VXM01 phase I study in patients with progressive glioblastoma - Final results

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Background

VAXIMM's oral T-cell vaccine platform is based on the approved, live attenuated *Salmonella* Typhi vaccine strain Ty21a, which has been applied in millions of individuals for prophylactic vaccination against typhoid fever. This strain has been thoroughly studied, and is safe and well tolerated. The bacteria are modified to deliver an eukaryotic expression plasmid which encodes the genetic information of a specific target antigen, via the oral route[1].

VXM01 encodes vascular endothelium growth factor receptor 2 (VEGFR2) to evoke an immune response directed to the tumor vasculature and VEGFR2-expressing tumor cells. It is currently in clinical development as a treatment for solid cancer types[2,3]. The murine analogue of VXM01 has shown consistent anti-angiogenic activity in different tumor types in several animal studies[4]. An increase in tumor immune cell infiltration was recently shown. A proposed mechanism of action of VXM01 is described in **Figure 1**.

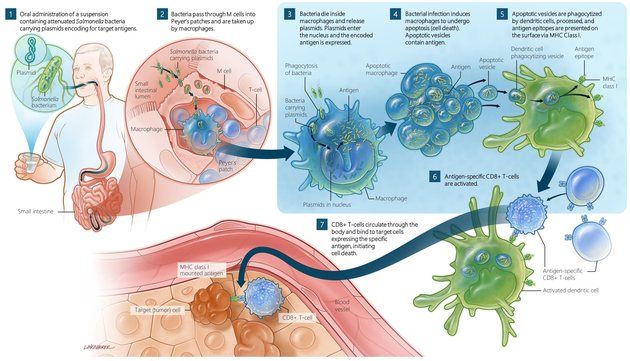

Figure 1. Intra-lymphatic delivery of *Salmonella* Typhi strain Ty21a vaccine VXM01 via the oral route leading to target specific T-cell activation.

This trial was set up to examine safety and tolerability, clinical and immunogenic response to VXM01 after treatment with at least four vaccinations [10^6 or 10^7 colony-forming units (CFU)] in patients with progressive glioblastoma who have failed at least radiochemotherapy with temozolomide and who are a candidate for a reoperation (clinical trials.gov #NCT02718443).

Methods

Patients with progressive operable glioblastoma were subjected to VXM01 in one oral administration each on day 1, 3, 5, and 7. In addition, VXM01 was allowed to be administered in 4-weekly single doses on week 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 during the tumor follow-up period after surgery. Follow-up was done by weekly safety laboratories and physical examinations in the treatment period and 4-weekly thereafter, magnetic resonance imaging (MRI) including perfusion maps (days 15 and 30 and six-weekly thereafter), 12-weekly T-cell immunomonitoring in the peripheral blood, and brain tumor immunohistochemistry (**Figure 2**). Patient-specific prolongation of VXM01 treatment was conducted for patients benefitting from treatment.

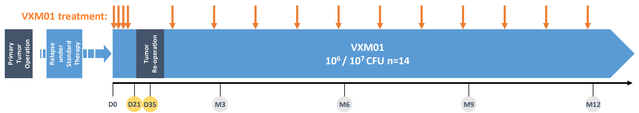

Figure 2. Study design with the vaccination schedule and the time points for analysis of the VEGFR2–specific T cell response by ELISpot (bullets).

Results

Fourteen patients have been treated with VXM01. Three out of them with additional nivolumab. Surgery has been performed in eight patients (**Figure 3**).

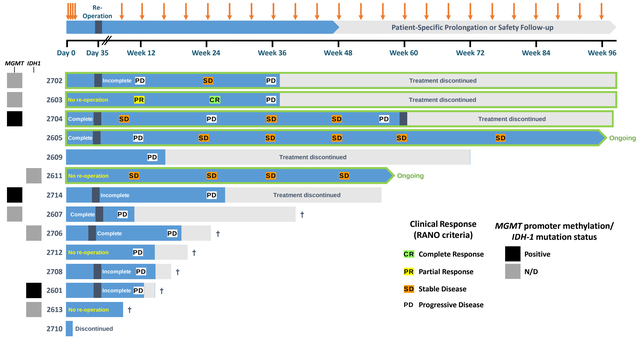

Figure 3. Swimmer plot and clinical responses observed in the patients accrued so far.

Under VXM01 treatment 129 adverse events, mostly unrelated to VXM01, were observed after a median of 8 doses per patient (**Table 1**). ELISpot analysis showed a detectable VEGFR2–specific T cell response in 7 out of 12 (58%) patients measured. In the observation period up to almost 2 years, 7 patients are alive and survived for more than 12 months after initiation of treatment (**Figures 3 and 4**).

	VXM01 (N=14)					
	F	n	n%	Maximum Severity		
All TEAEs	129	14	100	Mild/Moderate	Severe	Life-threatening
All drug-related TEAEs	6	5	35.7	80	14	1
Paresis (fascialis, hands, legs)	14	7	50.0	12	2	-
Lymphocyte count decreased	14	6	42.9	11	3	1
Aphasia	12	6	42.9	10	2	-
Cognitive slowing	8	6	42.9	8	-	-
Headache	7	5	35.7	6	1	-
Flu like syndrome	7	3	21.4	7	-	-
Fatigue	7	5	35.7	5	2	-
Nausea/vomiting	4	2	14.3	4	-	-
Brain oedema	4	3	21.4	4	-	-
Visual loss	4	2	14.3	3	1	-
Depression/anxiety attack	3	3	21.4	3	-	-
Seizure/syncope	3	3	21.4	1	2	-
Hemiplegia	3	3	21.4	2	1	-
Flatulence	2	2	14.3	2	-	-
Wound healing disorder	2	1	7.1	2	-	-

Table 1. Frequency of drug-related treatment emergent adverse events (data cut-off: 8 May 2018).

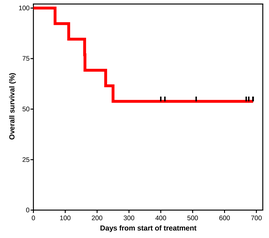

Figure 4. Kaplan-Meier survival analysis.

Survival seemed to be correlated with a higher CD8/Treg ratio in progressive and primary tumor (**Figure 5A**), which further increased after VXM01 treatment. CD8 infiltration was higher in recurrent compared to primary tumor (**Figure 5B**). In patients with prolonged survival a decrease in intratumoral PD-L1 was observed (**Figure 5C**) arguing for combination of VXM01 with an anti-PD-L1 checkpoint inhibitor.

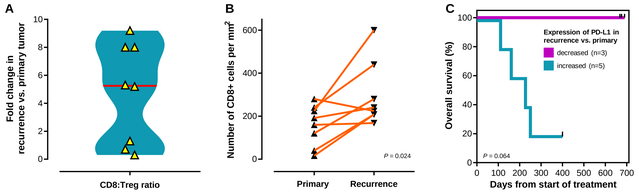

Figure 5. (A) CD8:Treg ratio (violin plot; median in red), (B) CD8 infiltration, and (C) Kaplan-Meier survival analysis in patients with increased and decreased PD-L1 expression in recurrent vs. primary tumor, as quantified by immunohistochemistry (n=8 complete pairs of data).

In total, five patients benefitted from a favorable course of disease, including:

- *Patient 2603* (male, 47 y), candidate for re-operation but not operated due to tumor shrinkage under VXM01 treatment. An objective an durable T1 response was observed (**Figure 6A**), including PR after 12 weeks under VXM01 monotherapy, and CR after additional 15 weeks under VXM01 and 6 doses of nivolumab treatment. Of note, high VEGFR2 expression was observed on the tumor neovasculature in the primary tumor.
- *Patient 2605* (female, 55 y), candidate for re-operation. Showed stabilization of tumor growth after VXM01 treatment before re-operation (**Figure 6B**). VXM01 treatment was given as monotherapy up to week 10, and combined with nivolumab from week 10 onwards. A favorable post-operative course of disease under VXM01 + chemotherapy from week 10 to week 36, and SD up to week 76 were observed. VEGFR2 was expressed on primary but not recurrent tumor cells after VXM01 treatment, which indicates a VEGFR2 targeting effect.
- *Patient 2611* (female, 44 y), candidate for re-operation. Showed stabilization of tumor growth after VXM01 treatment before re-operation (target lession size **14.6 mm × 10.8 mm** at baseline, **13.2 mm × 9.7 mm** at day 21, and **14 mm × 10 mm** at day 35), and refused the re-operation. VXM01 treatment was given as monotherapy up to week 8, and combined with nivolumab from week 8 onwards. SD was observed up to week 48 (target lesion size **14 mm × 10 mm** at week 24, and **11 mm × 10 mm** at week 36).

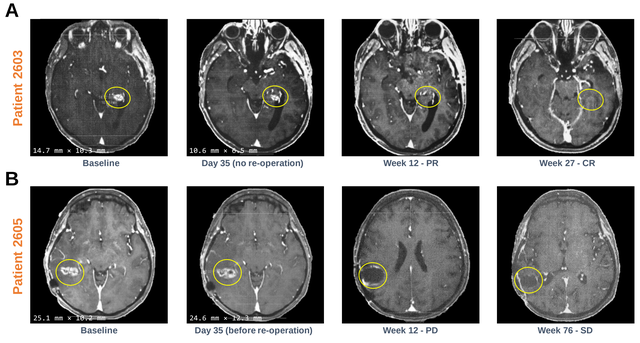

Figure 6. MRI images at the indicated time points in patients (A) 2603 and (B) 2605.

Discussion

VXM01 was safe and produces detectable specific peripheral immune responses as well as CD8/Treg ratio increase in post-vaccine tumor tissue. There was one patient with an objective response. As a next step, a combination study of VXM01 and anti-PD-L1 checkpoint inhibitor avelumab in patients with relapsed glioblastoma has been launched to investigate the synergistic mechanism of action changing the tumor microenvironment (**Figure 7**).

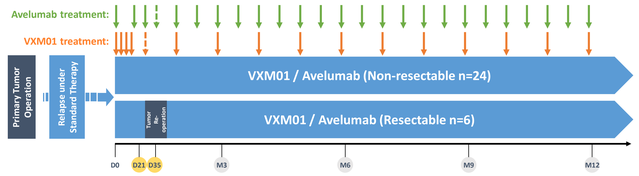

Figure 7. Study design of the new combination clinical trial in patients with relapsed glioblastoma describing the schedules of vaccination and treatment with avelumab.

Outlook

VXM01 is a potential sensitizer for checkpoint inhibitors

- **VXM01 treatment leads to**
  - **Increased immune cell / T-cell infiltration**
  - **Possible synergistic effects of VXM01 and anti-PD-1**
- **Strong partial response in one glioblastoma patient with VXM01 monotherapy**
- **Complete Response observed in this patient after nivolumab treatment was added to VXM01**
  - **No indicators of VXM01 / anti-PD-1 safety risks detected**
- **Excellent VXM01 safety profile confirmed in three cancer indications**
- **The combination of VXM01 and checkpoint inhibitor is very likely to not pose a safety concern due to minimal overlap in side effects**

References

1. Darji A. et al, Cell 1997. 2. Schmitz-Winnenthal FH. et al, OncoImmunology 2015. 3. Schmitz-Winnenthal FH. et al, OncoImmunology 2018. 4. Niethammer AG. et al, Nature Medicine 2002.

POSTER PDF

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