A Phase 1/2a, Open-label, Dose-finding Trial to Evaluate Safety, Immunogenicity, and Anti-tumour Activity of VB10.16 in Combination with Pembrolizumab in Patients with Unresectable Recurrent or Metastatic HPV16-positive Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

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Background

- **HPV16:** In the US and UK, Human Papilloma Virus (HPV) causes 71% and 52% of Oropharyngeal Squamous Cell Carcinoma (OPSCC), predominantly HPV16-induced. At least 10-25% of patients diagnosed with OPSCC develop disease recurrence after primary treatment, the majority within 2 years after initial diagnosis[1]
- **Treatment landscape in recurrent/metastatic (R/M) HNSCC:** Pembrolizumab with or without combination chemotherapy is approved by the European Medicines Agency (EMA) for R/M HNSCC patients with a combined positive score (CPS) ≥1. The approval was based on results from the KEYNOTE-048 trial (2). However, the treatment response to pembrolizumab alone is limited (19% objective response rate)[2]. There is still an unmet medical need to develop better therapeutic options for HPV16 positive OPSCC with CPS ≥1.
- **VB10.16:** The HPV oncogenes E6 and E7 are ideal targets for therapeutic HPV vaccines[3]. VB10.16, a DNA-based therapeutic vaccine encoding E6 and E7 proteins from HPV16 linked to natural human chemokine ligand 3-like 1 (CCL3L1), triggers strong HPV-specific T-cell responses. After VB10.16 monotherapy in patients with HPV16-positive high-grade cervical intraepithelial neoplasia, a PD-L1 upregulation post-vaccination was observed indicating that VB10.16 might sensitize tumours to anti-PD(L)1 treatment[4]. In a Phase 2 trial in R/M cervical cancer, VB10.16 combined with atezolizumab showed a favourable safety profile and promising efficacy[5]. Boosting T-cell responses with VB10.16 could be a valuable strategy in combination with the anti-PD-1 pembrolizumab to improve outcomes in HPV16-positive R/M OPSCC patients.

VB10.16 - Mode of action

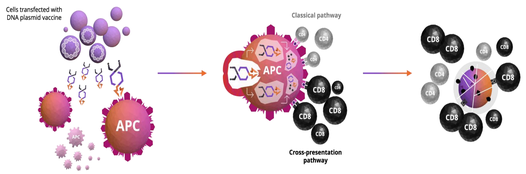
VB10.16 is an investigational non-integrating off-the-shelf DNA-plasmid therapeutic cancer vaccine under development to treat HPV16-associated premalignant and malignant lesions. VB10.16 encodes a recombinant fusion protein consisting of mutation-inactivated HPV16 E6 and E7 oncoprotein antigens linked, via a dimerization unit, to the natural human chemokine ligand 3-like 1 (CCL3L1).

Targeting Unit
CCL3L1: CCL3L1 targeted immunotherapies attract and stimulate antigen presenting cells (APCs), eliciting broad, strong and dominant CD8 T cell responses combined with supporting CD4 helper T cell responses

Dimerization unit:
The dimeric format is designed to facilitate attraction, activation and internalization into the APC by crosslinking receptors on the surface of the APC

Antigenic unit:
Contains mutation-inactivated full-length HPV16 E6 and E7 antigens

The DNA plasmid VB10.16 is delivered by needle-free intramuscular administration (PharmaJet® Stratis®) and enters myocytes at the injection site. After uptake, the plasmid is translated, and the newly encoded VB10.16 proteins is secreted from the cells. The CCL3L1 domain has two actions: recruiting antigen presenting cells (APCs) to the injection site and directly targeting the protein to APCs. Both mechanisms enhance antigen loading to APCs, which present HPV16 epitopes (E6 and E7) to CD4+ T-helper cells and CD8+ cytotoxic T-cells, leading to T-cell activation. The activated T-cells can target HPV16-positive tumours and mediate cell killing.



Trial Design

This phase 1/2a, open-label, dose-finding trial is designed to determine the biological optimal dose of VB10.16 in combination with a fixed dose of pembrolizumab based on the totality of data (i.e. safety, tolerability, immunogenicity with HPV16 E6/E7 specific cellular immune responses, and anti-tumour activity) in patients with HPV16-positive R/M HNSCC whose tumours express PD-L1 (CPS ≥ 1) and who are eligible for pembrolizumab monotherapy. The trial consists of 2 phases (Figure 1A), a VB10.16 dose escalation phase (Phase 1) with proportion of patients with dose-limiting toxicities as primary endpoint, and a dose expansion phase (Phase 2a).

After 48 weeks of combination treatment, patients can either continue with pembrolizumab with 200 mg Q3W or change to 400 mg Q6W at the discretion of the investigator and after consultation with the Sponsor corresponding to approximately 2 years of trial treatment (Figure 1 B).

Figure 1A. Trial phases

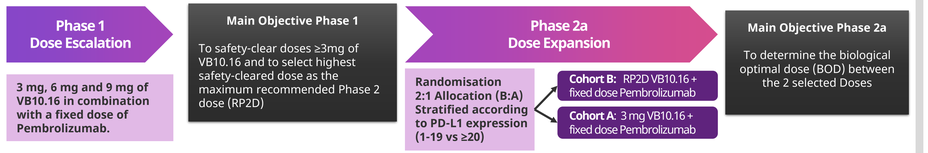
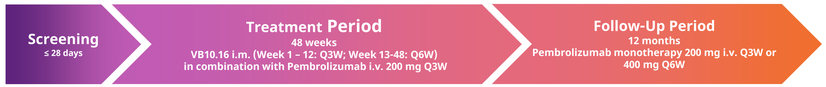


Figure 1B. Trial Treatment Schedule (for both trial phases)



Key Eligibility Criteria:

- Histologically or cytologically confirmed R/M HNSCC, located in the oropharynx, considered incurable by local therapy and eligible for monotherapy with pembrolizumab.
- HPV16 positivity of R/M oropharyngeal HNSCC confirmed by designated central laboratory.
- PD-L1 positivity (CPS ≥1) using the validated PD-L1 IHC 22C3 pharmDx (DAKO) assay.
- No prior systemic therapy administered in the R/M setting
- Immune checkpoint inhibitor naïve
- At least 1 measurable lesion per RECIST v1.1
- ECOG performance Status ≤1
- No progressive disease for at least 6 month after completion of curatively intended concurrent chemoradiotherapy for locoregionally advanced HNSCC
- No known history of HIV, Hepatitis B or C infection
- Rapidly progressing disease (e.g., tumour bleeding, uncontrolled tumour pain) in the opinion of the investigator is an exclusion criteria

Endpoints Dose Expansion Phase 2a:

Primary Endpoints:
- Objective Response Rate (ORR)
- Proportion of patients who discontinue due to an adverse reaction
- Change from baseline in HPV16 E6/E7-specific T-cell responses as measured by IFN-γ ELISpot in post-vaccination samples.
- Proportion of patients with AEs following treatment initiation by severity grade

Secondary endpoints:
- Disease control rate (DCR)
- Duration of response (DOR)
- Duration of complete response (DOCR)
- Duration of disease control (DODC)
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Proportion of patients who are progression-free
- Proportion of patients who are alive

Status

First patient dosed: December 2023

Estimated enrolment: 51 patients

Enrolment currently ongoing in 8 European countries

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