A Multi-Centre, Open-label Phase 2 Trial of the Combination of VB10.16 and Atezolizumab in Patients with Advanced or Recurrent, Non-resectable HPV16 Positive Cervical Cancer

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BACKGROUND

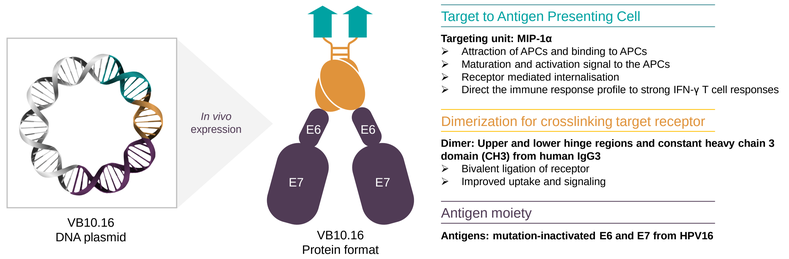
HPV16 accounts for almost 60% of the cervical cancer cases. There is an urgent need to develop novel treatment options, such as therapeutic HPV vaccines for the control of HPV induced neoplastic diseases. HPV16 oncogenes E6/E7 are truly cancer-specific viral antigens and represent ideal targets for a therapeutic HPV16 vaccine. VB10.16 is a targeted DNA-based immunotherapy designed to treat HPV16-associated pre- and malignant lesions. The DNA vaccine encodes a recombinant protein consisting of mutation-inactivated E6 and E7 proteins linked to the natural human chemokine macrophage inflammatory protein-1 alpha (MIP-1α). Atezolizumab is a PD-L1 inhibitor indicated for the treatment of urothelial carcinoma, non- small cell and small cell lung cancers, triple negative breast cancer and hepatocellular carcinoma. In a phase 1 trial, VB10.16 monotherapy demonstrated a beneficial safety and efficacy profile and upregulated PD-L1 in the least responsive patients. This provides a strong rationale for combining VB10.16 with a checkpoint inhibitor therapy.

This open-label phase 2a trial is designed to evaluate the safety and efficacy of multiple dosing with VB10.16 immunotherapy in combination with atezolizumab in patients with advanced or recurrent non-resectable HPV16+ cervical cancer, who failed or are not eligible for current standard of care.

The study will enroll 50 patients and is approved in 6 European countries and open for enrolment (NCT04405349).

MECHANISM OF ACTION (VB10.16)

VB10.16 is a potent **DNA plasmid vaccine** based on the pUMVC4a vector backbone encoding a single recombinant protein consisting of three modules.



VB10.16 DNA plasmid

VB10.16 Protein format

Target to Antigen Presenting Cell

Targeting unit: MIP-1α
- Attraction of APCs and binding to APCs
- Maturation and activation signal to the APCs
- Receptor mediated internalisation
- Direct the immune response profile to strong IFN-γ T cell responses

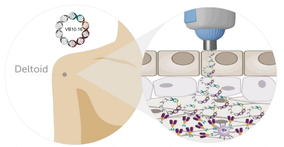
Dimerization for crosslinking target receptor

Dimer: Upper and lower hinge regions and constant heavy chain 3 domain (CH3) from human IgG3
- Bivalent ligation of receptor
- Improved uptake and signaling

Antigen moiety

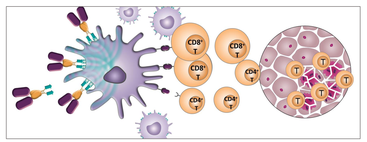
Antigens: mutation-inactivated E6 and E7 from HPV16

The VB10.16 vaccine is administered as intramuscular injections with the **PharmaJet® Stratis** injection system. Delivery and mode of action presented below.



Administration (i.m) of VB10.16 DNA plasmid

In vivo protein expression and secretion



Target – Attract – Mature – Deliver – Cross-present

- 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**

OBJECTIVES

Primary Objectives

- To assess the safety/tolerability and clinical efficacy by overall response rate (ORR) of multiple doses of 3 mg VB10.16 immunotherapy in combination with 1200 mg atezolizumab

Secondary Objectives

- To assess the immunogenicity of multiple doses of 3 mg VB10.16 immunotherapy in combination with 1200 mg atezolizumab
- To further assess efficacy of multiple doses of 3 mg VB10.16 immunotherapy in combination with 1200 mg atezolizumab in patients by progression-free survival (PFS), duration of response (DOR), and overall survival (OS)

Exploratory Objectives

- To investigate predictive biomarkers and changes in tumour microenvironment during therapy
- To evaluate correlation between HPV16 circulating tumour (ct) DNA and clinical response

KEY ELIGIBILITY CRITERIA

Key inclusion criteria

- Patients with persistent, recurrent, or metastatic non-resectable squamous cell carcinoma, adeno-squamous carcinoma, or adenocarcinoma of the cervix, who have failed or are not eligible for treatment with systemic chemotherapy, radiotherapy or other standard-of-care anticancer treatment
- Tumour must be HPV16 positive (mandatory archival tumour tissue sample not older than 2 years or new biopsy)
- Measurable disease as assessed by the local site investigator/radiology as per RECIST 1.1
- ECOG performance status of 0-1
- Life expectancy of > 6 months

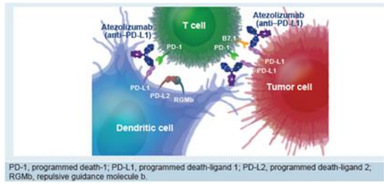
Key exclusion criteria

- Rapidly progressing disease while on anticancer treatment (or within 3 months from the last dose of this treatment)
- Brain metastases (unless they have received prior treatment and are controlled and stable for at least 6 weeks before Visit 1) or leptomeningeal spread of disease
- Other concomitant or prior malignant disease, except for: a) adequately treated basal cell carcinoma or other non melanomatous skin cancer, or low-grade urothelial cancer; b) other malignancies treated with curative intent, without disease recurrence and in complete remission with treatment completed 2 years or more before Screening
- Active, known or suspected autoimmune disease
- Active bleeding within last 2 weeks

MECHANISM OF ACTION (ATEZOLIZUMAB)

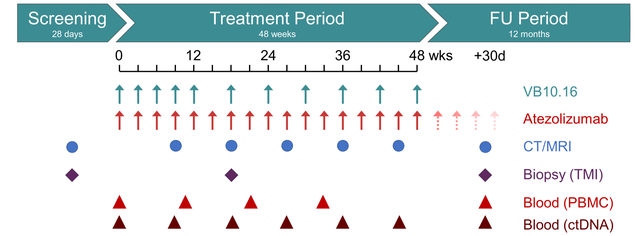
- Atezolizumab inhibits binding of PD-L1 to PD-1 and B7.1 and may thereby enable the activation of T-cells
- PD-L1 expression is present in a high proportion of cervical tumours* and has been postulated to be a predictive biomarker of tumor response to PD-1/PD-L1 inhibitors*

**Reference: Chung et al. J Clin Oncol. 2019*



STUDY INTERVENTIONS & ASSESSMENTS

Patients will receive:
- up to 11 intramuscular (i.m.) vaccinations of **VB10.16** (3 mg) for up to 48 weeks and
- up to 17 intravenously (i.v.) infusions of **atezolizumab** (1200 mg) for up to 48 weeks or as long as the patient may derive clinical benefit



Safety assessments
- Safety will be assessed by evaluating AEs, clinical laboratory test results, vital sign measurements, and physical examination findings.
- Immune-mediated AEs will be followed closely and management performed according to established standards of care and in accordance with the study protocol and the Investigator's Brochure.
- An interim safety review will take place after the first 10 patients have received their first 3 immunizations.
- A follow-up period of up to 12 months will follow the 48 week treatment period.

Efficacy assessments
- Tumour response will be assessed by computed tomography (CT)/magnetic resonance imaging (MRI) at every 9 weeks throughout the treatment period according to the RECIST 1.1 criteria (and iRECIST for exploratory endpoints).

Other assessments
- Tumour material to confirm HPV16 status at screening.
- Tumour material at up to 3 time points (screening, week 18 and early termination) to investigate predictive biomarkers (e.g. PD-L1) at screening and tumour microenvironment (e.g. T cell infiltration) during therapy.
- Blood samples for immune monitoring (PBMC) at baseline, 7-14 days after fourth dose, week 21, 33 and 30 days after end of treatment (EoT).
- Blood samples for ctDNA analyses at baseline and every 9 weeks throughout the treatment period, and 30 days after EoT.

SUMMARY

The VB C-02 study is currently enrolling patients in 6 European countries: Germany, Belgium, Bulgaria, Czech Republic, Poland and Norway (NCT04405349).

This study is sponsored by Vaccibody AS and conducted in collaboration with F. Hoffmann- La Roche Ltd

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