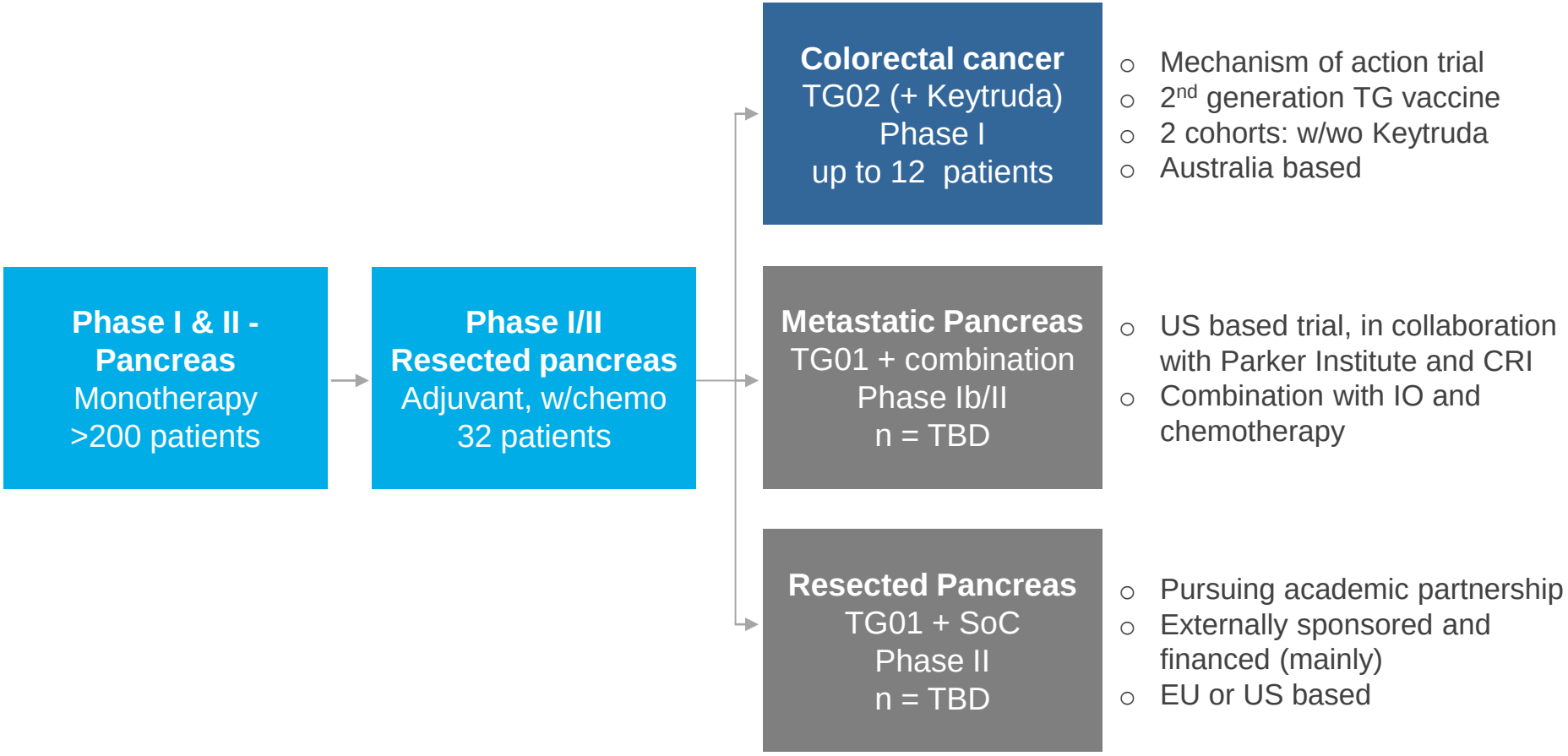
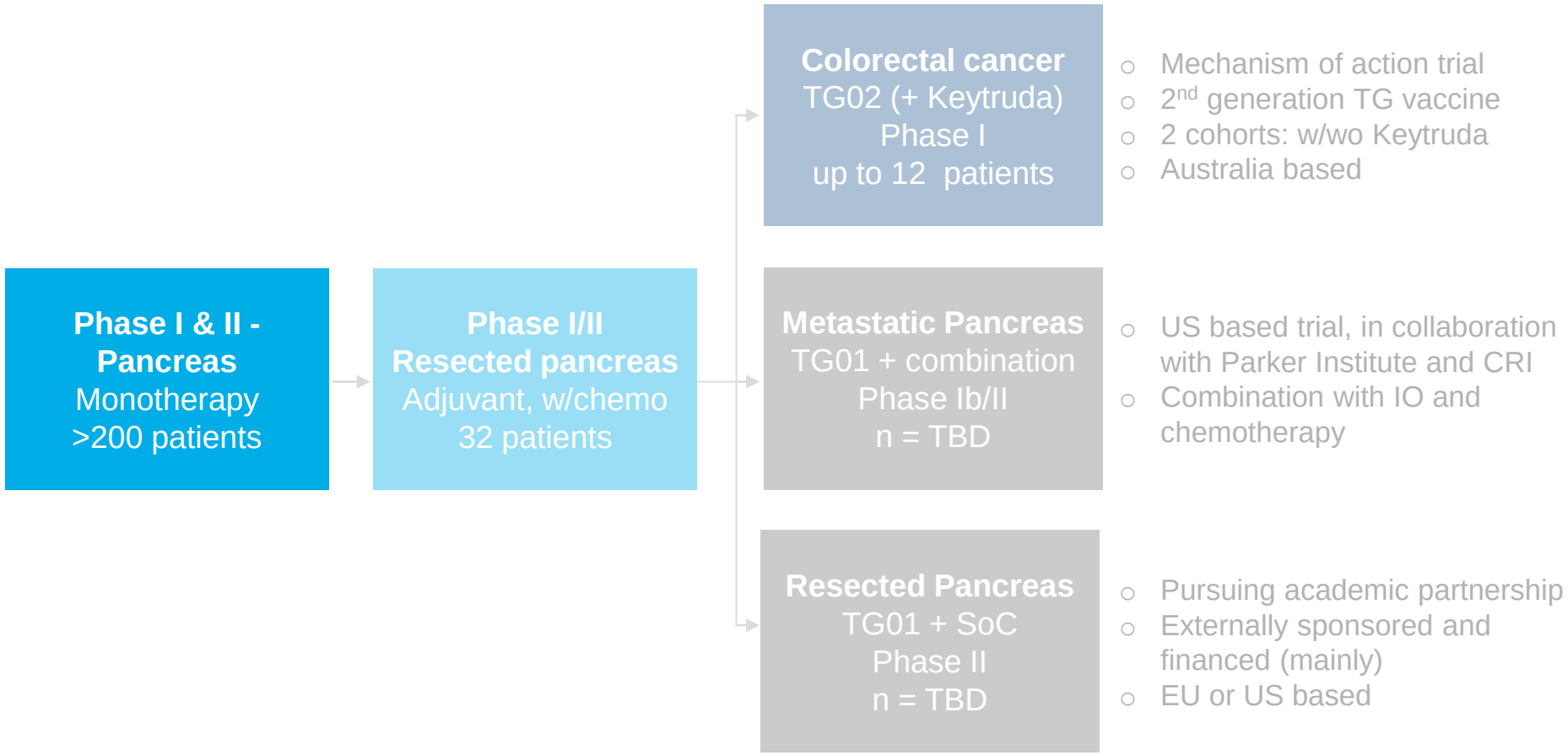
TG CLINICAL PROGRAM OVERVIEW



TG CLINICAL PROGRAM OVERVIEW



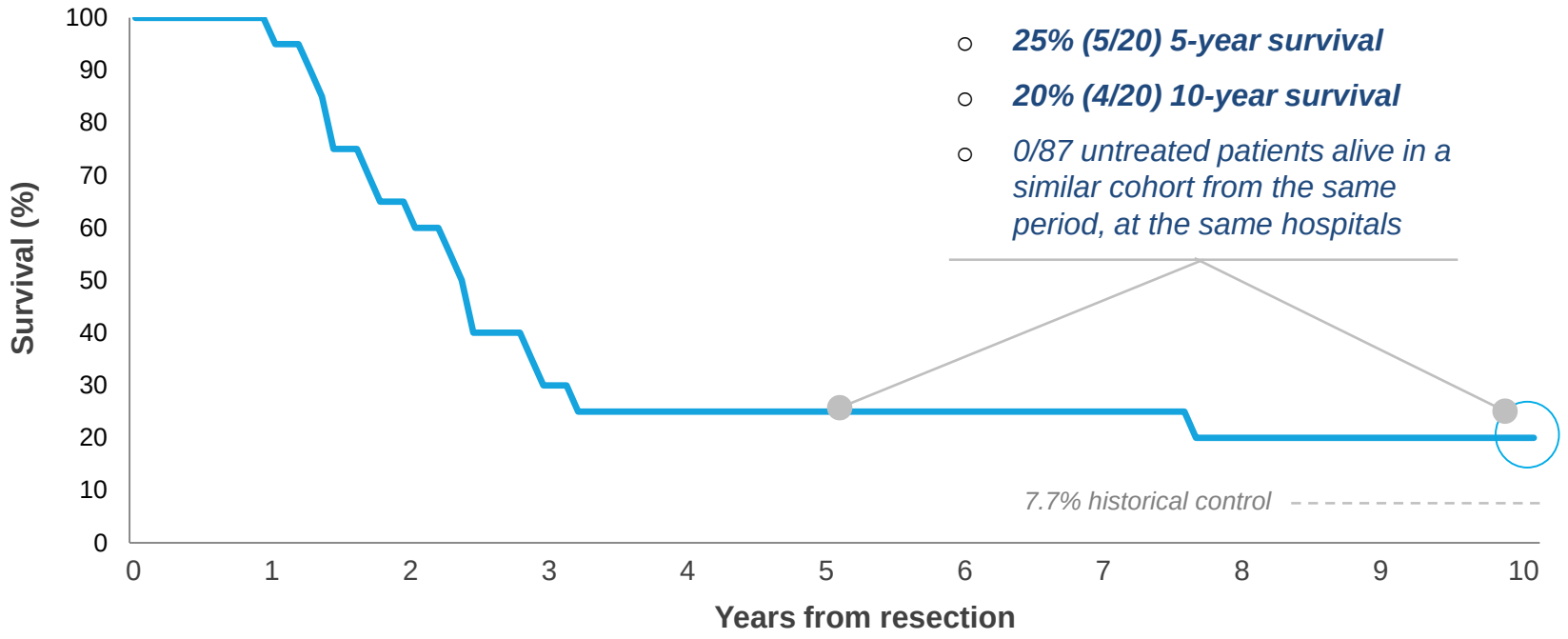
Completed trials | Ongoing trials | Trial sponsored by partner (under planning)

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]

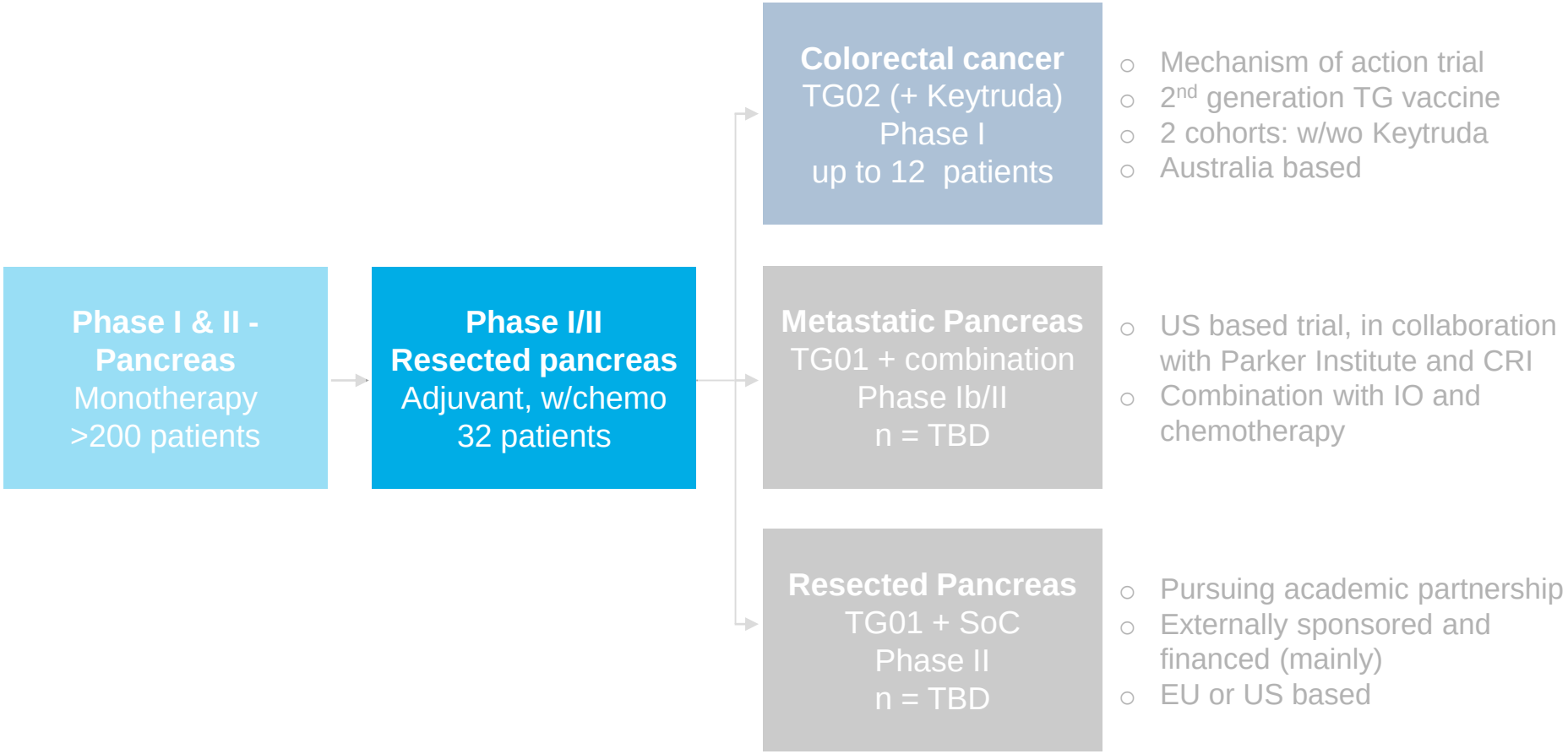
n=20, resected patients from two clinical trials, TG monotherapy



[1] Wedén et al., 2011

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

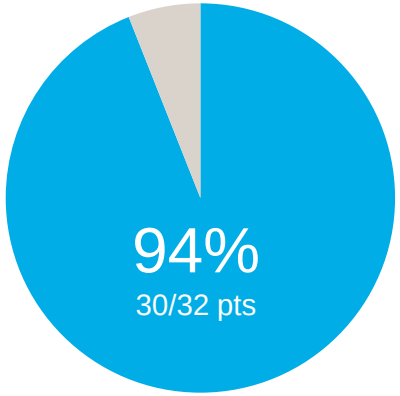
TG CLINICAL PROGRAM OVERVIEW



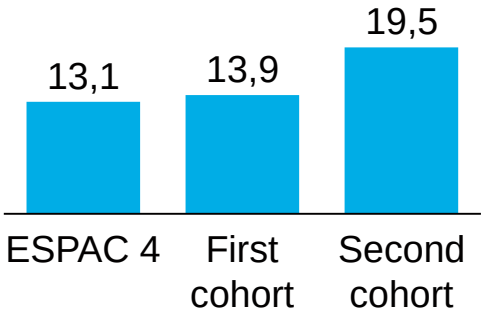
EFFICACY SIGNAL SEEN IN PHASE I/II TRIAL

in resected pancreatic patients

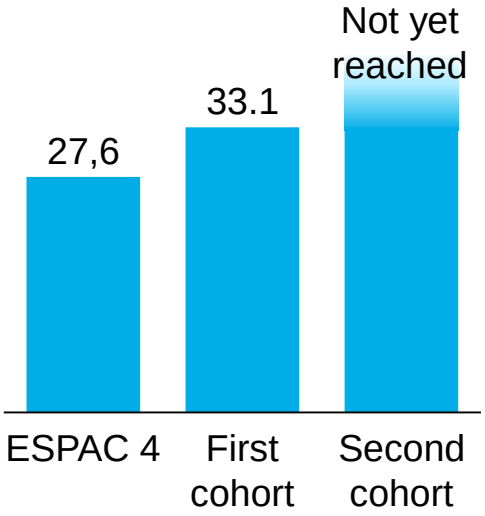
1 RAS-specific immune activation



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.
ESPAC4 trial for gemcitabine alone
DFS both cohorts: 16.1 months

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1

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 (69 %)	26 (81 %)
mutRAS Specific T-cells (PBMC proliferation assay)	14 (74 %)	12 (92 %)	26 (81 %)

**Immune responder defined as positive DTH hypersensitivity test or PBMC proliferation assay for at least one time point within 12 months on the trial*

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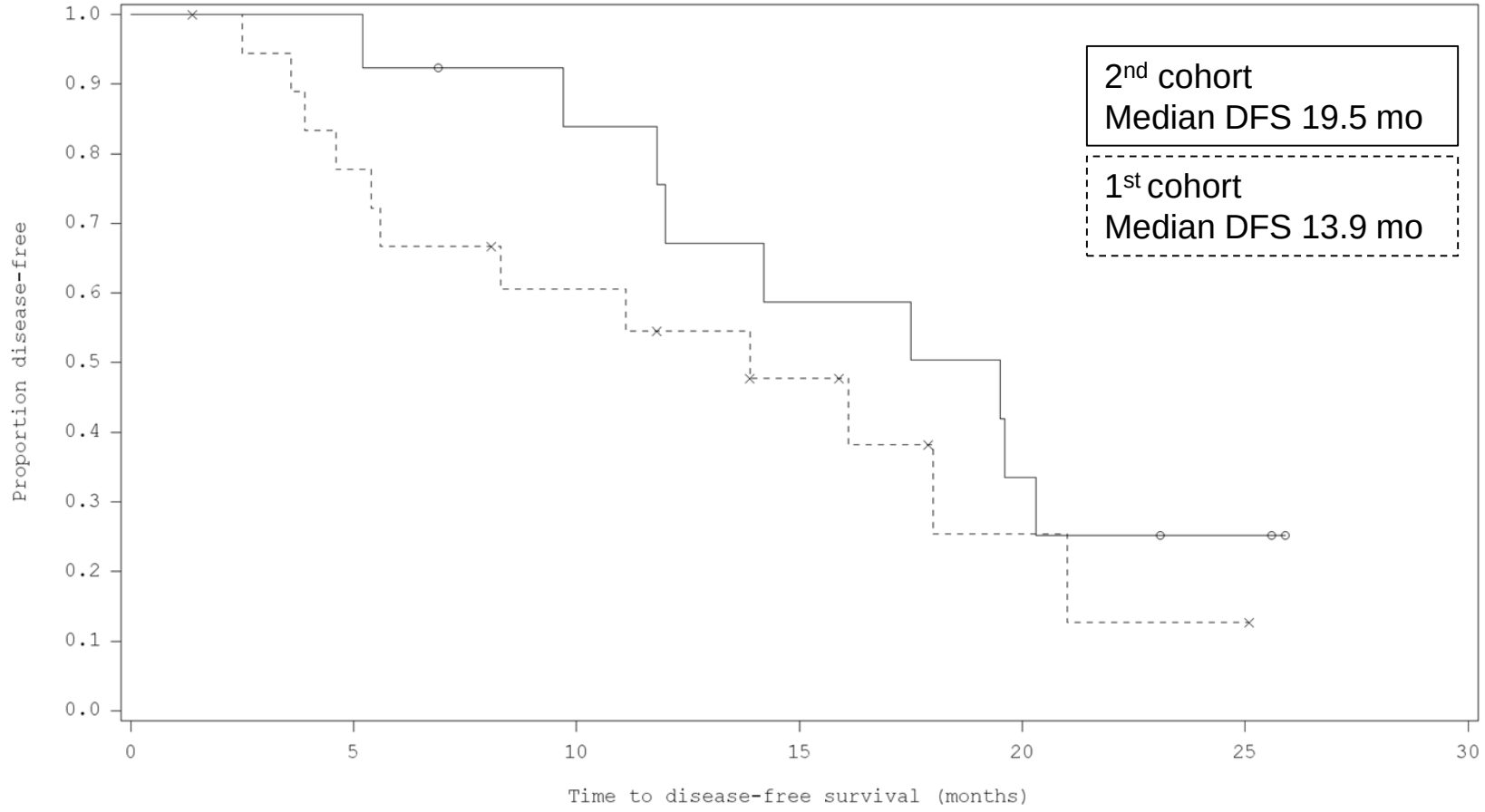
2 Six-month improvement in disease free survival for 2nd dose cohort



Censored= No progression on latest scan collected

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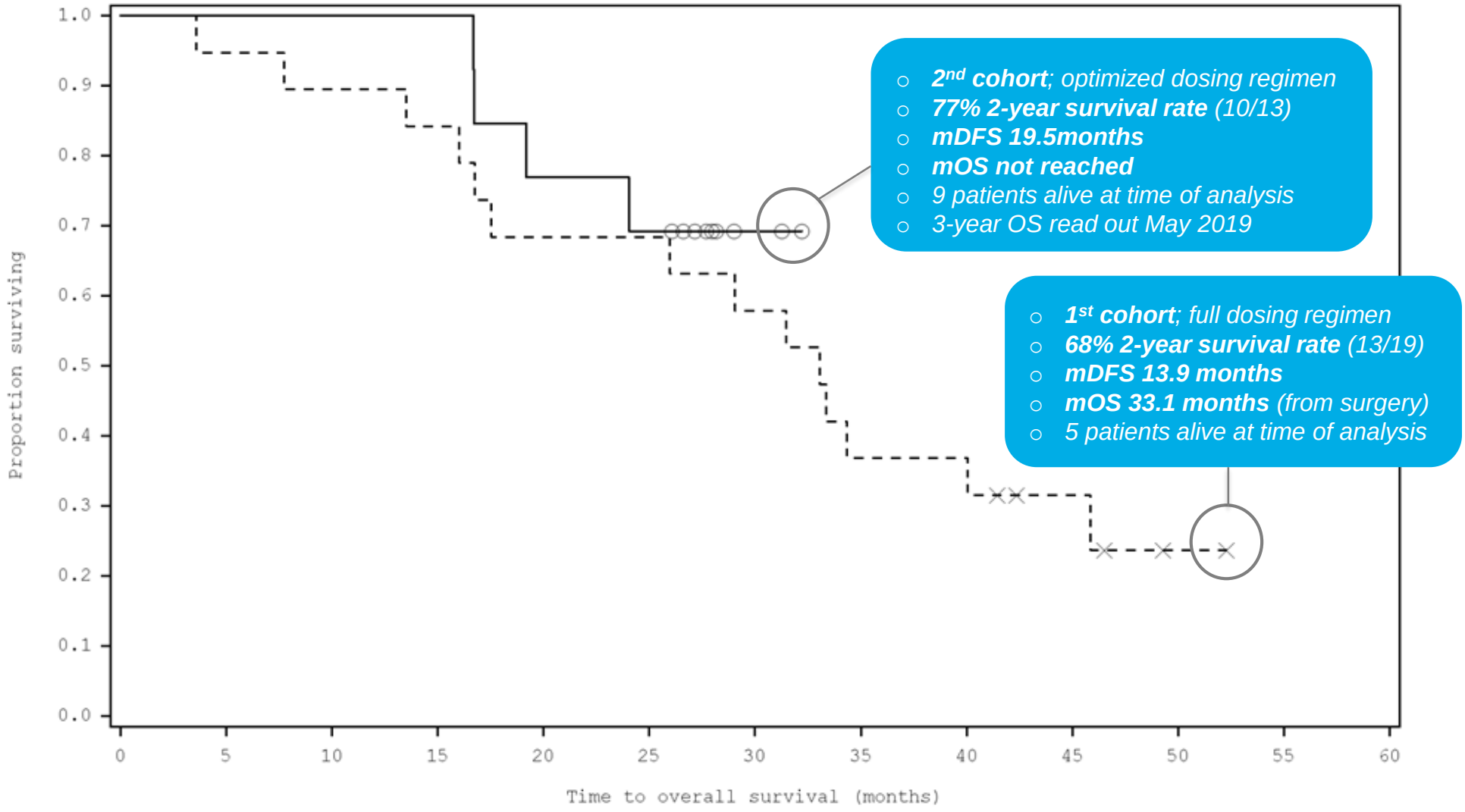
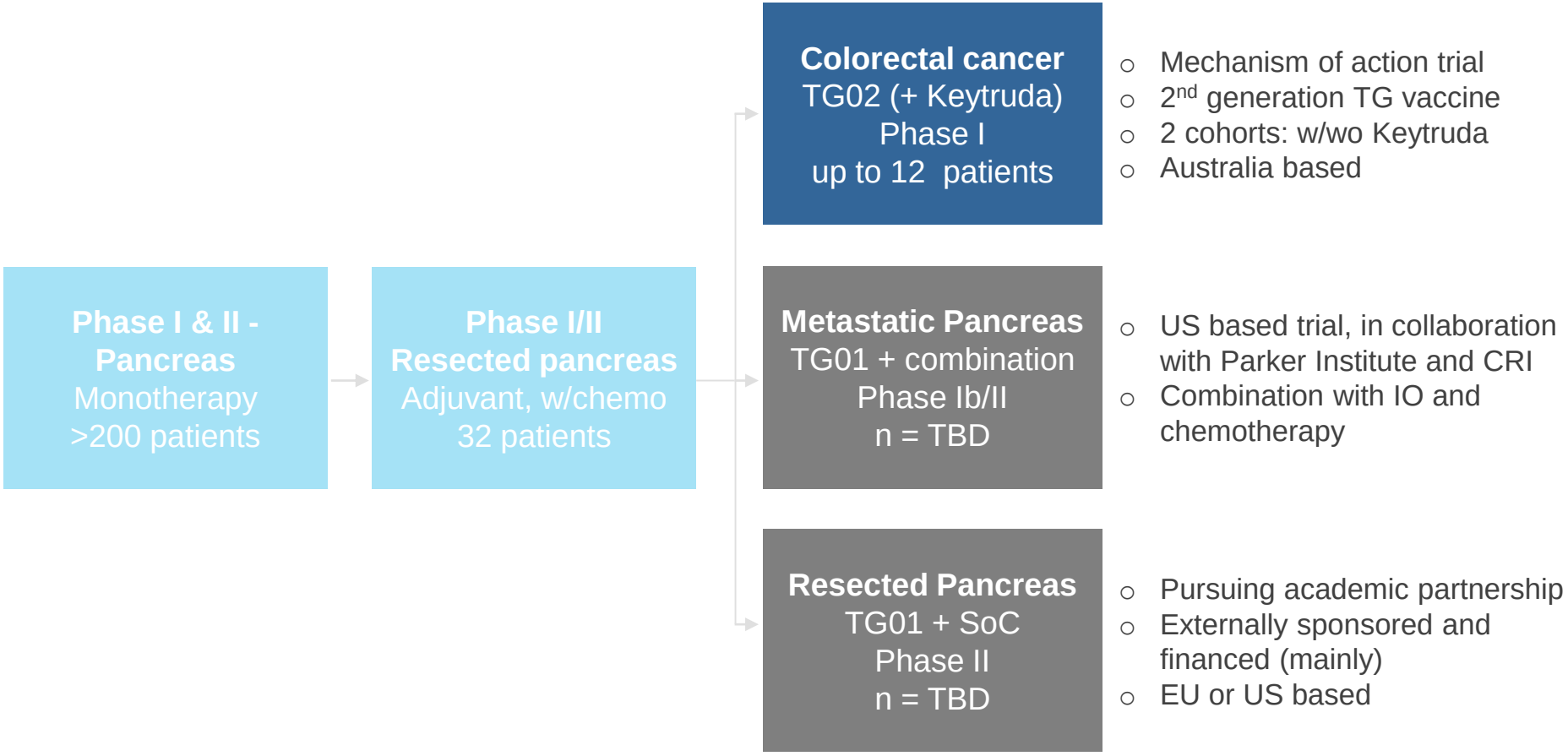
Signal of overall survival benefit observed at two-year read-out point



- ***2nd cohort**; optimized dosing regimen*
- ***77% 2-year survival rate** (10/13)*
- ***mDFS 19.5months***
- ***mOS not reached***
- *9 patients alive at time of analysis*
- *3-year OS read out May 2019*

- ***1st cohort**; full dosing regimen*
- ***68% 2-year survival rate** (13/19)*
- ***mDFS 13.9 months***
- ***mOS 33.1 months** (from surgery)*
- *5 patients alive at time of analysis*

TG CLINICAL DEVELOPMENT NEXT STEPS



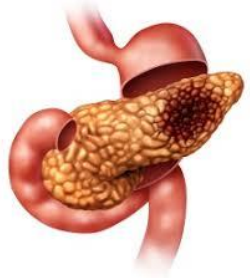
Completed trials | Ongoing trials | Trial sponsored by partner (under planning)

ALL RAS MUTATED CANCERS ARE POTENTIAL TARGETS

Opportunity for mutant RAS genetic marker approval?

1

Pancreatic cancer



TG01 indication

- Ph I/II completed
- Next trial(s) under planning
- ~300 000 incidents

2

Colorectal cancer

TG02 lead indication

- Ph I trial ongoing
- 40-50% mutRAS
- ~500 000 incidents

3

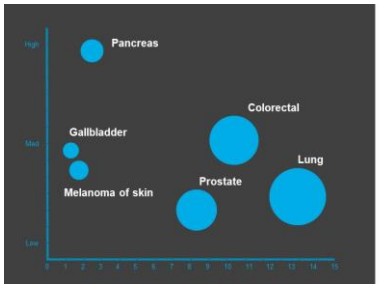
Lung cancer (NSCLC)

TG02 potential future indication

- 20-30% mutRAS
- ~500 000 incidents

4

All mutant RAS cancers



TG02 + TG03 long-term potential

- Genetic marker approval
- Up to 30% of all cancer patients

Source: Global data, Riva et al. Plos One 2017 Estimated total addressable patient number with RAS mutations in US, EU and China

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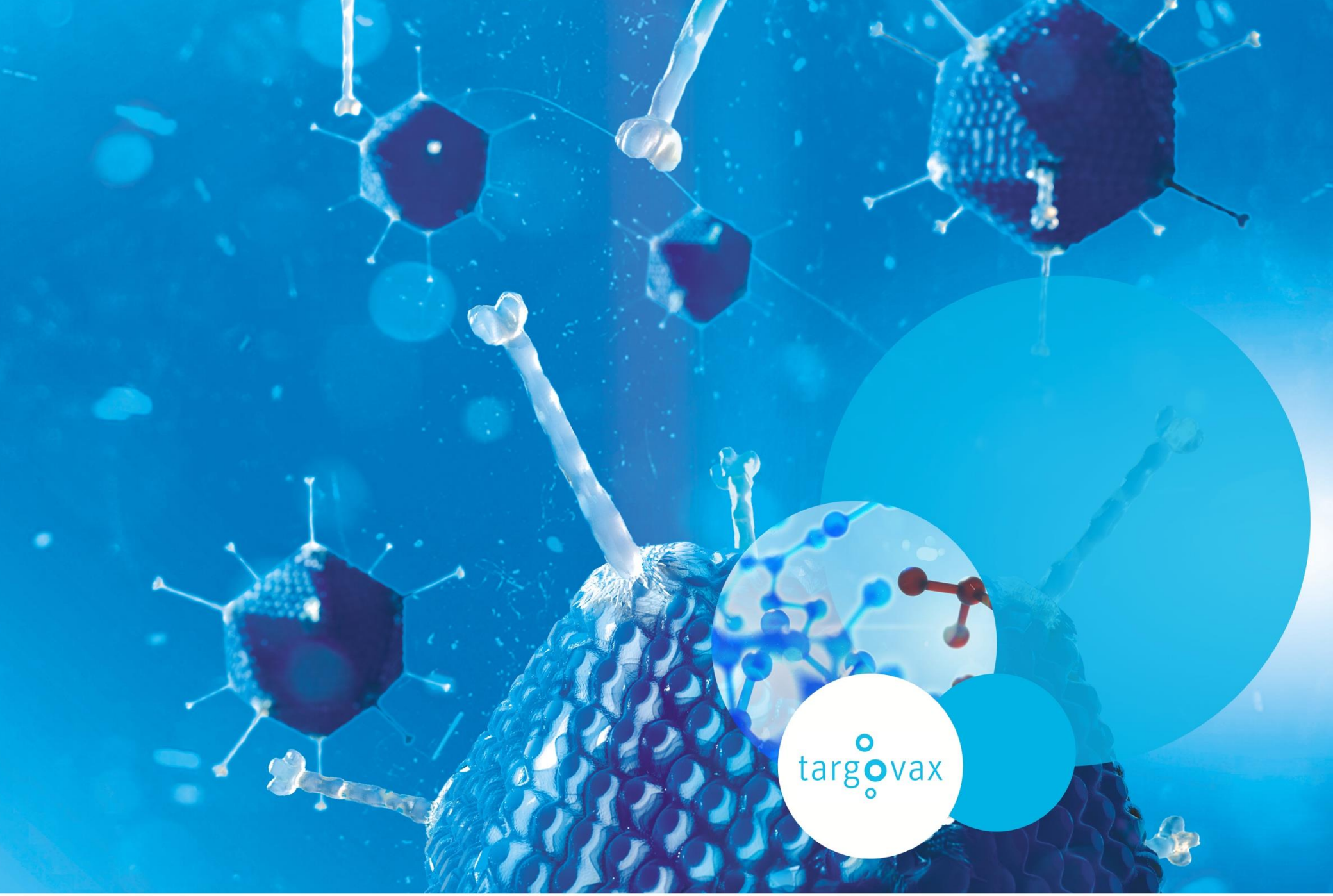
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