vaccibody

How the DNA Vaccine Format Used in a Novel Manner can Generate Potent CD8-Dominated Neoantigen-Specific T Cell Responses

Molecular Med TriCon
Neoantigen Based Immunotherapies
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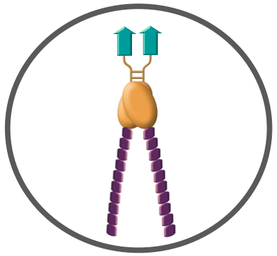
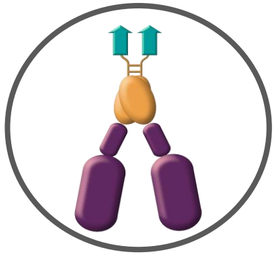
Vaccibody Product Pipeline

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		





The Workflow of Personalised Cancer Treatment

1. Tumour biopsy and sequencing

2. Neoepitope selection

3. Vaccine manufacturing (n=1)

4. Vaccine administration and immunogenicity

Rapid, cost-effective, efficacious

Vaccibody – Proprietary Vaccine Technology Platform

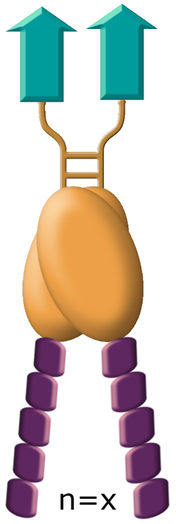
The Vaccibody Technology Platform was developed based on the concept of **targeting antigen to APC** in order to create more efficacious vaccines.

Exchangeable DNA Cassette

Vaccibody DNA Vaccine Plasmid

VB10.NEO

In vivo expression



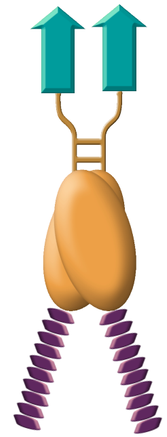
Vaccibody in Protein Format

Target to Antigen Presenting Cell

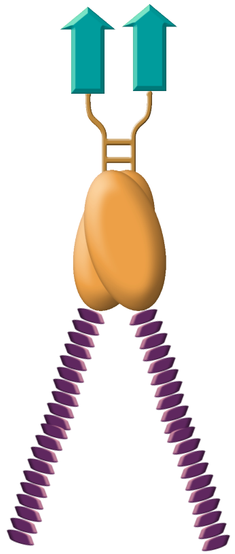
Dimerization for crosslinking target receptor

Antigen moiety

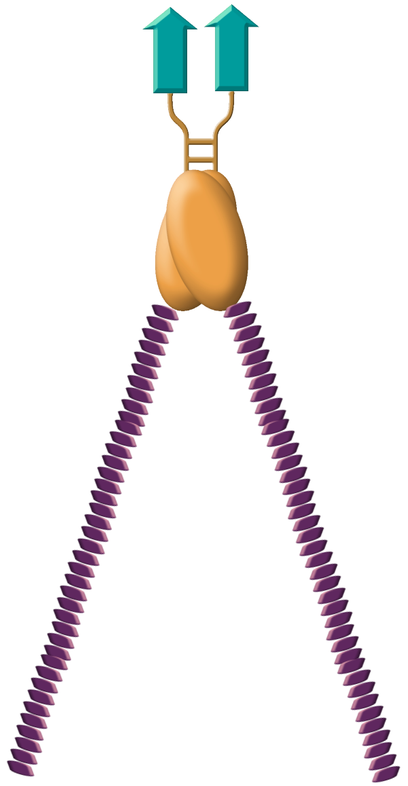
VB10.NEO – A Robust Vaccine Format



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

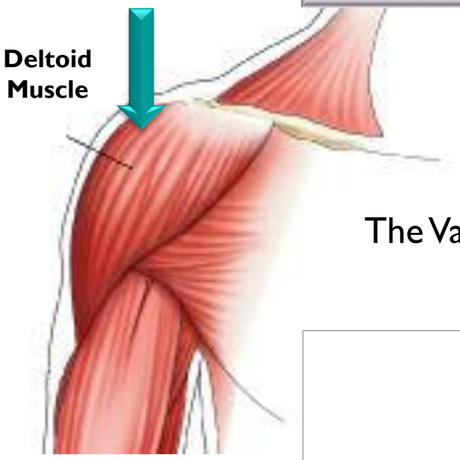
Mechanism of action: Intrinsic adjuvant for direct targeting

Administration (i.m.) of DNA plasmid

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

Target – Attract – Mature – Deliver – Cross-present

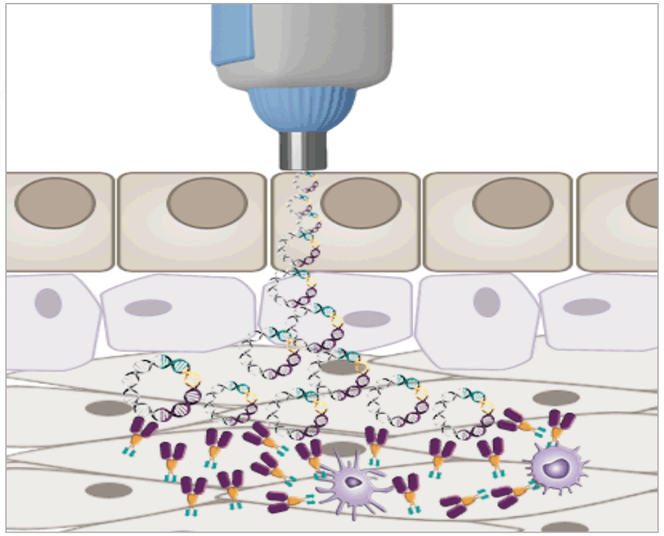
Skewing the immune system to a CD8+ killer T-Cell response

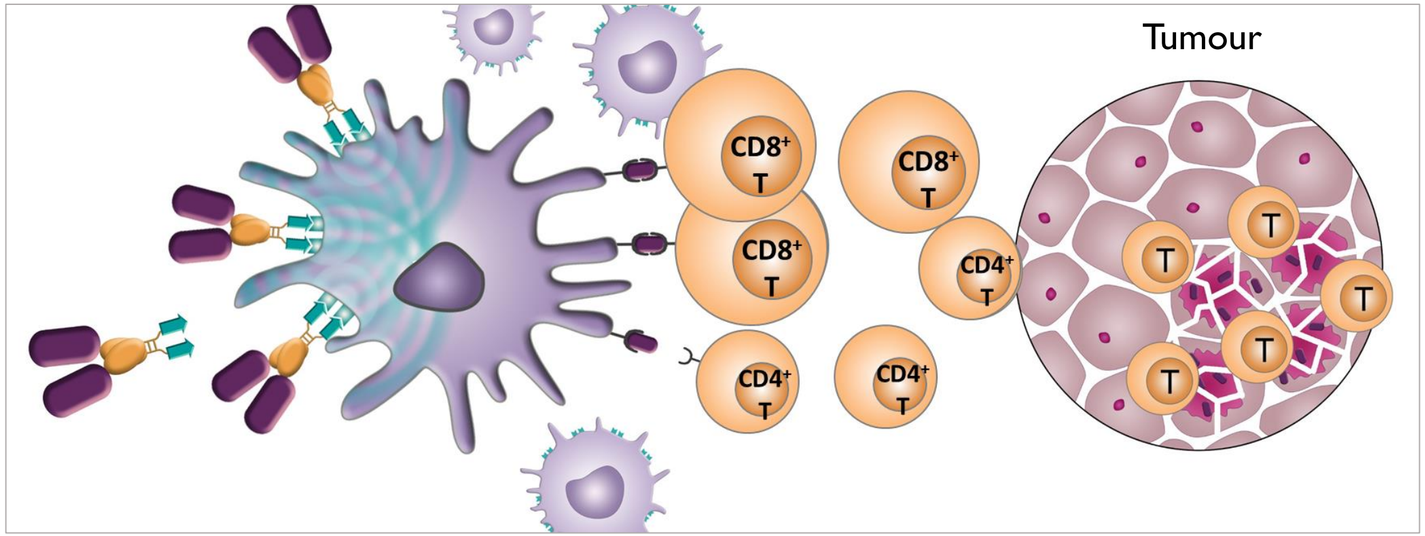


The Vaccibody uses the muscle cell as a factory

- 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**

PharmaJet®

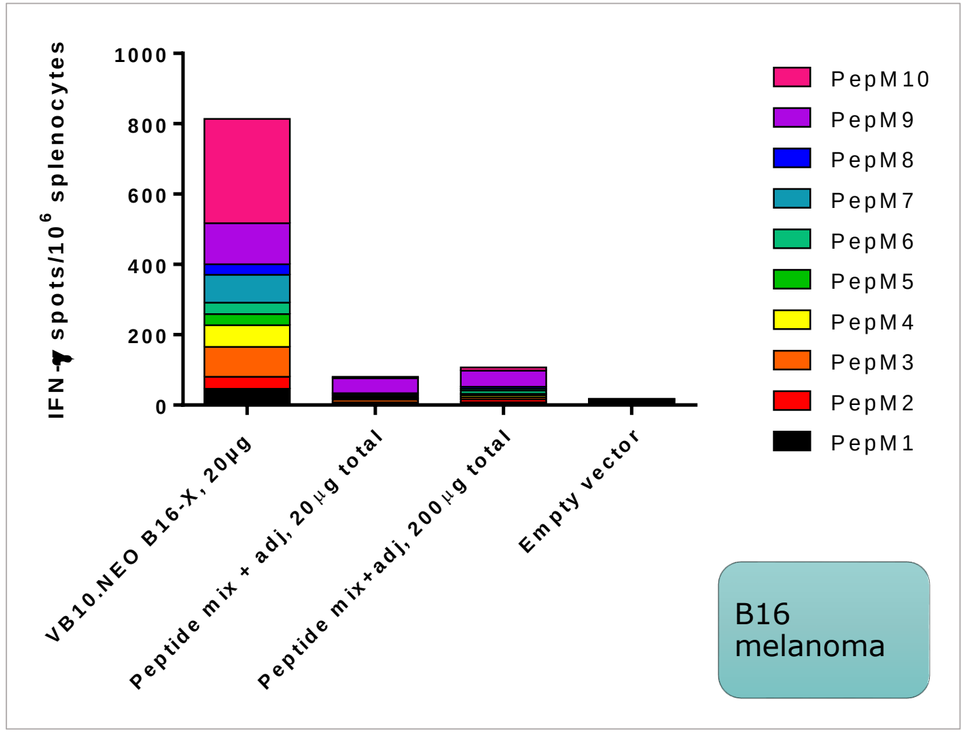




Targeting is elicited by the MIP-1α chemokine

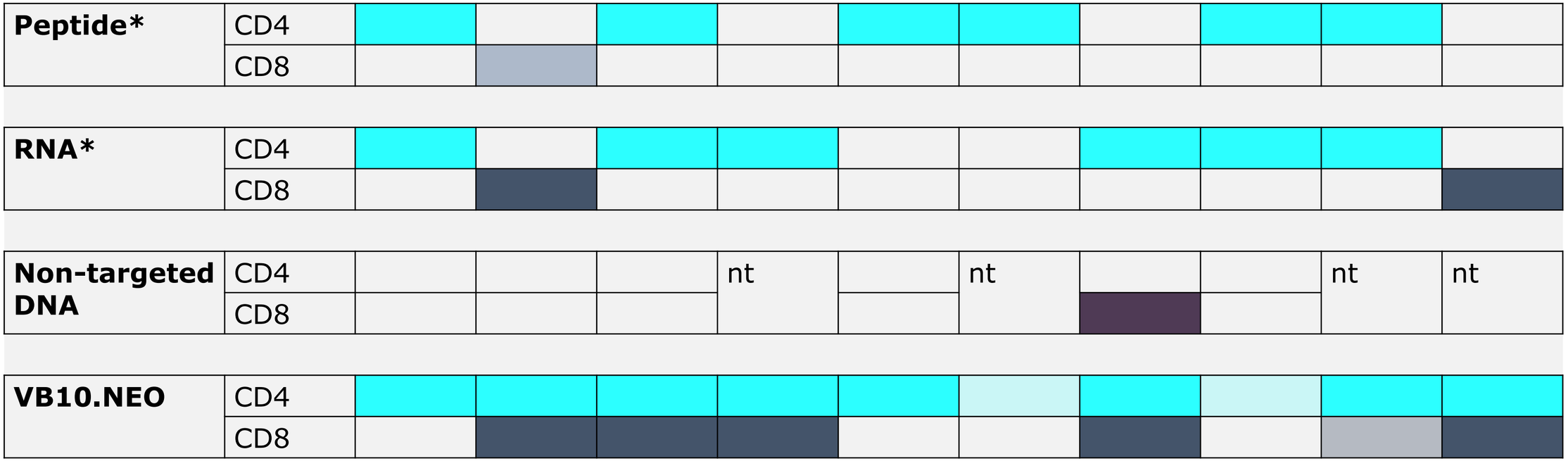
VB10.NEO induces Rapid, Broad and Strong responses to multiple Neoepitopes by single Vaccination

- VB10.NEO induces a broader and stronger response than Peptide + Poly (I:C) Adjuvant vaccines after a single immunization.
- VB10.NEO vaccinated animals respond to all 10 neoepitopes after a single immunization.
- Immunodominant neoepitopes differ between delivery vehicles



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

B16 melanoma



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

Non-targetd DNA vaccines induced a CD8+ response towards 1 of 6 tested neoepitopes

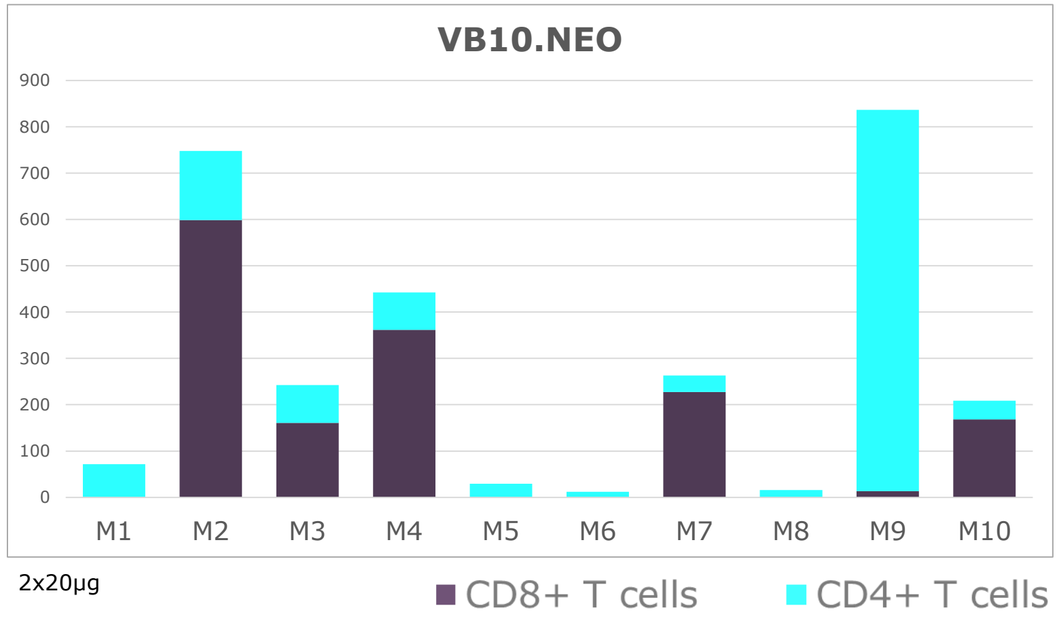
- Castle et al., 2012 and Kreiter et al., 2015
- Aurisicchio et al., 2019

VB10.NEO leads to a unique CD8+ dominated neoepitope response

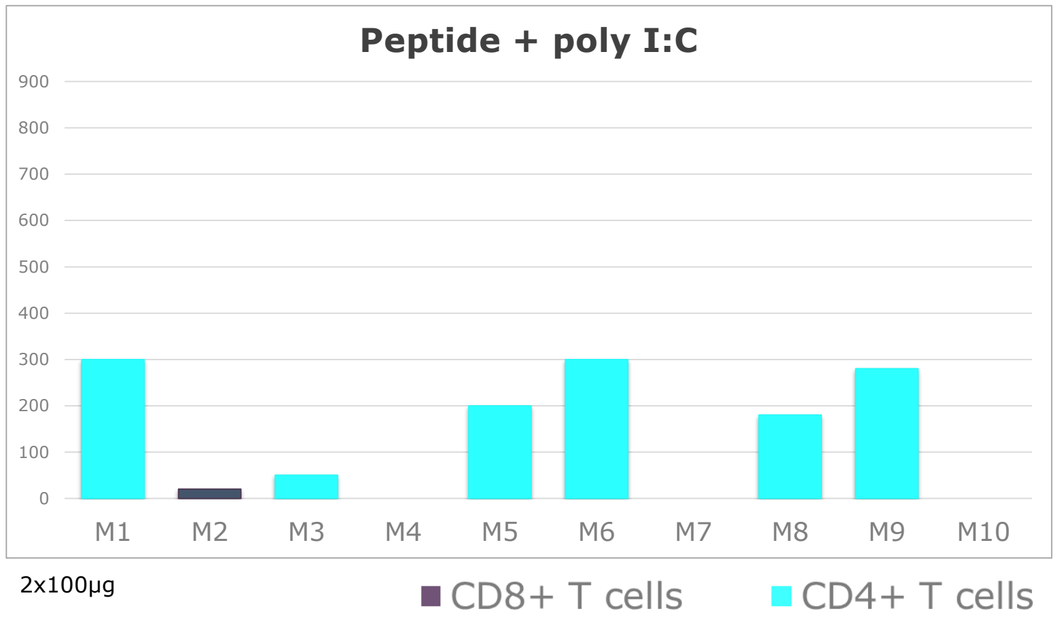
VB10.NEO induces a **strong, broad** immune response **dominated by CD8+** T cells

B16 melanoma

Peptide + poly I:C vaccination has been reported to induce responses **dominated by CD4+** T cells



2x20µg



2x100µg

VB10.NEO induces strong, dominantly CD8+ T cell response to identical neoepitopes that induces **no or weak** immune response if delivered as peptide vaccine

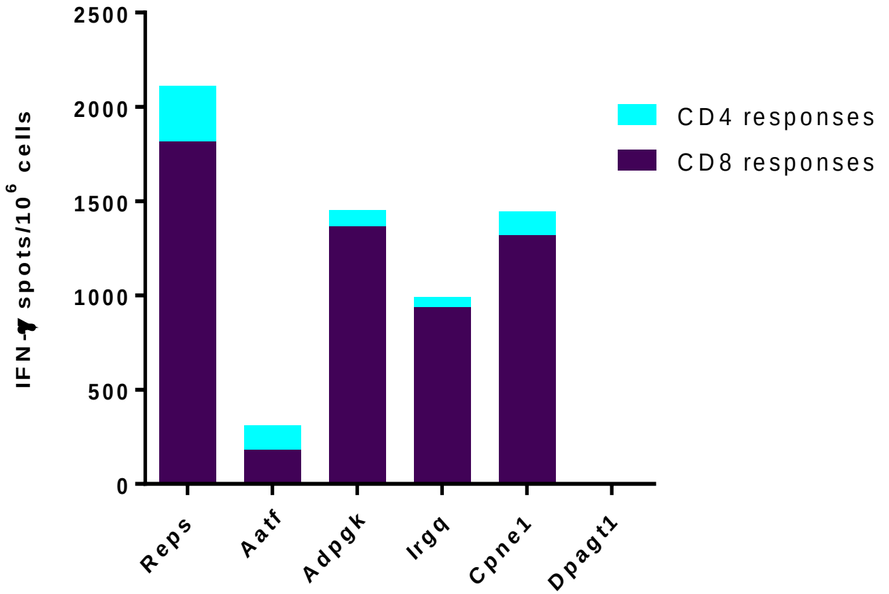
- Castle et al., 2012 and Kreiter et al., 2015-adapted figure based on B16 melanoma results

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

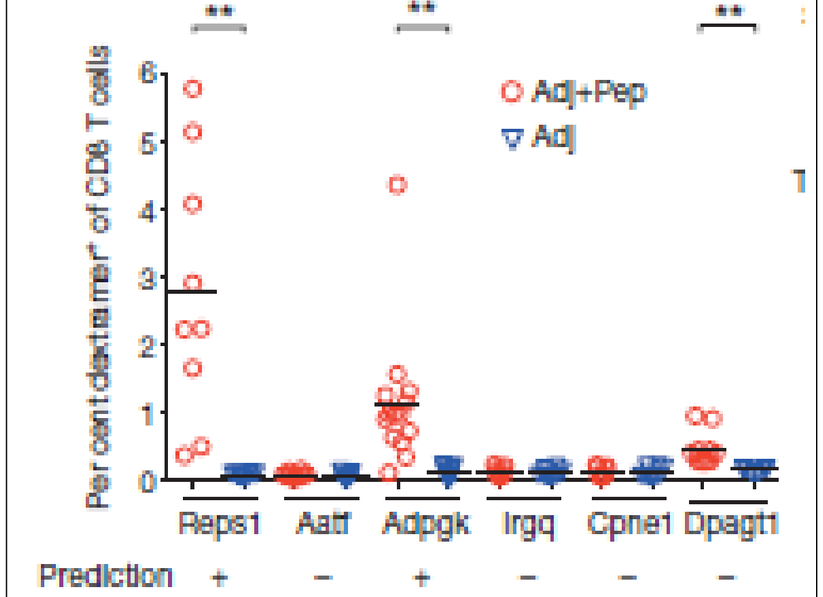
MC38 colon carcinoma

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.

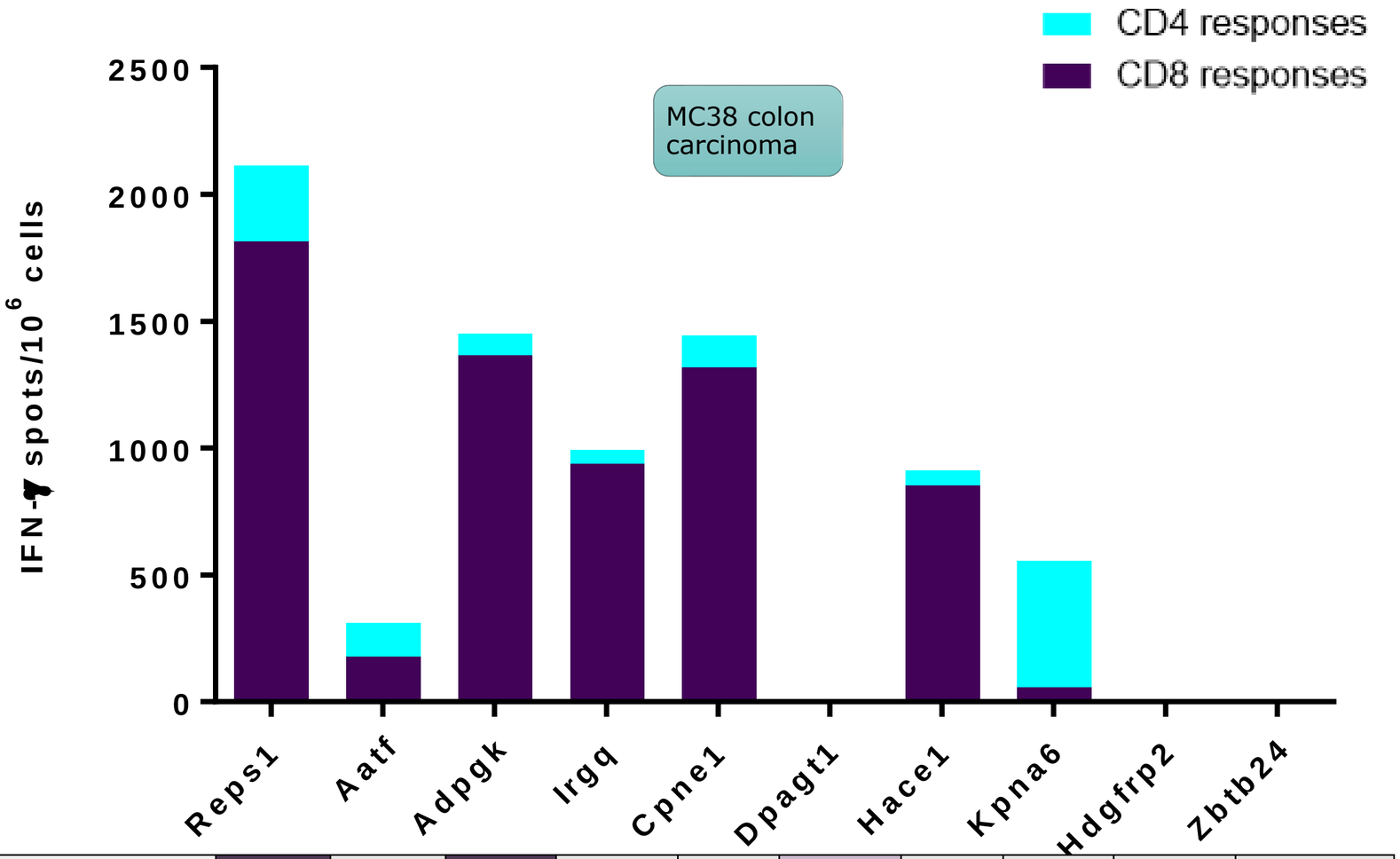
- 3 of these neoepitopes have been shown to be **non-immunogenic delivered as peptide + adjuvant**

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

Targeting of VB10.NEO to chemokine receptors is important for this unique ability to induce an immune response to multiple neoepitopes

DNA vaccine delivery alone is not explaining the ability to induce strong CD8 dominated immune responses to a higher number of neoantigens.

Vaccibody's unique *targeting* mechanism is essential for this observed feature.



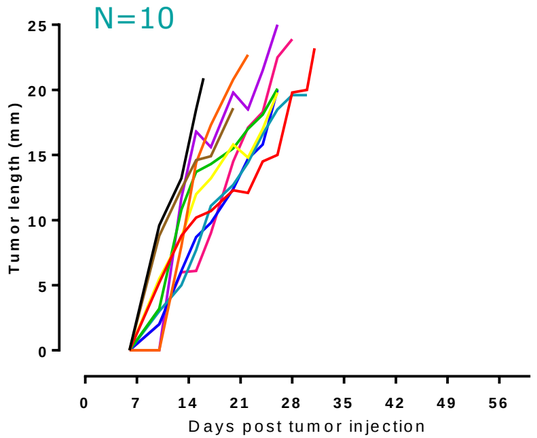
Peptide*	+	-	+	-	-	+	nt	nt	nt	nt
Non-targeted DNA	+	-	+	nt	-	nt	+	-	-	-

Yadav et al., 2014
Aurisicchio et al., 2019

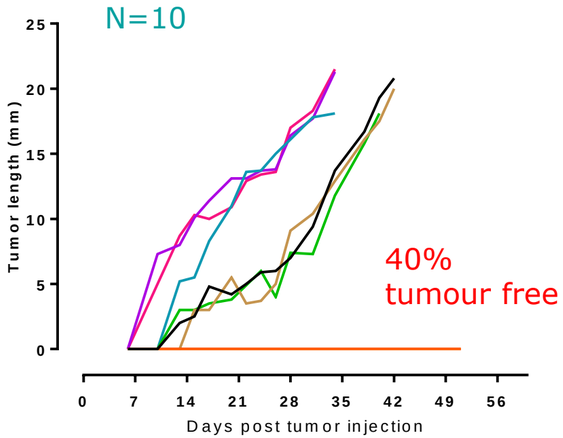
Vaccibody Induces Tumor Protection as Monotherapy

CT26 colon carcinoma model

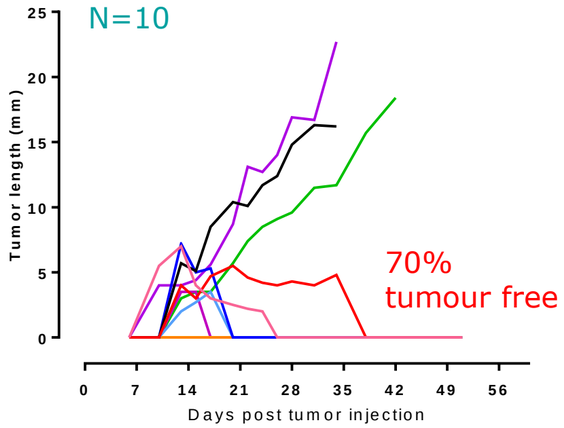
Control



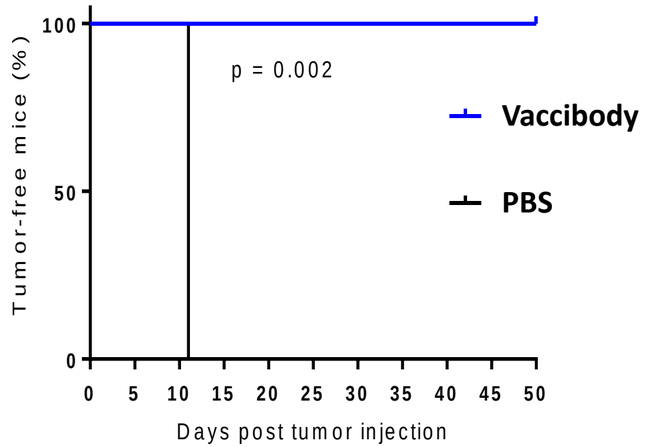
Vaccibody Monotherapy



Vaccibody Combination Therapy



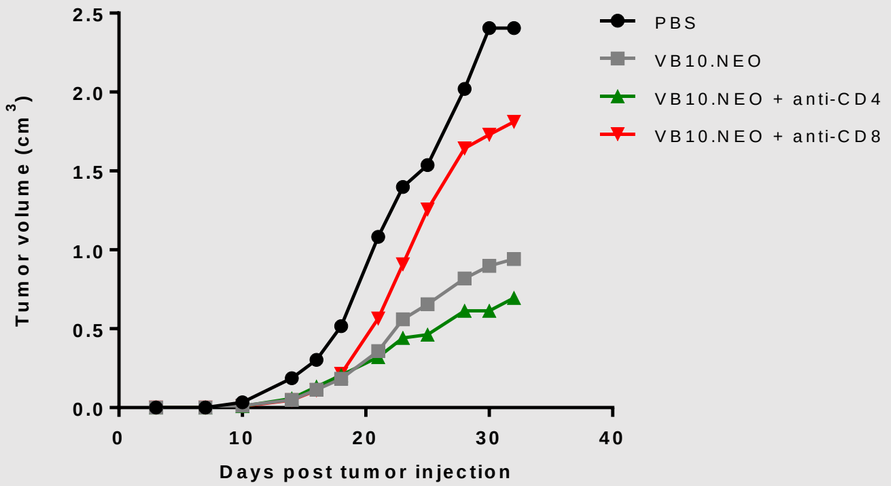
Re-challenged mice are protected



- Vaccibody vaccination induces strong CD8+ T cell responses and **tumour protection as Monotherapy**
- Combination with anti-PD-1 immunotherapy induced enhanced anti-tumour responses in mice involving **complete tumour regression** of large, established tumours
- **Long-term memory responses** ensure effective anti-tumour responses after a 2nd tumour challenge in surviving mice with no sign of tumour growth

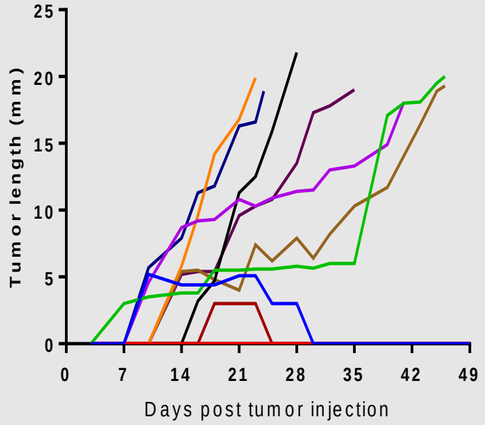
Neoepitope-specific CD8+ T cells are crucial for tumour protection

Average, all groups

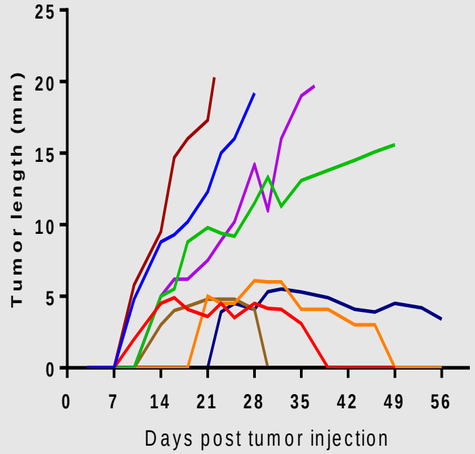


Individual growth curves

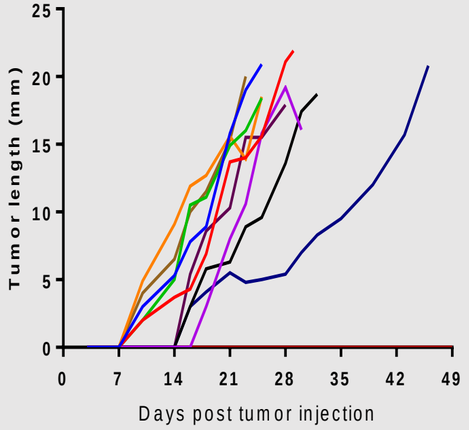
VB10.NEO



VB10.NEO + anti-CD4

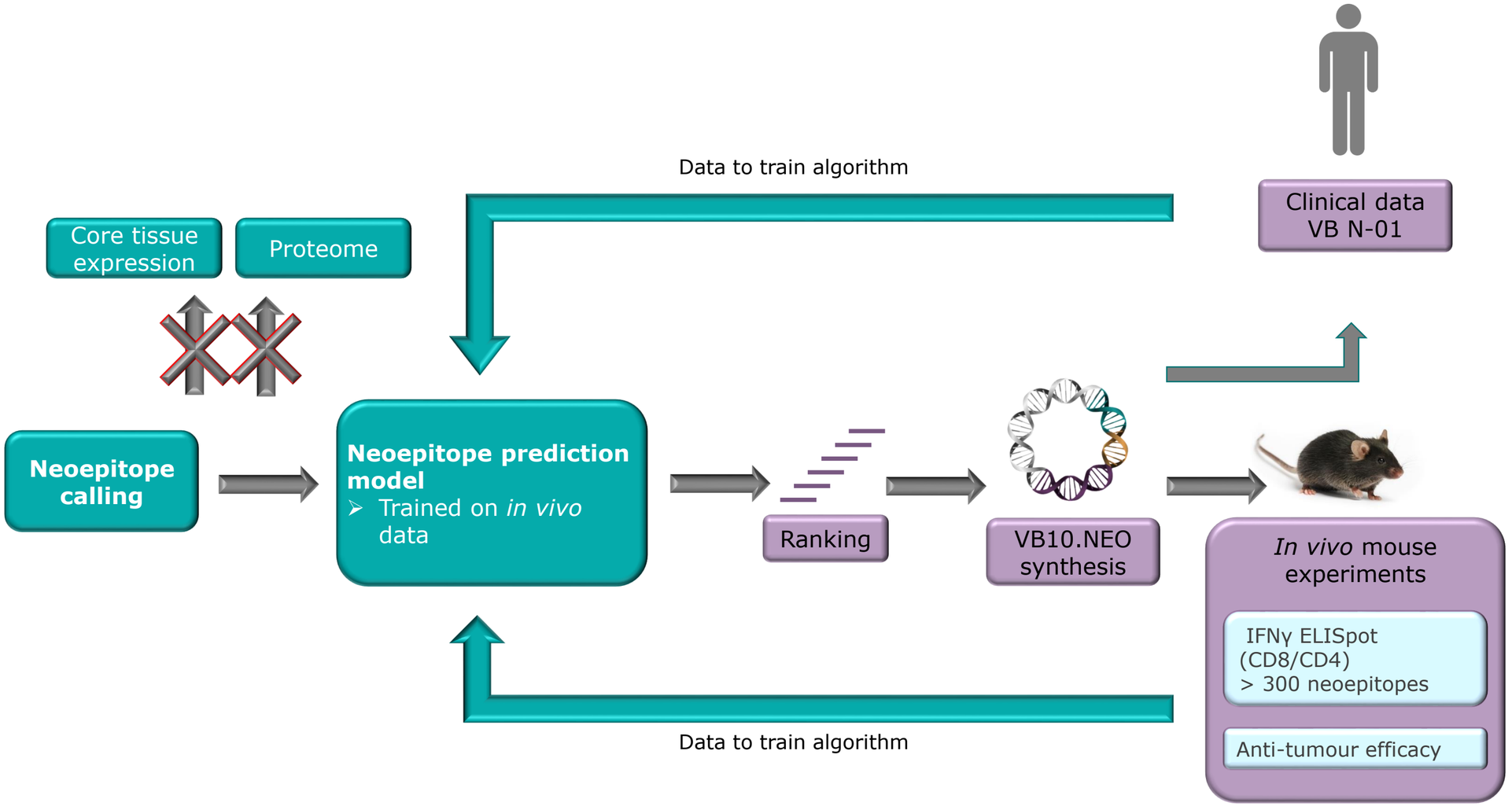


VB10.NEO+ anti-CD8

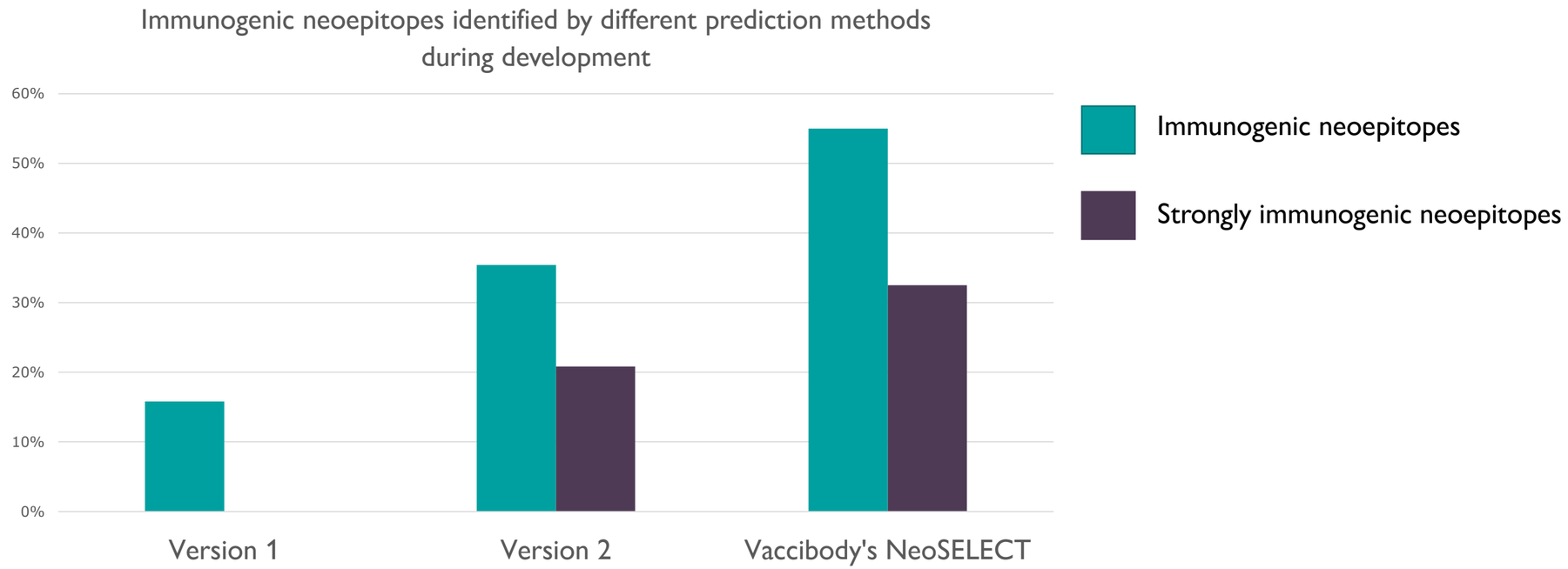


Depletion of CD8+ T cells prohibit tumour protection in VB10.NEO vaccinated mice, indicating a crucial role of neoepitope-specific CD8+ T cells for anti-tumour efficacy

Developing VB10.NEO specific Neoepitope Selection



Successful development of a strong proprietary neoepitope selection method NeoSELECT™



- Vaccibody has since 2017 successfully developed a proprietary neoepitope selection method able to identify a high number of immunogenic neoepitopes when used in VB10.NEO vaccines
- Majority of the induced responses are CD8+ restricted (measured ex vivo) with latest version
- This method, NeoSELECT, is used in the VB N-01 clinical trial

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®		
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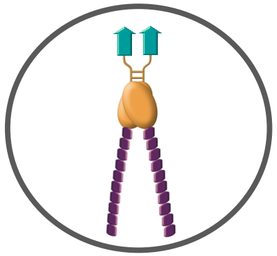
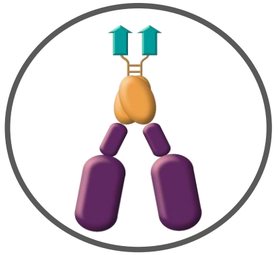
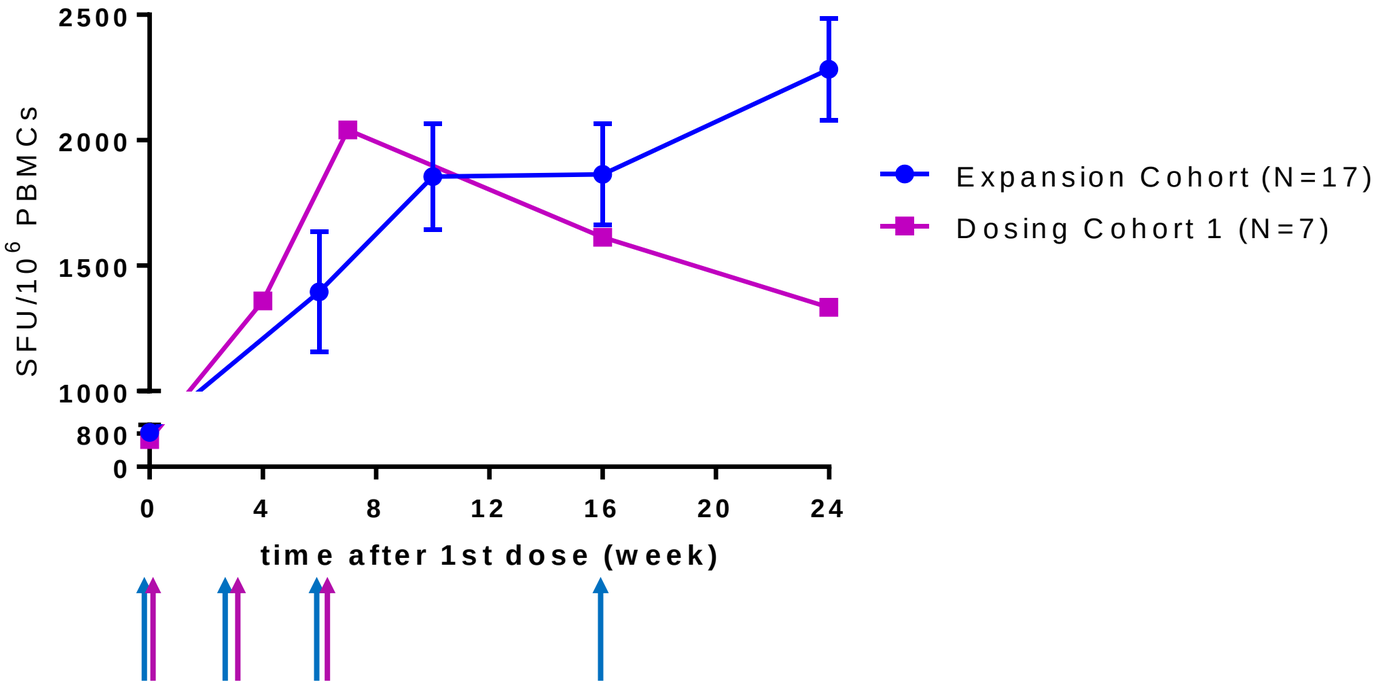
CERVICAL	VB10.16 + Atezolizumab (CPI)*		Roche		





Tecentriq® (Atezolizumab) is Roche's proprietary anti-PD-L1 checkpoint inhibitor (CPI)

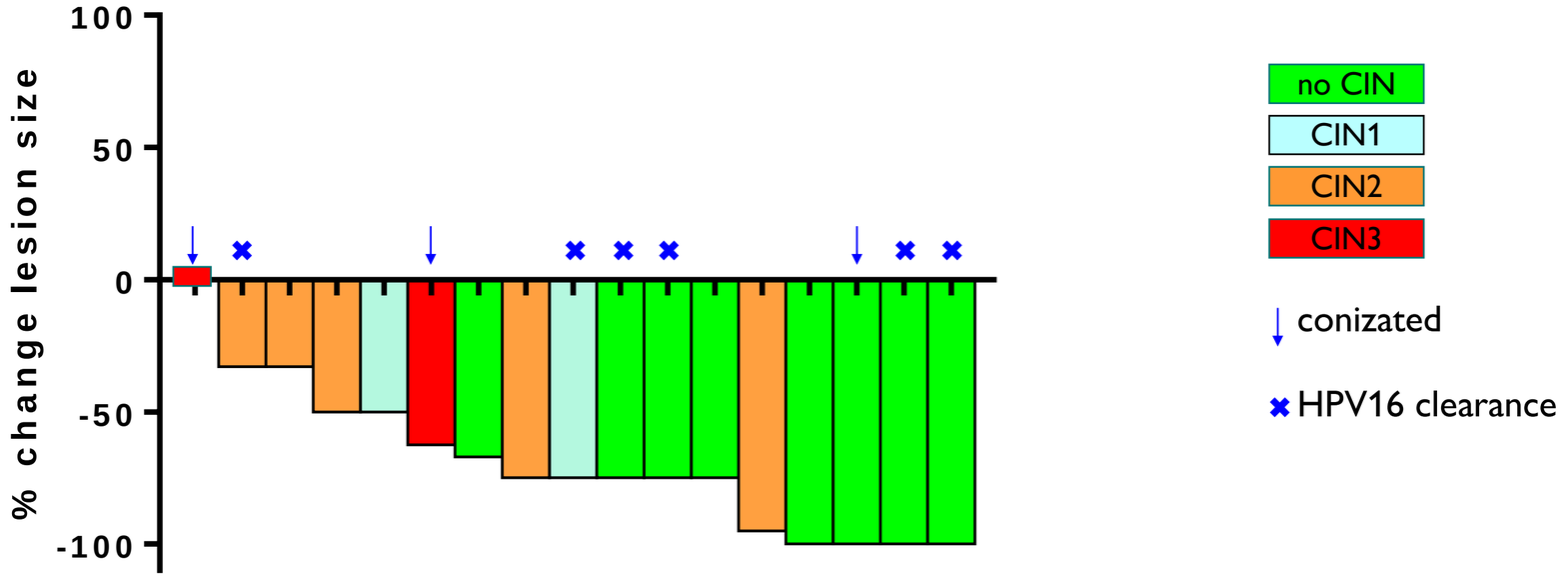
Strong, long-lasting immune responses elicited to HPV16, VB C-01



- The vaccination regiment from cohort 1 (week 0, 3 and 6) plus a booster vaccination at W16 was introduced in phase IIa
- 16 of 17 patients (94%) from phase IIa elicited increased HPV16-specific T cell responses after vaccination with VB10.16.
  - Rapid, strong and long-lasting

Promising clinical efficacy with excellent safety, VB C-01

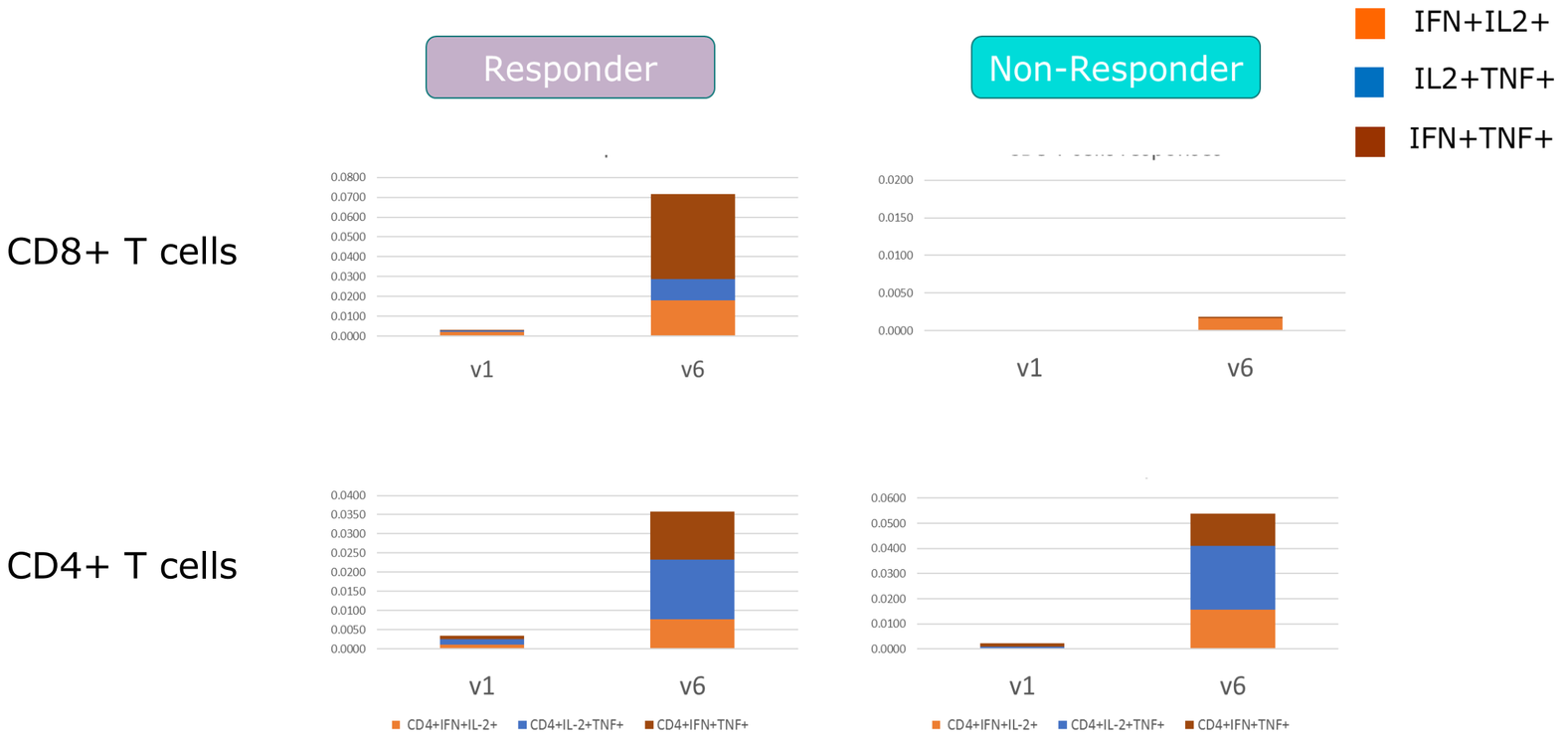
Best response data
(At enrollment: 10 CIN3 and 7 CIN2 patients)



VB10.16 as a monotherapy in HPV16-positive, precancerous cervical lesions induces:

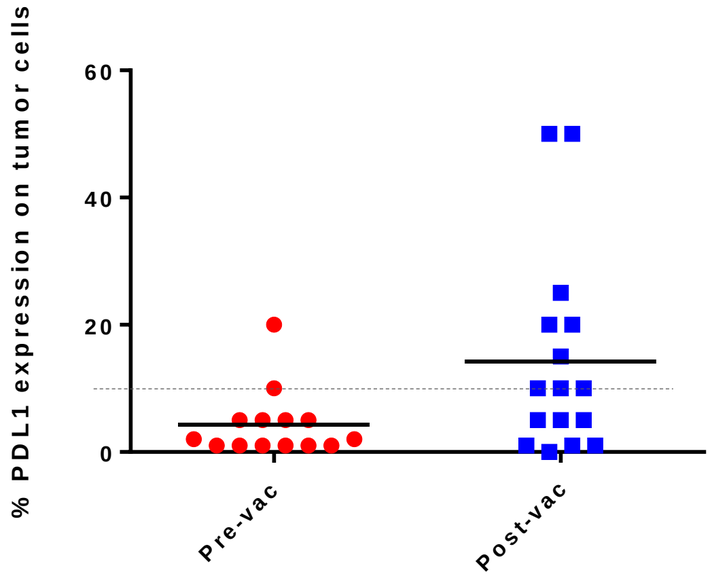
- Lesion size reduction in all patients followed >4 months
- CIN regression to CIN1 or no CIN in 10 patients
- HPV16 clearance in 6 patients

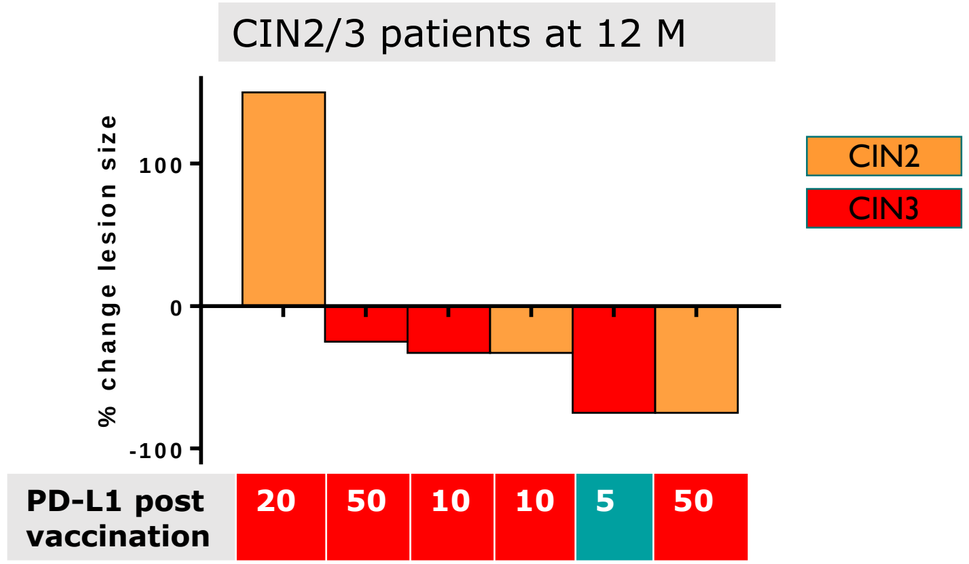
VB C-01: Strong multi-functional CD8+ and CD4+ T cell responses induced CD8+ T cell responses linked to clinical benefit



- In patients with CIN regression and HPV clearance, induction of multi-functional CD8+ T cells were significantly induced compared to non-responders.
- In contrast, CD4+ responses were similarly induced in all patients tested.

VB10.16 upregulates PD-L1, suggesting beneficial effect of combination therapy





- 5 of 6 patients that were CIN2/3 after completing the study (12M) showed **upregulation of PD-L1** ≥10%
- PD-L1 is upregulated by a strong local T cell response and may inhibit an efficacious long-term immune response
- Anti-PD-1/PD-L1 inhibitors blocks the brake and activates the immune system to attack PD-L1+ tumour cells
- VB10.16 induces a strong T cell response and creates a target for PD-1/PD-L1 inhibitors. Thus, there is a strong rationale for combination of VB10.16 with an anti-PD-1/PD-L1 checkpoint inhibitor to improve its effect, especially in PD-L1 negative patients

CPI: checkpoint inhibitor

VB C-02: combination of VB10.16 & Atezolizumab (Tecentriq™) in patients with advanced or recurrent, non-resectable HPV16+ cervical cancer

Advanced or Recurrent, Non-Resectable HPV16-Positive Cervical Cancer

12 months

6 weeks

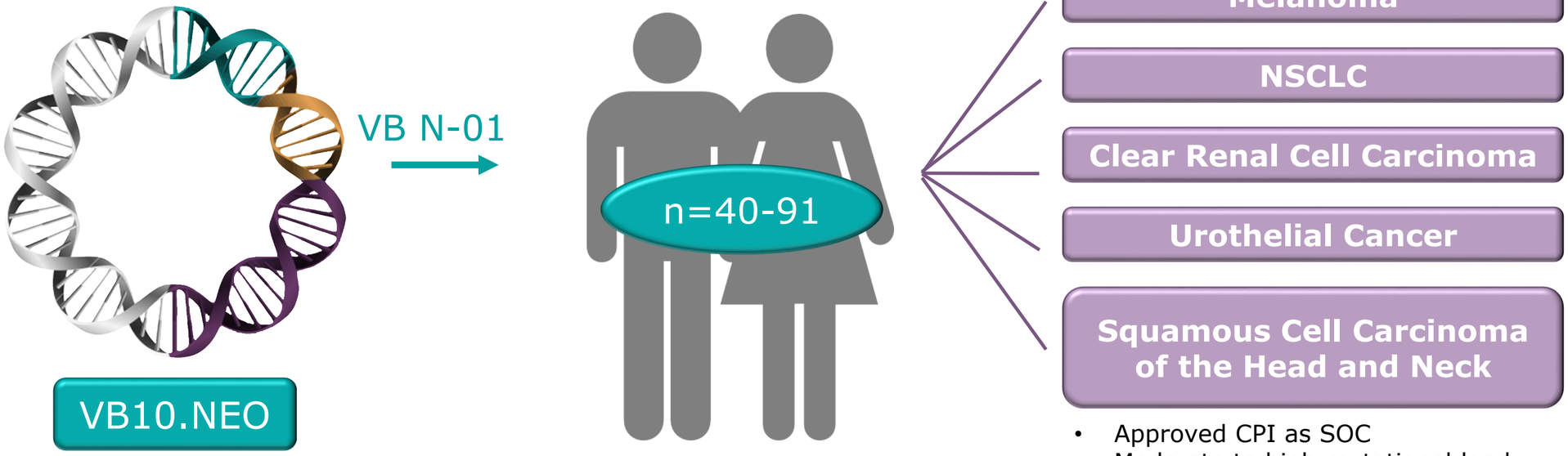
Vaccination Induction

Vaccination Maintenance

Visit	1	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
VB10.16 Dose #	1	2	3			4			5			6			7		
CPI Dose #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17

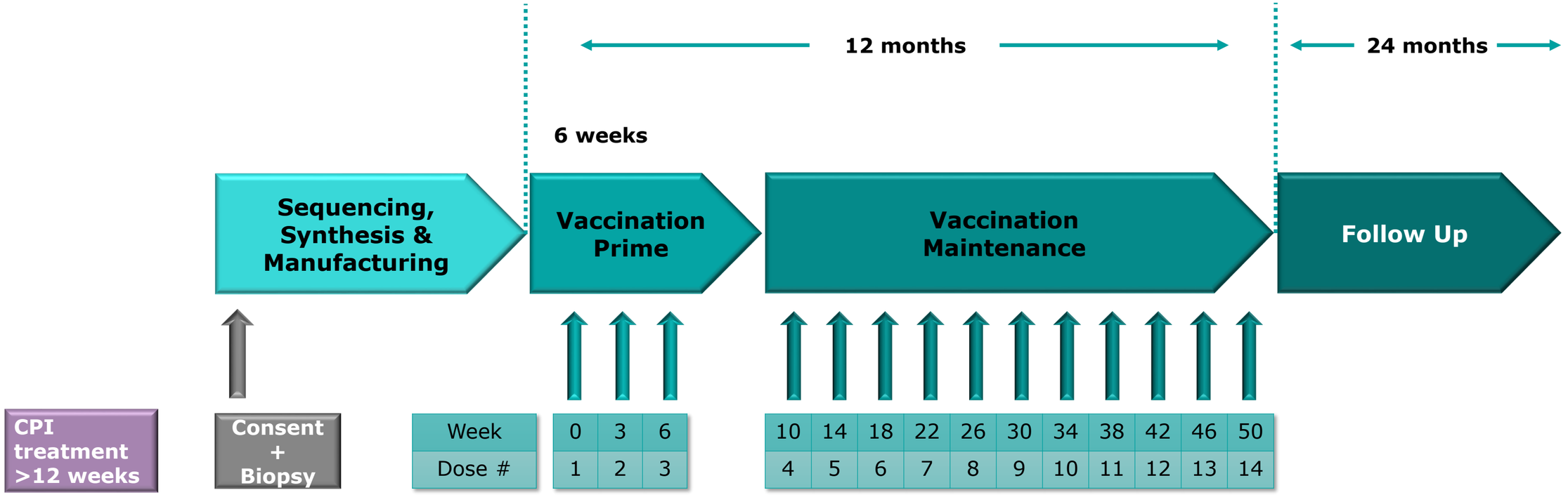
Clinical Trial VB N-01

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

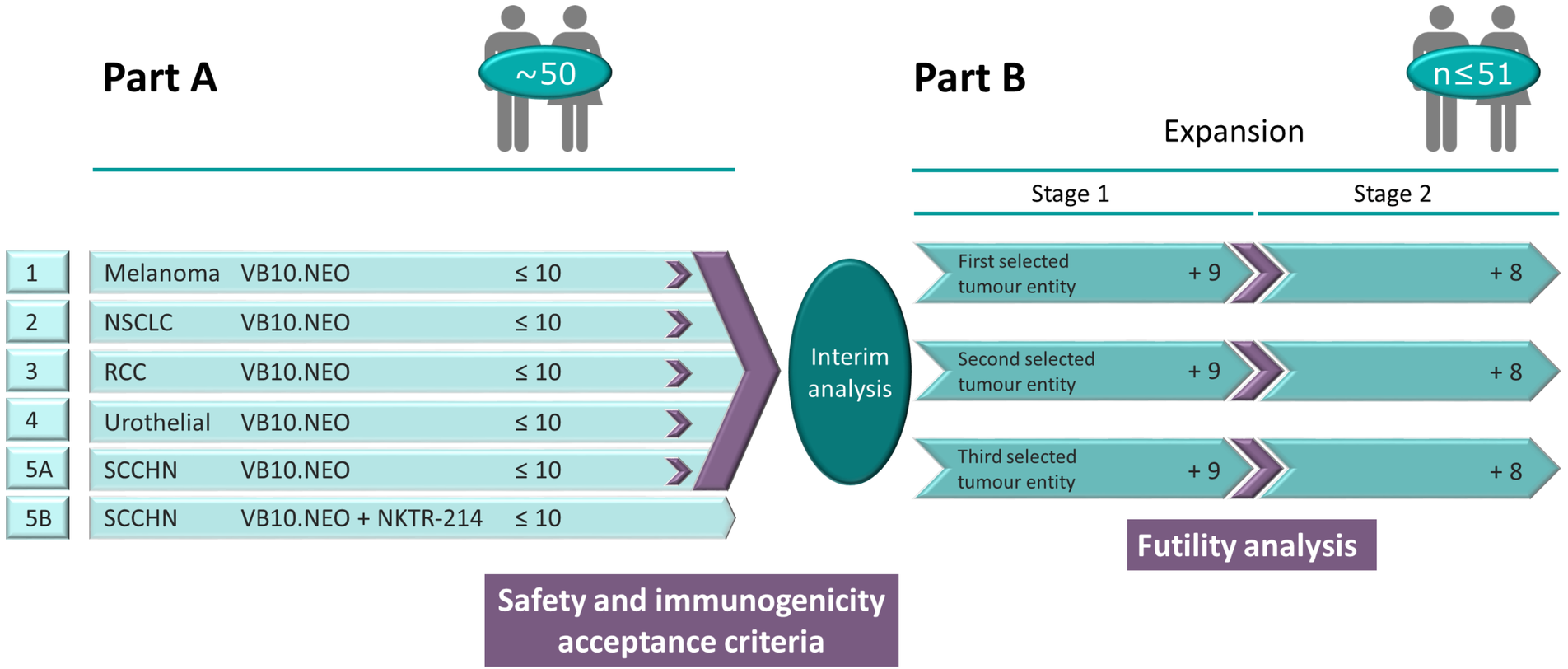


- Approved CPI as SOC
- Moderate to high mutational load

Study Design and Treatment Schedule VB N-01

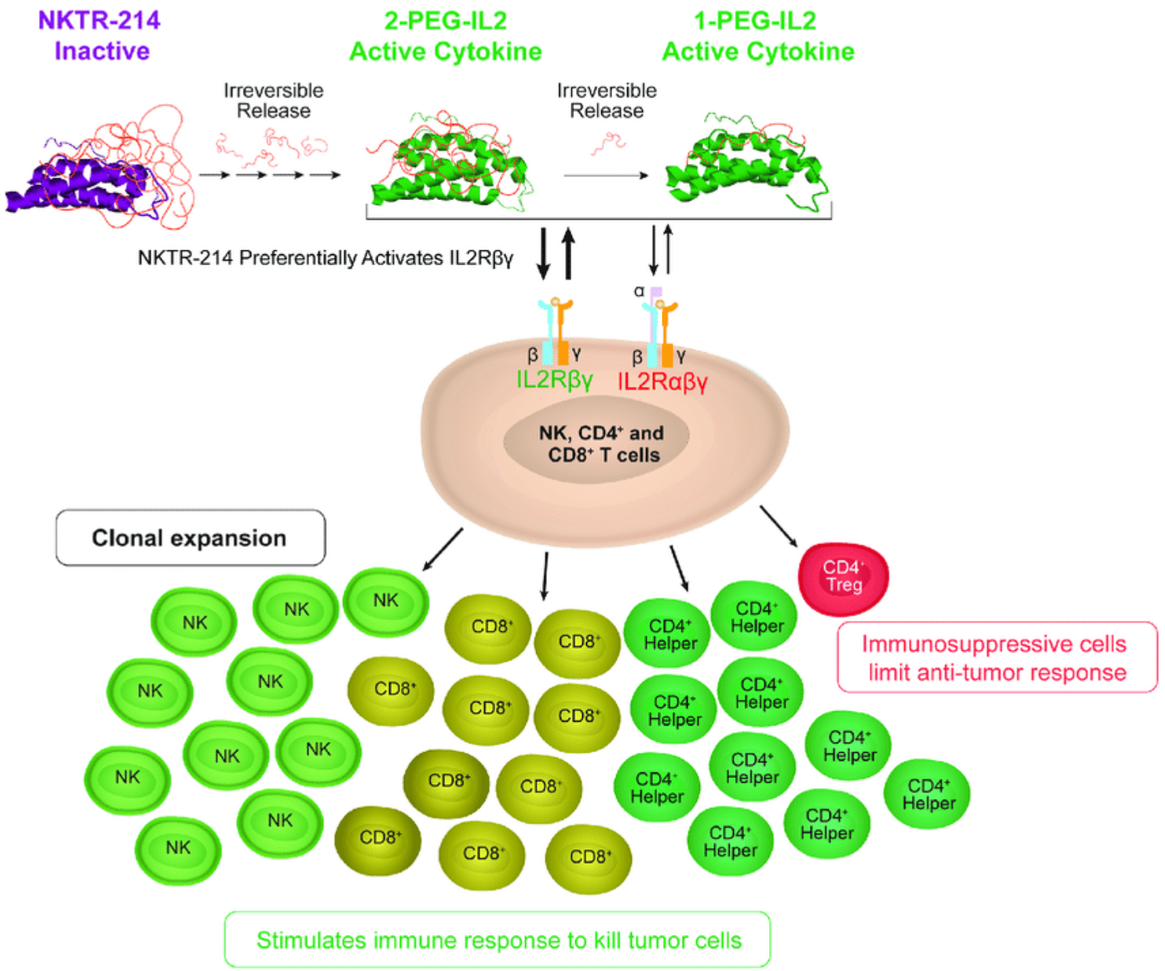


Plan to open expansion cohort(s) in 2H 2019



- 100% vaccine manufacturing success for all patients with a successful biopsy so far
- 20 neoepitopes selected for all patients in the trial
- First expansion cohort(s) could be initiated in H2, 2019

Combination with Bempegaldesleukin (NKTR-214) has the potential to significantly expand neoantigen-specific CD8+ T cells



NEKTAR®

Vaccibody's Solution to Personalised Cancer Treatment

1. Tumour biopsy and sequencing

NeoSELECT™

2. Neoepitope selection (TSNA)

-DNA: Robust, rapid, cost-effective, stable, safe, up to 40 neoepitopes

3. Vaccine manufacturing (n=1)

-Needle-free

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

-Rapid, strong, long-lasting

-unique CD8 dominated responses

4. Vaccine administration and immunogenicity

Vaccibody provide a Rapid, Cost-effective and Efficacious solution

vaccibody

www.vaccibody.com