vaccibody

# Update from Vaccibody's clinical trial with the personalized cancer neoantigen vaccine, VB10.NEO;

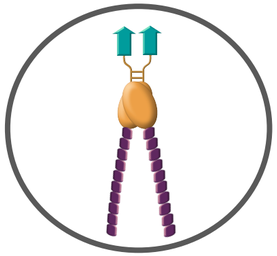
## insight into parameters correlating with improved clinical responses

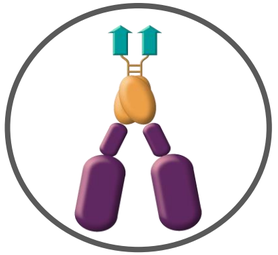
March 4, 2020

**Agnete B Fredriksen**
President & CSO

# Vaccibody Product Pipeline

| PROGRAM | DISCOVERY | PRE-CLINICAL | PHASE I | PHASE II | PHASE III |
|---|---|---|---|---|---|
| MELANOMA<br>LUNG (NSCLC)<br>BLADDER<br>RENAL<br>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

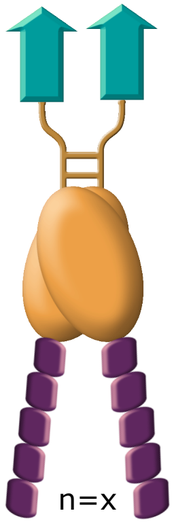
The Vaccibody Technology Platform is developed based on the concept of **targeting antigen to Antigen Presenting Cells (APCs)** in order to create more efficacious vaccines

**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**

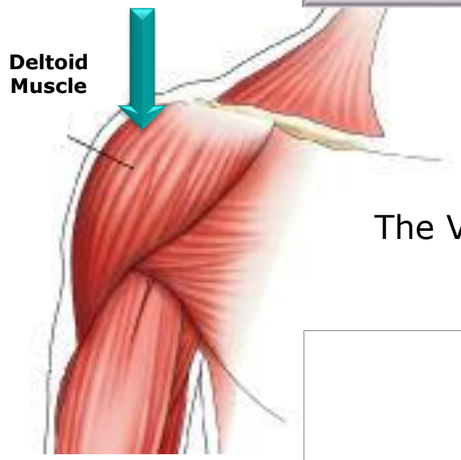
# Mechanism of Action: the Multiple Effects of MIP-1α as Targeting Unit

**Administration (i.m.) of DNA plasmid**

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

**Target – Attract – Mature – Deliver – Cross-present**

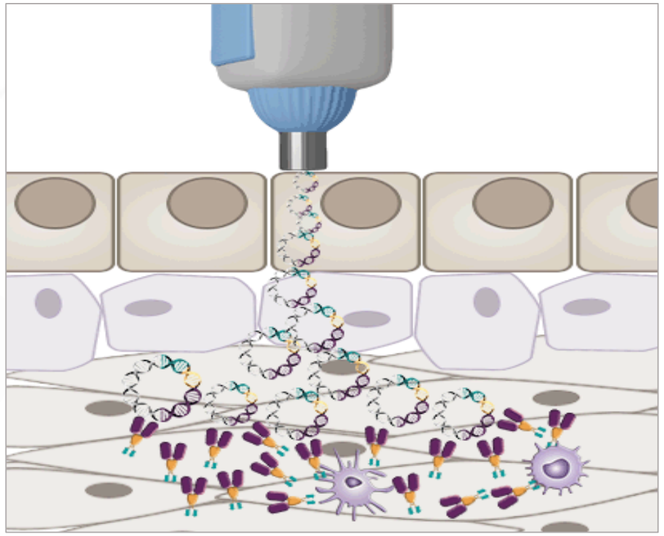
**MIP-1α: Skewing the immune system to a CD8+ killer T-Cell response**

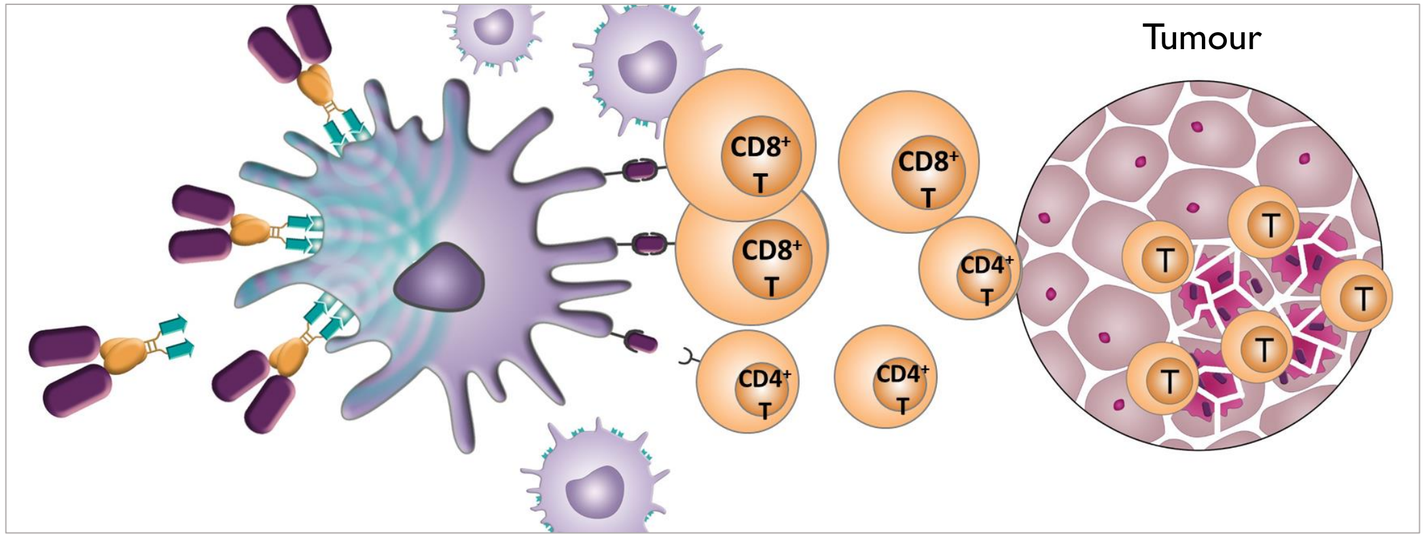



The Vaccibody uses the muscle cell as a factory

- 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 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 | | | | | | | | | | |

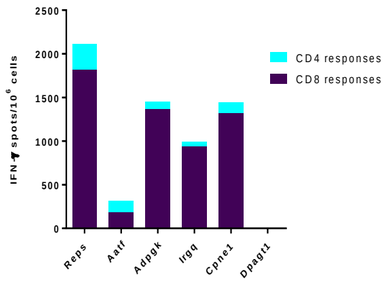
Peptide and RNA vaccines induces primarily CD4 T cell responses, while VB10.NEO induces strong, and **dominating** CD8 responses to the identical neoepitope sequences

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

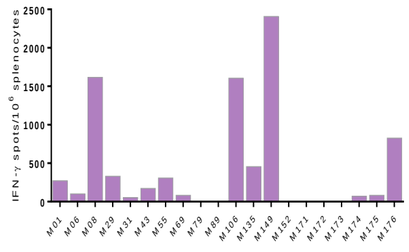
- Castle et al., 2012 and Kreiter et al., 2015
- Aurisicchio et al., 2019

# VB10.NEO Has Proven to Induce an Effective Anti-Tumour Response

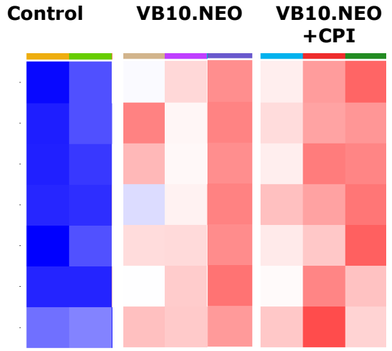
Neoepitope-specific CD8+ T cell response in spleen



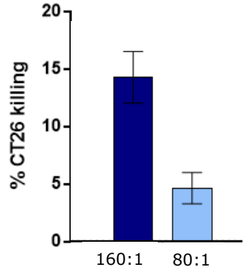

Neoepitope-specific T cell response in tumor




Influx of cytotoxic T cells in tumor (TILs)

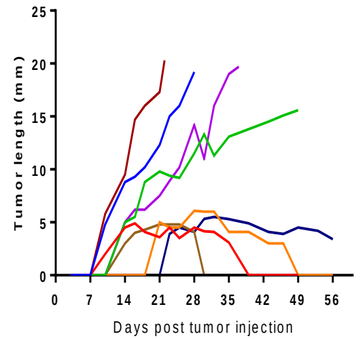



TILs recognize and kill tumor cells




Effector:target cell ratio

Tumor protective immune responses elicited in vaccinated mice (CD8 dependent)

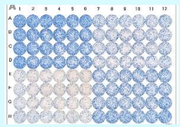



**Strong scientific rational and proven mechanism of action leading to anti-tumor efficacy**

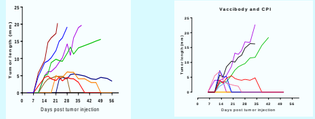
# Proprietary NeoSELECT Was Developed to Match VB10.NEO's Mode of Action

*In vivo* mouse experiments

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



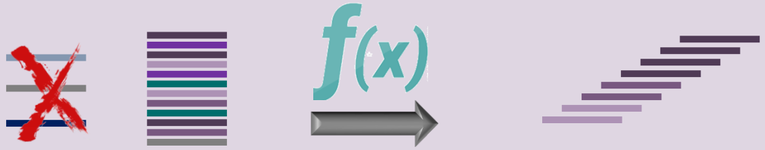
**Anti-tumour efficacy**



Literature
External data sets

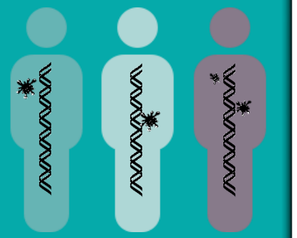
**NeoRANK™**

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




**+++ Criteria rel. for clinical response +++**

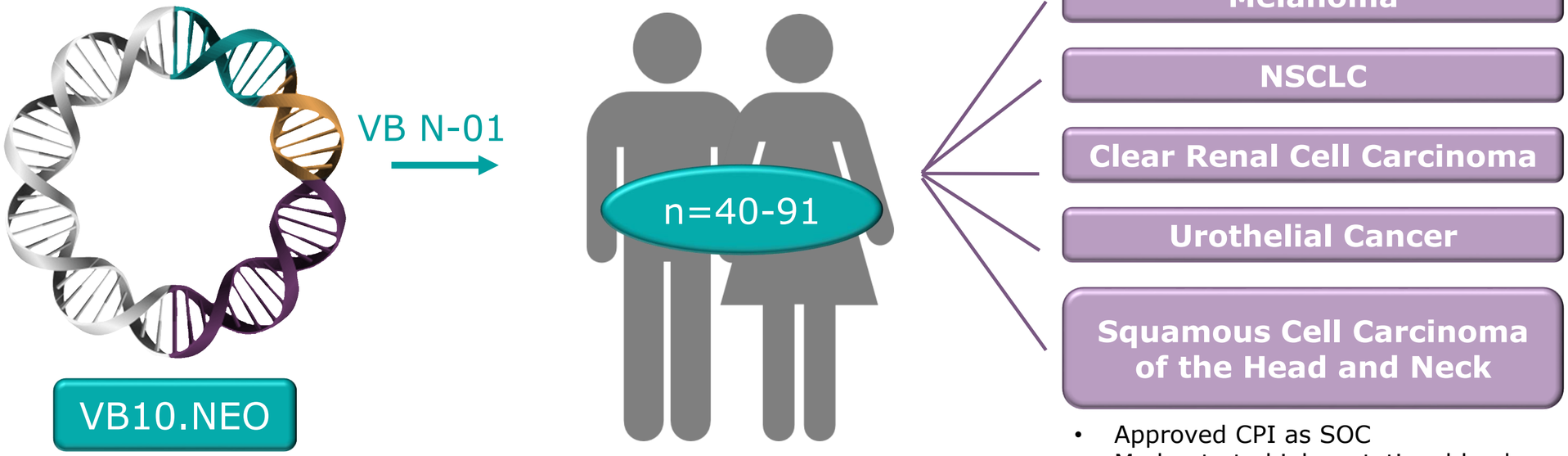
VB10.NEO Patients



Optimization in close collaboration with regulatory authorities

# VB N-01 Clinical Trial Was Designed to Evaluate VB10.NEO in Five Indications

**VB N-01**: An open labelled first human dose phase 1/2a study to evaluate safety, feasibility and efficacy of multiple dosing with individualized 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

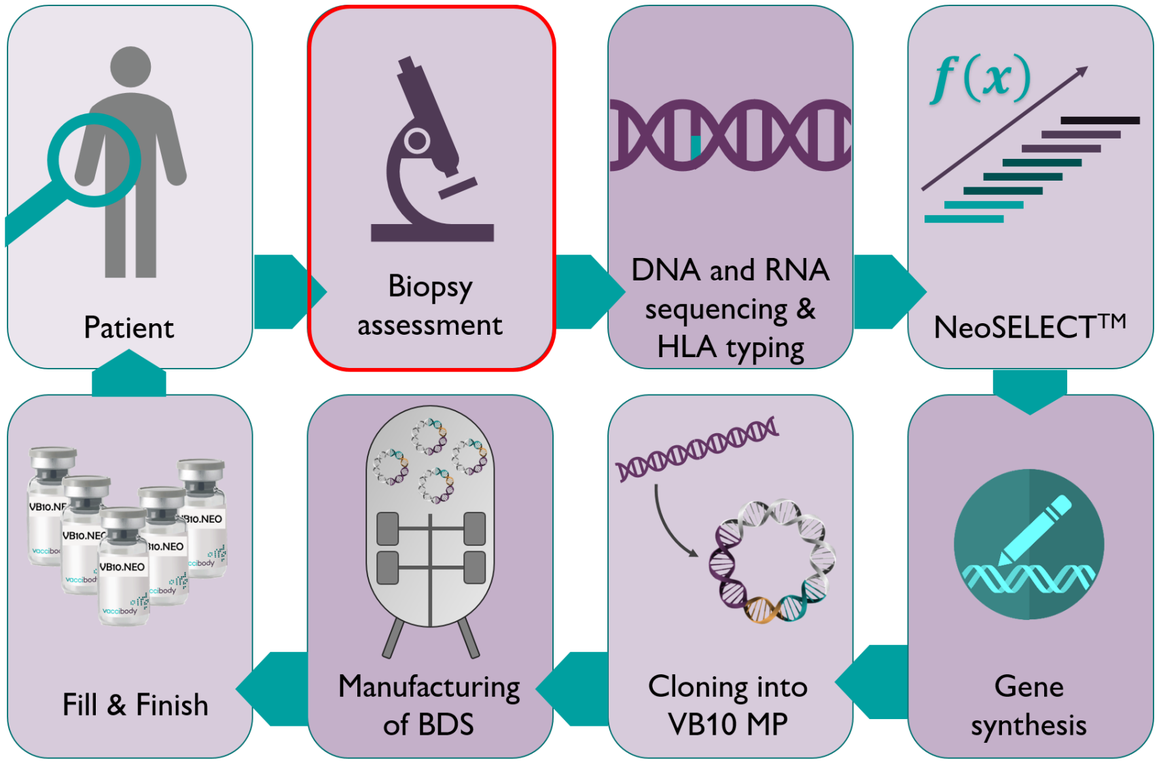



- Approved CPI as SOC
- Moderate to high mutational load

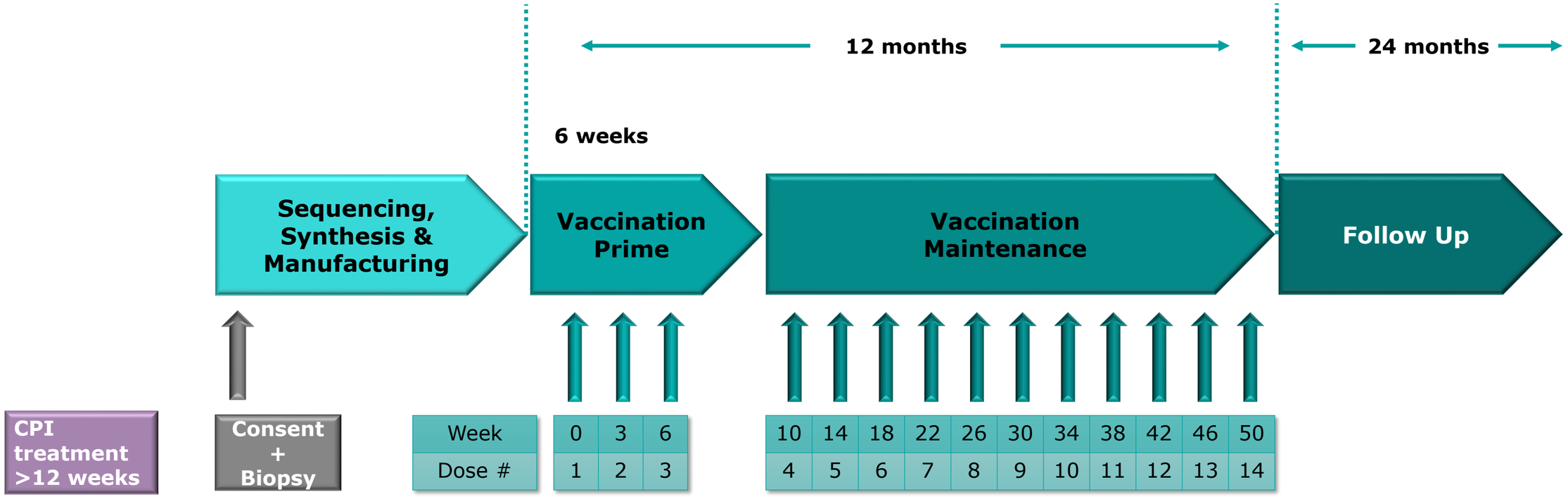
# High Focus on Successful, Robust and Fast Manufacturing

- So far, 100% manufacturing success rate for patients providing a successful biopsy
  - Top choice of 20 neoepitopes used for every patient
  - Proven feasibility and stability data from all initial batches

- Confidence in achieving **rapid and cost-effective** manufacturing before reaching market
  - Good dialogue with regulatory authorities
  - One roof strategy to be implemented before market approval

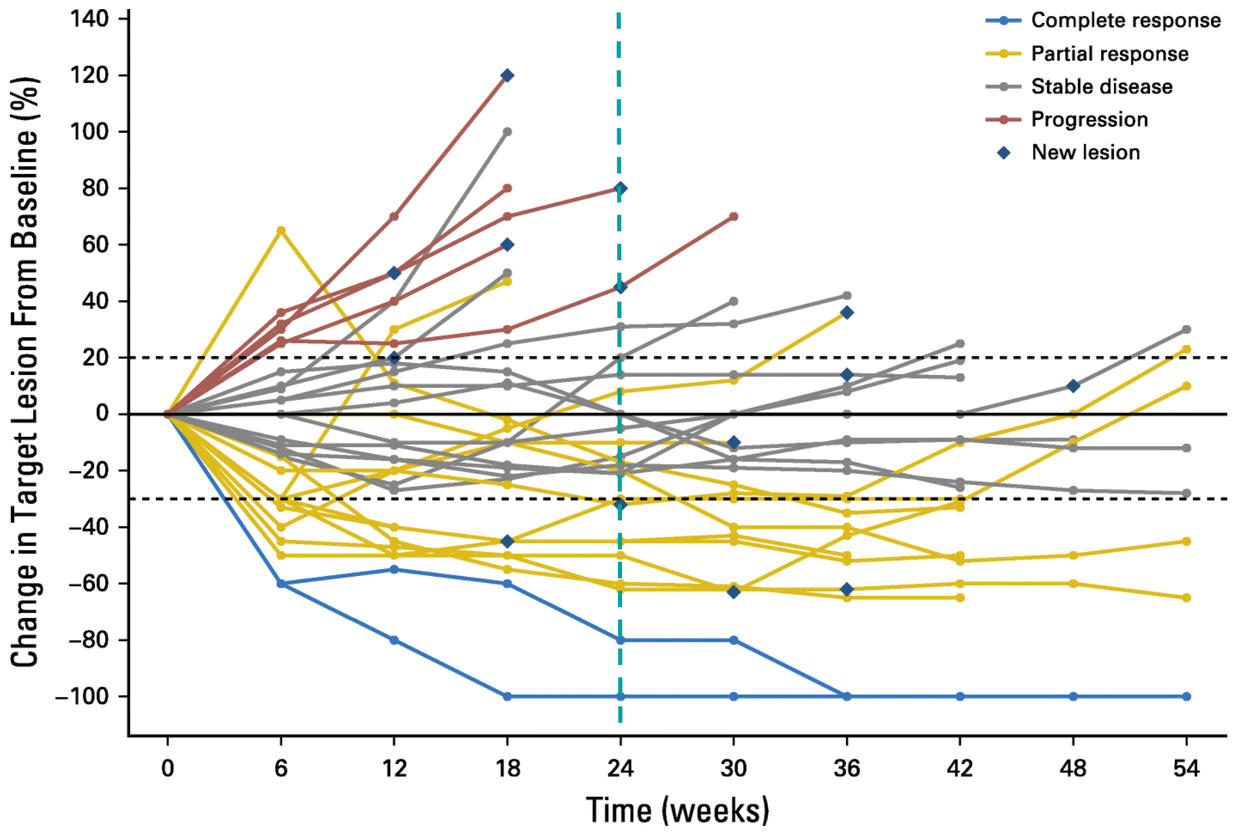


# Unique Study Design and Treatment Schedule VB N-01




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 (post >6 months)

# Treatment Design Allows Evaluation of VB10.NEO-Induced Clinical Responses




*Not Vaccibody data*

- After 6 months on CPI treatment, most patients are stable or relapse (progressive)
- If they progress, they normally continue to progress

Tsimberidou et al., 2018

# Heavily Pre-Treated Patients Treated with CPI Monotherapy for 9-32 Months Before Adding VB10.NEO

| patient | indication | diagnosed | age | prior therapy | TNM | TMB | months CPI before VB10.NEO | Best response on CPI | status at screening | status at start VB10.NEO |
|---|---|---|---|---|---|---|---|---|---|---|
| 01-002 | SCCHN | 2005 | 53 | S, Rt, T, ct, o | N2M1 | low | 32 | SD | SD | PD |
| 01-004 | SCCHN | 2015 | 69 | S, Rt, ct, ch | T4Nx | low | 15 | SD | SD | SD |
| 01-006 | SCCHN | 2017 | 68 | S, ch, ct, ipi | T2N2M1 | med | 18* | SD | SD | PD |
| 01-010 | SCCHN | 2015 | 60 | S, Rt, ct | T4N2M1 | low | 12 | SD | SD | *PR* |
| | | | | | | | | | | |
| 02-003 | melanoma | 2000 | 81 | S | M1 | high | 10 | PR | SD | SD |
| | | | | | | | | | | |
| 02-007 | NSCLC | 2018 | 54 | S, Rt, ch | T2N1M1 | med | 9 | SD | SD | PD |
| | | | | | | | | | | |
| 01-001 | RCC | 2014 | 69 | S | T1N1M1 | low | 16 | SD | SD | SD |
| 01-003 | RCC | 2005 | 64 | S, T, o | T1aN1M1 | low | 5* | PD | PD mixed | PD |
| 01-005 | RCC | 2006 | 58 | S, Rt, T | T1bN1M1 | low | 11 | SD | SD | SD |
| 02-002 | RCC | 2013 | 76 | S, IT | T3bN0M0 | low | 8+15 | PR | SD | PD |
| 01-007 | RCC | 2017 | 55 | S, T | T3aN1M1 | low | 14 | PR | SD | SD |
| 01-008 | RCC | 2017 | 62 | S, T | T2N1M1 | low | 14 | SD | SD | SD |
| 01-009 | RCC | 2011 | 57 | S, Rt, o | T1bNXM1 | low | 31 | SD | SD | SD |
| 01-011 | RCC | 2007 | 58 | S, o | T2N0M0 | low | 26 | PR | SD | SD |

S: Surgery
Rt: Radiotherapy
T: Targeted Therapy
Ct: Cetuximab
Ch: Chemotherapy
ipi: Ipilimumab
O: Other

TMB: Tumor Mutational Burden

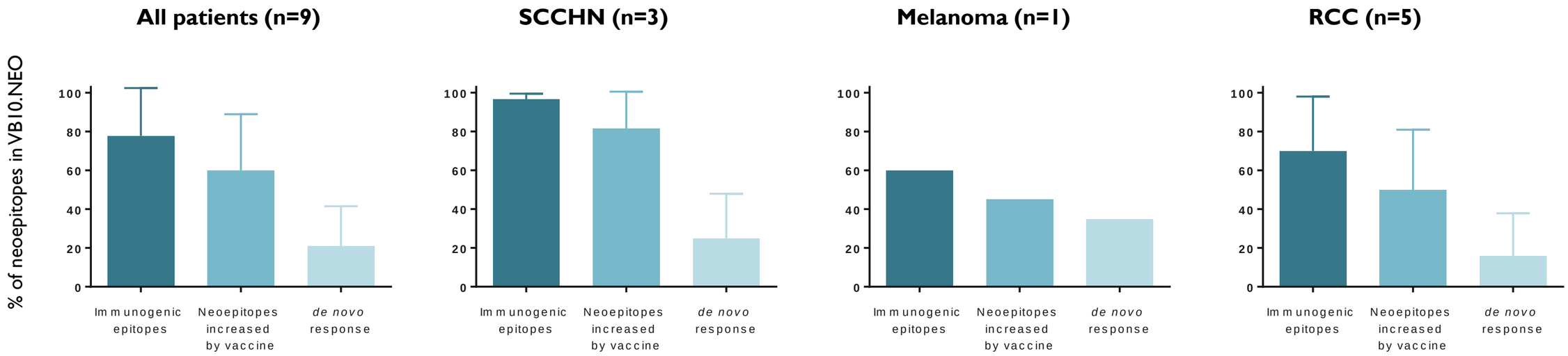
SD: Stable Disease
PD: Progressive Disease
PR Partial Response
* Stopped CPI

- 14 patients have been evaluated for clinical response to VB10.NEO (2-9 months follow up time)
- All patients had been treated with CPI for 9-32 months before adding VB10.NEO. 5 patients relapsed before the first vaccination
- 11 patients showed low TMB, 2 medium TMB (SCCHN, NSCLC) and 1 high TMB (melanoma)

# VB10.NEO Induces Immune Responses to the Majority of Selected Neoepitopes

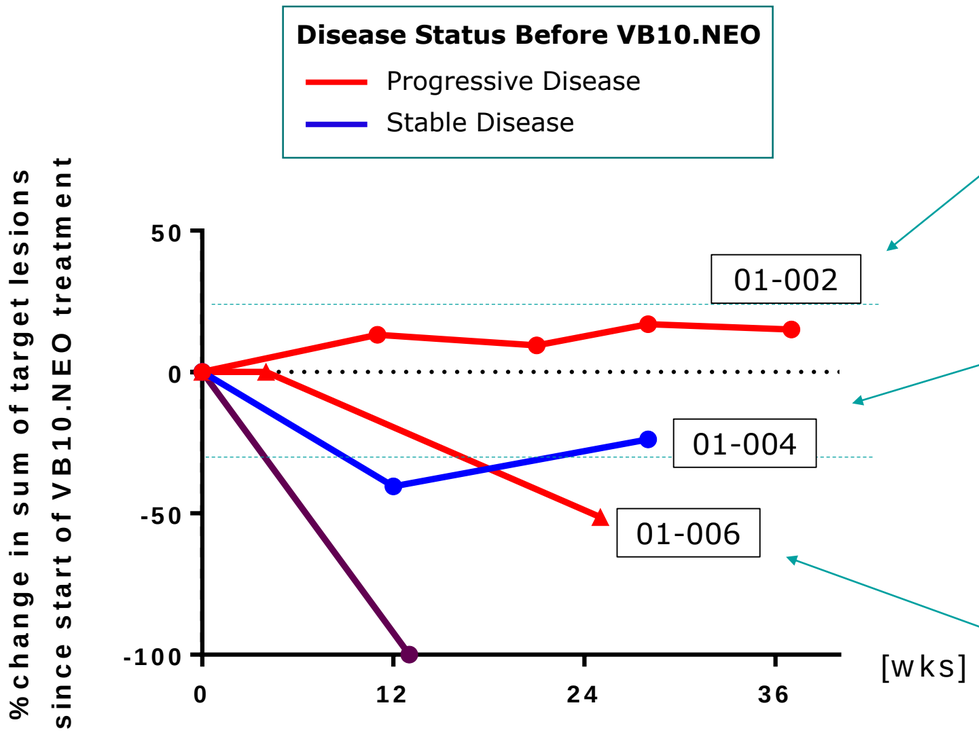
9 patients have been assessed for immunogenicity (IFN-γ ELISpot) after six vaccinations (week 22) :

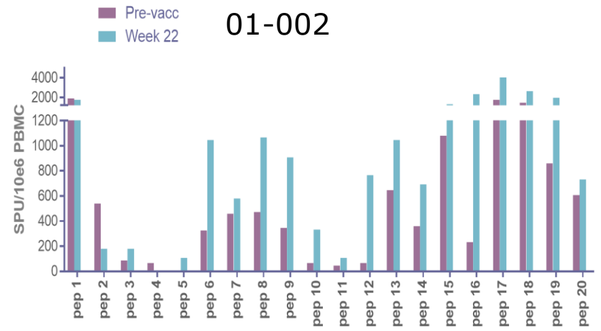
- ✓ NeoSELECT identifies a high percentage of immunogenic neoepitopes
- ✓ Increased immune response to majority of selected neoepitopes
- ✓ Induction of *de novo* reponses

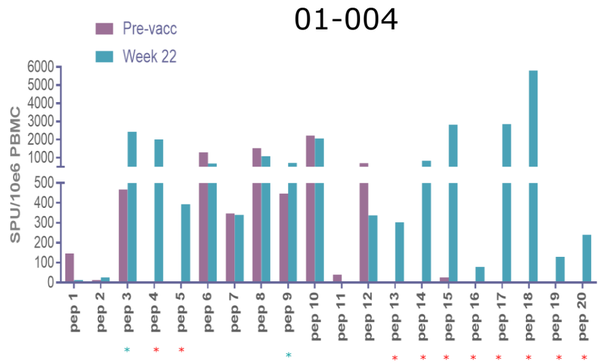


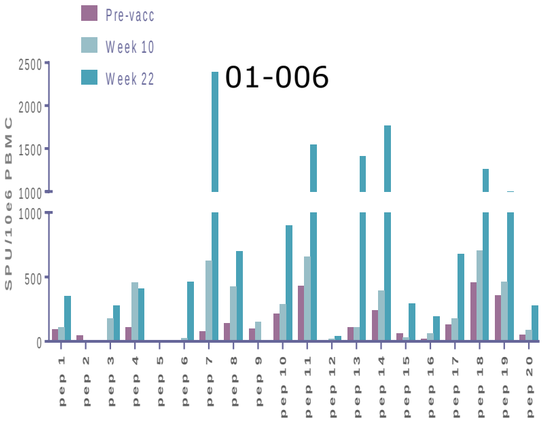
# SCCHN (Head & Neck): Clinical Responses Observed After VB10.NEO Initiation in All Patients

Tumour shrinkage or stabilization of progressing lesions




**Strong immune responses in all assessed patients**

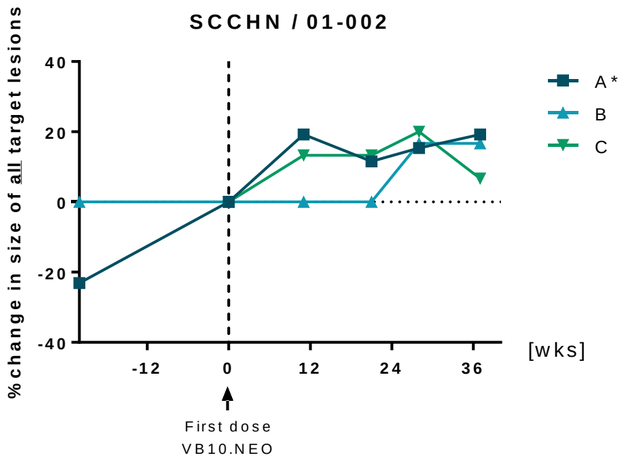
- 60-95% increased post vaccination

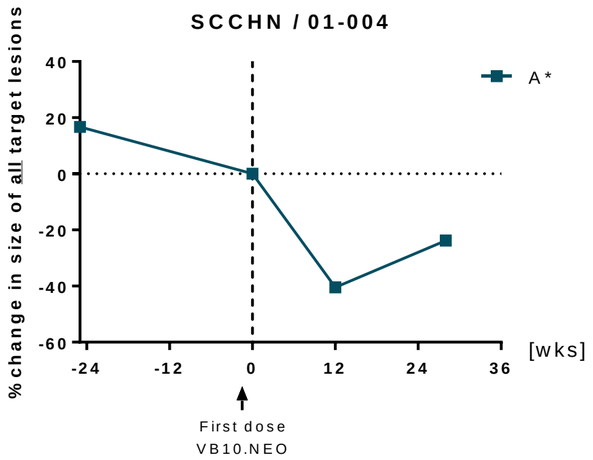
**Head & Neck (SCCHN;** 4 patients)

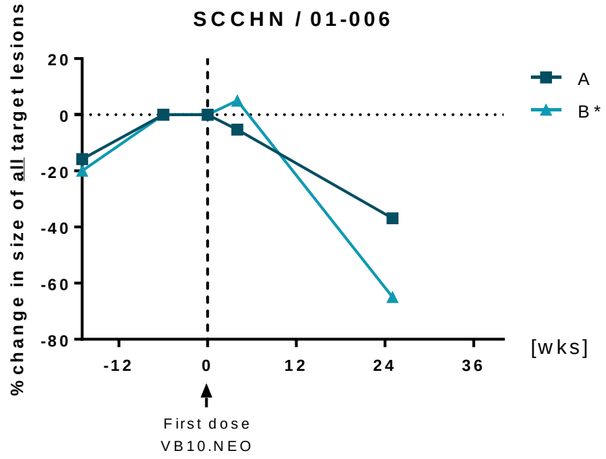
- VB10.NEO induced strong immune responses leading to clinical responses in all assessed SCCHN patients

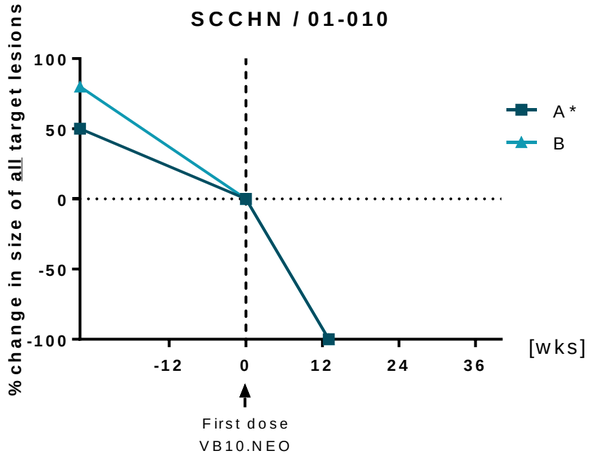
SCCHN: Squamous Cell Carcinoma of the Head and Neck

# SCCHN: Change in All Individual Target Lesions Before and After VB10.NEO Treatment



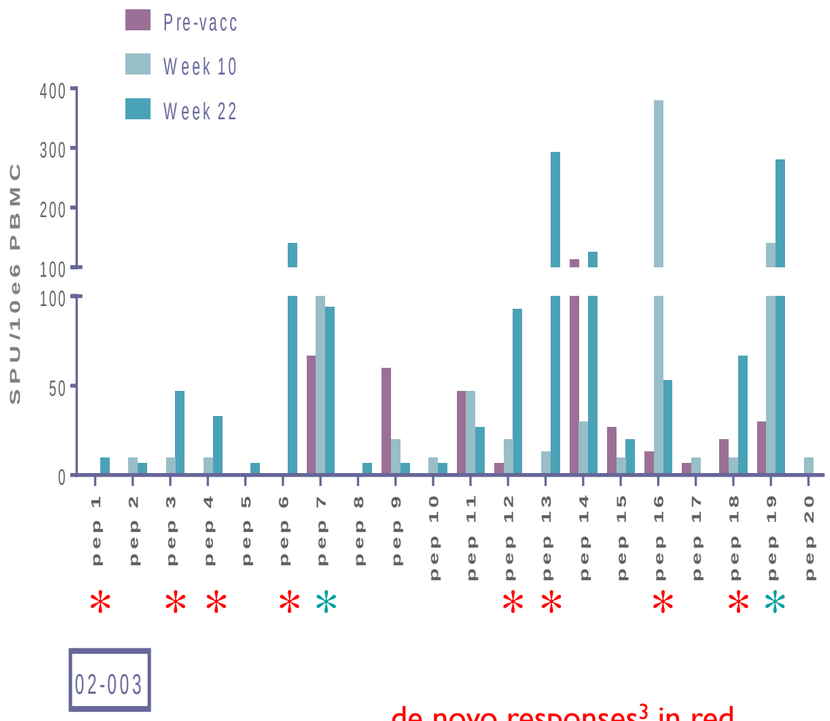




## Key Learnings (Head & Neck)

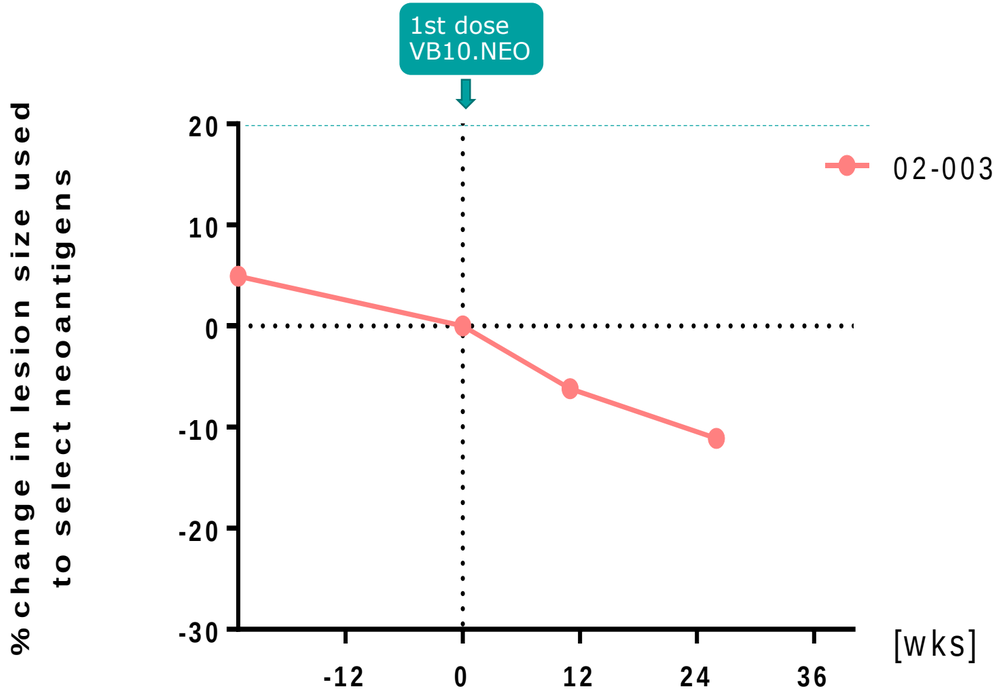
- All SCCHN patients show a positive change in the lesion size development after VB10.NEO treatment start
- Multiple lesions respond
- The lesion used to select neoepitopes responds best. Next best response is seen in lesions from the same region

SCCHN: Squamous Cell Carcinoma of the Head and Neck

# Melanoma (Skin): VB10.NEO Induce Several de novo T Cell Responses and Increased Tumour Shrinkage



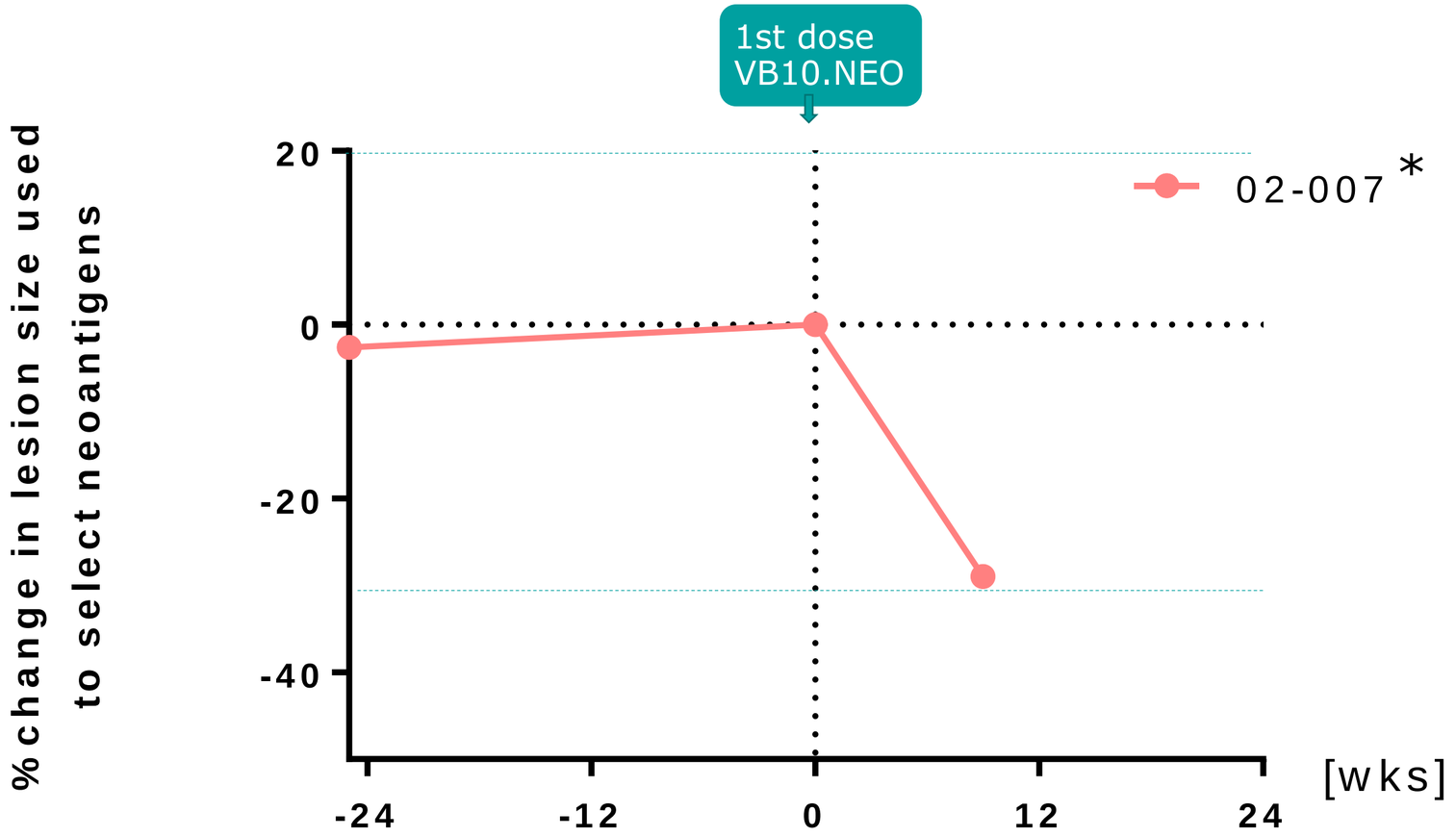

de novo responses[3] in red




**Melanoma** (1 patient)

- VB10.NEO induces an increased T cell response against several of the selected neoepitopes
- Immune responses are weaker than tested in SCCHN so far, but the majority are *de novo* responses
- An increased reduction in is observed after the first dose VB10.NEO in the large target lesion (81-72mm)

# NSCLC: Rapid Reduction in Target Lesion Size after VB10.NEO Treatment



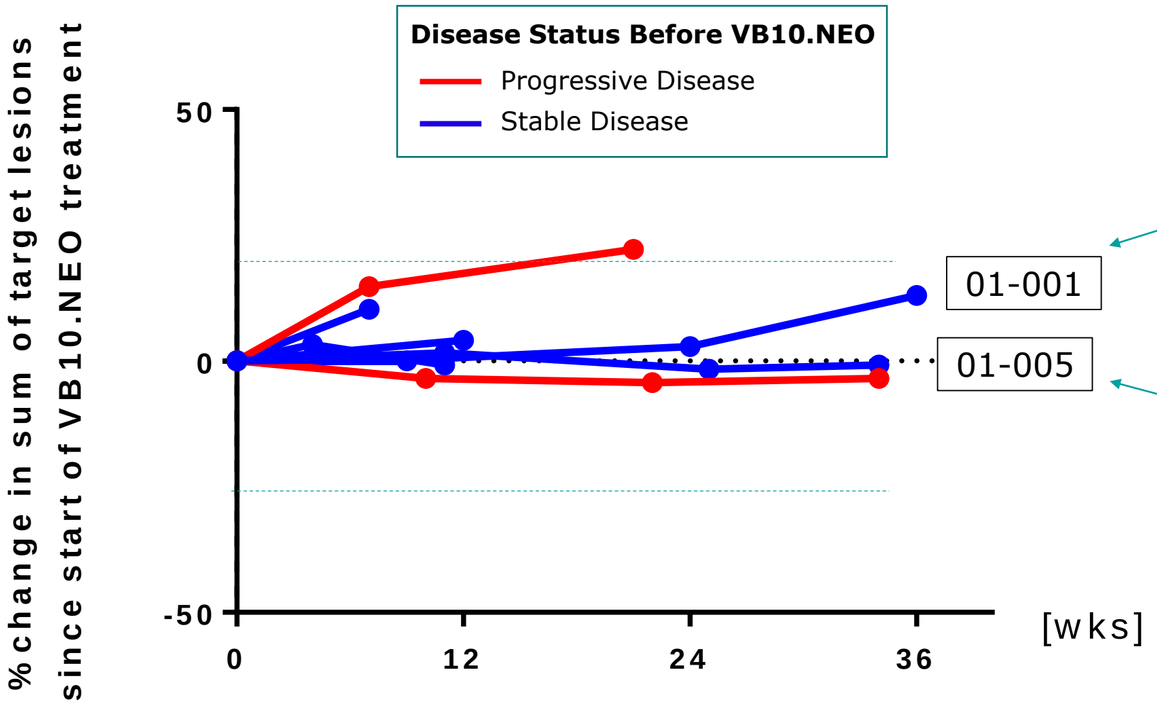

* Immune response not yet assessed (too early)

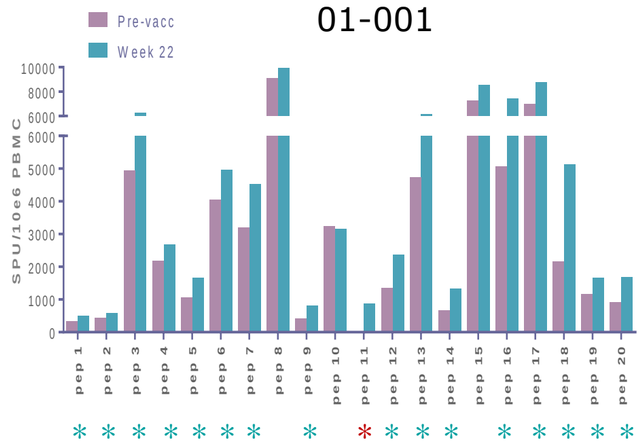
NSCLC (Lung Cancer):

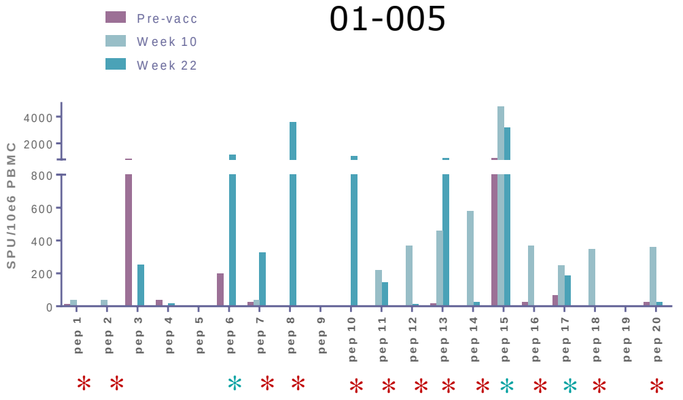
- Rapid reduction in the target lesion (lung lesion used to select neoantigens) 9 weeks after VB10.NEO was started

# RCC: Reduced Growth and Long-Term Continuous Stable Lesions

## Clinical responses after VB10.NEO initiation




Data shown for the two RCC patients with strongest immune response

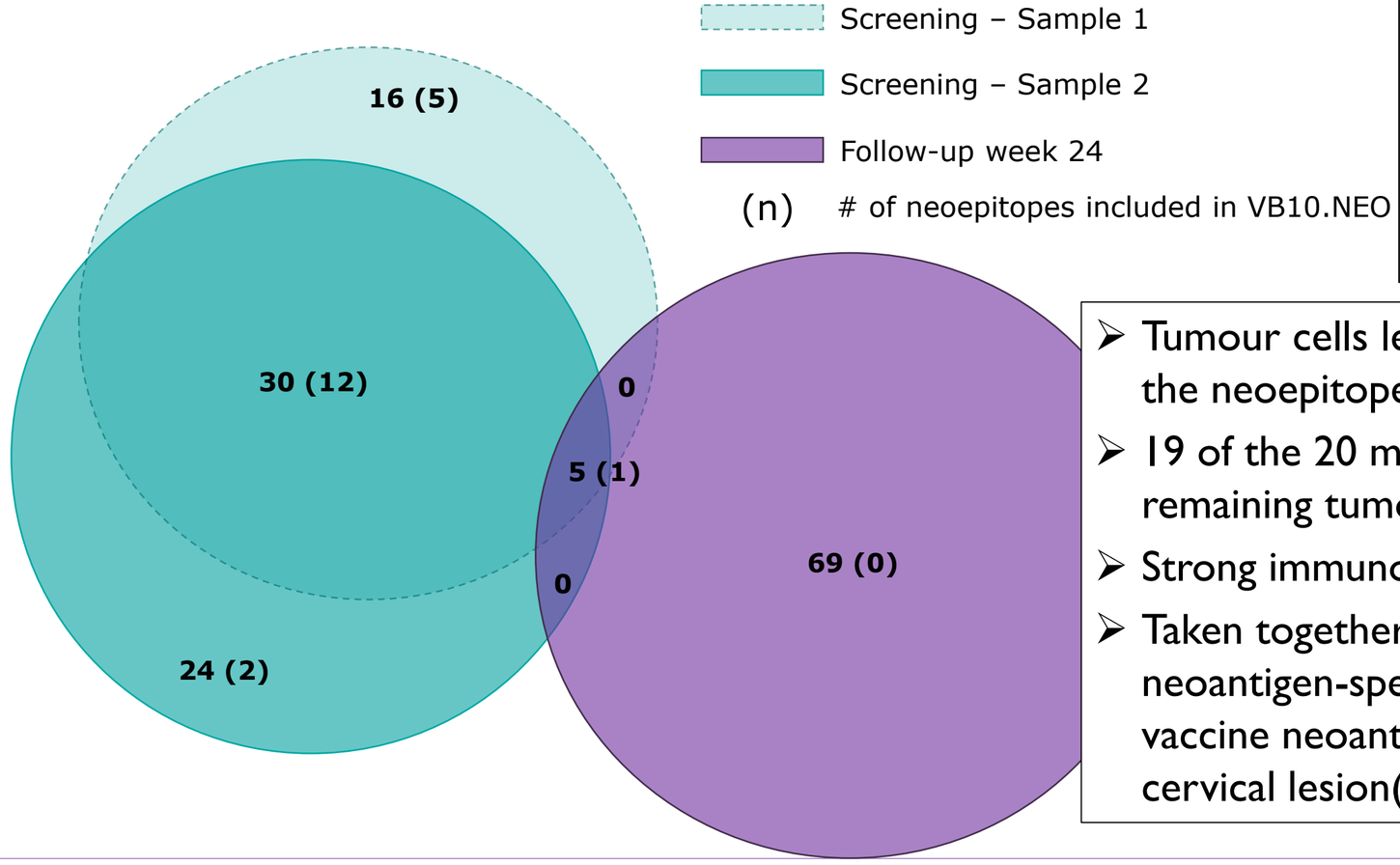
**Renal Cell Carcinoma:**

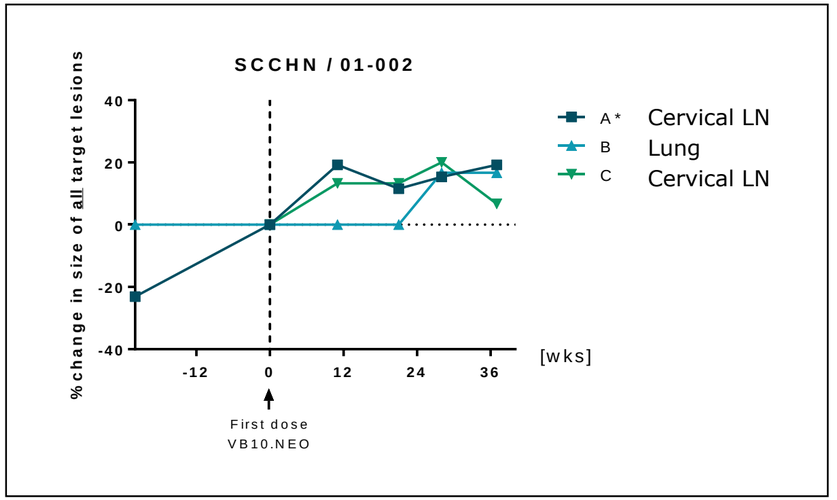
- Limited changes were observed in the RCC patients post VB10.NEO treatment
- Importantly, none of the lesions used to select neoantigens have progressed (>20%) post 1st dose VB10.NEO

RCC: Renal Cell Carcinoma

# Neoepitope Analysis in Follow-up Biopsy Indicate Specific Tumour Cell Killing

Follow-up biopsy week 24 – 1 sample from cervical area

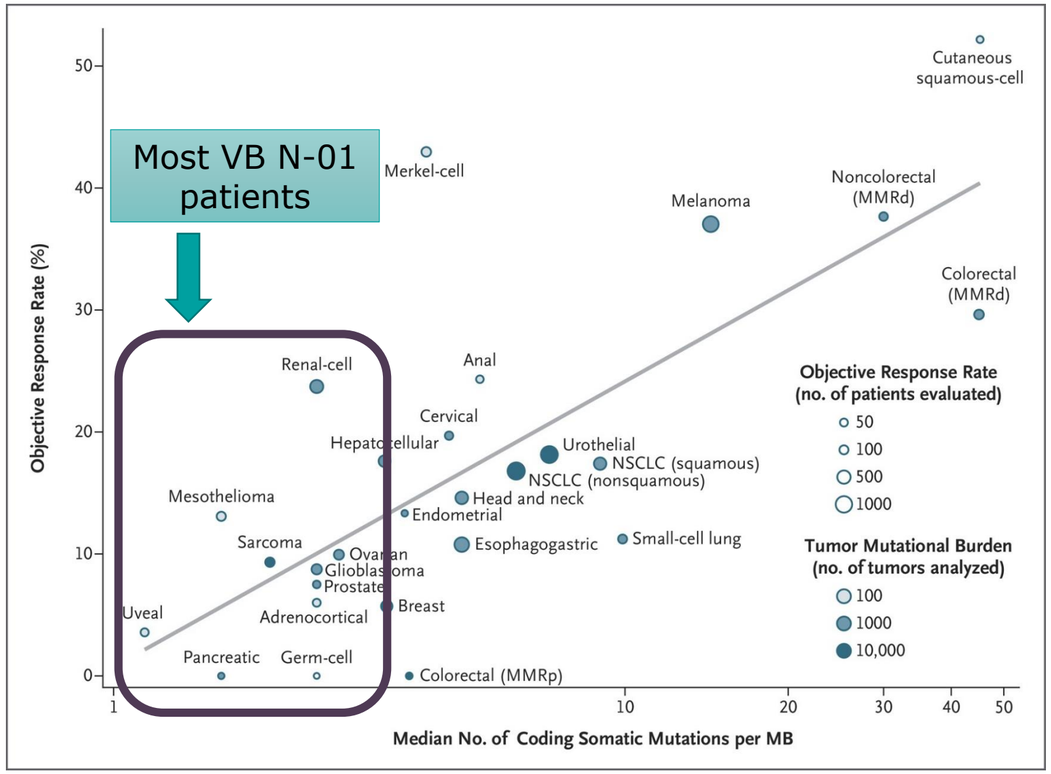



- Tumour cells left in the cervical area no longer contained the neoepitopes targeted by the vaccine
- 19 of the 20 mutations were no longer found in the remaining tumour cells
- Strong immunogencity data and stabilization of lesions
- Taken together, this may indicate that the induced neoantigen-specific T cells have killed all tumour cells with vaccine neoantigens and a different clone is now left in the cervical lesion(s)

Tumour cell content (TCC) in screening samples 40 and 60%, respectively. TCC in follow-up sample 40%.

# Patients with High TMB Responds Better to Immunotherapies




Strong relationship between Tumor Mutational Burden (TMB) and response to CPI

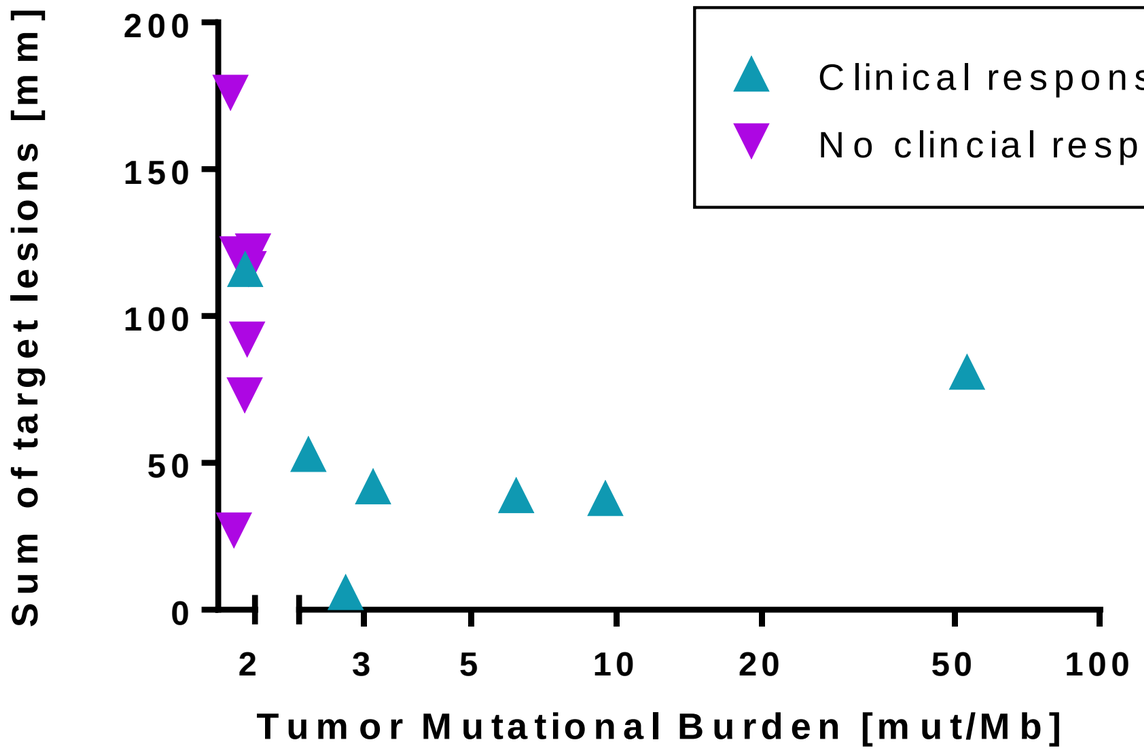
Limits response to already existing neoantigen-specific T cell repertoire

Patients with low TMB have worse prognosis on CPI

Our patient population is at the lower end of the TMB scale for their indications

Source: Yarchoan et al., 2017 NEJM
TMB: Tumor Mutational Burden

# Clinical Response Was Seen Even in Patients with Low TMB, Indicating Potential in a Broad Setting and Large Number of Indications



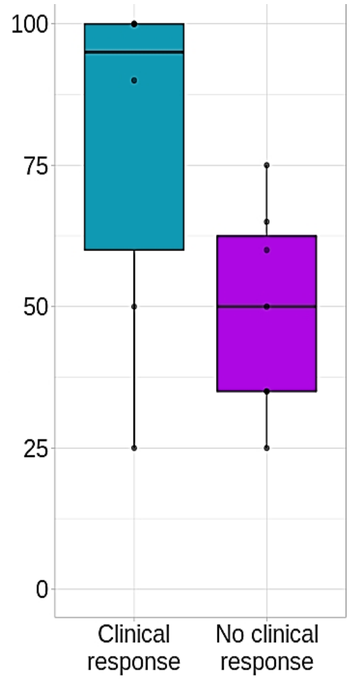

Broad potential for vaccine-induced clinical responses identified

- The Renal Cell Cancer patients in our VB N-01 trial have the lowest TMB and the largest tumour burden among all included patients
- Data indicates a broad potential for vaccine-induced clinical responses

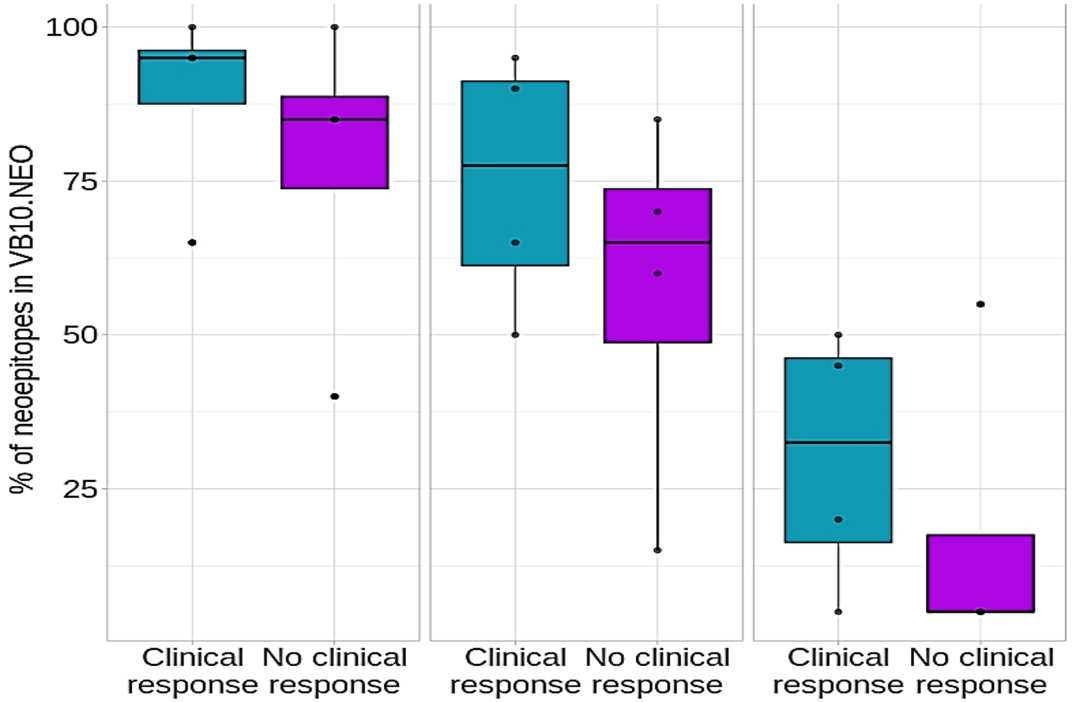
TMB: Tumor Mutational Burden

# Patients With Clinical Responses Have the Strongest Immune Response Profile and Highest Frequency of High-Quality Neoepitopes

## Frequency of high quality neoepitopes vs change in lesion size




## Frequency of immunogenic neoepitopes vs change in lesion size




Patients with clinical response after VB10.NEO vaccinations have

- Highest frequency of high quality neoepitopes

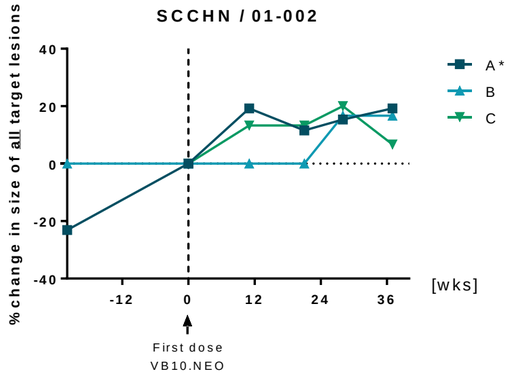
Patients with clinical reponse after VB10.NEO vaccinations have

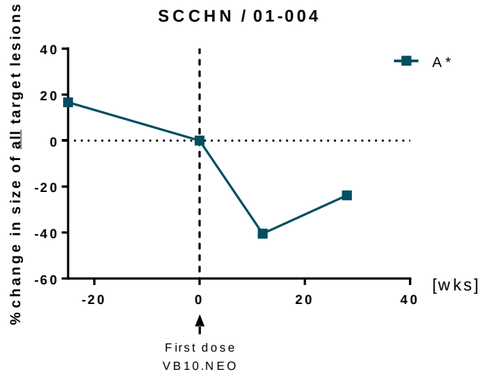
- A) Highest frequency of immunogenic neoepitopes
- B) Highest frequency of increased response after vaccination
- C) Highest frequency of de novo immune responses

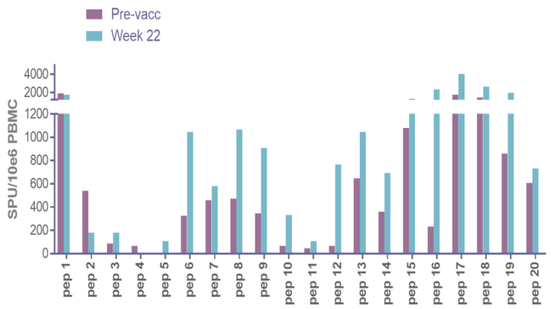
Clinical response is here defined as reduction in the sum of target lesions by at least 10% or stabilization of prior progressing lesions

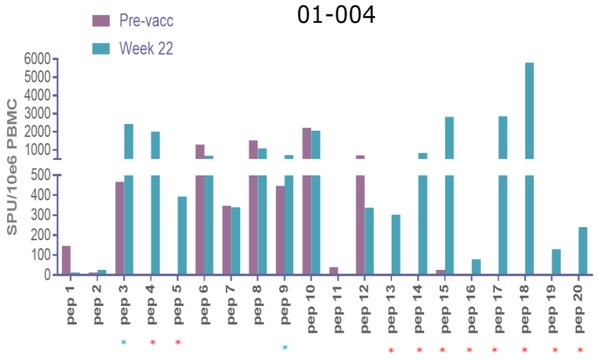
# Strong, Dominating CD8 T Cell Responses Are Correlated with Clinical Responses

## CD8 dominated responses

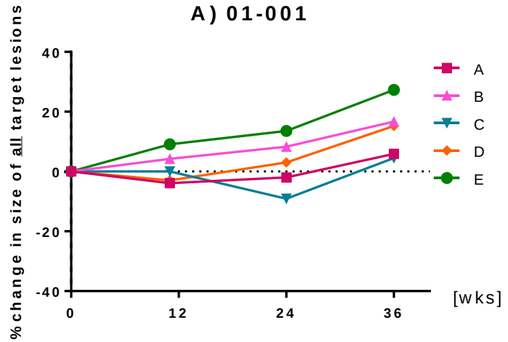


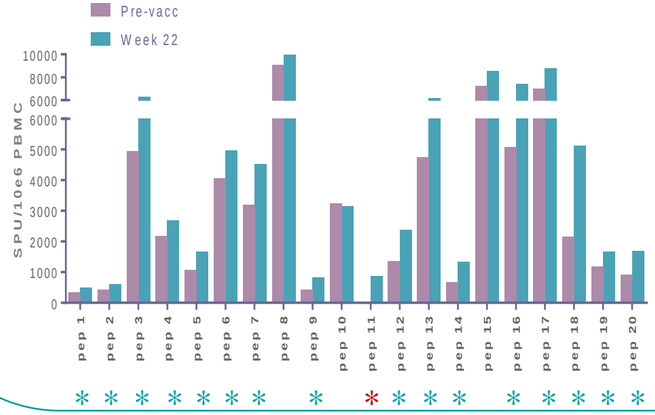



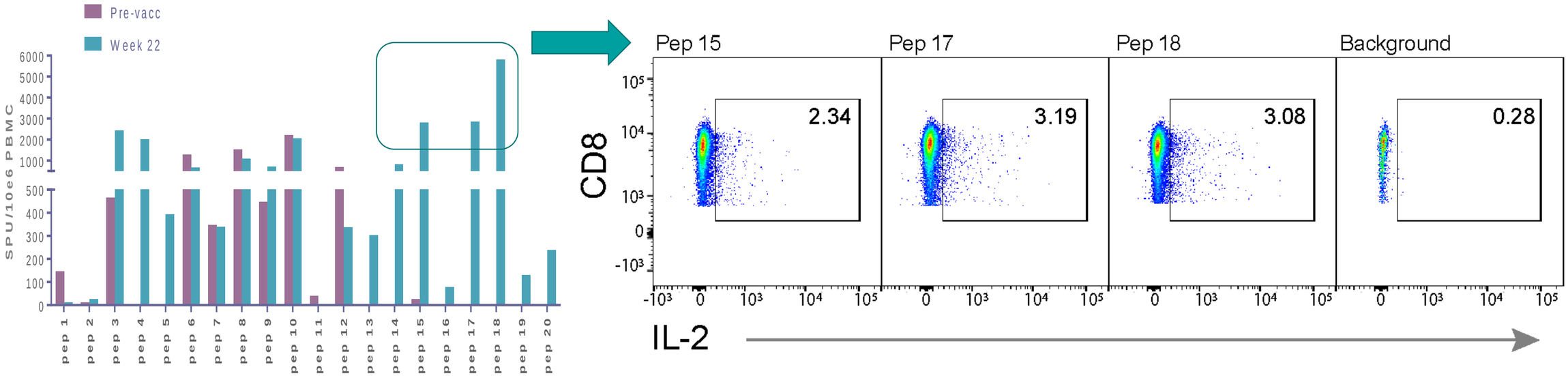

## CD4 dominated responses



# Neoepitope-specific CD8 dominating immune responses in SCCHN patients with clinical response

3 epitopes from 01-004




- The strongest de novo responses* were characterized as dominating CD8 T cell responses by FACS analysis in SCCHN patient 01-004. Also secreting IL-2.

* As identified by IFN-γ ELISpot

# Summary of Clinical Observations: VB10.NEO Causes Shrinkage of Tumours and Stabilization of Progressing Lesions

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VB10.NEO is able to shrink tumours or stabilize progressing lesions in multiple patients with advanced metastatic disease after long-term CPI treatment

- Shrinkage occurs 9-24 weeks after first dose VB10.NEO
- Optimal shrinkage in lesion used to select neoepitopes
- Tumour cells with neoantigens targeted by the vaccine are specifically killed
- Optimal clinical responses in patients with highest frequency of high-quality neoepitopes
- Optimal clinical responses in patients with strongest immune responses
- Strong, dominant CD8 responses in patients with clinical responses

# Acknowledgements

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