P424

VB10.NEO, an individualized neoepitope cancer vaccine, induces positive clinical responses in patients with locally advanced or metastatic solid tumours

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BACKGROUND

Fully personalized cancer neoantigens vaccines are a new class of cancer therapies. These vaccines are customized to trigger an immune response to each patient's unique set of mutations that are tumour specific and not subject to central tolerance.

VB10.NEO is a DNA vaccine with intrinsic adjuvant effect designed for efficient delivery of personalized neoepitopes and holds up to 20 unique neoepitopes specific for each patient's tumour (Fig. 1). Preclinical data support VB10.NEO's unique ability to generate CD8 responses translating into anti-tumour efficacy.

VB N-01 (DIRECT-01) is an open-label phase 1/2a study (NCT03548467) in up to 40 patients with locally advanced or metastatic solid tumours including

- Melanoma
- Non-small-cell lung carcinoma (NSCLC)
- Clear renal cell carcinoma (RCC)
- Urothelial cancer
- Squamous cell carcinoma of the head and neck (SCCHN)

in combination with checkpoint inhibitors as standard of care (SOC).

Here, we present the first interim clinical response data from 14 heavily pre-treated patients that were followed for 9-37 weeks after the first dose of VB10.NEO at data cut-off (1st October 2019).

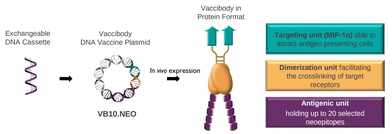

Figure 1. Vaccibody's proprietory DNA vaccine technology.

VB N-01 STUDY

Before enrolment, the patients have been treated for at least 12 weeks with CPI (nivolumab or pembrolizumab) as standard of care (SoC), often in addition to multiple lines of prior anti-cancer treatments. Most patients had stable disease with one patient showing a mixed response when enrolled into the study (Table 1).

Manufacturing of the DNA vaccine commenced upon tumour tissue collection. So far, Vaccibody succeeded in manufacturing all patient batches with the top 20 neoepitopes selected. During manufacturing, five patients progressed, one had a partial response, while all other patients started VB10.NEO treatment with stable disease (Table 1).

Patients were given Q3W VB10.NEO vaccinations for an induction period of 6 weeks, with Q4W vaccinations following until week 50. The vaccine is administered intramuscularly with a needle-free jet injector (PharmaJet Stratis).

12 out of 14 patients continued treatment with the CPI as SoC during VB10.NEO treatment.

So far, treatment with VB10.NEO has been well tolerated. The most common adverse events attributable to VB10.NEO treatment (TRAEs) were injection-related hypertensive episodes and injection site reactions.

EFFICACY

Patient ID	Indication	Year of initial diagnosis	Age	Prior therapy	TMB	Months CPI before VB10.NEO	Best response on CPI	Status at screening	Status at start VB10.NEO
02-003	Melanoma	2000	81	S	high	10	PR	SD	SD
02-007	NSCLC	2018	54	S, Rt, ch	med	9	SD	SD	PD
01-001	RCC	2014	69	S	low	18	SD	SD	SD
01-003	RCC	2005	64	S, T, o	low	5*	PD	PD mixed	PD
01-005	RCC	2006	58	S, Rt, T	low	11	SD	SD	SD
02-002	RCC	2013	76	S, IT	low	8+15	PR	SD	PD
01-007	RCC	2017	55	S, T	low	14	PR	SD	SD
01-008	RCC	2017	62	S, T	low	14	SD	SD	SD
01-009	RCC	2011	57	S, Rt, o	low	31	SD	SD	SD
01-011	RCC	2007	58	S, o	low	26	PR	SD	SD
01-002	SCCHN	2005	53	S, Rt, T, ct, o	low	32	SD	SD	PD
01-004	SCCHN	2015	69	S, Rt, ct, ch	low	15	SD	SD	SD
01-006	SCCHN	2017	68	S, ch, ct, ipi	med	17	SD	SD	PD
01-010	SCCHN	2015	60	S, Rt, ct	low	12	SD	SD	PR

Table 1. Patient disposition for all patients with at least one scan after VB10.NEO (n=14).
* Patient stopped CPI 2 months prior first dose VB10.NEO.

Most responses to checkpoint inhibitors occur within the first 3-5 month. After this period, further reductions in lesions size are unexpected and lesions that progress usually continue to grow without further interventions.

50% of all analyzed patients (n=14) showed clinical responses to VB10.NEO treatment, defined as a reduction in the sum of target lesions by at least 10% or stabilization of prior progressing lesions.

The seven patients showing clinical responses include the melanoma, the NSCLC, one of the eight RCC patients (01-003), as well as all four SCCHN patients (Fig. 3). These patients had all been treated with CPI for 9-32 months before the first dose of VB10.NEO.

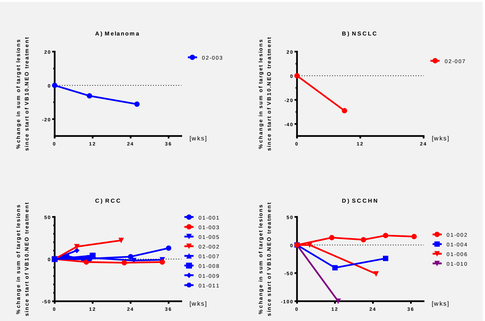

Figure 2. % change in sum of target lesions vs. time for all patients by entity. Patients stable at start of VB10.NEO treatment are indicated in blue; two show lesion size reduction. Patients progressing between enrolment and first dose of VB10.NEO are indicated in red; two of which show lesion stabilization while two have a lesion size reduction. One patient had a partial response to CPI, indicated in purple, with a further lesion size reduction after start of VB10.NEO treatment. (Four patients were reported with new lesions.)

Figure 3 provides a more detailed overview of the development of the individual target lesions in the responding patients with SCCHN, melanoma and NSCLC before and after VB10.NEO treatment start. The clinical responses are observed within 9-24 weeks after the first dose of VB10.NEO.

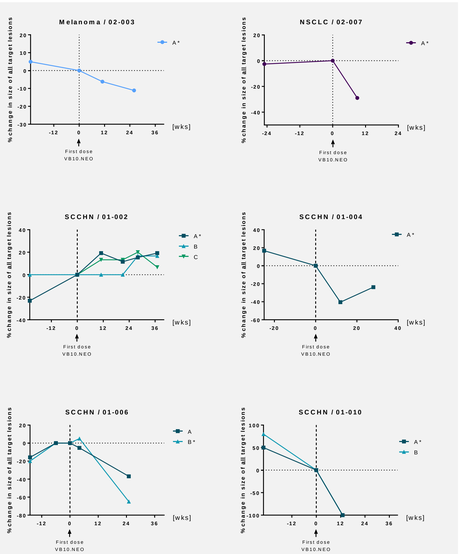

Figure 3. % change in all target lesions vs. time for all melanoma, NSCLC and SCCHN patients. Prior measurements (3-6 months pre first dose of VB10.NEO) are included. First dose VB10.NEO is indicated with a dotted vertical line. Target lesions that were used to select neoepitopes for the vaccines are marked with an asterisk.

Clinical responses are observed even in patients with low tumour mutational burden (TMB) and large tumour burden (Fig. 4). This demonstrates the broad potential for VB10.NEO.

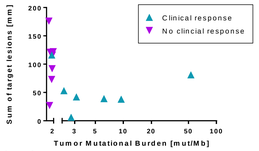

Figure 4. TMB vs lesion sizes.

IMMUNOGENICITY

Immunogenicity to each individual neoepitope was assessed in 8 patients after six vaccinations by *in vitro* pre-stimulated IFN-γ ELISpot. The breadth and strength of neoepitope-specific T cell responses were increased with the number of vaccinations (data not shown). Strikingly, clinical responses correlate with the number of selected immunogenic neoepitopes (Fig. 5A), an increased immune response to the majority of selected neoepitopes (Fig. 5B), as well as the induction of *de novo* responses (Fig. 5C). Furthermore, there is a clear correlation between the frequency of high-quality neoepitopes included in the vaccine, as predicted by Vaccibody's proprietary neoepitope selection algorithm **NeoSELECT™**, and clinical responses (Fig. 5D).

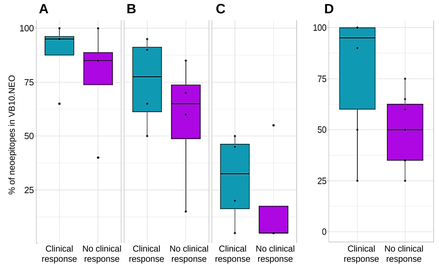

Figure 5. Correlation of clinical efficacy with A) % of immunogenic neoepitopes in VB10.NEO, B) increased neoepitope-specific T cell responses after VB10.NEO start, C) *de novo* responses and D) the number of high-quality neoepitopes.

Flow cytometry analysis characterizing CD8+ and CD4+ T cell responses were performed in two SCCHN patients with clinical responses. Patient 01-004 had increased T cell responses after vaccination towards 12 of 20 neoepitopes of which 10 were *de novo* responses as identified by *in vitro* pre-stimulated IFN-γ ELISpot. The three strongest *de novo* responses were confirmed by flow analysis to be dominated by CD8+ T cells (Fig. 7). Additionally, CD4+ T cell responses were observed to multiple neoepitopes.

In patient 01-002, the neoepitope-specific T cell responses were amplified against 19 of 20 neoepitopes. The strongest neoepitope-specific T cell responses were also in this patient confirmed to be CD8+ T cell dominated. The strongest neoepitope-specific T cell responses identified by *in vitro* pre-stimulated IFN-γ ELISpot and flow cytometry were confirmed to be the strongest response also in *ex vivo* ELISpot analysis (data now shown).

Interestingly, in patient 01-001 that showed no clinical response, neoepitope-specific immune responses were dominated by CD4+ T cells.

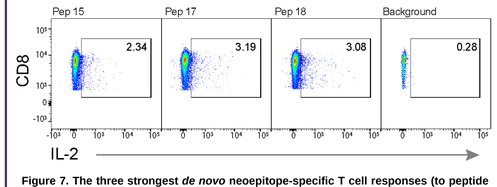

Figure 7. The three strongest *de novo* neoepitope-specific T cell responses (to peptide 15, 17 and 18) in patient 01-004 were confirmed to be CD8+ T cells by flow cytometry.

EFFICACY

One of the SCCHN patients, 01-002, showed progression of two target lesions in the cervical area prior to VB10.NEO treatment. Post treatment and up to week 37, these lesions were stabilized (Fig. 3 – SCCHN / 01-002). Interestingly, a follow-up tumour biopsy at week 24 showed that the tumour cells left in the cervical area no longer contained the neoepitopes targeted by the vaccine (Fig. 6). 19 of the 20 mutations were no longer found in the remaining tumour cells indicating that the vaccine had successfully killed all tumour cells with these mutations.

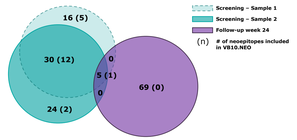

Figure 6. Venn diagram of neoepitopes found in tumour samples at screening (cyan) and at follow-up biopsy (purple).

SUMMARY

- **VB10.NEO demonstrates the ability to induce clinical responses in multiple patients with metastatic or locally advanced solid tumours**
- **The clinical responses were observed within 9-24 weeks after first dose of VB10.NEO**
- **The clinical responses correlate with frequency of high quality neoepitopes as well as strong *de novo* neoepitope-specific CD8+ T cell responses induced by the vaccine**
- **The lesion used for neoepitope selection by NeoSELECT™ showed the most evident tumour shrinkage**
- **All patient-specific VB10.NEO vaccine batches have to date been produced successfully with the 20 highest ranked neoepitopes**
- **VB10.NEO is well tolerated**

vaccibody

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