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

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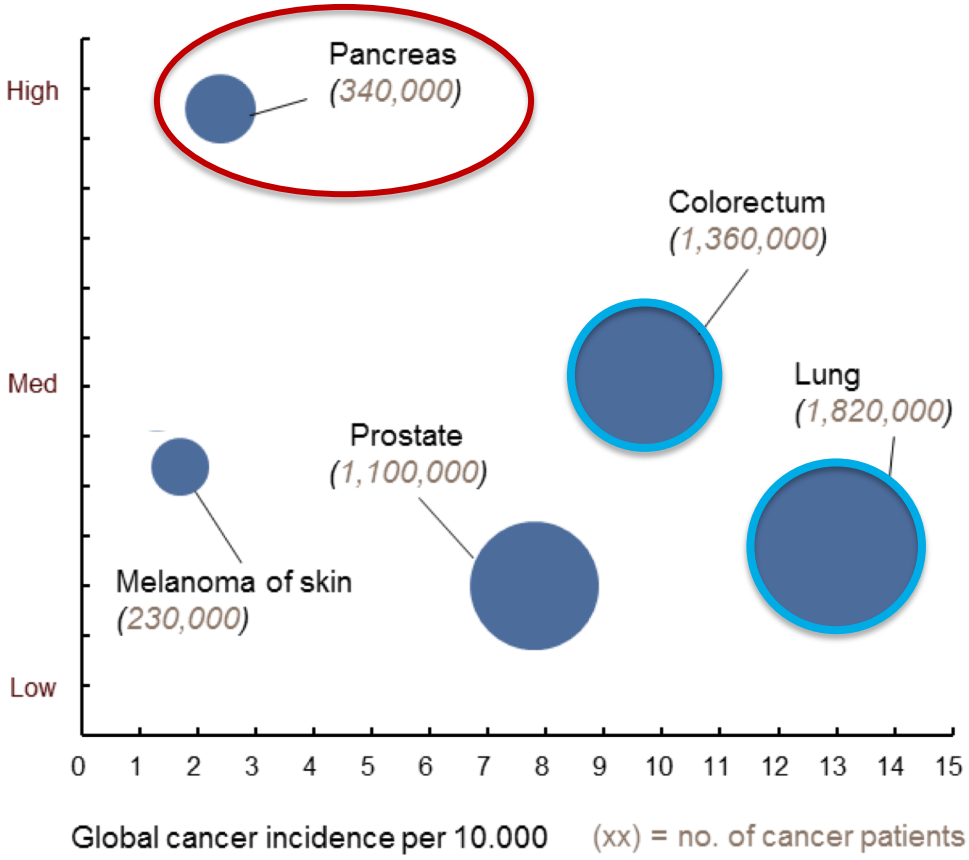
NeoAg Summit, 16th November, Boston

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

Frequency of RAS mutations



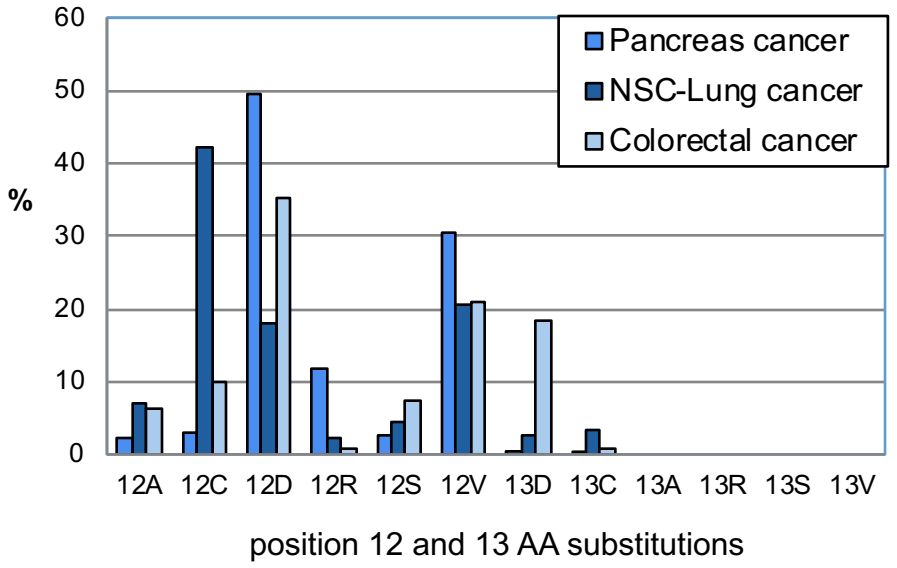
- RAS mutations result in **uncontrolled cell division**
- **There are no existing therapies** targeting RAS
- Targovax has developed a unique **vaccine against mutant RAS**

RAS exon 2 codon 12 and 13 mutation

RAS protein amino acid sequence: 1 … 12 13 **MTEYKLVVVGAGGVGKSALTIQLIQ ……**

- Usually only one mutation
- Different lesions in same patient can have different mutations
- Undetected mutRAS sub-clones in primary tumour drive recurrence and metastasis formation

Exon 2 mutRAS amino acid (AA)substitutions



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

GOAL: One vaccine targeting all codon 12 and 13 mutations

targovax

Peptide cocktails for mutRAS immunisation

TG01

7 peptides covering > 99% of mutations in Pancreatic cancer

TG02

8 peptides covering > 99% of mutations in NSCL 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 adjuvant**

Why the Targovax approach may work

where other cancer vaccines have failed

Historical lessons learned	*The Targovax approach*
Target often not known or poorly defined and not cancer specific, mainly TAAs	Mutated **RAS is a well-defined, cancer-specific neo-antigen**, driving the cancer
No or insufficient immune activation of the adaptive immune system	TG peptides are **clinically proven** to induce both **CD4+ and CD8+ mutRAS T-cells**
Most clinical trials have been in **progressive metastatic disease**	Initial focus on **earlier stage patients, with stronger immune system**

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

1. Activate immune system

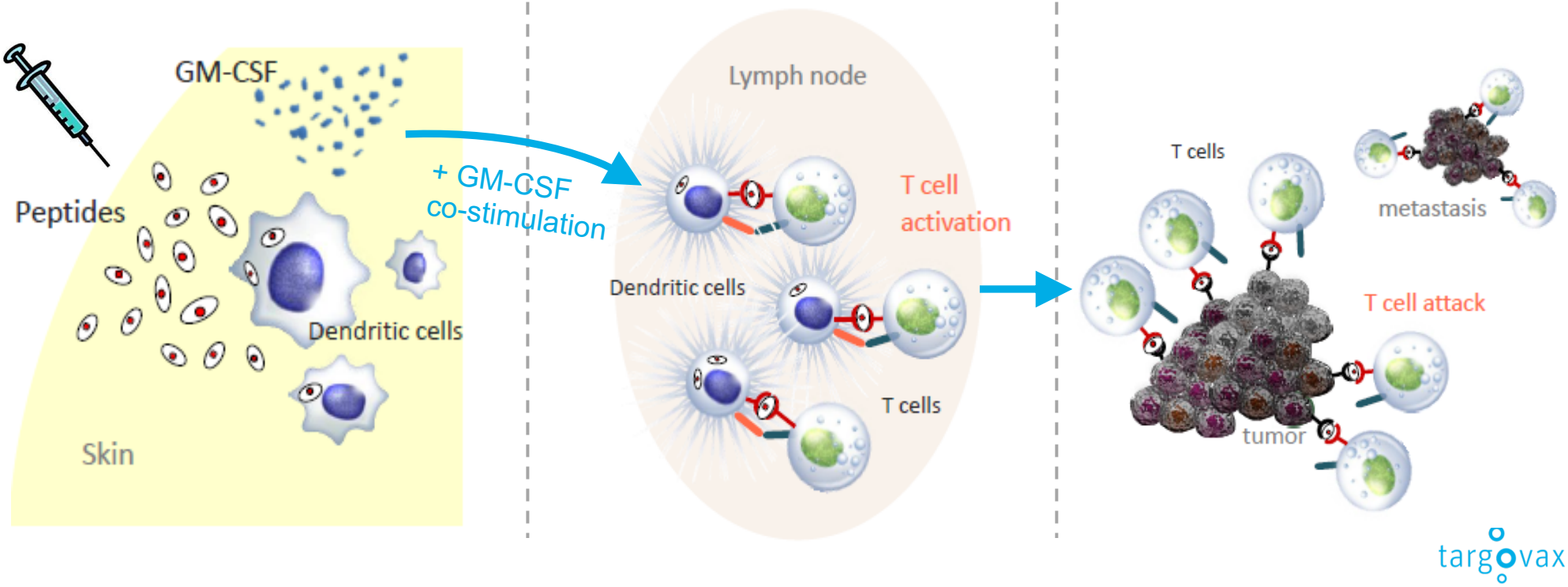
- TG vaccine **injected intradermally** and picked up by APCs

2. Induce mutRAS T-cells

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

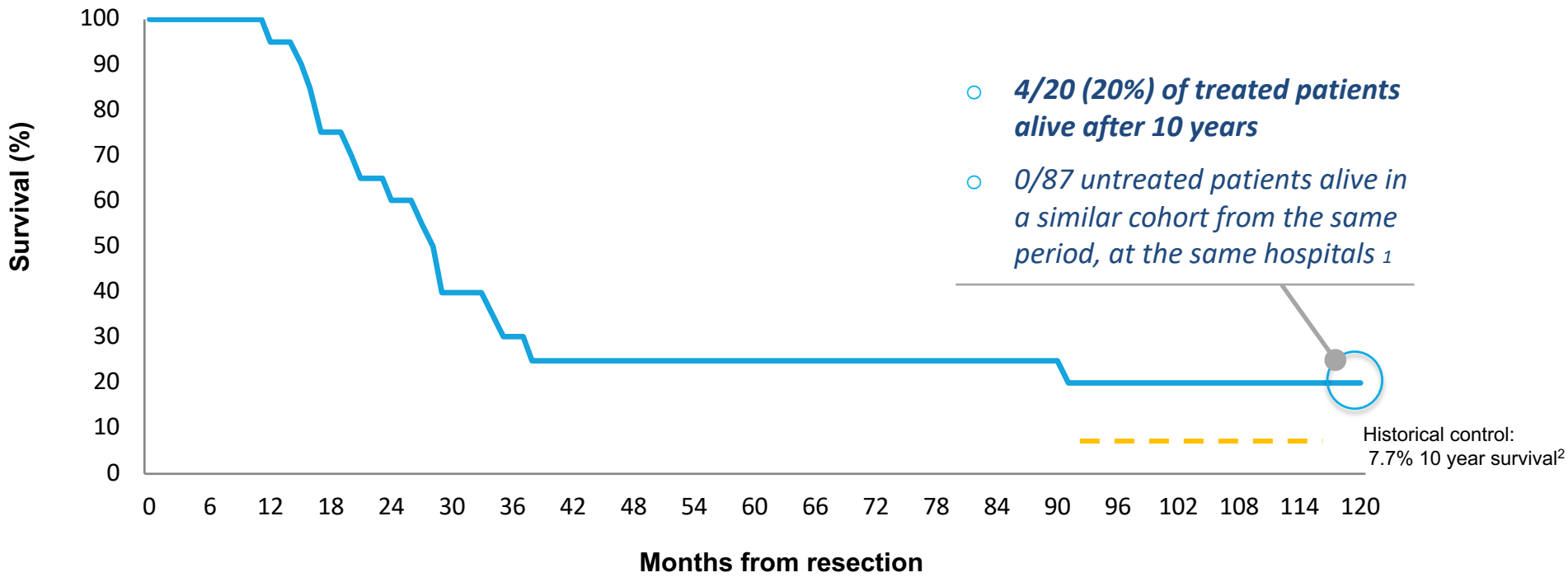
3. Attack the cancer

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



”Reason to believe” data in resected PC

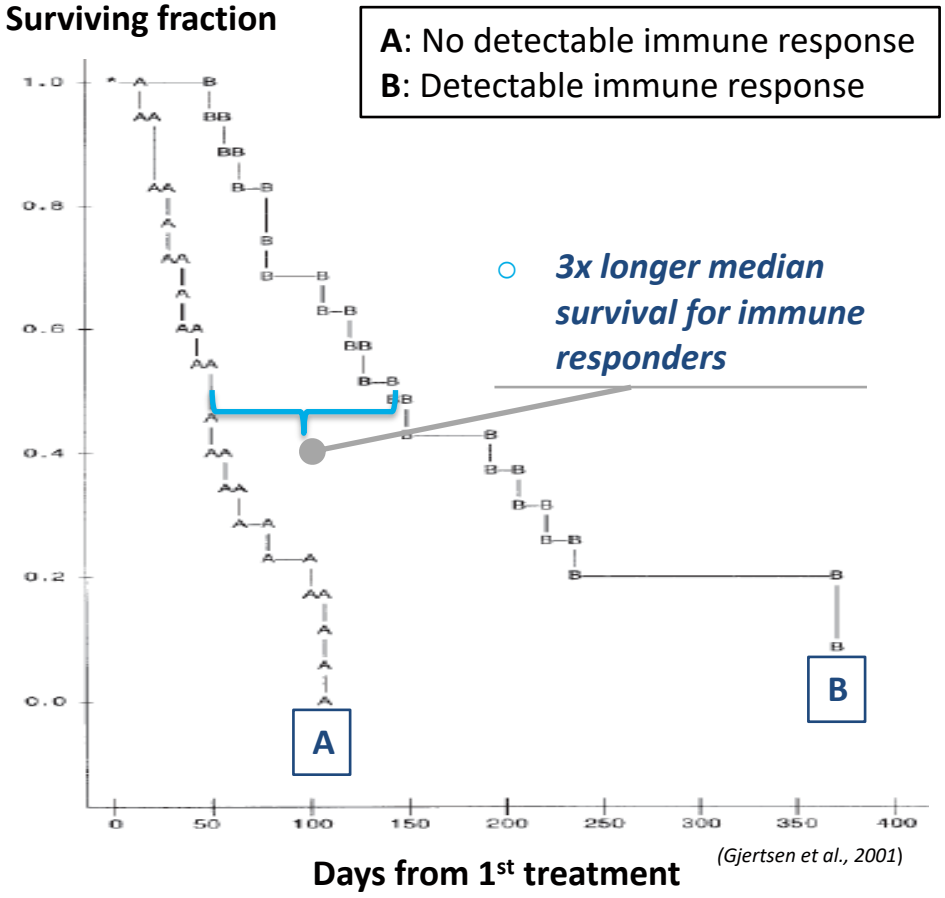
Retrospective 10 year survival data from TG trials in resected pancreatic cancer (n=20, TG monotherapy)



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

“Reason to believe” data in advanced PC

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

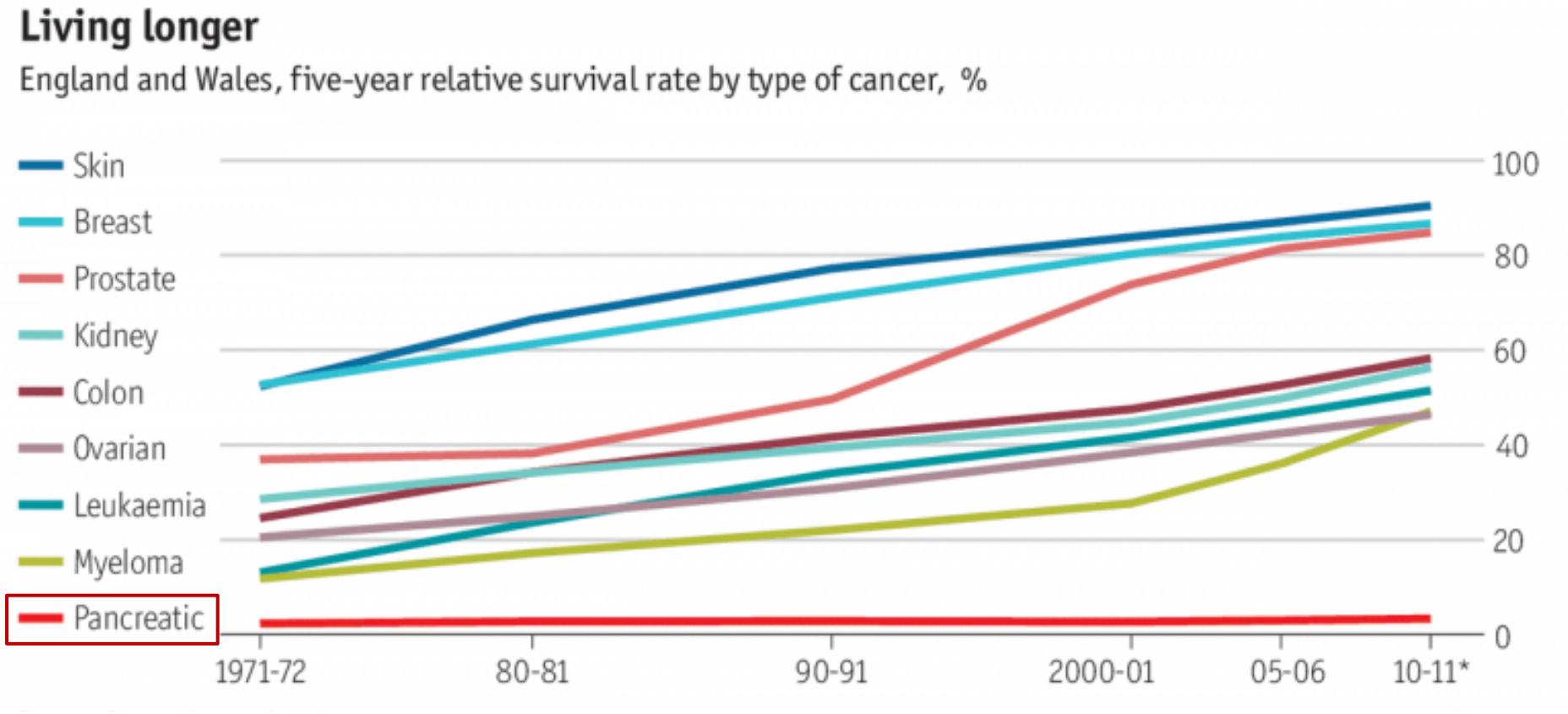


(Gjertsen et al., 2001)

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

- **19 of 36 (52%) patients had mutRAS immune response**
- **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



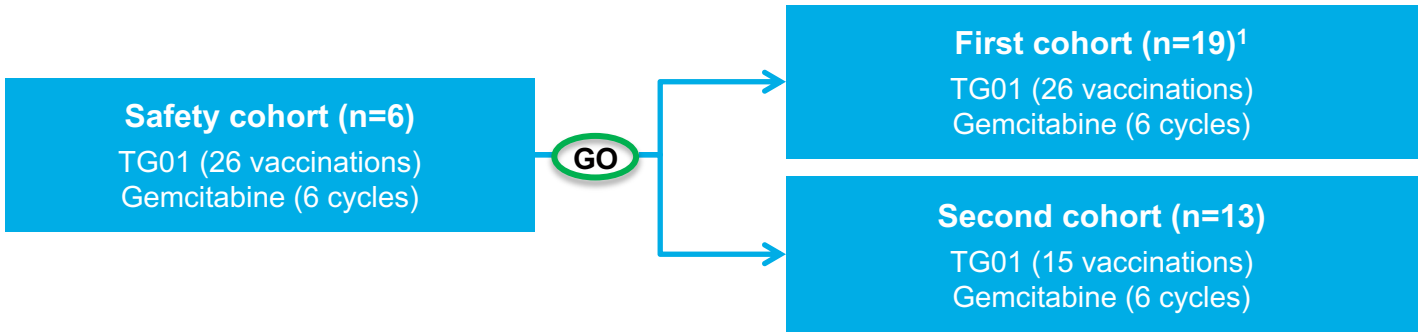
SOURCE: Cancer Research UK, graphic adapted from The Economist September 16 2017

TGO1-01 STUDY DESIGN

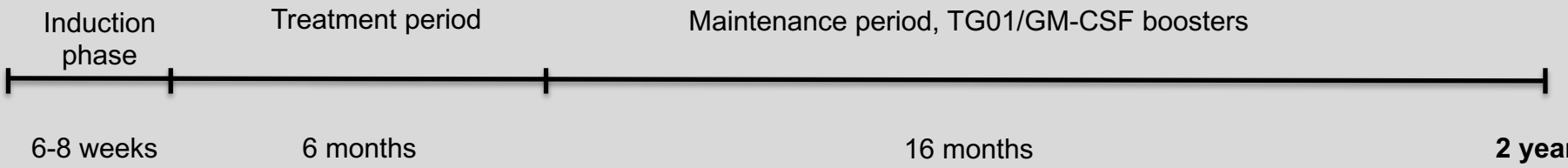
Patient population	Resected adenocarcinoma of the pancreas and candidates for adjuvant chemotherapy
Objective	Assess safety, immune response and clinical efficacy

Treatment	TG01/GM-CSF + Gemcitabine in 6 months
Study design	Safety lead-in Open-label, Non-randomized 2 cohorts with different dosing regimen

Study cohorts



Treatment schedule



Dosing regimen

	Number of vaccinations	Gemcitabine regimen	Vaccinations relative to gem.		
			Induction	During	Boosters
Main 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
Modified 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

Baseline characteristics

Parameters	Main Cohort (n=19)	Modified Cohort (n=13)	Overall (N=32)
Age (years)			
Median (min, max)	67 (49, 79)	59 (46, 74)	65 (46, 79)
Gender, n (%)			
Male	10 (53%)	11 (85%)	21 (66%)
Female	9 (47%)	2 (15%)	11 (34%)
ECOG, n (%)			
0	8 (42%)	6 (46%)	14 (44%)
1	11 (58%)	7 (54%)	18 (56%)
CA19-9 (U/ml)			
Median (min, max)	15 (5, 240)	25 (9, 2166)	16 (5, 2166)
Hemoglobin (g/L)			
Median (min, max)	124 (104, 153)	127 (109, 148)	124.5 (104, 153)

Baseline characteristics

Parameters	Main Cohort (n=19)	Modified Cohort (n=13)	Overall (N=32)
Disease staging at diagnosis			
T stage			
T1	1 (5%)	0	1 (3%)
T2	1 (5%)	0	1 (3%)
T3	**17 (90%)**	**13 (100%)**	**30 (94%)**
N stage			
N0	7 (37%)	2 (15%)	9 (28%)
N1	12 (63%)	11 (85%)	23 (72%)
M stage			
M0	19 (100%)	13 (100%)	32 (100%)
Resection surgical outcome, n (%)*			
R0	6 (32%)	4 (31%)	10 (31%)
R1	**13 (68%)**	**9 (69%)**	**22 (69%)**
KRAS mutation detected, n (%)			
Yes	16 (84%)	10 (77%)	26 (81%)
No	3 (16%)	3 (23%)	6 (19%)
Time from surgery to first IMP adm (week)			
Median (min, max)	8 (7, 12)	9 (7, 12)	9 (7, 12)

*Surgical resection of the five historical reference studies (PR): R0 60-100% . Then ESPAC-4 (R0 40%) showed >10% improved 2 year OS comparing R0 v R1

Adverse Events similar to chemotherapy alone

Serious Adverse Events Preferred term	Number of Events Main cohort (n=19)	Number of Events Modified cohort (n=13)	CTCAE grade	Relationship to study treatment
Total treatment-emergent SAEs	13	7		
Anaphylactic reaction	2	0	4	Related to TG01 plus gemcitabine
Hypersensitivity	1	0	2	
Dyspnoea	1	0	1	Possibly related to TG01 plus gemcitabine
Pyrexia	2	0	1, 2	Related to Gemcitabine
Anaemia	1	0	3	
Lung infection	1	0	2	
Pulmonary embolism	0	1	3	
Transient ischaemic attack	0	1	1	
Abdominal pain	0	1	2	Unrelated to study treatment
Anaphylactic shock (related to a concomitant medication	1	0	3	
Biliary sepsis	0	1	3	
Femoral neck fracture	0	1	3	
Gastroenteritis	0	1	2	
Hyperglycaemia	1	0	4	
Pneumonia	1	0	5	
Urosepsis	1	0	3	
Upper respiratory tract infection	0	1	3	
Viral upper respiratory tract infection	1	0	2	

IMMUNE RESPONSE

Parameters	1st Cohort (n=19)	2nd Cohort (n=13)	Overall (N=32)
Immune responder	*18 (95 %)*	*12 (92 %)*	*30 (94 %)*
DTH Positive	18 (95 %)	8 (62 %)	27 (84 %)
mutRAS Specific T-cells	14 (74 %)	12 (92 %)	26 (81 %)

Immune response = positive DTH and/or PBMC.
Immune responder = at least once during the entire study period

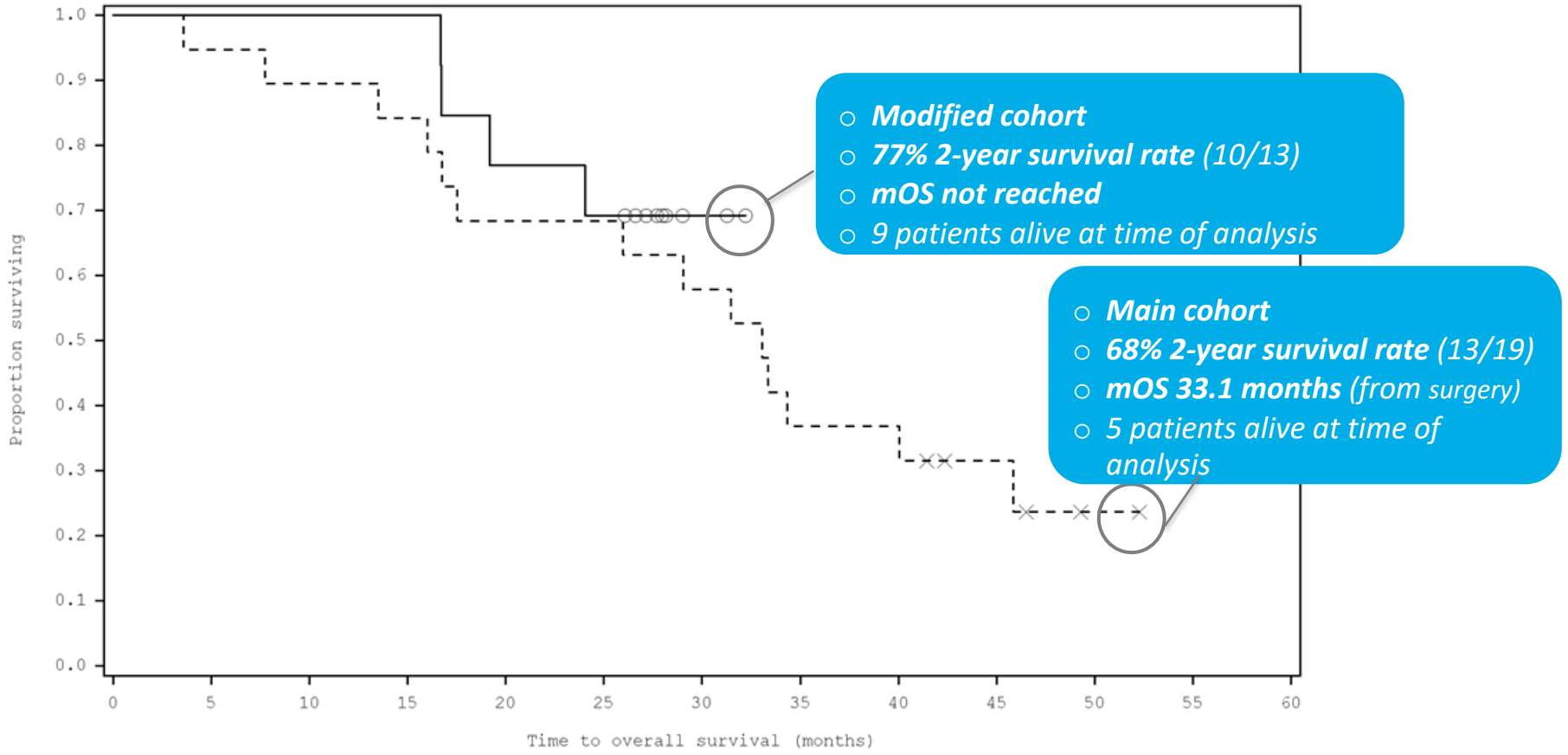
Efficacy (survival rate)

	1 year survival rate			2 years survival rate		
	Main Cohort (n=19)	Modified Cohort (n=13)	Overall (N=32)	Main Cohort (n=19)	Modified Cohort (n=13)	Overall (N=32)
Assessed from surgery*	17 (90%)	13 (100%)	30 (94%)	13 (68%)	10 (77%)	23 (72%)

* ~8 weeks before first IMP

OS from time of surgery

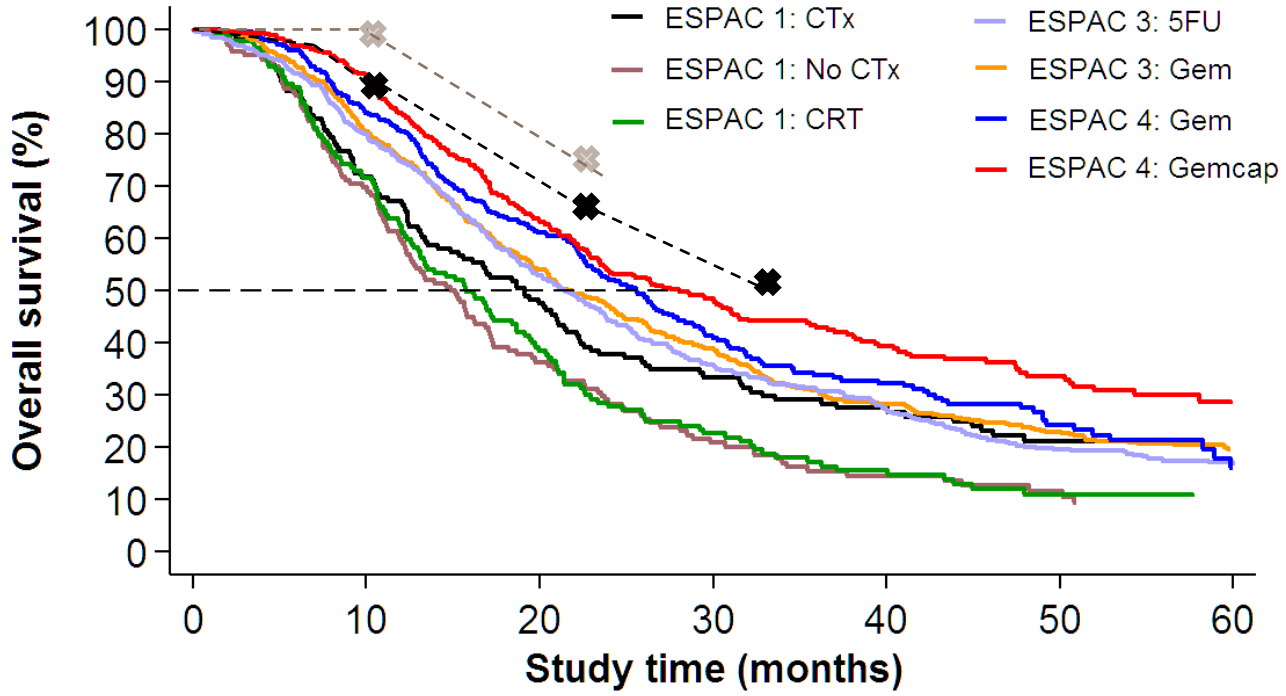
Note: mOS not yet reached as 9 patients still alive in May 2018 when censored at the end of the trial (2 years) – next censoring planned May 2019



- ***Modified cohort***
- ***77% 2-year survival rate*** *(10/13)*
- ***mOS not reached***
- *9 patients alive at time of analysis*

- ***Main cohort***
- ***68% 2-year survival rate*** *(13/19)*
- ***mOS 33.1 months*** *(from surgery)*
- *5 patients alive at time of analysis*

TG study data in the context of ESPAC Trials Overall Survival (Ref. Prof D Palmer, Liverpool, UK)



No. at Risk							
E1 - CTx	149	105	68	46	34	19	16
E1 - No CTx	143	99	50	28	17	10	8
E1 - CRT	145	103	54	30	19	10	8
E3 - Gem	539	422	283	187	126	93	64
E3 - 5FU	551	430	283	180	131	81	56
E4 - Gem	366	302	207	109	61	27	9
E4 - GemCap	364	328	219	139	83	50	19

Study time = time from surgery for ESPAC 1/3, study time = time from randomisation for ESPAC 4

Overall conclusion

- TG01 is well tolerated
- TG01 generated a RAS specific immune response in 94% of the patients
- Overall survival results were encouraging compared to reports published for similar patient population

Clinical development overview for the TG program

Historical trials

Phase I
Resected & non-resected
>200 patients

- *10 year survival data*
- *Correlation between immune response and survival*
- *Large safety database*

Completing trial

Phase I/II
Resected pancreatic cancer
32 patients

- *Encouraging mOS*

Planned / recruiting trials

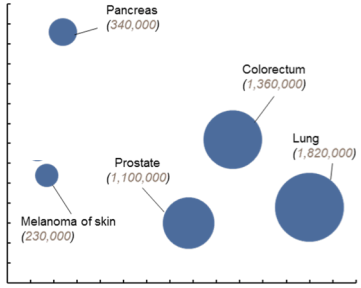
Pancreas cancer
TG01 - Phase IIb/III
n = tbd

- *Cancer network collaboration in resected disease (planning stage)*
- *Targovax sponsored in Locally Advanced PC (planning stage)*
- *TG + Check Point Inhibitor*

Colorectal - TG02
Phase I immune marker study
12-20 patients

- *TG02, targets 8 mutations*
- *Monitor changes to the micro tumour environment (TILs, PD expression) and PBMC*
- *1st cohort just TG02*
- *2nd cohort in combination w/KEYTRUDA®*

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	**TG02 lead indication**	**TG02 potential future indication**	**TG ultimate long-term potential**
Completed phase I/II	Phase I trial recruiting	30% RAS mutated	Biomarker license
40.000 patients	**Up to 500.000 patients**	**Up to 500.000 patients**	**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