VXM01 phase 1 study in patients with progressive glioblastoma - Final results

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Background

VXM01, our 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 extensively tested, 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 route1. VXM01 encodes vascular endothelial 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 types2. The murine analogue of VXM01 has shown consistent anti-tumor activity in different tumor types in several animal studies3. An increase in tumor immune cell infiltration was reported. A proposed mechanism of action of VXM01 is described in Figure 1.

Methods

Patients with progressive operable glioblastoma were subjected to VXM01 in one oral administration each on days 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-week T-cell immunomonitoring in the peripheral blood, and brain tumor immunohistochemistry (Figure 2). Patient-specific prolongation of VXM01 treatment was conducted for patients benefiting from treatment.

Results

Under VXM01 treatment 125 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%) response to VXM01 after treatment, and 38 out of 48 patients (83%) were alive and survived for more than 12 months after initiation of treatment (Figures 3 and 4).

Discussion

VXM01 was safe and produces detectable specific peripheral immune responses in patients with at least two vaccinations (Figure 5). VXM01 treatment leads to increased and decreased PD-L1 checkpoint inhibitor expression. In total, five patients benefited from a favorable course of disease, including: - Patient 2601 (male, 47 yr), candidate for re-operation but not operated due to tumor shrinkage under VXM01 treatment. An objective response in the primary tumor (Figure 6A), including PD-L1 expression pattern in the primary tumor. - Patient 2602 (female, 55 yr), candidate for re-operation. Increased tumor growth after second operation, increased PD-L1 expression in the primary tumor (Figure 6B). VXM01 was applied. - Patient 2603 (male, 50 yr), candidate for re-operation. Increased tumor growth after second operation, increased PD-L1 expression in the primary tumor (Figure 6C). VXM01 was applied. - Patient 2604 (male, 63 yr), candidate for re-operation. Increased tumor growth after second operation, increased PD-L1 expression in the primary tumor (Figure 6D). VXM01 was applied. - Patient 2605 (female, 55 yr), candidate for re-operation. Increased tumor growth after second operation, increased PD-L1 expression in the primary tumor (Figure 6E). VXM01 was applied.

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 multimodal treatment approach
- No indicators of VXM01 / anti-PD-1 safety risks detected
- Excellent VXM01 safety profile confirmed in all patients
- The combination of VXM01 and checkpoint inhibitor is very likely to not pose a safety concern due to minimal overlap in side effects

References


Poster #171 presented during the “Central Nervous System Tumors Session at the ASCO Annual Meeting on June 2-8 2018 in Chicago.”

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