VXM01 phase I study in patients with operable progression of a glioblastoma to examine safety, tolerability, immune and biomarker response to the VEGFR-2 DNA vaccine VXM01

VAXIMM

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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, 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[1].

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

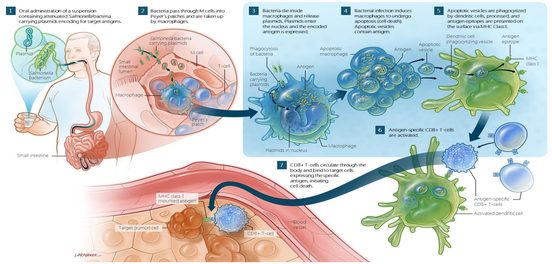

Figure 1. Intra-lymphatic delivery of VXM01 via the oral route leading to target specific T-cell activation.

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 recurrent 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.

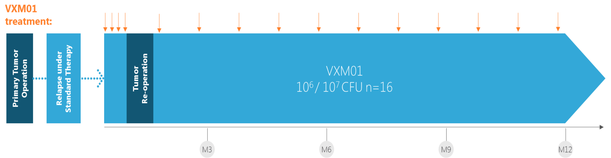

Figure 2. Scheme of the study design describing the vaccination schedule, as well as the time points selected for blood sampling for analysis of the VEGFR2-specific T cell response by ELISpot.

Results

Eight patients have been treated according to the schedule in the initial phase I part of the study and surgery has been performed in seven of them. Under VXM01 treatment 47 adverse events, mostly unrelated to VXM01, were observed after a median of 7 doses per patient. Four out of eight patients (50%) showed a VEGFR-2 specific T cell response. In four patients there was a relevant increase in cerebral blood volume and apparent diffusion coefficient on post-vaccination MRI. In one patient there was an objective and durable T1 response, whereas three further patients remained stable prior to surgery and thereafter. Evaluation of infiltrating T cells in the tissue from re-operation revealed an increase in CD8+ T-cells in 5 out of 7 patients relative to the primary tumor tissue.

Until date, a total of 14 patients have been included into the (expanded) phase I trial.

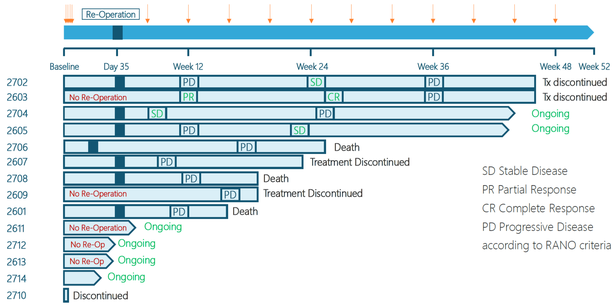

Figure 3. Schedule of events and status of the phase I patients accrued so far. Patients 2702-2609 have been accrued in the completed phase I part. Further patients are part of the expanded cohort.

Figure 4a. Patient 2603 (male, 47 y), candidate for re-operation, **not operated** due to tumor shrinkage under VXM01 treatment. VXM01 treatment without other anti-cancer therapy during study up to week 12. **Partial response (PR)** after 12 weeks under VXM01 monotherapy. **Complete response (CR)** after additional 15 weeks under VXM01/anti-PD1 treatment (follow-up ongoing). High VEGFR-2 expression on tumor neovasculature in primary tumor.

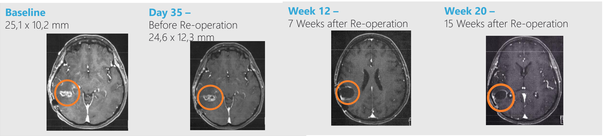

Figure 4b. Patient 2605 (female, 55 y), candidate for re-operation **showed stabilization** of tumor growth after VXM01 treatment before re-operation VXM01 monotherapy treatment up to week 10. Initiation treatment plus boosting after reoperation. Favorable post-operative course of disease – under VXM01 + chemotherapy started at week 10. **Stable Disease (SD)** at week 20 VEGFR-2 expression on tumor cells in primary tumor, but no expression on recurrent tumor cells after VXM01 treatment. Indicator of VEGFR-2 targeting effect.

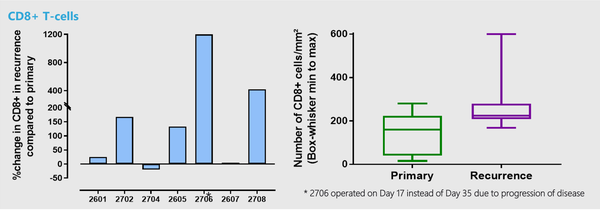

Figure 5. CD8+ Tumor T-cell infiltration increased in 5 out 7 patients

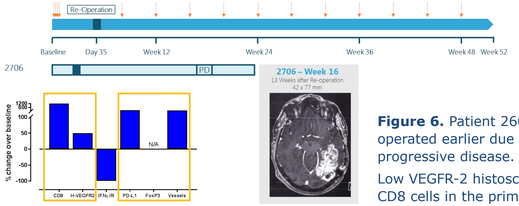

Figure 6. Patient 2607 operated earlier due to progressive disease.

Low VEGFR-2 histoscore and CD8 cells in the primary tissue.

Discussion

VXM01 was safe and produces specific peripheral immune responses as well as enumeration of tumor-infiltrating T-cells in post-vaccine tumor tissue. MRI parameters of tumor angiogenesis were affected by the treatment implying vascular normalization and there was one patient with an objective response, which continued with boost vaccinations.

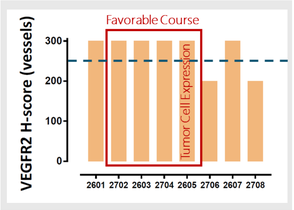

Figure 6. Hypothesis-generating immune biomarker set.

Favorable course of disease associated (i) with high VEGFR-2 H-score in tumor vasculature in primary tumor, (ii) decrease in PD-L1 post-VXM01 compared to pre-VXM01, (iii) high CD8+ T-cell level in primary tumor, VEGFR-2 expression on tumor cells in primary tumor and (v) decrease in Tregs post-VXM01 compared to pre-VXM01.

Outlook

VXM01 is potentially synergistic with checkpoint inhibitors

- VXM01 treatment leads to
  - Increased immune cell / T-cell infiltration
- 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., Cell. 1997; 91(6):765-75.* ***2.*** *Niethammer et al., Nature Medicine. 2002; 8(12):1369-1375.*