vaccibody

Considerations and experiences from taking a fully personalized targeted cancer neoantigen DNA vaccine into the clinic

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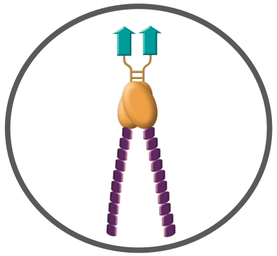
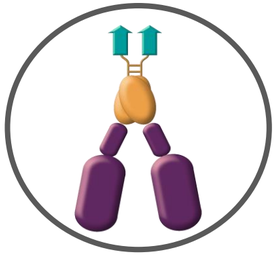
Vaccibody Product Pipeline

PROGRAM	DISCOVERY	PRE-CLINICAL	PHASE I	PHASE II	PHASE III
MELANOMA LUNG (NSCLC) BLADDER RENAL HEAD AND NECK	**VB10.NEO**				
HEAD AND NECK	**VB10.NEO + NKTR-214**			NEKTAR®	
PRECANCEROUS CERVICAL LESIONS	**VB10.16**				
CERVICAL	**VB10.16 + Atezolizumab (CPI)***		Roche		





Vaccibody – Proprietary Vaccine Technology Platform

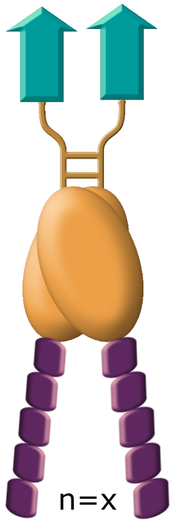
The Vaccibody Technology Platform was developed based on the concept of **targeting antigen to APC** in order to create more efficacious vaccines.

Exchangeable DNA Cassette

Vaccibody DNA Vaccine Plasmid

VB10.NEO

In vivo expression



Vaccibody in Protein Format

Target to Antigen Presenting Cell

Dimerization for crosslinking target receptor

Antigen moiety

Mechanism of action: the multiple effect of MIP-1α as targeting unit

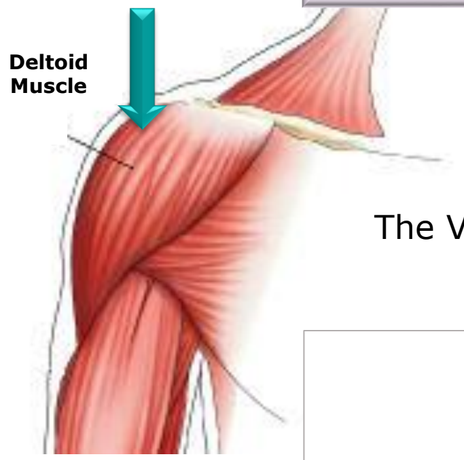
Administration (i.m.) of DNA plasmid

***In vivo* protein expression and secretion**

Target – Attract – Mature – Deliver – Cross-present

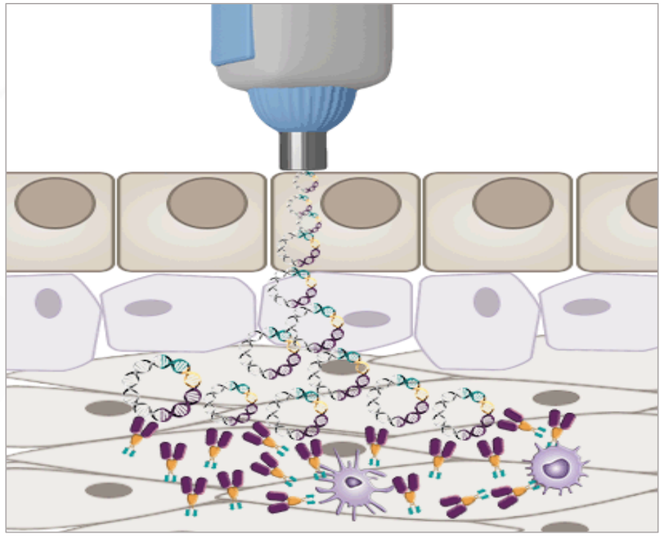
MIP-1α: Skewing the immune system to a CD8+ killer T-Cell response

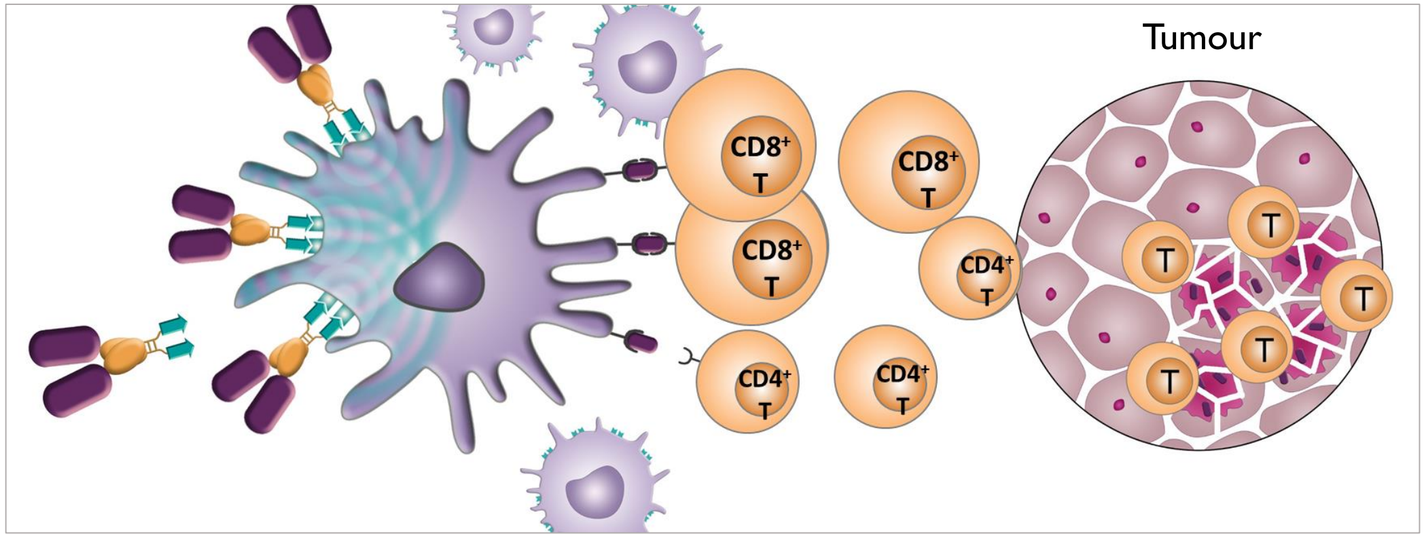
- Direct targeting & attraction of antigen presenting cells, high local vaccine concentration
- Enhanced T cell immunity obtained with fewer and lower doses
- Faster and longer lasting immune responses
- **Stronger potential to kill cancer cells**



The Vaccibody uses the muscle cell as a factory

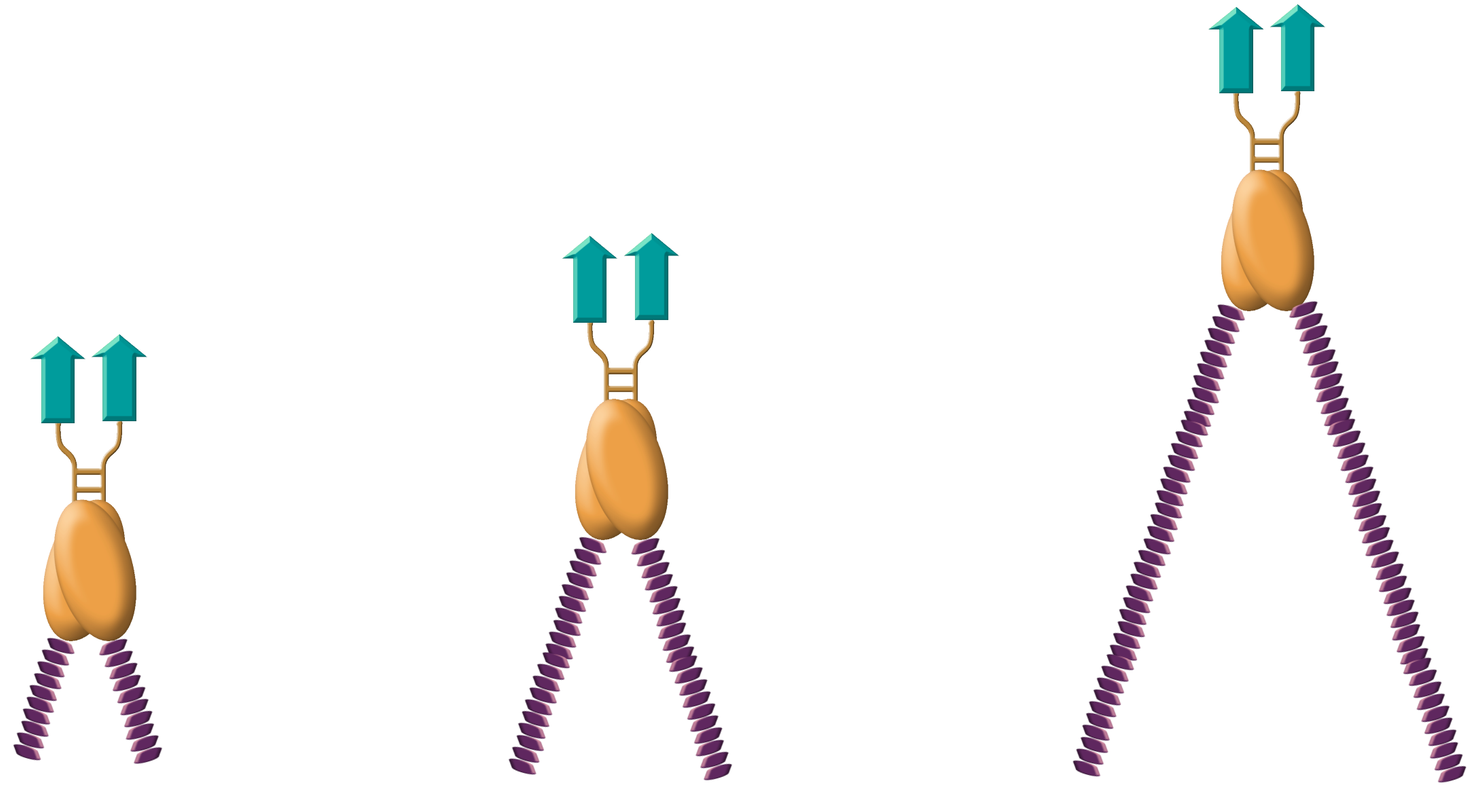
PharmaJet®





Targeting is elicited by the MIP-1α chemokine

VB10.NEO – A Robust Vaccine Format



VB10.NEO-X

VB10.NEO-XX

VB10.NEO-XD

- >90 different VB10.NEO constructs with >450 neoepitopes constructed to date with up to 40 neoepitopes.
- Order or position of neoepitopes generally do not affect their immunogenicity

VB10.NEO generates a broader immune response profile dominated by CD8+ T cells than competing technologies

B16 melanoma model

		Pep 1	Pep 2	Pep 3	Pep 4	Pep 5	Pep 6	Pep 7	Pep 8	Pep 9	Pep10
Peptide*	CD4										
	CD8										
RNA*	CD4										
	CD8										
Non-targeted DNA	CD4				nt		nt			Nt	nt
	CD8										
VB10.NEO	CD4										
	CD8										

Peptide and RNA vaccines induces primarily CD4 T cell responses, while VB10.NEO induces strong, and **dominating** CD8 responses to the identical neoepitope sequences

Non-targetd DNA vaccines induced a CD8 response towards 2 of 6 tested neoepitopes

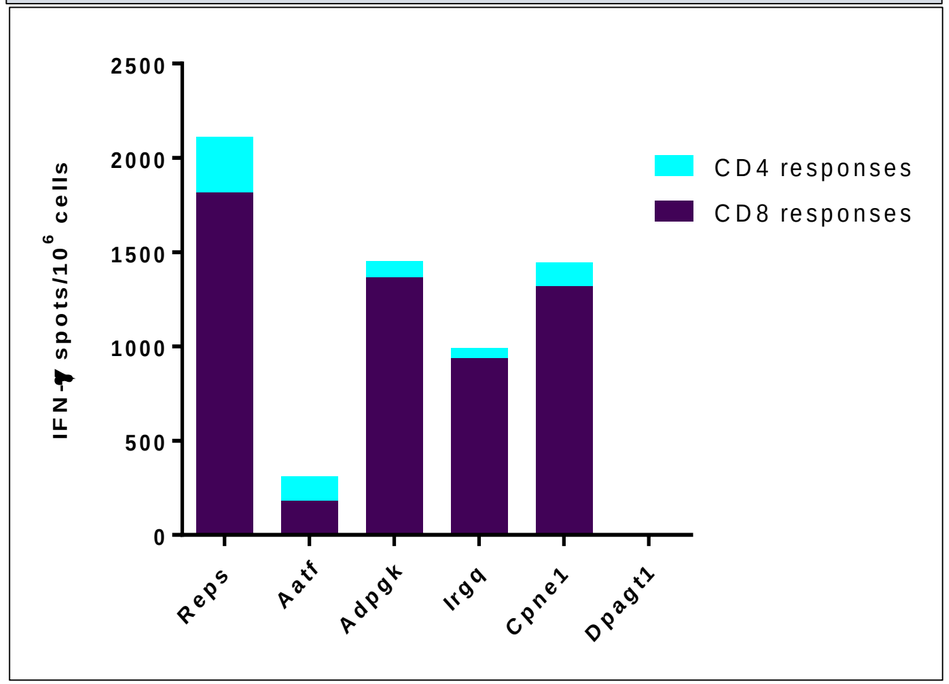
- Castle et al., 2012 and Kreiter et al., 2015
- Aurisicchio et al., 2019

Confirmation of VB10.NEO's unique ability to induce strong neoepitope-specific CD8 responses

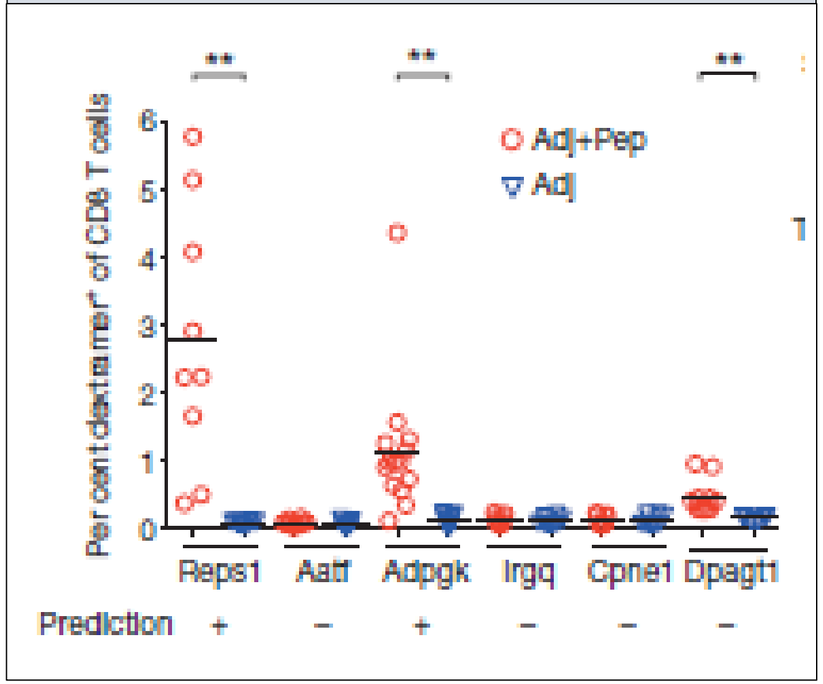
MC38 colon carcinoma

Yadav et al., 2014

VB10.NEO



Peptide + poly I:C + anti-CD40 mAb



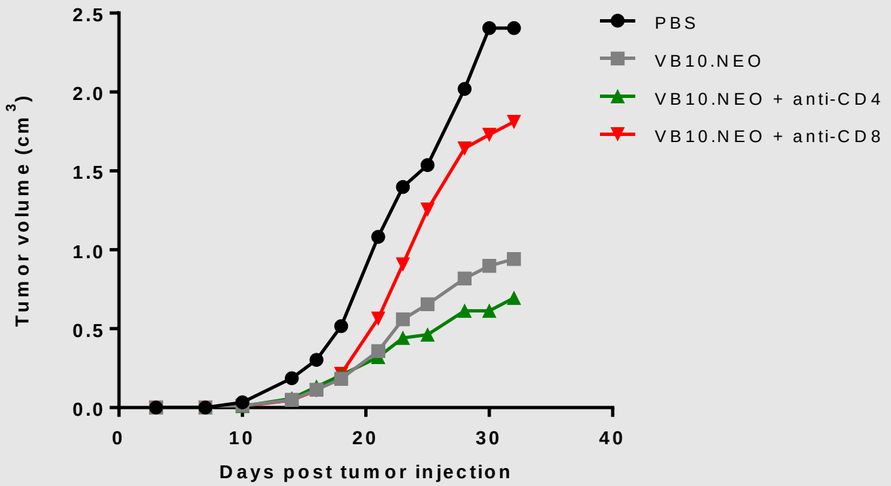
-VB10.NEO induces a strong CD8 T cell response, combined with a CD4 response **to 5 of 6** MC38 neoantigens.

-3 of these neoepitopes have been shown to be **non-immunogenic delivered as peptide + adjuvant**

-Confirmation of VB10.NEO's ability to induce stronger CD8 responses to neoantigens

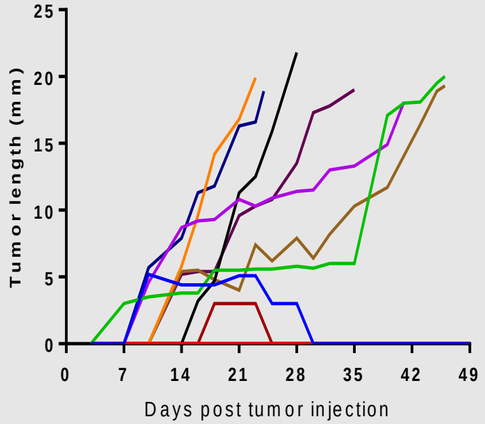
Neoepitope-specific CD8 T cells are crucial for tumour protection

Average, all groups

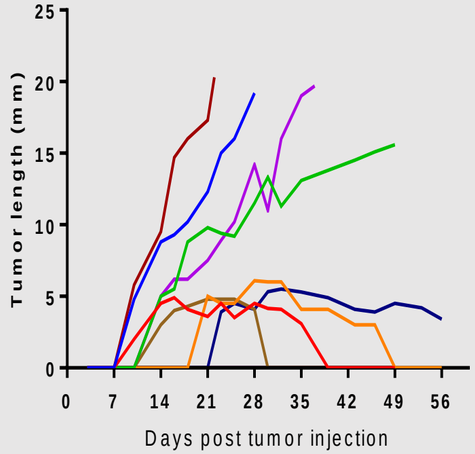


Individual growth curves

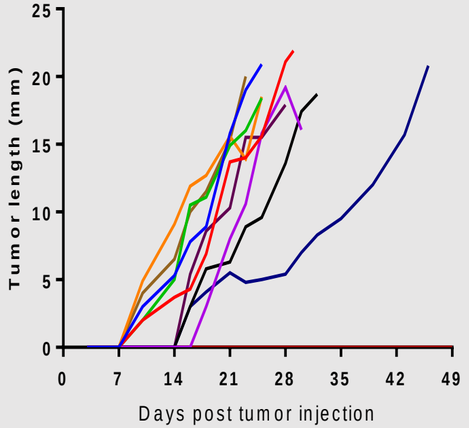
VB10.NEO



VB10.NEO + anti-CD4



VB10.NEO+ anti-CD8

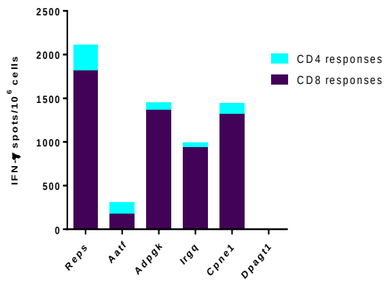


Depletion of CD8 T cells prohibit tumour protection in VB10.NEO vaccinated mice, indicating a crucial role of neoepitope-specific CD8 T cells for anti-tumour efficacy

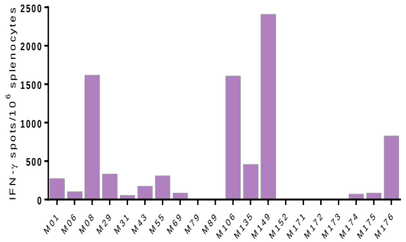
VB10.NEO proven to induce an effective anti-tumour response

VB10.NEO induce unique neoepitope-specific CD8+ T cell responses → T cells traffic to the tumor → Creates «hot» immune signatures in tumor-bearing mice → T cells in tumor are able to kill tumor cells *in vitro* → Complete tumour regression is observed *in vivo*

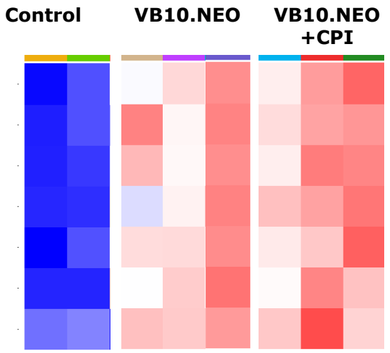
Neoepitope-specific CD8+ T cell response in spleen



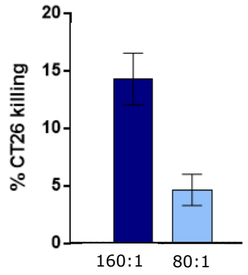
Neoepitope-specific T cell response in tumor



Influx of cytotoxic T cells in tumor (TILs)

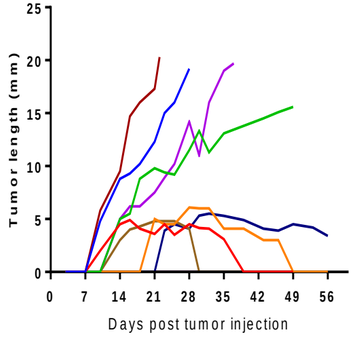


TILs recognize and kill tumor cells



Effector:target cell ratio

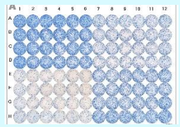
Tumor protective immune responses elicited in vaccinated mice



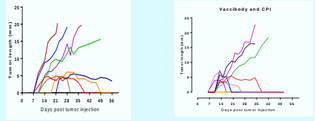
Development of NeoRANK™

In vivo mouse experiments

IFN-γ ELISpot (CD8/CD4)
- > 350 neoantigens
- 2 mouse strains
- 4 tumour models



Anti-tumour efficacy



Literature External data sets

NeoRANK™

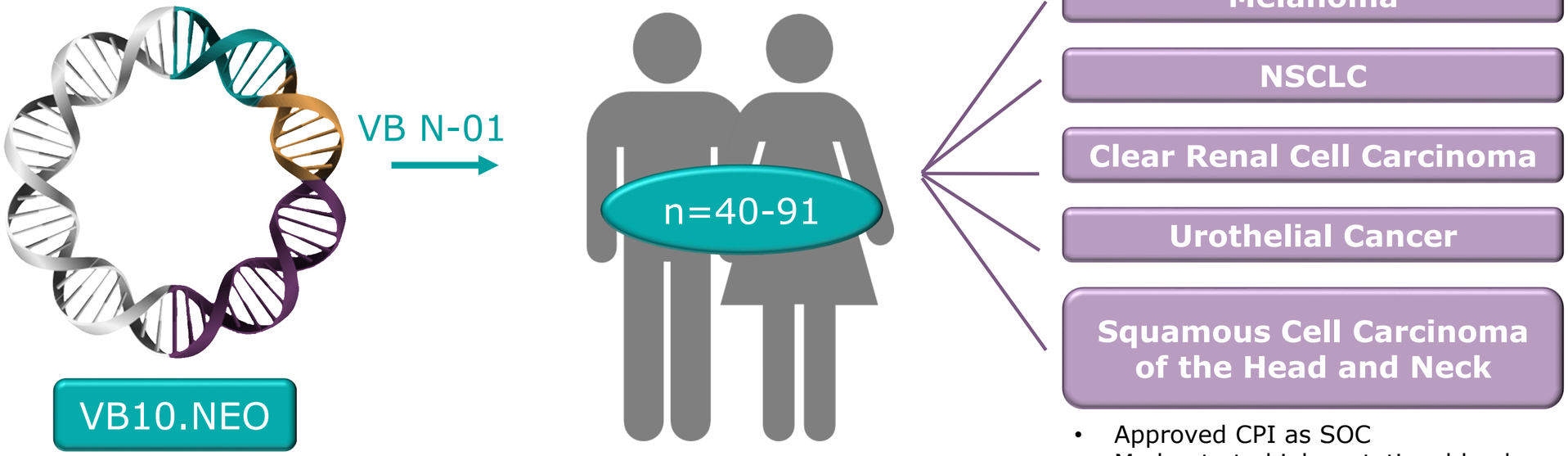
Neoantigen filtering and ranking
Trained and verified on *in vivo* mouse data

+++ criteria rel. for clinical response +++

VB10.NEO Patients

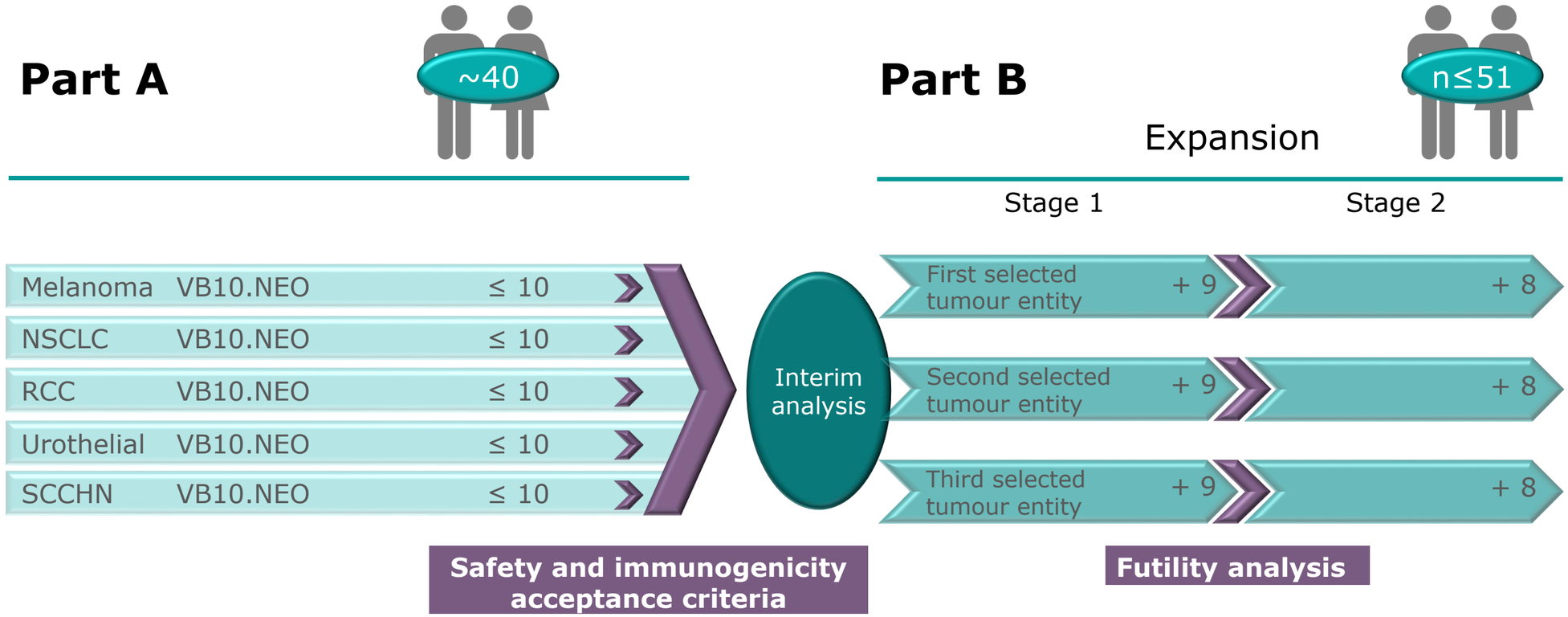
Clinical Trial VB N-01

VB N-01: An open labelled first human dose phase 1/2a study to evaluate safety, feasibility and efficacy of multiple dosing with individualised VB10.NEO immunotherapy in patients with locally advanced or metastatic melanoma, NSCLC, clear renal cell carcinoma, urothelial cancer or squamous cell carcinoma of head and neck, who did not reach complete responses with current standard of care immune checkpoint blockade



- Approved CPI as SOC
- Moderate to high mutational load

Study Design and Current Status, VB N-01

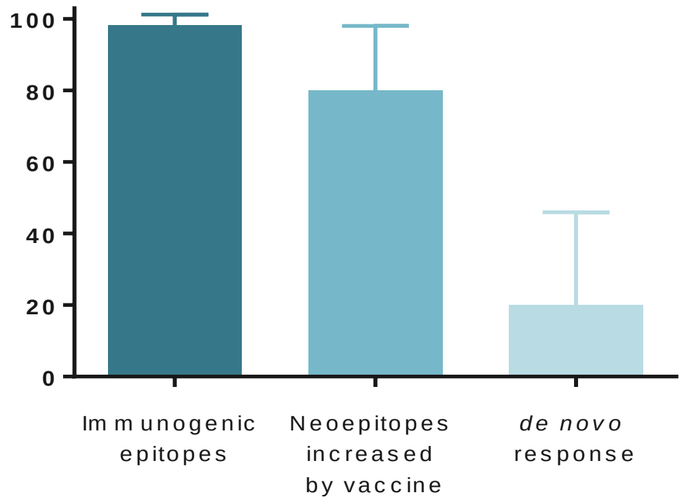


- 100% vaccine manufacturing success for all patients with a successful biopsy so far
- 20 neoepitopes selected for all patients in the trial

VB10.NEO induce immune responses to the majority of selected neoepitopes

Patient	Indication	TMB	#months on CPI before VB10.NEO	Disease at VB10.NEO start
A	SCCHN	Low	32	Relapsed
B	SCCHN	Low	15	stable
C	RCC	Low	18	stable

- First patients are all low TMB and with SD as best response to long-term CPI treatment.
- 1 patient progressed before VB10.NEO treatment.



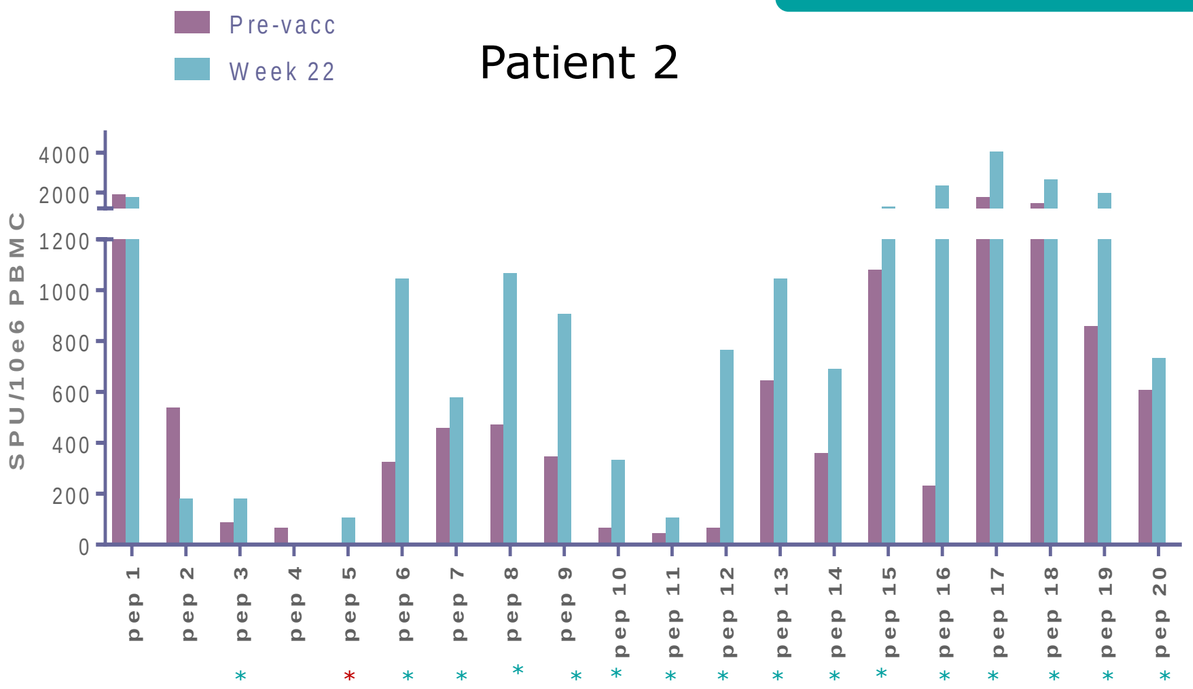
First 3 patients tested after 6 vaccinations:

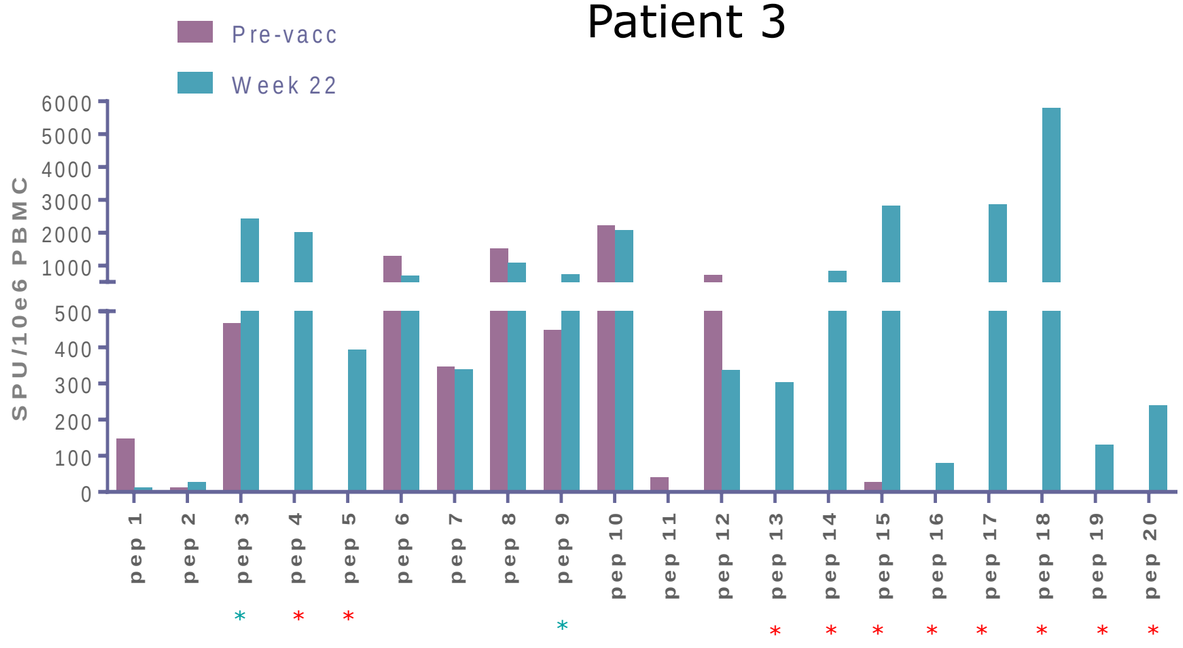
- High % of immunogenic neoepitopes selected with NeoSELECT prediction.
- Majority of neoepitopes increased by VB10.NEO
- Boosting pre-existing as well as *de novo* responses

VB10.NEO induces strong immune responses in SCCHN patients even with low TMB

2 Head & Neck patients (week 22)

de novo responses[3] in red



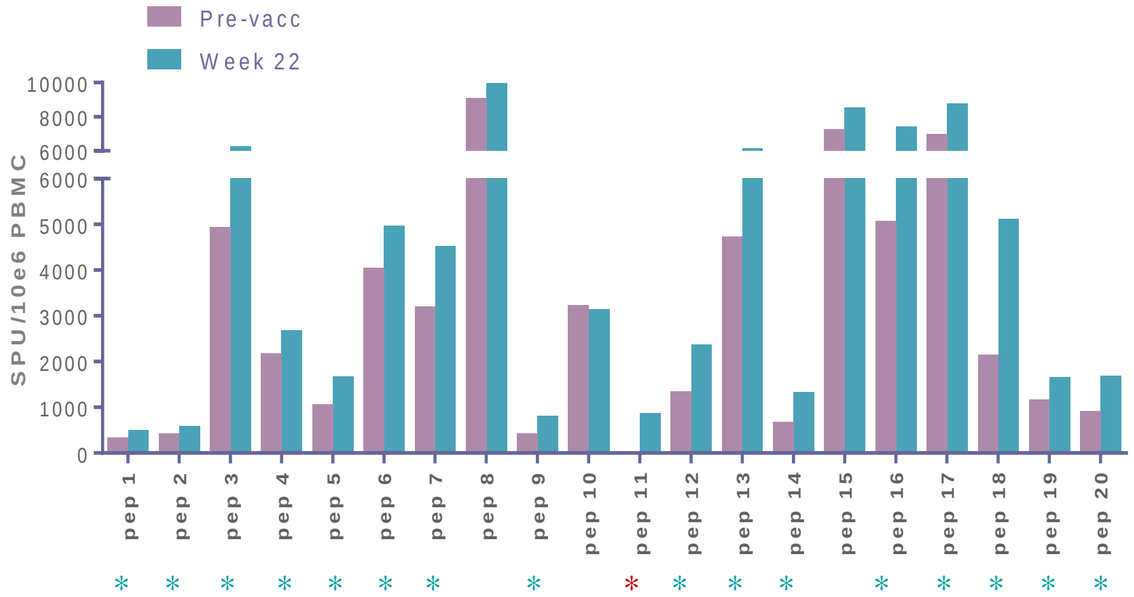


- Strongly increased T cell responses to the majority of the selected neoepitopes after VB10.NEO vaccination.
- Highest number of neoepitopes increased for patient 2 (85%), but biggest fold increase (~>1000 times) and highest number of *de novo* responses observed for patient 3 (83%).

VB10.NEO increases neoantigen-specific T cell responses in the two first RCC patient analysed after 6 vaccinations

Patient 1

de novo responses[3] in red

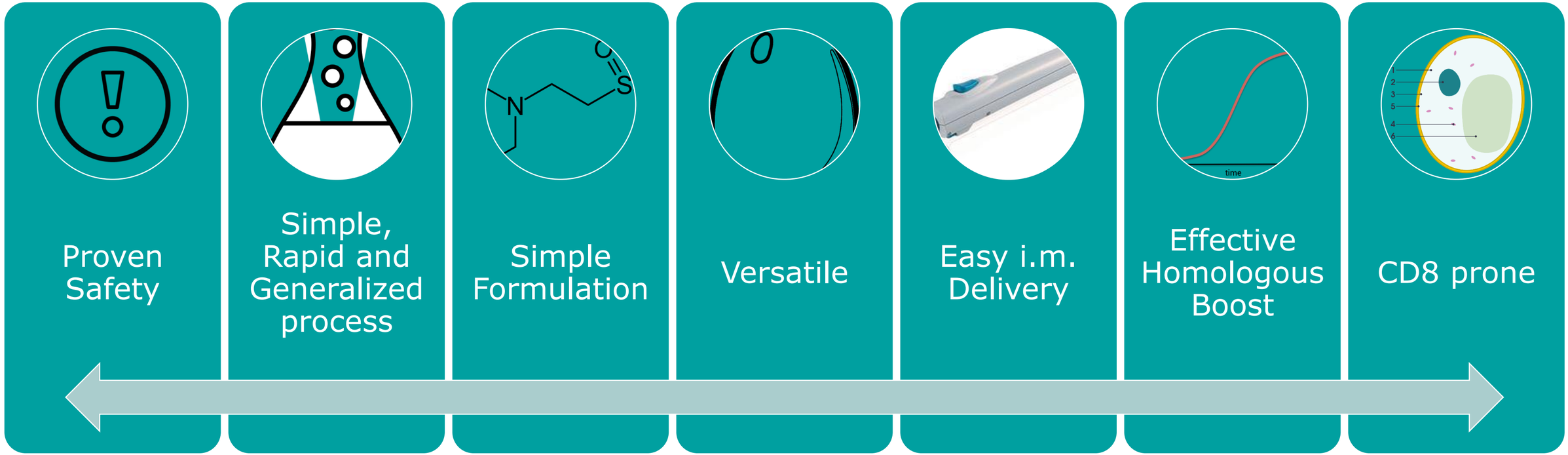


- RCC is also low on TMB. Few neoepitopes to select. Still strong neoantigen-specific immune responses detected.
- Very strong baseline response in this particular patient. One de novo repsonse.

Main findings and interesting questions

- Patients with stable disease after long-term CPI treatment seem to have low TMB.
- NeoSELECT has a strong ability to identify immunogenic neoepitopes.
-
- VB10.NEO is able to increase the immune response to the majority of the selected neoepitopes.
- The baseline response and the number of de novo responses were surprisingly different among the patients tested so far.
- Is boosting pre-existing T cell responses and/or induction of de novo responses the most important to improve clinical responses?
- How important is the breadth of the immune response?
- Is a certain level of T cells needed?

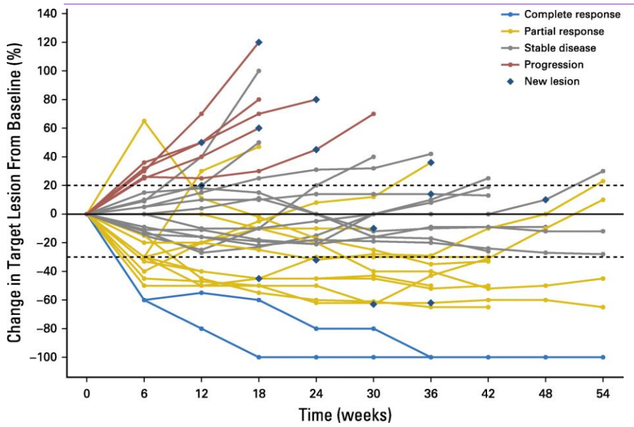
Naked DNA plasmid ideal for personalized manufacturing

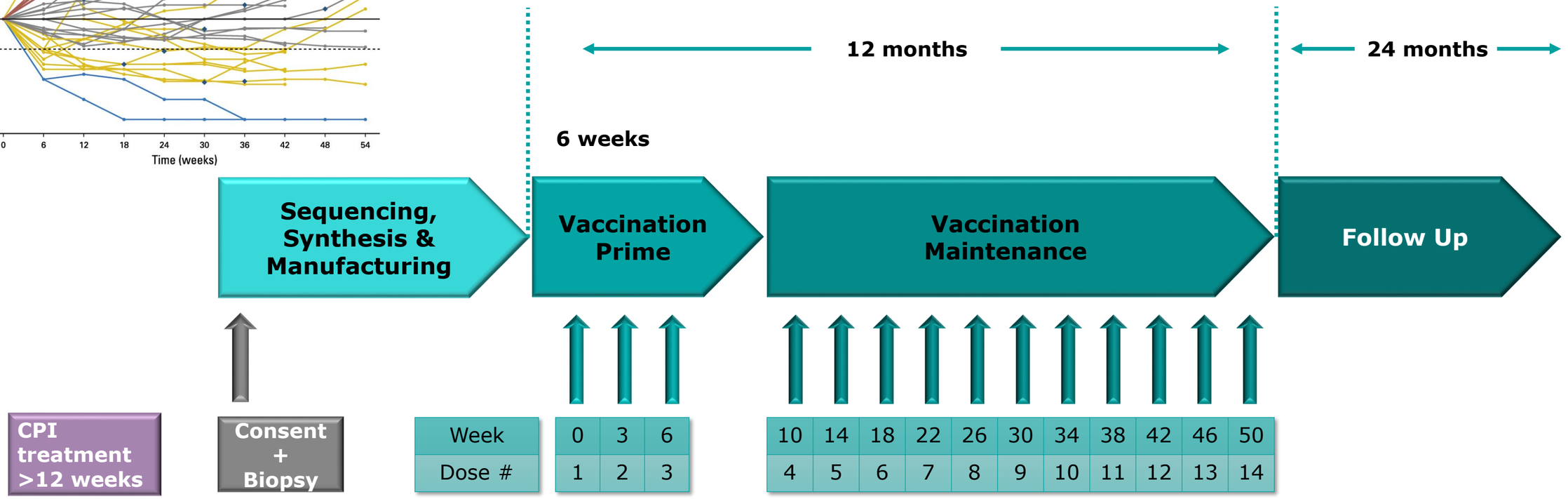


DNA plasmid is an ideal platform for bringing individualized neoantigen vaccines to the market as a viable product at reasonable COGS

100% success in manufacturing VB10.NEO with top 20 neoepitope choice

Unique Study Design and Treatment Schedule VB N-01

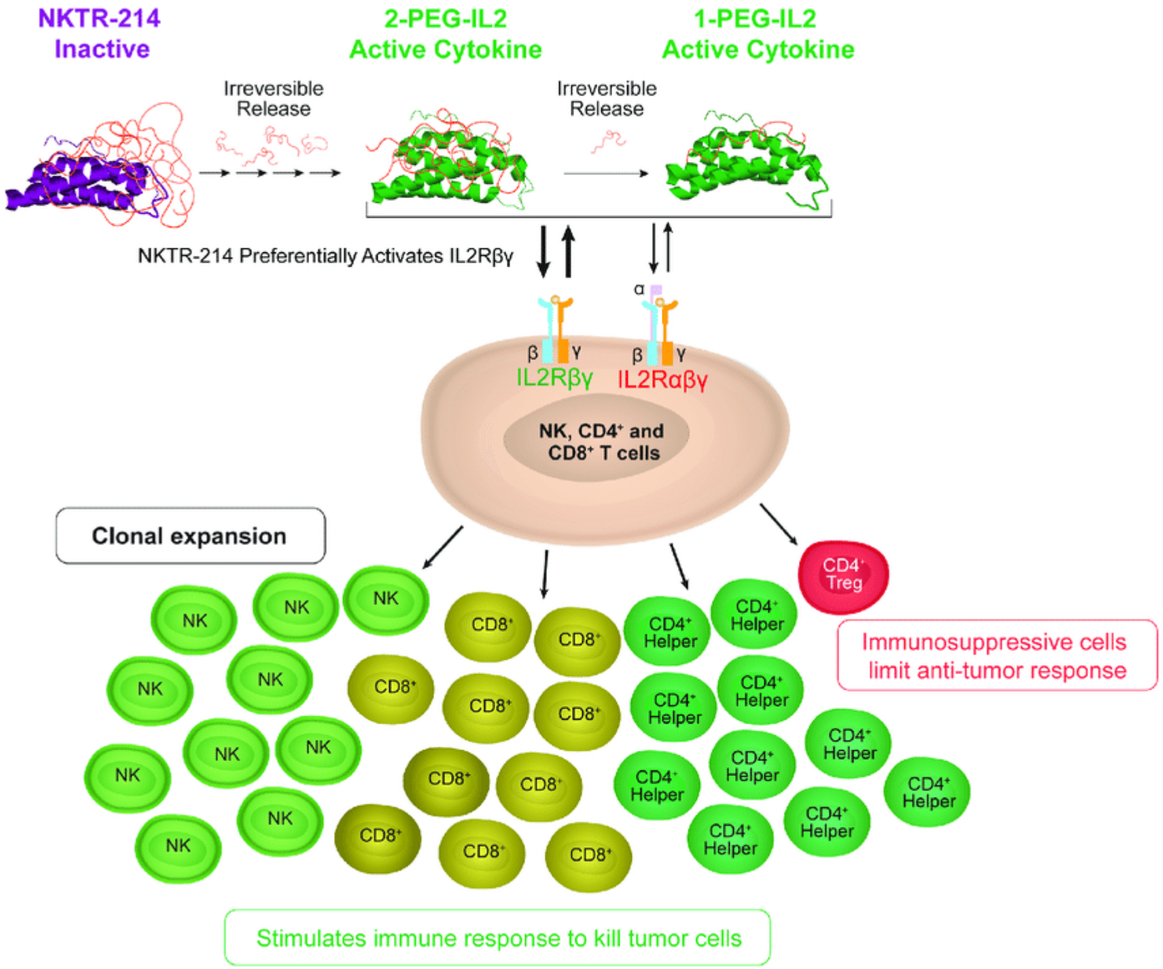




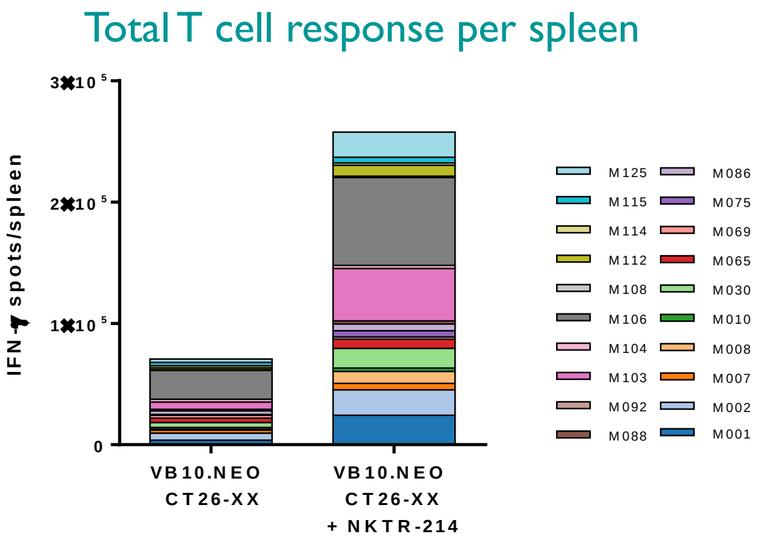
- Inclusion criteria: previous treatment with CPI for >12 weeks and stable disease (or partial response or mixed response) at enrollment. Limited tumour reduction expected from continuous CPI treatment only

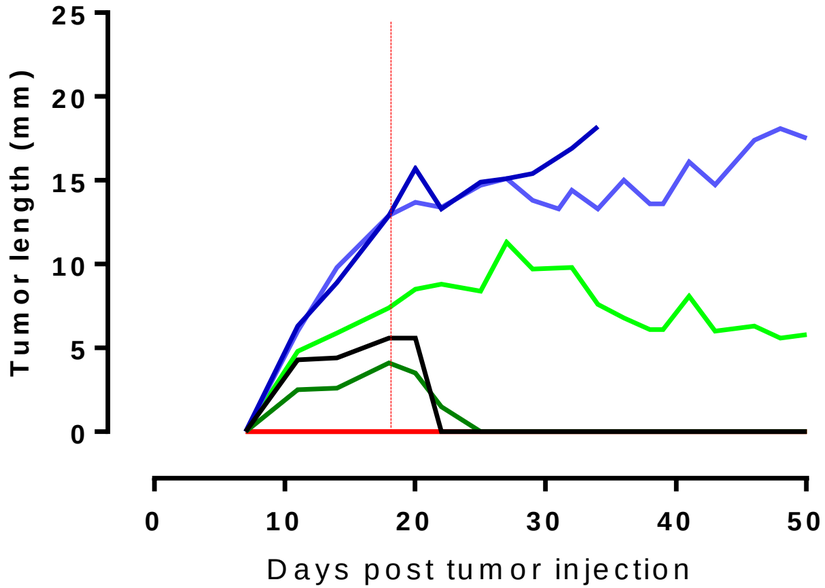
Tsimberidou et al., 2018

Bempegaldesleukin (NKTR-214) has the potential to significantly expand T cells



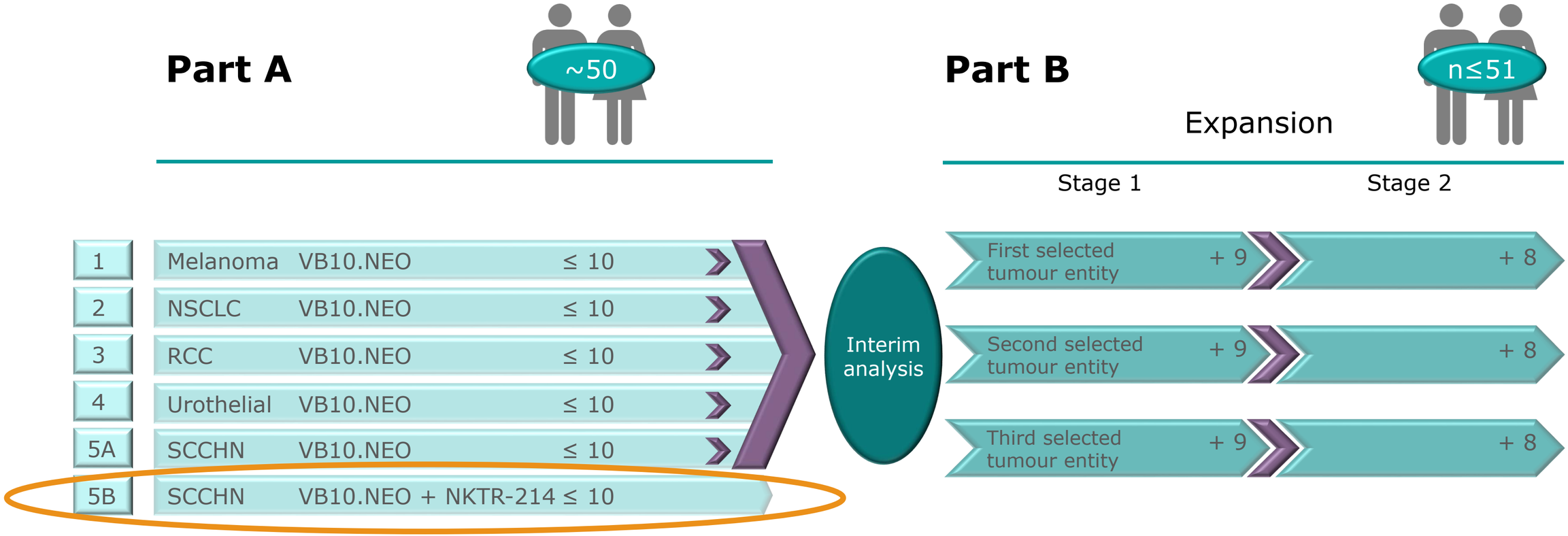
Combination of VB10.NEO and NKTR-214 greatly synergizes





- Combination of VB10.NEO and bempegaldesleukin (NKTR-214) synergizes to elicit greater breadth and depth of neoantigen-specific T cell responses than each individual treatment
- Adding NKTR-214 (from day 18) to a VB10.NEO and anti-PD-1 treatment induce rapid, complete and durable tumour regression of small tumours and long-lasting stabilization of large tumours.

Expansion of the study planned in 2019– add NKTR-214 and expansion cohorts



- First patient enrolled planned 2019
- Prepare for interim analysis first indication to trigger expansion

Vaccibody's Solution to Personalised Cancer Treatment

Insight from clinical experience

NeoSELECT™

-DNA: Robust, rapid, cost-effective, stable, safe

-up to 40 neoepitopes

-Needle-free

-Target, Attract, Mature, Deliver, Cross-present

-Rapid, strong, long-lasting

-CD8 dominated

1. Tumour biopsy and sequencing

2. Neoepitope selection (TSNA)

3. Vaccine manufacturing (n=1)

4. Vaccine administration and immunogenicity

Vaccibody provide a Rapid, Cost-effective and Efficacious solution

Vaccibody Dreamteam!

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