TG01, a neo-antigen specific peptide vaccine targeting RAS mutations in solid tumours

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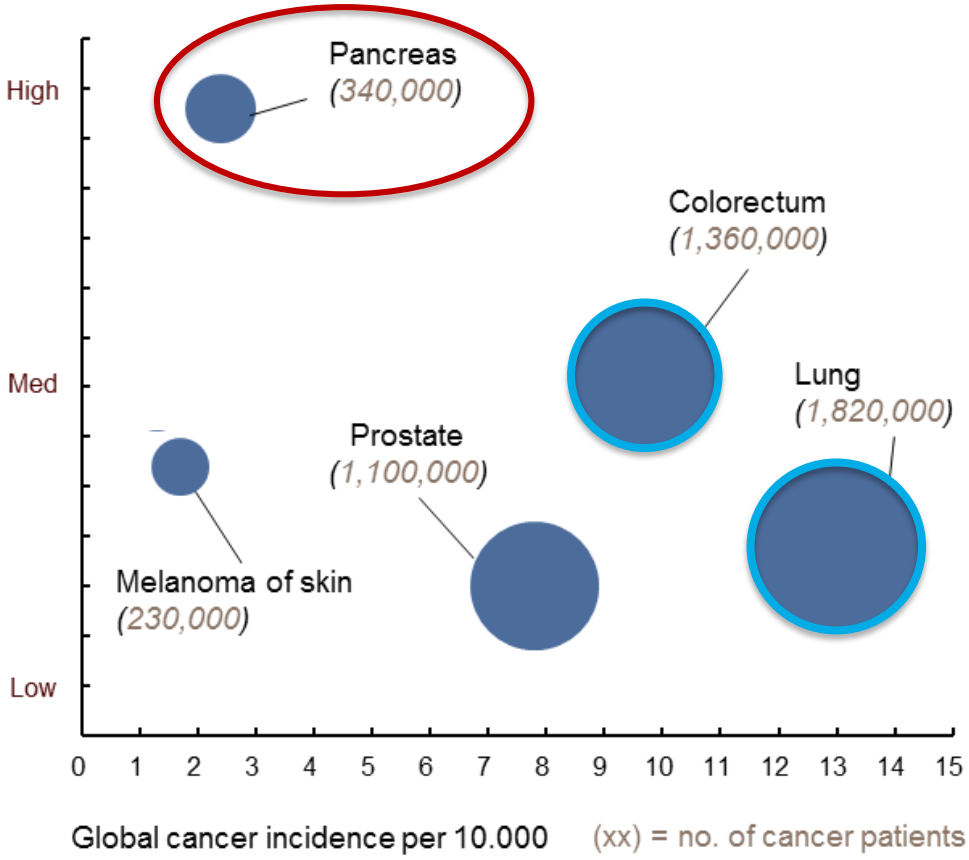
The RAS gene is mutated in 90% of pancreatic cancer patients, making it an ideal target

Frequency of RAS mutations



- RAS mutations result in **uncontrolled cell division**
- **There are no existing therapies** targeting RAS
- Targovax has developed a unique **vaccine against mutant RAS**

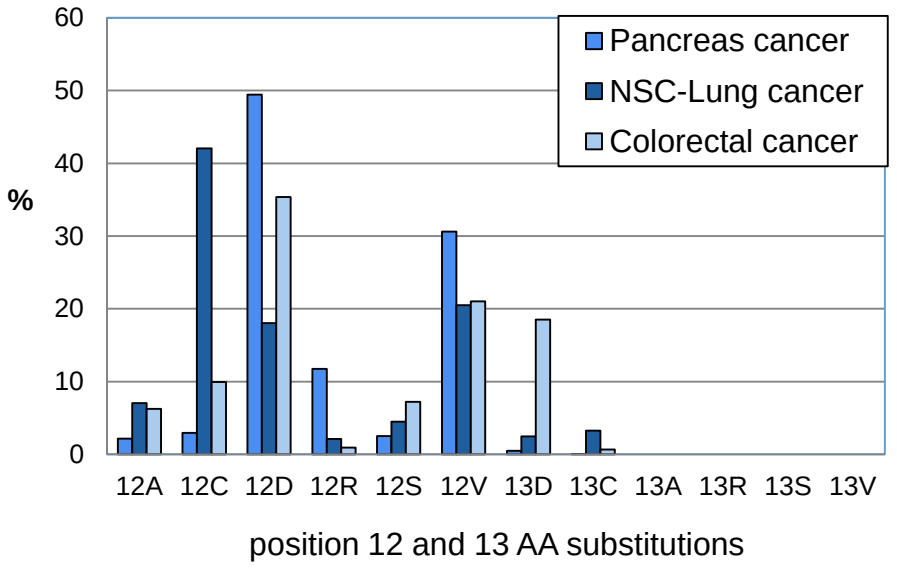
RAS exon 2 codon 12 and 13 mutation

- mutRAS proteins are trunk neoantigens and potential targets for T cells

RAS protein amino acid sequence: 1 MTEYKLVVVGA**GG**VGKSALTIQLIQ …… (12 13)

- Usually only one mutation present in tumor but tumours with more than one mutation occur
- Different lesions in same patient can have different mutations
- Undetected mutRAS sub-clones in primary tumour drive recurrence and metastasis formation
- 3 isoforms of RAS (K, N, H) but identical protein sequences

Exon 2 mutRAS amino acid (AA)substitutions



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

GOAL: One vaccine targeting codon 12 and 13 mutations

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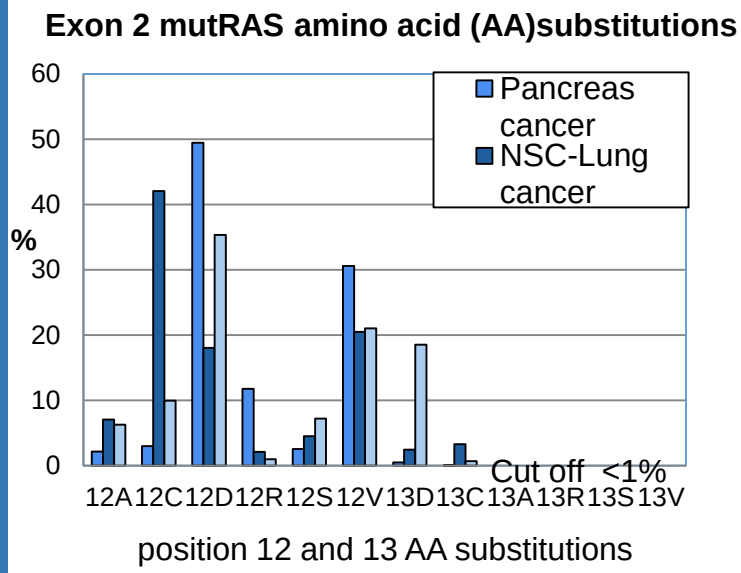
Peptide cocktails for mutRAS immunisation

TG01

7 peptides covering > 99% of mutations in Pancreatic cancer

TG02

8 peptides covering > 99% of mutations in NSC-Lung cancer and Colorectal cancer (TG01 + 13C peptide)



- **17 amino acid peptides used as antigens**
- **HLA unrestricted - activate both mutRAS specific CD4+ and CD8+ T cells**
- **Recombinant human GM-CSF is used as local immune-modulator**
  - The peptides lack inherent immunogenicity

The TG vaccine induces T-cells that recognize and destroy RAS mutated cancer cells

1. Activate immune system

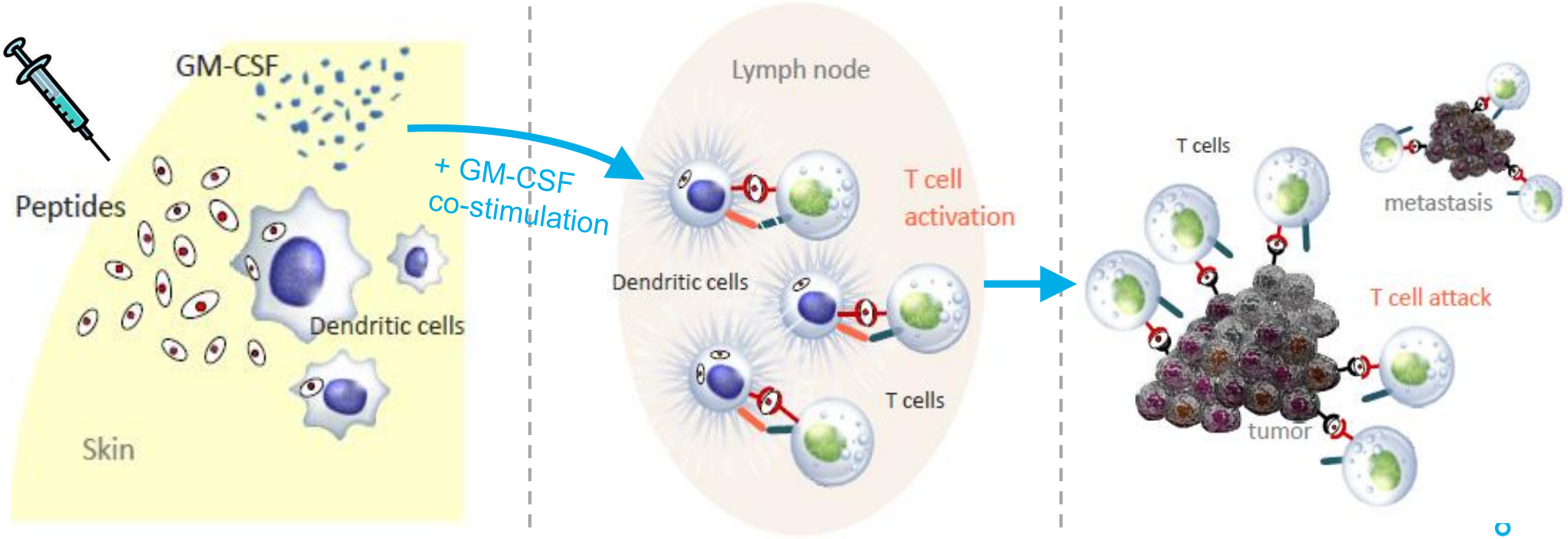
- TG vaccine **injected intradermally** and picked up by APCs

2. Induce mutRAS T-cells

- CD4+ and CD8+ **mut-RAS T-cells induced** in the lymph node

3. Attack the cancer

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

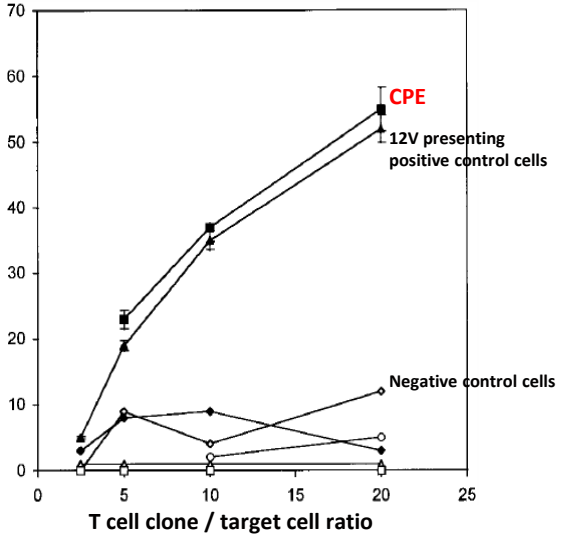


Formation of mutRAS specific CD4+ and CD8+ T-cells were validated in patients, both in blood and tumor biopsies

1 mutRAS specific CD4+ T cells kill the patient's tumor cells *in vitro*

CD4+ T cell clone from a RAS peptide vaccinated patient that recognize the same mutation (12V) as found in the patient's tumor, can lyse and kill cancer cells (CPE) from the same patient (*in vitro*)

% Specific lysis (killing) of cells by CD4+ T cell clone

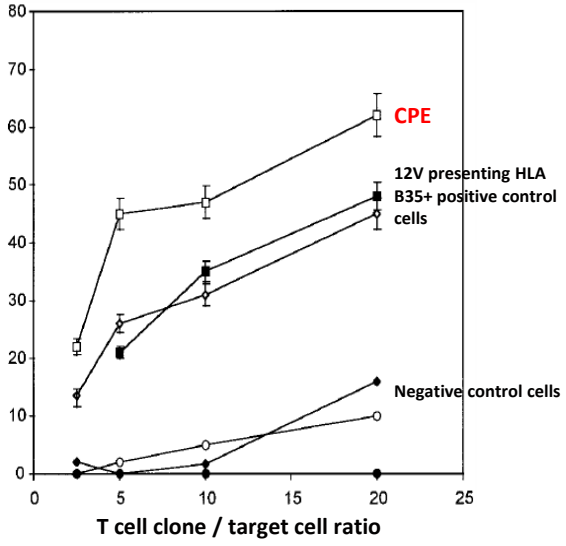


(Gjertsen et al., 1997)

2 mutRAS specific CD8+ T cells kill the patient's tumor cells *in vitro*

HLA B35 (tissue type) restricted CD8+ T cell clone from a RAS peptide vaccinated patient that recognize the same mutation (12V) as found in the patient's tumor, can lyse and kill cancer cells (CPE) from the same patient (*in vitro*).

% Specific lysis (killing) of cells by CD8+ T cell clone



(Gjertsen et al., 1997)

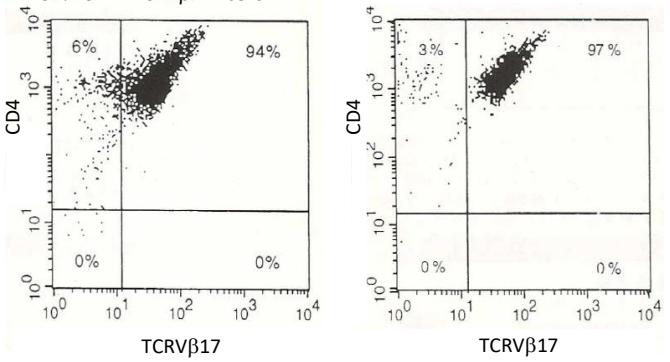
3 mutRAS specific T-cell clones identified both in blood and tumor

CD4+ T cells with same T cell receptor clonality (TCR Vβ17), and recognizing the same mutation (12R) as found in the patient's tumor, was found in both blood (PBMC) and tumor biopsy (TIL) from vaccinated patient.

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

PBMC Clone
94% CD4+ TCRVβ17+ cells

TIL Clone
97% CD4+ TCRVβ17+ cells



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

(Gjertsen et al., 2001)

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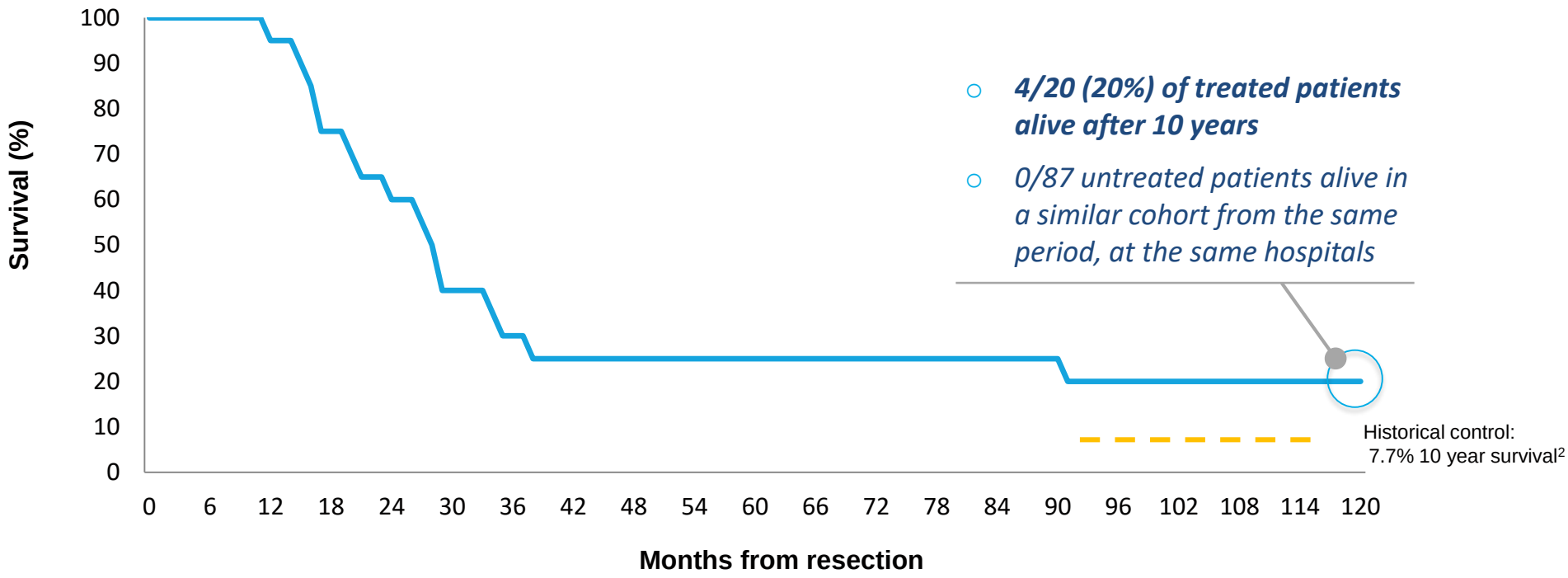
”Reason to believe” in resected disease

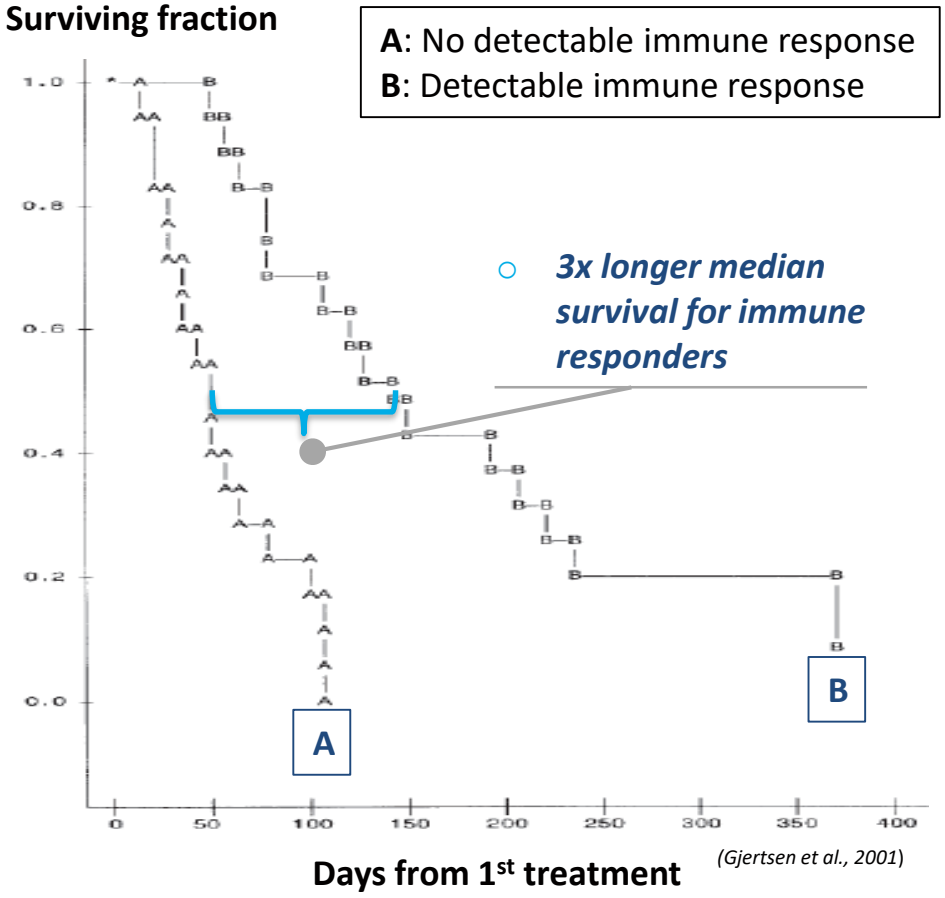
Retrospective 10 year survival data from TG trials in resected pancreatic cancer (n=20, TG monotherapy)



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

“Reason to believe” in advanced disease

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

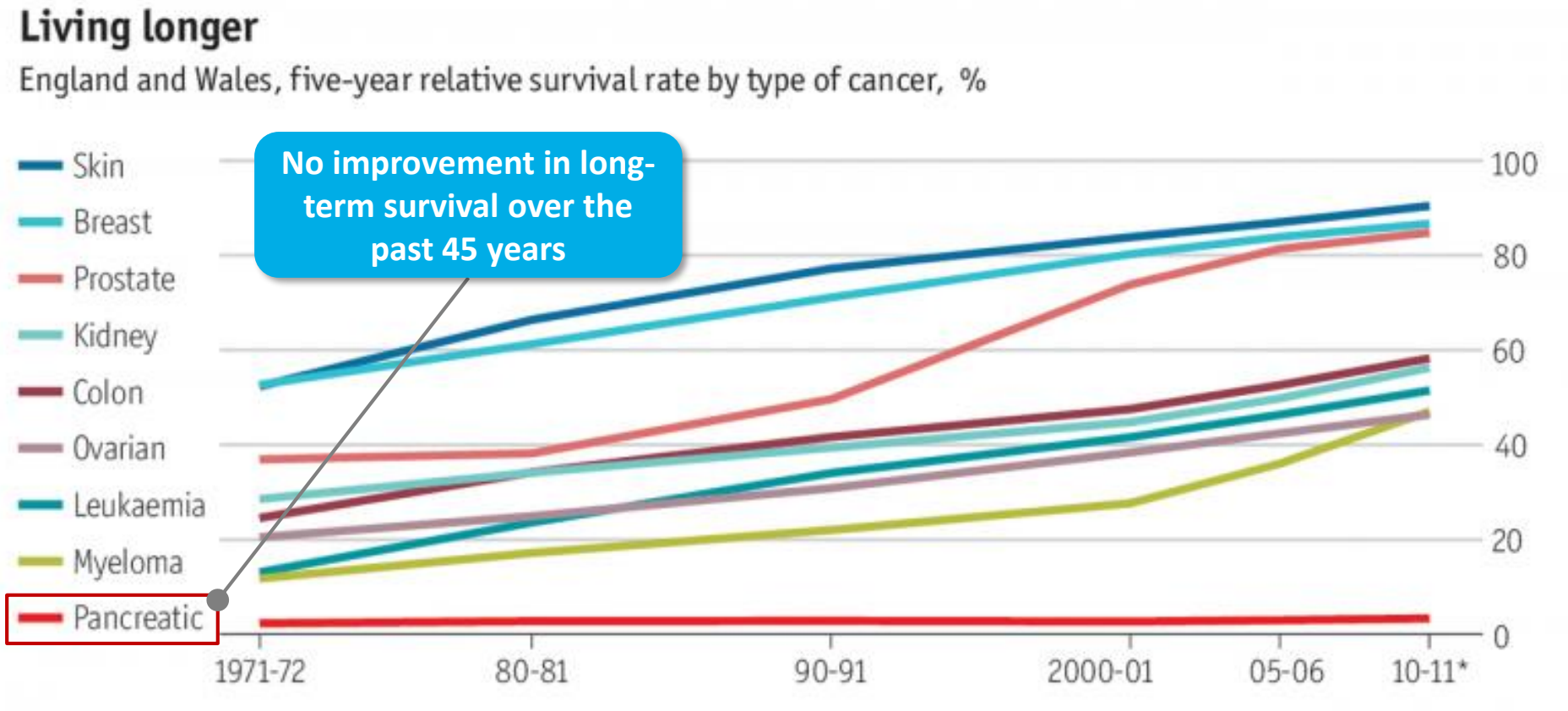


(Gjertsen et al., 2001)

- ***3x longer median survival for immune responders***

- **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)*

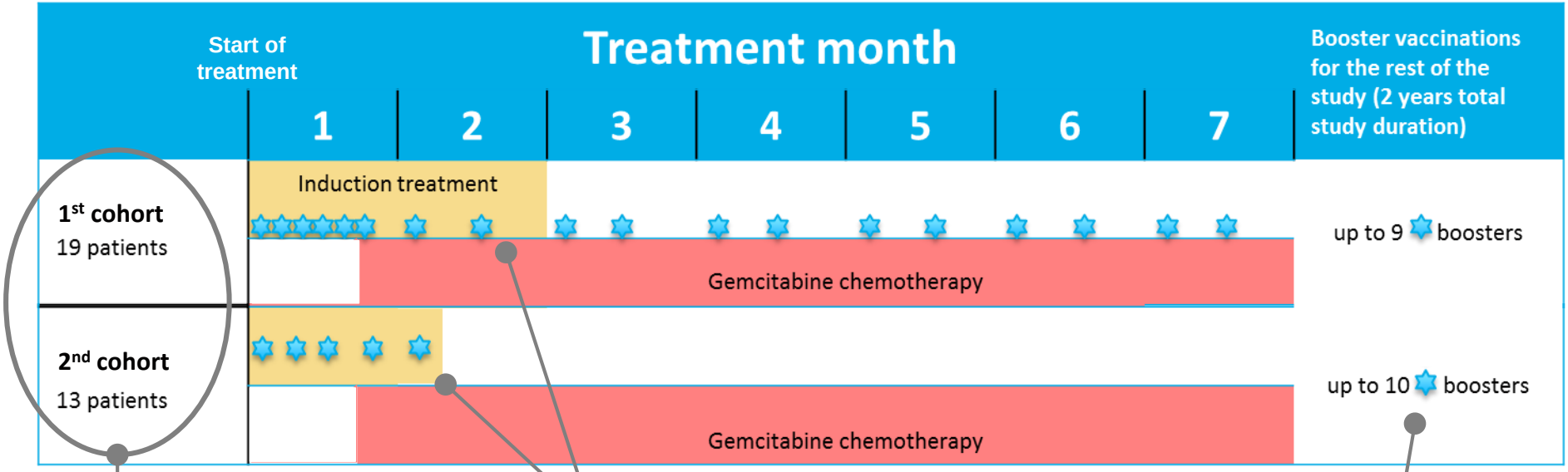
The five year survival rate for pancreatic cancer patients has not improved since the 1970s



SOURCE: Cancer Research UK, graphic adapted from The Economist September 16 2017

Targovax was set up to validate the TG concept with adjuvant chemotherapy

Ongoing Phase I/II trial in resected pancreatic cancer with adjuvant Gemcitabine (SoC)



- 32 patients in 2 cohorts
- Single arm design, no control group

- The cohorts have different dosing regimens
- Chemo given with/wo TG

- TG booster injections up to 2 years post surgery

Interim data from soon completed phase I/II (ASCO 2017)

1st cohort (19 patients)

- **Median survival 33.1 months vs. 27.6 for historical control**
- **13 of 19 patients (68%) alive 2 years after surgery**, vs. 30-53% in historical controls

2nd cohort (13 patients)

- **13 of 13 patients (100%) alive 1 year after surgery**

mutRAS immune response (1 yr)

- **90% of patients** (29/32) had **RAS-specific immune activation**

Safety

- TG01 and gemcitabine **combination treatment is well-tolerated**
- **Four allergic reactions reported in 1st cohort, none in 2nd cohort** (up to 1 year)

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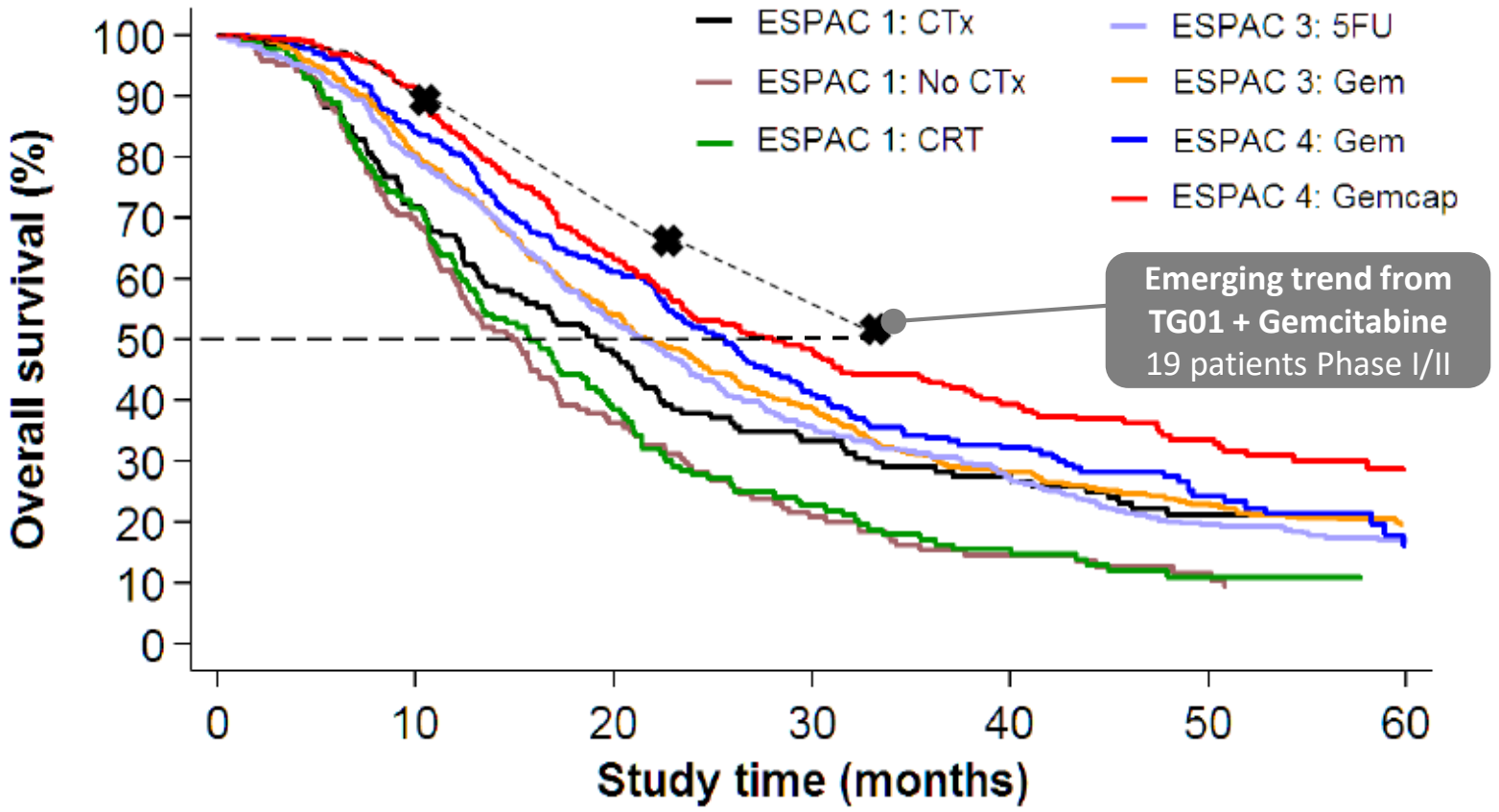
Interim TG01 data in context

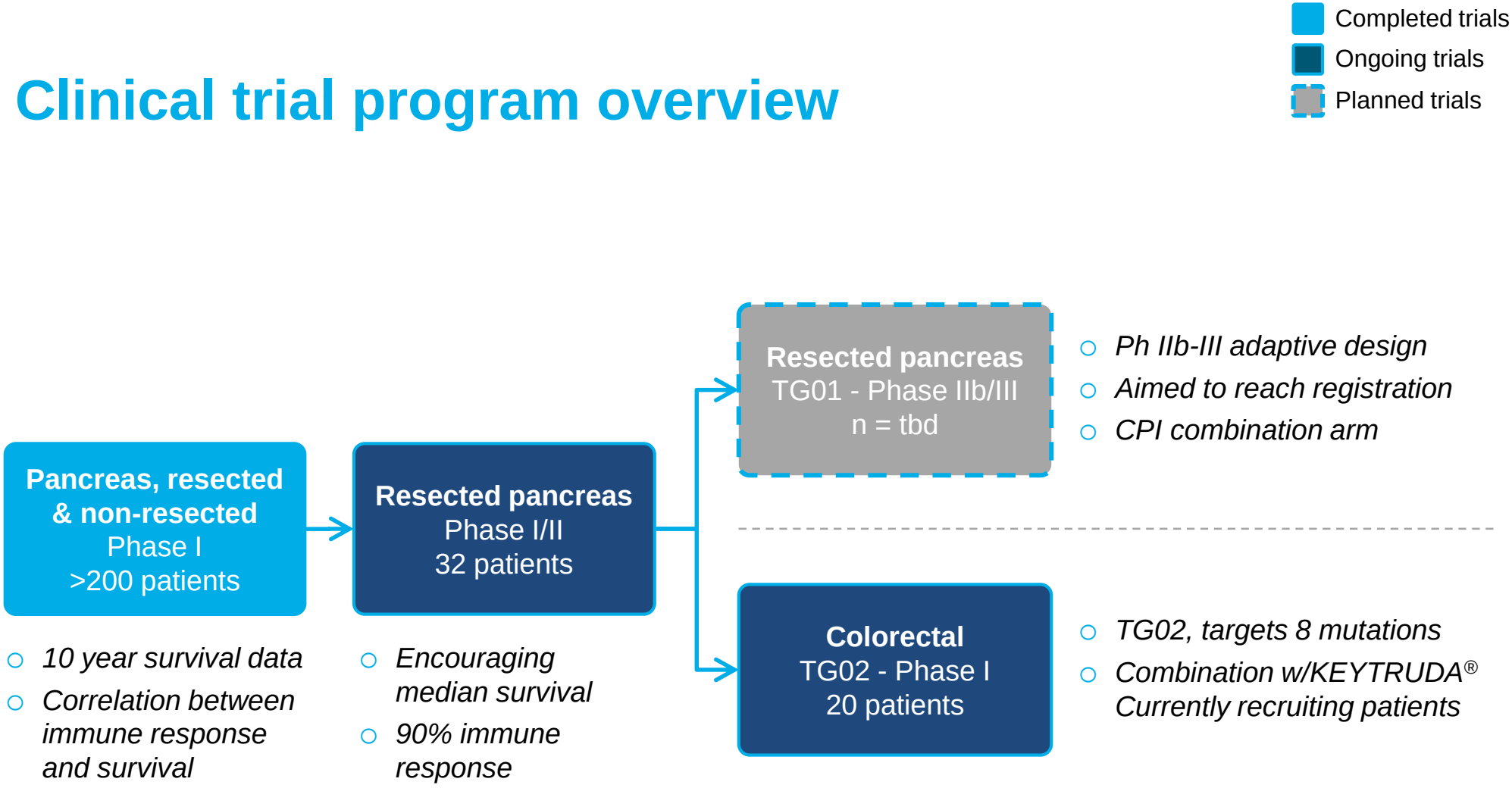
As presented by TG01 PI Prof. Daniel Palmer, London, June 2017

Comparative survival rates across trials in resected pancreatic cancer



NOTE: Relative survival curves across studies (ESPAC), meant for indicative comparisons only. No Kaplan Meier analysis has been done of the TG01 study data. Instead 1 and 2 year survival as well as median OS have been plotted.

Clinical trial program overview

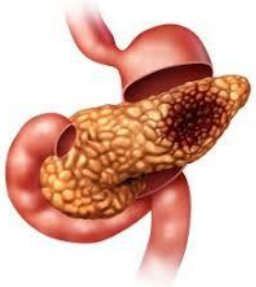


Why TG may succeed where others have failed

Lessons Learned	The TG approach
Target often poorly defined *and not cancer specific*	✓ Mutated **RAS is a well-defined neo-antigen**, and a driving cause of cancer
Insufficient immune activation *of CD4+ helper and CD8+ killer T-cells*	✓ TG peptides are **proven** to induce both **CD4+ and CD8+ mutRAS T-cells**
Most clinical trials have been done in ***advanced disease***	✓ Initial focus on **resected patients, with stronger immune system**

Resected pancreatic cancer is the lead indication, but all RAS mutated cancers are potential TG targets

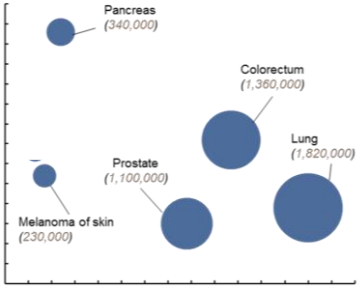
1. **Pancreatic cancer** (resected)
2. **Colorectal cancer**
3. **Lung cancer** (NSCLC)
4. **All mutRAS cancers**



- **TG01 lead indication**
- Completing phase I/II
- Planning phase IIb/III
- **40.000 patients**

- **TG02 lead indication**
- Phase I trial recruiting
- 50% RAS mutated
- **Up to 500.000 patients**

- **TG02 potential future indication**
- 30% RAS mutated
- **Up to 500.000 patients**



- **TG02 + TG03 ultimate long-term potential**
- 30% of all cancers
- **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

Thank you