Safety, efficacy and immunogenicity of VB10.16, a therapeutic DNA vaccine targeting human papillomavirus (HPV) 16 E6 and E7 proteins for high grade cervical intraepithelial neoplasia (CIN 2/3): 6-month data from an exploratory open-label phase 1/2a trial

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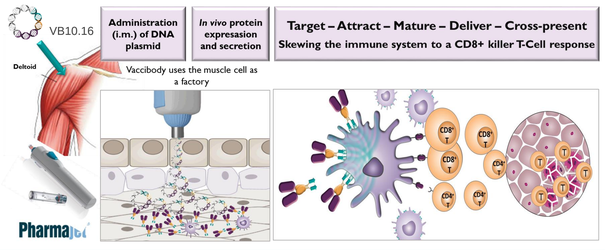
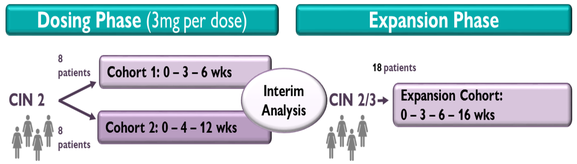
BACKGROUND

Persistent HPV infection can lead to high-grade squamous intraepithelial lesions (HSIL) in cervical cells; current treatments are exclusively ablative which can lead to long-term reproductive morbidity.

VB10.16, an investigational immunotherapy designed to treat precancers and cancers induced by HPV16, is a potent DNA plasmid vaccine with intrinsic adjuvant effect designed for efficient delivery of antigens E6 and E7 from HPV16 to elicit strong immune responses.



STUDY DESIGN

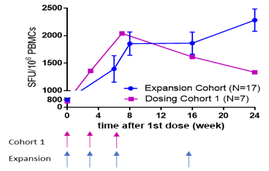


VB C-01 is a first-in-human dose, open-label, multicenter phase 1/2a study of VB10.16 immunotherapy for the treatment of high grade Cervical Intraepithelial Neoplasia (CIN 2/3) caused by HPV16.

The **primary objective** of the study was to evaluate the safety and tolerability of VB10.16. The **secondary objectives** were to assess peripheral T cell immunogenicity and to evaluate early signs of efficacy by means of CIN regression and HPV clearance.

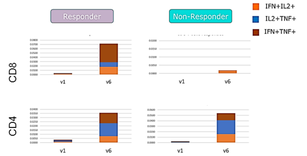
IMMUNOGENICITY

VB10.16 induced strong, long-lasting HPV16-specific immune responses



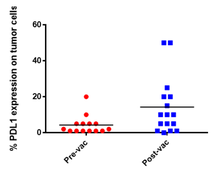
Patients in the Expansion cohort, receiving a booster dose at week 16, showed a stronger and longer-lasting T cell response to HPV16 E6 and E7 proteins in IFNγ ELISpot.
HPV16-specific T cell responses were observed in all patients and responses were increased after vaccination in 16 of 17 patients.

Multifunctional CD8+ T cell elicited post vaccination in responders



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

PD-L1 up-regulated in patients after vaccination



PD-L1 was up-regulated in patients after vaccination, which is in line with the vaccine VB10.16 inducing strong IFNγ T cell responses.
PD-L1 may block an efficacious long-term immune response and combining the VB10.16 vaccine with an anti-PD-1/PD-L1 checkpoint inhibitor could be beneficial to improve its effect,

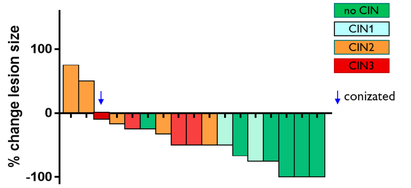
SAFETY

Vaccinations were well tolerated. The AEs were mainly mild to moderate, of short duration and related to the injection site.

Majority of the events reported were grade 1-2, only one patient reported a drug-related treatment emergent grade 3 event. No SAEs were reported.

CLINICAL EFFICACY

CIN grading and lesion size regresssion at 6-months



16 of 17 patients in the expansion cohort were followed for 24 weeks (1 conizated before week 24 visit).

Of the remaining 16 patients, 15 patients were assessed as responders by investigator at 6 months (2 CR, 13 PR and 1 SD).

14 patients showed a regression in lesion size from colposcopic examination at 6 months (median reduction was 50%).

Histopathological regression to low grade neoplasia (CIN1) or no disease was seen in 8 patients.

Of the 8 patients that have not regressed to CIN1 or less at 6 months, 6 patients showed upregulation of PD-L1 in the lesions which may delay or inhibit elimination of all affected cells.

CONCLUSIONS

- We report strongly encouraging interim phase 1/2a safety, tolerability, immunogenicity and signs of clinical efficacy results for a therapeutic HPV16 DNA plasmid vaccine VB10.16 in women with HSIL
- VB10.16 is capable of eliciting HPV16-specific CD4+ and CD8+ T cells contributing to elimination of HPV16-infected and transformed cells, leading to reduction in lesion size and CIN grading
- Up-regulation of PD-L1 post vaccination provides a rationale for investigating the combination of checkpoint inhibitors with VB10.16 in HPV16-associated cancers
- A phase 2 clinical trial in HPV16 positive cervical cancer in combination with atezolizumab (Tecentriq®) is planned to start early 2020

DEMOGRAPHICS & TREATMENT

Demographic Characteristics	Cohort 1	Cohort 2	Expansion	Overall
Number of Patients	8	8	18	34
Age (years)				
Mean	31.4	27.4	29.1	29.2
Min - Max	25 - 46	25 – 30	24 – 41	24 - 46
Cervical Dysplasia Categorization				
CIN2	8 (100.0%)	8 (100.0%)	8 (44.4%)	24 (70.6%)
CIN3	0	0	10 (55.6%)	10 (29.4%)
Number of vaccinations				
Two	0	0	1 (5.6%)	1 (2.9%)
Three	8 (100%)	8 (100%)	0	16 (47.1%)
Four	0	0	17 (94.4%)	17 (50.0%)

Cohort 1 from the Dosing phase induced the strongest T Cell responses which correlated with lesion size reduction.
The dosing schedule 0, 3, 6, with a booster dose week 16 was selected for the Expansion phase.
18 patients were enrolled in the Expansion cohort. One was an error (HPV16 negative) and results are reported on 17 patients.

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Abstract #CT209

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