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

Wolfgang Wick1,2, Antje Wick1, Michael J. Platten1,2, Olivier Chino1, Martin van den Bent3, Frederic Dhermain5, Marc Mansour6, Lilli Podola6, Heinz Lubena6

1Department of General Neurology, Neurology Clinic, University of Heidelberg; 2German Cancer Consortium, German Cancer Research Center, Heidelberg; 3CHU Timone, Aix-Marseille-University, Marseille, France; 4Erasmus MC Cancer Institute, Rotterdam, Netherlands; 5Gustave Roussey, Université-Paris Saclay Villejuif, France; 6Vaximm GmbH, Mannheim; 7Neurology Clinic, University of Heidelberg, University Hospital Mannheim; all German

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 serve 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 15022017). 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.)

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. 2017-00376-31, 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

Main Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male or female subjects. Female subjects post-menopausal or 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
  - Active autoimmune disease; 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, 6 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 cytokine staining, FACS immunophenotyping and ELISpot

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, cell-mediated anti-tumor response, immunofluorescence, immunohisto-chemistry staining to analyse tumor infiltrating T-cells, MDSCs and characterize tumor tissue.

References


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