Background

VXM01’s oral T-cell vaccine platform is based on the approved, live attenuated Salmonella typhimurium vaccine strain Ty21a, which has been applied in millions of individuals for prophylactic vaccination against typhoid fever. This strain has thus been thoroughly studied, is safe and well tolerated. The bacteria are modified to deliver a eukaryotic expression plasmid, which encodes the genetic information of a specific target antigen. VXM01 is encoding vascular endothelial growth factor receptor 2 (VEGFR2) in order to evaluate 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 demonstrated antitumor activity in different tumor types in several animal studies. An increase in tumor immune cell infiltration was recently shown. A proposed mechanism of action of VXM01 is described in Figure 1.

Methods

Patients with progressive operable glioblastomas were subjected to VXM01 in one oral administration each on day 1,2,3, 7, and 14. 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 (class 15 and 30 and six-weeks thereafter), 12-week T-cell immunophenotyping in the peripheral blood, and brain tumor immunohistochemistry.

Results

Eight patients have been treated according to the schedule in the initial phase 1 part of the study and surgery has been performed in seven of them. Under VXM01 treatment, 47 adverse events were observed of which 10 (21%) were related to vaccine administration in the primary tumor. According to Week 27 of follow-up, no indicators of VXM01/anti-VEGFR2 antibodies were detected. There was no evidence of VXM01 safety implications in any of the patients. No indicators of VXM01 / anti-VEGFR2 antibodies were detected. There was no evidence of VXM01 safety implications in any of the patients.

Figure 1. Intra-lumbar 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 x 10^9 colony forming units (CFU)) in patients with recurrent glioblastoma who have failed at least radiationchemotherapy with temodar and who are a candidate for a reoperation (clinicaltrials.gov NCT01701943).

Discussion

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

Outlook

VXM01 is possibly 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 rituximab treatment was added. Additional VXM01/anti-VEGFR2 antibodies were detected. The combination of VXM01 and checkpoint inhibitor is very likely to not pose a safety concern due to minimal overlap in side effects.

References