An open-label, phase 1/2a study of VB10.NEO (DIRECT-01) in combination with checkpoint blockade in patients with locally advanced or metastatic solid tumors including melanoma, NSCLC, renal cell carcinoma, urothelial cancer or SSCHN

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#CT217

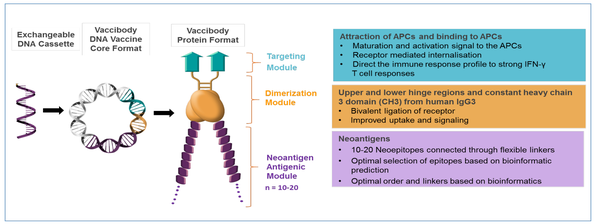
BACKGROUND

Neoantigens are ideal for developing personalized cancer vaccines as they are tumor specific and not subject to central tolerance. Targeting neoantigens to generate potent tumor-specific T-cell responses has shown both promising preclinical efficacy as well as clinical responses. VB10.NEO is a DNA plasmid vaccine with intrinsic adjuvant effect designed for efficient delivery of personalized neoepitopes and can hold up to 20 unique neoepitopes specific for each patient's tumor. Here we describe VB N-01 (DIRECT-01), an open-label phase 1/2a study, designed to evaluate the safety, immunogenicity and efficacy of administrating personalized VB10.NEO in combination with checkpoint blockade in up to 91 patients with locally advanced or metastatic solid tumors including melanoma, NSCLC, renal cell carcinoma, urothelial cancer or head and neck cancer, who have not achieved a complete response by at least week 12 on checkpoint blockade as respective standard of care (SOC).

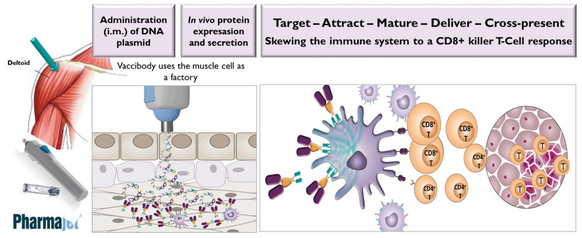
MECHANISM OF ACTION

VB10.NEO is a potent DNA plasmid vaccine based on the pUMVC4a vector backbone encoding a single recombinant protein consisting of three modules.

- **Targeting Module:** human chemokine macrophage inflammatory protein-1 alpha (hMIP-1α)
- **Dimerisation Module:** upper and lower hinge regions and the constant heavy chain 3 (CH3) domain from human IgG3
- **Neoepitope antigen module**



- The VB10.NEO vaccine is administered as intramuscular injections with the PharmaJet® Stratis injection System. Delivery and mode of action presented below.



OBJECTIVES

Primary objectives:

- To assess the safety/tolerability of VB10.NEO immunotherapy
- To determine the feasibility of the VB10.NEO vaccine manufacturing

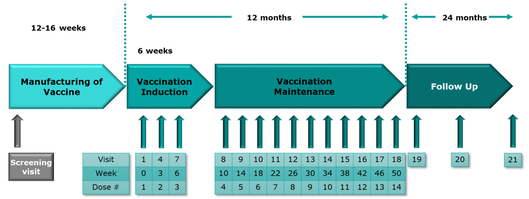
Secondary objectives:

- To assess the immunogenicity of multiple doses of 3 mg VB10.NEO immunotherapy
- To make a preliminary assessment of the efficacy of multiple doses of 3 mg VB10.NEO

Exploratory objectives

- To investigate immune signature alterations during therapy
- To investigate the correlation between immunological response and clinical efficacy

VISIT SCHEDULE & ASSESSMENTS



Study scheme

Safety assessments

- Patients will be assessed for safety by adverse events (AEs), serious adverse events (SAEs) physical examination, vital signs, safety laboratory assessments and ECOG status

Staggered treatment was performed for the first 3 patients

Continuous safety data evaluation by Study Safety Group and Independent Data Safety Monitoring Board (IDSMB)

Efficacy assessments

- Tumor response will be assessed by iRECIST at regular intervals according to standard of practice (baseline scan within 4 weeks of visit 1)

Efficacy will be based on:

- Objective Response Rate (ORR)
- Duration of Response (DOR)
- Overall survival (OS)

Immunogenicity and other assessment

- Systemic immune response to each neoepitope in the vaccine will be evaluated by IFN-γ ELISpot and other immune assays
- A descriptive analysis of serial biopsies will also be assessed, including analysis of the mutagenic landscape by exome and RNA sequencing, and IHC to study tumor microenvironment

KEY ELIGIBILITY CRITERIA

Eligible patients who have not achieved a confirmed complete response by week 12 on checkpoint blockade as respective standard of care (SOC) can be enrolled.

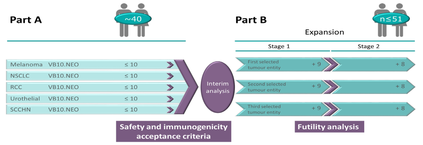
Key inclusion criteria

- Histologically confirmed locally advanced or metastatic melanoma, NSCLC, RCC, urothelial carcinoma or SCCHN
- Been on CPI (i.e., anti-PD-1 or anti-PD-L1) for at least 12 weeks before screening
- >18 years
- RECIST evaluation at screening:
  - partial response or;
  - stable disease or,
  - in progression, i.e., in case of a mixed response to CPI, provided at least one lesion shows measurable regression and according to the investigator will have a clinical benefit of continued immunotherapy
- Adequate tumor specimen available for exome sequencing
- Measurable disease per RECIST 1.1
- ECOG performance status ≤ 1

Key exclusion criteria

- Ocular melanoma
- Brain metastases (unless controlled and stable for at least 6 weeks) or leptomeningeal spread of disease
- Positive serological test for hepatitis C virus or hepatitis B virus surface antigen (HBsAg) or human immunodeficiency virus (HIV)
- Other concomitant or prior malignant disease, except for adequately treated basal cell carcinoma or other non-melanomatous skin cancer, low-grade urothelial cancer or other malignancies treated with curative intent within 2 or more years pre study entry and in complete remission at study entry

STUDY DESIGN



Part A

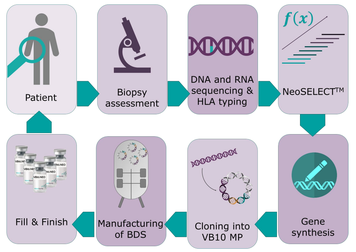
- Basket trial with five different indicated tumor entities
- Maximum 40 patients will be enrolled, with max. 10 patients per tumor entity

Part B

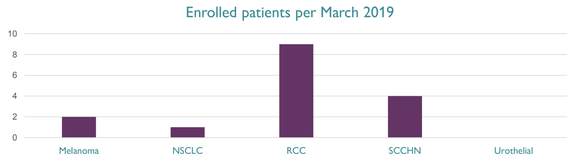
- Tumor entity-specific expansion cohorts can be opened once the safety (overarching), and immunogenicity (tumor entity-specific) criteria are met (indicated with purple arrows) and regulatory approval to proceed into part B has been obtained (interim analysis)
  - At least 30% (12 patients) of the total patient number have completed week 10 (visit 8)
  - IDSMB recommends continuation of the study (safety)
  - At least 2 patients out of at least 6 patients in one tumor entity-specific part A cohort demonstrate a positive immunogenicity result (immunogenicity)

VB10.NEO SUPPLY CHAIN

At screening, mandatory biopsy and blood samples are used to identify the patient-specific tumor mutations. A personalized VB10.NEO holding up to 20 unique neoantigens will be designed based on Vaccibody's proprietary neoepitope selection algorithm NeoSelect™. One GMP batch is produced per patient.



STUDY STATUS



- 16 patients have been enrolled as of March 2019.
- The staggered treatment scheduled for the first patients was completed uneventful.
- Safety surveillance and the trial is continuing as planned.

SUMMARY

- The study is ongoing at 3 clinical sites in Germany (NCT03548467)
- Regulatory approval was received in March 2018 for the VB N-01 (DIRECT-01) basket trial
- The VB N-01 study is currently enrolling
- Patient-specific VB10.NEO vaccine batches have to date been produced successfully for all patients enrolled
- The initial accrual goal has been met

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