VAXIMM

Oral DNA vaccination targeting VEGFR-2 combined with anti-PD-L1 avelumab in patients with progressive glioblastoma, a phase I/II study

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Background

Glioblastoma WHO grade IV is the most aggressive form of gliomas. Patient median survival after first diagnosis is still below 15 months in study cohorts, nearly all patients suffer from tumor recurrence, and only 25% survive more than 1 year. Since 2005 surgery followed by radiotherapy in combination with temozolomide serves as the standard first line treatment in glioblastoma. After failure of initial treatment further therapeutic options are limited. There is no standard treatment for recurrent glioblastoma. New and more effective immunotherapeutic approaches are highly needed to increase patients' survival.

VXM01 is a VEGFR-2 coding DNA vaccine, using a Salmonella Ty21a carrier for oral administration. High expression of VEGFR-2 on glioblastoma tumor tissue and tumor vasculature serves as a promising target for VEGFR-2 primed T cells. A proposed mechanism of action of VXM01 is described in **Figure 1**.

In a previous phase I/II VXM01 study in glioblastoma administration of VXM01 in 14 recurrent tumor patients showed an acceptable safety profile. Objective clinical responses in 2 patients (CR and PR) and prolonged overall survival could be associated with the VEGFR-2-specific immune response, J Clin Oncol 36, 2018 (suppl; abstr 2017). In this trial a combination therapy of VXM01 with an anti PD-L1 checkpoint inhibitor (CPI) is administered to glioblastoma patients with the intention to further enhance anti-VEGFR-2 tumor immunity induced by VXM01. Blocking of PD-L1/PD-1 interaction enhances the T cell immune function and is therefore a promising compound to boost the patients intrinsic immune defense against the tumor **(Figure 2. and 3.)**

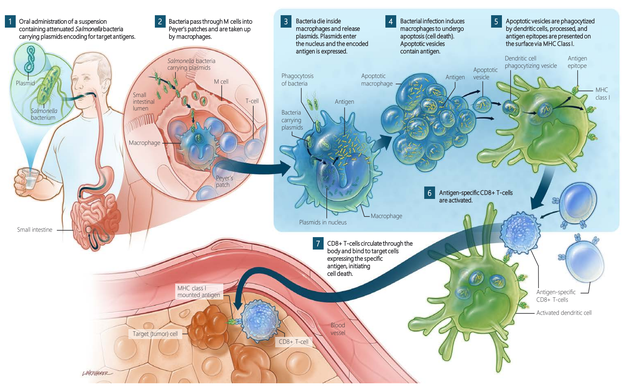

Figure 1. Intra-lymphatic delivery of *Salmonella* Typhi strain Ty21a vaccine VXM01 via the oral route leading to target specific T-cell activation.

Mode of Action Avelumab

Avelumab targeting PD-L1

- Blockade of immune-inhibitory PD-1/PD-L1 interaction leading to activation of T-cell mediated anti-tumor responses
- Induction of natural killer cell-mediated antibody-dependent cellular cytotoxicity

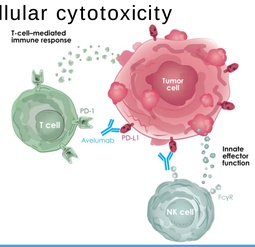

Figure 2. Mode of action avelumab

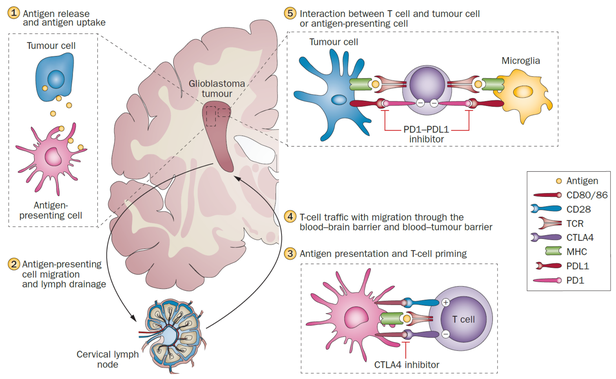

Figure 3. Tumor antigen-uptake and recirculation of primed T cells from the draining lymph node to the tumor (1-4). Blocking of PD-1/PD-L1 interaction of T cells and tumor cell/microglia during antigen presentation (5). *Weller et al., Nature Reviews 2017*

Potential synergistic mechanism of action

- **Increased effector function of vaccine induced T cells due to blocking of PD-L1 / PD-1 interaction**
- **Induction of natural killer cell-mediated antibody-dependent cellular cytotoxicity**
- **Increase of tumor T-cell infiltration**

Trial design

The trial is conducted as a multicenter, open-label, Phase I/II trial (*EudraCT.gov no. 2017-003076-31, NCT03750071*) in collaboration with Merck KGaA and Pfizer, Inc., to evaluate the efficacy and safety as well as the clinical and immunogenic response of VXM01 in combination with avelumab in patients with non-resectable (n=24) and resectable (n=6) progressive glioblastoma following tumor resection and radiochemotherapy containing temozolomide.

30 patients will be enrolled in 8 study centers in Germany, Netherlands and France. The enrolment of cohort 1 **(Figure 5.)** started with inclusion of the 1st patient in November 2018. Currently, patients of the 2nd cohort of the safety run-in are treated.

Treatment Scheme: Patients are treated with 10^6 or 10^7 CFU of VXM01+ avelumab. Vaccinations for all patients will be on day 1, 3, 5, and 7, followed by 4-weekly boosts until progression. Avelumab 800 mg will be administered intravenously every two weeks until progression. The end of study is week 60. Follow up visits after the end of study will be on months 1, 3, 6, 12 and 24. (**Figures 4 and 5**). Samples for biomarker and immunogenicity testing will collected at several time points before and after treatment.

This study receives a free supply of drug from Merck KGaA, a part of the alliance between Merck KGaA and Pfizer, Inc, New York, NY, USA

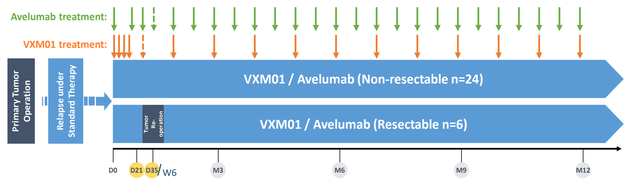

Figure 4. Study design with the vaccination schedule and the time points for analysis of the VEGFR-2–specific T cell response by ELISpot (bullets).

Safety run-in: Two cohorts of non-resectable patients are vaccinated with one of 2 doses of the oral vaccine (10^6 or 10^7 CFU), and treated with concurrent intravenous avelumab administration. After vaccination of patient 1 with 10^6 CFU and a 5-weeks observation period 2 additional patients of cohort 1 were included. Five weeks after inclusion of the latter patients, a safety evaluation and recommendation for dose escalation to 10^7 CFU was done by the **Data Safety Monitoring Board**. The same procedure will be followed for cohort 2 (10^7 CFU). After safety evaluation and recommendation of the DSMB, enrolment of cohort 3, comprising 18 non-resectable and 6 resectable patients, will be initiated in parallel at 8 study sites. (**Figures 5**).

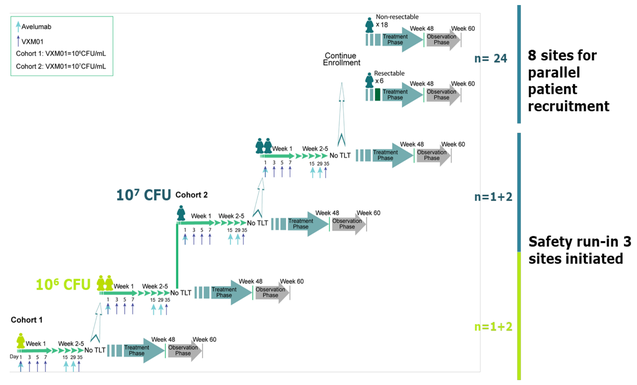

Figure 5. The safety run-in includes 6 non-resectable patients; for cohort 1 (10^6 CFU) 1+2 patients followed by cohort 2 (10^7 CFU) 1+2 patients. A 5-week observation time is held after each step. The DMSB will evaluate safety data and give recommendation about dose escalation to dose 10^7 CFU and also parallel recruitment of cohort 3.

Primary Endpoints

The primary objective is to evaluate safety and tolerability of the vaccine in combination with the anti-PD-L1 monoclonal antibody avelumab.

Secondary / Exploratory Endpoints

Objective response rate (ORR), clinical response using iRano criteria, immunological correlates before and after treatment using ELISpot, FACS immunophenotyping, TCR-sequencing, immunofluorescence, immunohisto-chemistry staining to analyse tumor infiltrating T-cells, MDSCs and characterize tumor tissue.

Main Inclusion / Exclusion Criteria

Inclusion Criteria:

- Male or female subjects. Female subjects post-menopausal surgically sterile; Age ≥18 years
- Histologically diagnosed intracranial supratentorial malignant glioma (glioblastoma WHO Grade IV)
- Evidence of tumor progression by RANO criteria following at least one prior therapy regimen that must have contained radiation and chemotherapy with temozolomide, as measured by MRI. Neurosurgical intervention should be postponable for 30 days
- Karnofsky performance status ≥70

Exclusion Criteria:

- Cardiovascular disease
- Non-healing wound, incomplete wound healing, bone fracture or gastrointestinal ulcers within three years before inclusion, or positive gastroscopy within 3 months before inclusion
- Active autoimmune disease: diabetes ; Other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis
- Women of childbearing potential
- Chronic concurrent therapy within 2 weeks before and during the treatment period with: Corticosteroids (except steroids up to equivalent of dexamethasone 4 mg daily dose); Immunosuppressive agents; Antibiotics

Summary

- **Objective clinical responses (CR and PR) and prolonged survival were observed in previous VXM01 trial in recurrent glioblastoma patients.**
- **Synergistic effects of vaccination and anti-PD-L1 are expected.**
- **VXM01 oral vaccination has been well tolerated so far.**
- **24 non-resectable, a6 resectable patients will be included in 8 study sites in Germany, France and the Netherlands.**
- **Safety run-in with Data Safety Monitoring Board approval.**
- **First patient was treated in November 2018.**
- **Extensive immunological read-out program for peripheral and intra-tumoral analysis, including TCR Seq, multiplex tumor staining, FACS immunophenotyping and ELISpot**

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. 5. Weller et al, Nature Review 2017. 6. Hamilton et al, Expert Opin Biol Ther 2017. 7. Preusser, Nature Rev Neurol 2015

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