CLINICAL STUDY REPORT

An Open-Label, Phase I/II Multicenter Clinical Trial of VXM01 in Combination with Avelumab in Patients with Progressive Glioblastoma Following Standard Treatment, with or without Second Surgery

Protocol Number:	VXM01-AVE-04-INT
Investigational Product:	VXM01
Indication:	Patients with progressive glioblastoma
Phase:	I/II
Sponsor:	VAXIMM GmbH Landteilstraße 24 68163 Mannheim Germany
Principal/Coordinating Investigator	Prof. Dr. med. Wolfgang Wick Neurology Clinic and National Center for Tumor Diseases University Clinic Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg Germany
First Patient, First Visit:	*20 Nov 2018*
Last Patient, Last Visit:	*15 Aug 2022*
Date of Report:	*22 March 2023*
Report Version:	1.0

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

Study Title: An open-label, Phase I/II multicenter clinical trial of VXM01 in combination with avelumab in patients with progressive glioblastoma following standard treatment, with or without second surgery.

Study Author: Dr. Simone Langeveld, Allucent

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

04.05.2023

Prof. Dr. med. Wolfgang Wick Date:
Coordinating Investigator
Neurology Clinic and National Center for Tumor Diseases

4.5.2023

Dr. Heinz Lubenau Date:
On behalf of
Vaximm GmbH

2. SYNOPSIS

Name of Company: Vaximm	**Volume:**	(For national authority use only)
Name of Finished Product: VXM01	**Page:**	
Name of Active Ingredient(s): *Salmonella typhi Ty21a carrying pVax10-VEGFR-2*		

Title of Study:
An open-label, Phase I/II multicenter clinical trial of VXM01 in combination with avelumab in patients with progressive glioblastoma following standard treatment, with or without second surgery

Protocol Number:
VXM01-AVE-04-INT

Study Period: **Study Phase:** I/II
Date of first patient, first visit: *20 Nov 2018*
Date of last patient, last visit: *15 Aug 2022*

Study Center(s):
The study was conducted in 3 centers (2 centers in Germany and 1 center in France) in 28 enrolled patients.

Publication(s):
None to date.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Safety and tolerability of VXM01 vaccine in combination with avelumab	• Safety and tolerability up to 60 weeks after first investigational medicinal products (IMP) administration (including end of study [EoS] visit, week 60)
Secondary	
• Efficacy of VXM01 vaccine in combination with avelumab by assessment of tumor objective response rate (ORR) per Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria and according to (Okada et al. 2015) in non-resected and resected patients (up to re-operation)	• Best overall response (BOR) and Duration of Response (DoR) on magnetic resonance imaging (MRI) according to iRANO in patients with or without surgery prior to trial entry (up to re-operation)
• Efficacy of VXM01 vaccine in combination with avelumab by assessment of clinical response	• Clinical response as assessed by time-to-progression (TTP), progression free survival (PFS) recurrence-free survival after re-operation (RFS) and overall survival (OS) up to end of trial
Exploratory	
• Effect of VXM01 vaccine plus avelumab on immuno- and biomarkers in tumor tissue and blood samples pre-and post-treatment	• Patient-individual vascular endothelial growth factor receptor 2 (VEGFR-2) specific interferon (IFN)-gamma T cell responses pre- and post-vaccination, determined by Enzyme Linked Immuno Spot (ELISpot) using cryopreserved peripheral blood mononuclear cells (PBMCs) (all patients) • Frequency of peripheral regulatory T cells (T_{regs}) and myeloid derived suppressor cells (MDSCs) measured using flow cytometry analysis • Tumor tissue immunohistochemistry and immunofluorescent staining evaluations including, but not limited to, VEGFR-2 expression on tumor cells and tumor vasculature, effector T cell infiltration, T_{reg}, MDSCs, programmed death 1 (PD-1), programmed death ligand 1 (PD-L1) (primary tumors of all patients and recurrent tumor of re-operated patients) • T cell receptor (TCR) sequencing of tumor-infiltrating lymphocytes (TILs) and peripheral T cells • Tumor phosphatase and tensin homolog (PTEN) mutation/deletion status (primary tumors of all patients and recurrent tumors of re-operated patients)
• To characterize the pharmacokinetics (PK) of avelumab in combination with VXM01	• PK profile of avelumab in combination with VXM01

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• To characterize the immunogenicity of avelumab in combination with VXM01	• Microsatellite instability (MSI)/ DNA mismatch repair (MMR) status • Anti-avelumab anti-drug antibodies (ADA)	
• To characterize the gut microbiome pre- and post-treatment	• Gut microbiome status	

Study Design:

This trial was conducted as a multicenter, open-label, Phase I/II trial to evaluate the efficacy and safety of VXM01 vaccine in combination with avelumab in patients with resectable (R) and non-resectable (NR) progressive glioblastoma following tumor resection and radiochemotherapy containing temozolomide.

The trial enrolled 28 patients with progressive glioblastoma:

- 25 patients who were not candidates for a tumor re-operation (non-resectable patients)
- 3 patients who were candidates for a tumor re-operation (resectable patients)

Patients who were candidates for tumor re-operation but, for any reason, did not have this routine surgical resection were allowed to enter the NR cohort if this was agreed by the investigator and medical monitor.

The trial started with a safety run-in to determine which dose of VXM01 vaccine (10^6 or 10^7 colony forming units [CFU]/mL) in combination with avelumab (800 mg) to take forward. This part of the trial was performed in the patients with non-resectable glioblastoma only.

For each patient, the trial consisted of a screening period (approximately 3 weeks), a treatment period (up to 48 weeks), and an observation period (12 weeks). During the treatment period, the patient received prime and boosting administrations of VXM01 vaccine in combination with avelumab.

Patients received VXM01 vaccine in combination with avelumab up to Week 48.

The EoS visit assessment was performed at Week 60.

Follow-up visits were performed 1, 3, 6, 12, and 24 months after the EoS examination.

If the investigator deemed appropriate, treatment with the combination of VXM01 vaccine and avelumab could continue beyond Week 48 and under a patient-specific treatment prolongation phase. Patients could continue to receive trial treatments as long as, in the investigator's or delegate's opinion, they were benefiting from treatment and did not meet any of the protocol specific discontinuation criteria, or withdrawal of consent. VXM01/avelumab combination was not to be given concomitantly with other anti-cancer treatment.

During the prolongation phase VXM01 vaccine in combination with avelumab was administered from Week 52 to Week 96 (VXM01 in a 4 weekly administration scheme and avelumab in a 2-weekly administration scheme), followed by an observation phase of 8 weeks. The end of patient-specific treatment prolongation visit (EoP) was performed at Week 104. Follow-up visits were performed 1, 3, 6, 12, and 24 months after the EoP.

In case of patient-specific prolongation, the duration of the trial was approximately 107 weeks (from screening to end of prolongation). The entire trial including follow-up lasted approximately 5 years (recruitment phase of approximately 10 months, treatment phase of up to 24 months, follow-up phase of 24 months).

A Data Safety Monitoring Board (DSMB) was convened to periodically assess the trial conduct and data in terms of risk-benefit balance and provide recommendations to Vaximm regarding the trial's continuation or modification. Furthermore, the DSMB was consulted in case a treatment-limiting toxicity (TLT) was classified as possibly related to either of the IMPs.

Safety Run-In: The safety run was planned to investigate 2 doses of VXM01 vaccine, 10^6 CFU/mL and 10^7 CFU/mL.

The first 3 non-resectable patients treated with the VXM01 10^6 CFU/mL dose in combination with avelumab were included in a staggered fashion (1+2). For safety reasons, there was a time interval of at least 5 weeks between dosing of the first patient and the following 2 patients (TLT observation period). If no TLTs were observed, the VXM01 vaccine dose was to be increased to 10^7 CFU/mL, after review of the safety data by the DSMB.

Similarly, also the first 3 patients treated with the VXM01 10^7 CFU/mL dose in combination with avelumab were included in a staggered fashion (1+2). If the safety and tolerability were considered acceptable for the VXM01 10^7 CFU/mL dose in combination with avelumab, all patients treated with VXM01 10^6 CFU/mL dose in combination with avelumab could be treated with the higher dose (intra-dose escalation allowed) after general approval by the DSMB, at the investigator's discretion.

The decision to escalate the dose from the 10^6 CFU /mL to the 10^7 CFU /mL VXM01 dose and to proceed with the 10^7 CFU /mL beyond the run-in part of the trial, was made after agreement between the investigators, Vaximm and the medical monitor, after involvement of the DSMB, and considered the "Discontinuation of Treatment" rules.

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Number of Patients (planned and analyzed): Thirty patients including 24 non-resectable patients (not candidates for tumor re-operation) and 6 resectable patients (candidates for tumor re-operation) were planned to be enrolled. In total 25 non-resectable patients and 3 resectable patients were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion:

The trial was performed in patients with progressive glioblastoma.

Male or female patients were included in this trial because the product is intended for use in men and women. However, as no data about reproductive toxicity of VXM01 vaccine are available, only postmenopausal (for at least 2 years) or surgically sterile women were included in the trial.

The main criteria for inclusion were:

- Had histologically diagnosed intracranial supratentorial malignant glioma (contrast-enhancing glioblastoma WHO Grade IV)
- Had evidence of tumor progression by Response Assessment for Neuro-Oncology (RANO) criteria following at least one prior therapy regimen that had contained radiation and chemotherapy with temozolomide, as measured by MRI. Radiotherapy had been completed at least 3 months prior to the inclusion visit
- Were candidates for a tumor reoperation (for the resectable arm [n=6] only). Neurosurgical intervention had to be postponable for 30 days
- Had adequate bone marrow, hepatic, and renal function
- Were able to undergo MRI
- Had no active bacterial infection requiring antibiotic treatment
- Had a Karnofsky performance status (KPS) ≥70
- Had primary (or most recently obtained available) tumor samples available for pathology review, panel sequencing, as well as central detection of T cell responses in the peripheral blood and in the tumor tissue.

Test Product, Dose and Mode of Administration, and Lot Number(s):

- VXM01 vaccine (10^6 or 10^7 CFU/mL, batch numbers VXM01-14/2018-P6, VXM01-15/2018-P7, VXM01-16/2019-P7) was administered as 4 single oral prime administrations on Day 1, 3, 5 and 7, followed by single oral boosting administrations every 4 weeks (from Week 4 to 48 in non-resectable patients and from Week 8 to 48 in resectable patients).
- Avelumab (800 mg, packaging batch AVE-01/2018 using drug product batch PD1H005/1, and packaging batch AVE-02/2019 using drug product batch PD1J002/2) was administered as single intravenous administrations every 2 weeks (in resectable patients the treatment was stopped after the third dose on Day 29 due to re-operation and continued from Week 8 to 48).

Reference Therapy, Dose and Mode of Administration, and Lot Number(s):

Not applicable.

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Duration of Treatment:

The total duration of the trial for each patient was up to approximately 63 weeks (from screening to end-of-trial visit). In case of patient-specific prolongation, the duration of the trial was approximately 107 weeks (from screening to end of prolongation). The entire trial including follow-up lasted approximately 5 years (recruitment phase of approximately 10 months, treatment phase of up to 24 months, follow-up phase of 24 months).

For the purpose of data analysis the trial started with first patient signing informed consent (who was also not a screen failure) and ended when the last patient performed the EoS visit under the standard protocol.

Criteria for Evaluation:

Efficacy:

All lesions radiographically identified at screening/baseline were consistently followed by MRI using the unique lesion number assigned at screening/baseline. Routine tumor follow-up by MRI was done at the time points given in the Schedule of Assessments.

Routine tumor follow-up included tumor assessment of the primary tumor and metastasis, e.g. determination of primary tumor size, number and size of metastasis. Tumor response or progression on MRI was determined according to the RANO criteria plus their adaption for immunotherapy trials (iRANO; (Okada 2015)). The iRANO assessment classified patients as having progressive disease, complete remission, partial remission, or stable disease. MRI comprised the National Brain Tumor Society/European Organisation for Research and Treatment of Cancer protocol for gliomas including perfusion MRI (Ellingson et al. 2014).

Pharmacodynamics:

Specific T cell-response against VEGFR-2 was determined by IFN-gamma ELISpot using cryopreserved PBMCs at the time points provided in the schedules of assessment. In addition, flow cytometry analysis using PBMCs was performed to determine the frequency of T_{regs} and MDSCs.

Primary (archival) tumor material of all patients and recurrent tumor material of re-operated patients was used for analysis. Tumor samples were processed according to local standards. Tumor tissue staining was performed provided there was access to sufficient tissue (formalin-fixed paraffin-embedded [FFPE]), *post hoc*, batchwise during the study or at the end of the trial and from the most recent available tissue. Staining was performed for the following:

- Immune cell infiltrates (CD3, CD4, CD8, PD-L1, PD-1, CD68, T_{regs}, Forkhead box P3 [FoxP3])
- Vessels (VEGFR-2)
- Tumor tissue characterization (expression of VEGFR2 on vessels and tumor cells, PTEN mutation/depletion status, MMR/MSI status, PD-L1)

Additional staining for other factors based on emerging scientific understanding of the combination therapy could also be performed.

TCR sequencing was performed for primary and recurrent tumor samples and blood T cells of the respective time point (if available) to assess overlap of T cell clones of periphery and intratumoral T cells in respect to expansion as well as breadth of T cell clonality before and after vaccination.

Specific IgM and IgG antibody responses against the lipopolysaccharide (LPS) of the carrier bacterium (anti-LPS IgG and anti-LPS IgM) were determined by validated enzyme linked immunosorbent assay (ELISA) methods using peripheral blood samples.

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Safety:

Safety was assessed by recording the following types of events: adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs). In addition, safety was assessed by clinical laboratory assessments, physical examination, vital signs and electrocardiograms (ECGs). Concomitant medications were recorded as well.

Each AE was classified and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.3. The relationship of an AE to either VXM01 vaccine or avelumab treatment was categorized as either unrelated or related.

Statistical Methods:

The full details of the performed statistical analyses are provided in the final Statistical Analysis Plan (SAP). Statistical analyses were in accordance with the final SAP. Analysis populations were defined as:

- **Full analysis set (FAS)**: included all patients who received any trial drug after trial entry.
- **Per-protocol analysis set (PPS)**: included all patients who received trial drug in compliance with the scheduled treatment regimen, underwent re-operation if in the resectable subgroup and without any major protocol deviations.
- **Safety analysis set (SAF)**: all patients who received at least one dose of the trial drug and for which at least one post-dose safety assessment is available

The FAS and PPS was used for efficacy analyses and the SAF was used for safety analysis.

The demographics and baseline characteristics of patients in the SAF were summarized for the total population, by dose level of VXM01 administered, and by patient category (NR/R).

Efficacy: Efficacy data included tumor and response data, KPS, and pharmacodynamics and other biomarkers, including anti-LPS, PBMC immunomonitoring, and tumor biomarkers. Efficacy results were analyzed for both the FAS and the PPS.

Safety: Results of all safety measurements were listed individually and summarized.

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Efficacy Results:

- The tumor response was assessed by ORR and DoR according to iRANO (2015). Overall, in the NR patients the ORR was 12.0% (95% CI: 2.5 – 31.2), with 3 of 25 patients (12.0%) who had a partial remission. In addition, overall 1 of 25 NR patients (4.0%) had stable disease. Of the patients with partial remission, 1 patient in the 10^6 CFU/mL group had a DoR of 5.6 months, while the patients in the 10^7 CFU/mL group had a DoR of 2.7 and 11.1 months. All patients who had stable disease received 10^7 CFU/mL VXM01.
- The clinical response was assessed by RFS (in the 10^7 CFU/mL R group), TTP, PFS, and OS. In the patients who underwent tumor resection (10^7 CFU/mL R group), disease progression occurred only in Patient 01-17 with an RFS of 1.8. Patient 01-14 was censored with an RFS of 20.9 months. The results for TTP and PFS were identical, with an overall median of 2.7 months (95% CI: 2.7 – 2.7) and range of 1.2 to 13.8 months in the non-resected patients (Total NR group). The median OS in the Total NR group was 11.1 months (95% CI: 8.5 – 15.1) with a range of 3.8 to 38.2 months. At the time of database lock, 1 patient in the 10^7 CFU/mL R group was alive and had stable disease without post-resection recurrence, while 3 patients in the 10^7 CFU/mL NR group were alive with progressive disease in long-term follow-up.
- The effect of VXM01 plus avelumab was explored by evaluating the VEGFR-2 specific T cell response and frequency of immune cells in peripheral blood, and by staining of immune- and biomarkers in tumor tissue obtained during resection. Overall, 12 of 28 patients (42.9%, all in the 10^7 CFU/mL NR group) had a VEGFR-2 specific T cell response classified as negative for all peptides at all time points tested. Two of the long-term survivors in the study (Patient 01-14 and Patient 01-27) had an increase found in peptide pool 169 – 210, indicating an increased VEGFR-2 specific T cell response. However, overall no clear trend could be observed in the VEGFR-2 specific T cell response classified as positive. Similarly, no clear trends could be observed in the change from baseline in peripheral MDSCs and T_{regs}, and in the tumor biomarkers evaluated in localized tumor tissue.

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Safety Results:

- Overall, 277 AEs were reported for 28 patients and 11 SAEs in 7 patients.
- No TLTs related to VXM01 or avelumab, infusion-related AEs, or AEs leading to study discontinuation were recorded for any group. No SAEs and no treatment-emergent SAEs were recorded for the 10^6 CFU/mL and 10^7 CFU/mL R groups. No VXM01- or avelumab-related SAEs or treatment-emergent SAEs were recorded for any group. There was one AE reported as leading to discontinuation of the study treatment, which was recorded after the first 5 weeks of treatment and thus not reported as TLT. Four patients experienced a total of 5 immune-related AEs.
- Overall, the most frequently reported treatment-emergent adverse events (TEAEs) were a decreased lymphocyte count in 16 patients (57.1%, 46 events), fatigue in 14 patients (50.0%, 19 events), and decreased white blood cell count in 8 patients (28.6%, 20 events). The system organ class with most reported TEAEs was investigations (21 patients [75.0%] with 116 events), followed by nervous system disorders (17 patients [60.7%] with 38 events), and general disorders and administration site conditions (15 patients [53.6%] with 34 events).
- The majority of TEAEs, 228 of 256 events (89.1%), were mild or moderate (Grade 1 or Grade 2). No TEAEs of Grade 5 (AEs leading to death) were reported.
- All TEAEs related to VXM01 occurred in the 10^7 CFU/mL group, in total 32 events in 12 patients. Treatment-emergent AEs related to avelumab occurred at both VXM01 vaccine dose levels, with 56 events in 16 patients. Of the 32 events considered related to VXM01 treatment, 29 events were also considered related to avelumab treatment. The 3 events considered only related to VXM01 treatment were diarrhea, myalgia, and pruritus. The majority of events were considered not related to VXM01 treatment (224 of 256 events [87.5%]) and none of the reported SAEs were considered related to study treatment.
- Treatment-emergent AEs related to the target disease (77 events [90.6%]) were reported for the majority of patients (21 of 28 [75.0%]).
- All 24 patients who died during the study, died of target disease progression. Three patients were alive and in the long-term follow-up phase at the time of database lock and 1 patient completed the study.
- The majority of laboratory findings, including hematology, chemistry, and urinalysis, were in the normal range or of mild to moderate severity. For vital signs and ECGs, changes from baseline were small and not clinically meaningful. The majority of physical examination findings were not clinically significant or of mild to moderate severity, with most findings reported for the neurological system related to the target disease.

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Conclusions:

- With the non-resected patients showing an ORR of 12.0% (partial remission) and 10.7% having stable disease as well as an OS of 2.2 to 23.1 months in resected patients, it appears that this combination therapy may be suitable for some patients with recurrent glioblastoma.
- Additionally, increases in peptide pool 169-210 may serve as potential biomarker for a VEGFR-2 specific T cell response in these patients.
- Due to the study design being an uncontrolled trial, no conclusion can be made regarding the extent of VXM01 treatment efficacy compared with the standard of care treatment for patients with recurrent glioblastoma, although a threshold of 20% with objective responses is usually regarded to be of interest (Galanis et al. 2012).
- VXM01 treatment in combination with avelumab was generally safe and well-tolerated.
- The majority of safety events were of mild to moderate severity. Of the SAEs, 9 of 11 events (81.8%) were target disease-related and no SAEs were considered related to the study treatment.

Date of Report, version: 22 March 2023, v1.0

3. TABLE OF CONTENTS

Tables in Text

Figures in Text

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

Abbreviation	Definition
AE	Adverse event
ADA	Anti-drug antibody
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}336h}$	Area under the concentration-time curve from 0 to 336 hours post-dose
BOR	Best overall response
CD	Cluster of differentiation
CFU	Colony forming units
C_{min}	Minimum plasma concentration
CRO	Contract research organization
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTLs	Cytotoxic T lymphocytes
C_{trough}	Trough concentration
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immuno spot
EoP	End of patient-specific treatment prolongation visit
EoS	End of study
EoT	End of treatment
FAS	Full analysis set
FDA	U.S. Food and Drug Administration

Abbreviation	Definition
FFPE	Formalin-fixed paraffin-embedded
FoxP3	Forkhead box P3
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
IDH	Isocitrate dehydrogenase
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IMP	Investigational medicinal product
INN	International Nonproprietary Name
INR	International normalized ratio
irAE	Immune-related adverse events
iRANO	Immunotherapy Response Assessment in Neuro-Oncology
IRB	Institutional review board
IRR	Infusion-related reactions
i.v.	Intravenous(ly)
KPS	Karnofsky performance status
LLOQ	Lower limit of quantification
LPS	Lipopolysaccharide
MCC	Merkel cell carcinoma
MDSC	Myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O6-methylguanine DNA methyltransferase
MMR	DNA mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability

Abbreviation	Definition
NCI	National Cancer Institute
NCS	Not clinically significant
NCT	Nationales Center for Tumor Disease
NR	Non-resectable
OR	Overall Response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PFS	Progression free survival
PK	Pharmacokinetic(s)
PPS	Per-protocol analysis set
PTT	Partial thromboplastin time
PT	Preferred Term
PTEN	Phosphatase and tensin homolog
Q2W	Every 2 weeks
QTcB	QT interval corrected for by Bazett’s formula
QTcF	QT interval corrected for heart rate by Fridericia’s formula
R	Resectable
RANO	Response Assessment for Neuro-Oncology
RBC	Red blood cells
RCC	Renal cell carcinoma
RFS	Recurrence-free survival after re-operation
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SoA	Schedule of Assessments
SOC	System organ class

Abbreviation	Definition
SOP	Standard operating procedure
StD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	T cell receptor
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocyte
TLT	Treatment-limiting toxicity
TMZ	Temozolomide
T_{reg}	Regulatory T cell
TSH	Thyroid stimulating hormone
TTP	Time-to-progression
ULN	Upper limit of normal range
U.S.	United States
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor receptor 2
WBC	White blood cell
WHO	World Health Organization

5. ETHICS

5.1 Ethics Committee or Institutional Review Board

In accordance with regulatory requirements copies of the protocol, amendments, and informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC) of each investigational center prior to the start of the trial at that center. Information about the IRB/IEC is provided in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

This study was designed and monitored in accordance with the contract research organization's (CRO's) standard operating procedures (SOPs), which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the current version of the Declaration of Helsinki.

5.3 Patient Information and Consent

In accordance with regulations, written informed consent was obtained from all patients (or their guardians or legal representatives, as applicable for local laws). The investigator had both ethical and legal responsibility to ensure that each individual being considered for inclusion in this trial was given a full explanation of the protocol. Informed consent was obtained and documented prior to initiation of any procedures that were performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). All patients received copies of their signed and dated ICFs.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted in 28 patients at 3 centers.

All aspects of the study were managed by Vaximm or the CRO. The responsibilities of the CRO included project management, medical monitoring, clinical monitoring, pharmacovigilance, maintenance of the Trial Master File, data management, biostatistics, and medical writing. Clinical laboratory, bioanalytical, and study medication supply services were used, as listed below.

CRO:	Allucent (previously CATO-SMS, initially SMS-Oncology) Stationsplein Noord-Oost 438 1117 CL Schiphol The Netherlands
Coordinating Investigator:	Prof. Dr. med. Wolfgang Wick Neurology Clinic and National Center for Tumor Diseases University Clinic Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg Germany
Tumor tissue analysis laboratory:	Prof Dr. med. Felix Sahm, PhD Universitätsklinik Heidelberg Neuropathologie Im Neuenheimer Feld 224 69120 Heidelberg Germany
Immuno-monitoring laboratory:	Dr. Isabel Poschke Nationales Center for Tumor Disease (NCT) Immun Monitoring Einheit (G808) Im Neuenheimer Feld 460 69120 Heidelberg Germany
Anti-lipopolysaccharide (LPS) analysis laboratory:	Dr. Szilveszter Toth ATRC Aurigon Toxicological Research Center Dunakeszi Pálya utca 2 H-2120 Hungary

Drug packaging:	Richter-Helm BioLogics, Hannover, Germany Catalent, Schorndorf, Germany Merck KgaA, Darmstadt Germany
Medication supplies:	Annette Kuhn Vaximm GmbH Landteilstraße 24 68163 Mannheim Germany

7. INTRODUCTION

7.1 Background

Four grades of malignancy for astrocytic glial tumors are defined in the 4th edition of the World Health Organization (WHO) classification of brain tumors (Louis et al. 2007). The treatment of Glioblastomas (WHO Grade IV) is an area of much controversy. There is a role for surgery, radiotherapy and chemotherapy, but their sequence and timing have remained a matter of debate. Such tumors may arise anywhere in the brain but the frontal and temporal lobes are most commonly affected. Genetically, these tumors may harbor more than 60 distinct mutations and common features comprise alterations in the epidermal growth factor receptor pathway and angiogenic growth involving vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) (Parsons et al. 2008).

Glioblastomas may develop *de novo* by clinical history (primary isocitrate dehydrogenase [IDH] wild-type glioblastoma) or *via* malignant progression from a Grade II or III astrocytoma (secondary or IDH-mutated glioblastoma). The primary IDH wild-type glioblastoma have a dismal prognosis with median survival of trial cohorts between 15-24 months. The secondary IDH-mutated glioblastoma has a better outcome. Approximately 5% of the malignant gliomas are multifocal by neuroimaging at diagnosis, and 5-10% seed in the subarachnoid space in the course of the disease. Features often noted at the time of diagnosis of glioblastoma are a short history of less than 6 months, a developing focal neurological deficit, either motor or sensory, headaches which may be intermittent or constant, focal or generalized epileptic seizures, or an alteration in personality. Magnetic resonance imaging (MRI) as the imaging method of choice demonstrates irregular intrinsic, poorly demarcated area of mixed intensity surrounded by vasogenic edema with a variable pattern of contrast enhancement, predominantly at the tumor periphery. The center of the tumor is typically a low-intensity region without contrast enhancement, reflecting necrosis. The histological hallmarks of glioblastoma include enhanced mitotic activity, nuclear atypia, vascular proliferation and necrosis. For the present trial patients with progressive growth of a contrast-enhancing (and though VEGF-driven) Grade IV glioma irrespective of *IDH* mutation will be eligible.

Up to 2005, the classical treatment for newly diagnosed glioblastoma included surgical resection when feasible and radiotherapy of the tumor with a peritumoral safety margin of 2-3 cm. Temozolomide (TMZ) chemotherapy with concomitant radiotherapy has a demonstrated survival advantage in the front-line setting (Stupp et al. 2005) and is now the world-wide standard of care. However, patients are rarely cured and novel agents in the recurrent setting are urgently needed. Tumor progression is inevitably associated with declining quality of life, clinically significant (CS) morbidity (such as neurological deficits) and death; therefore, additional progression free survival (PFS) time gained, or reduced risk of disease progression is of clinical benefit.

There is no standard of care for patients with recurrent disease, but rechallenge with TMZ or nitrosoureas are probably the most commonly used option at recurrence (Weller et al. 2013) especially with tumors harboring a hypermethylated *O6-methylguanine DNA methyltransferase* (MGMT) promoter (Taal et al. 2014, Weller et al. 2015). A number of other chemotherapeutic agents, including carboplatin, etoposide, irinotecan, fotemustin and imatinib (Brandes et al. 2005, Reardon et al. 2005, Rich 2008, Dresemann et al. 2010) have been used as salvage therapy either alone or in combination, but are either not tested in controlled trials or failed. For patients

who progress on TMZ, other combination therapies may be possible; several recent trials have evaluated various combinations containing angiogenesis inhibitors combined with cytotoxic chemotherapy. Many new and targeted agents, including immune directed therapies, have been evaluated in small and mostly uncontrolled clinical trials, however to date none suggested convincing activity (Wen and Kesari 2008).

It has been shown that brain tumors are accessible to immune cells including T cells (Khan-Farooqi et al., 2005). This is facilitated by a tumor-induced breakdown of the blood-brain barrier (Dunn et al. 2007), but T cell trafficking through the blood-brain barrier occurs even in healthy brain (Ransohoff et al. 2003). Therefore, activated cytotoxic T lymphocytes (CTLs) may even reach and efficiently fight tumor cell infiltrates into normal tissues or unresectable portions of the tumor mass. Moreover, CTL-induced tumor cell death is induced by a different mechanism of action from that in radio- and chemotherapy, thus decreasing the chance of malignant cells being able to develop resistance against a therapeutic approach combining both principles. Some evidence for this hypothesis has been provided by Liu and colleagues who demonstrate with clinical and preclinical data that glioblastoma cells are sensitized to chemotherapy after tumor-targeting immunotherapy (Liu et al. 2005).

Since conventional therapies for glioblastoma are of limited efficacy and fail to target tumor cells exclusively, immunologic targeting of tumor-specific gene mutations may allow more precise eradication of neoplastic cells. VXM01 therapy has been demonstrated to be safe and potentially beneficial in a previous trial in pancreatic cancer and colorectal cancer as well as recurrent glioblastoma patients. In addition, there is no indicator that VXM01 has any negative impact on the quality of life of glioblastoma patients.

7.2 VXM01

VXM01 is a VEGF receptor 2 (VEGFR-2) plasmid deoxyribonucleic acid (DNA) vaccine. Its target indication is the treatment of malignancies with or without metastases.

VXM01 is a gene transfer medicinal product as it consists of a plasmid, which is delivered to the body by a bacterium (*Salmonella typhi Ty21a*) serving as a vector. It is subject to the guidance and regulations of gene therapy medicinal products. VXM01 has been classified as “Advanced Therapy Medicinal Product”.

The vector *Salmonella typhi Ty21a* used is a live, attenuated bacterial carrier that allows for the oral delivery of the vaccine VXM01. It is itself an approved vaccine against typhoid fever (Vivotif®, Crucell, formerly Berna Biotech Ltd., Switzerland) that has been demonstrated to be safe regarding patient toxicity and transmission to third parties, as described in the Summary of Product Characteristics (SmPC) of Typhoral® L.

The vaccine construct has been designed to express VEGFR-2 protein after entry in the Peyer’s plaques, internalization by macrophages and release of the plasmid DNA.

The VEGFR-2 specific $CD8^+$ T cell mediated immune reaction elicited by VXM01 is expected to disrupt the tumor neovasculature by lysis of endothelial cells expressing VEGFR-2 within the tumor vasculature and, consequently, inhibit tumor growth and to support the development of an immune memory against proliferating endothelial cells. The VXM01 vaccine potentially combines the advantages of anti-angiogenic therapy and active immunotherapy. In glioblastoma, VEGFR-2 is expressed on tumor cells in a high percentage of patients. Therefore, VEGFR-2

specific $CD8^+$ T cells are also expected to directly target tumor cells. In such patients, dual targeting of the tumor neovasculature and the tumor cells is postulated.

Further details on the investigational medicinal products (IMP) used in this trial, including references, are provided in the VXM01 Investigator's brochure (IB).

7.3 Avelumab

The second medicinal product to be used in this trial together with VXM01 vaccine is a 20 mg/mL concentrate for solution for infusion with the active substance avelumab (anti-PD-L1 monoclonal antibody MSB0010718C), an antineoplastic agent that is directed against programmed death ligand 1 (PD-L1).

The programmed death 1 (PD-1) receptor and PD-1 ligands 1 and 2 (PD-L1, PD-L2) play integral roles in immune regulation. PD-1 is expressed on activated T cells and activated by PD-L1 and PD-L2 expressed by stromal cells, tumor cells, or both, initiating T cell death and localized immune suppression (Dong et al. 1999, Freeman et al. 2000, Dong et al. 2002, Topalian et al. 2012). PD-1 activation potentially provides an immune-tolerant environment for tumor development and growth. Conversely, inhibition of the interaction between PD-1 and PD-L1 can enhance local T cell responses and mediate antitumor activity. In the clinical setting, treatment with antibodies that block the PD-1 – PD-L1 interaction have been reported to produce objective response rates (ORRs) of 7% to 38% in patients with advanced or metastatic solid tumors, with tolerable safety profiles (Brahmer et al. 2012, Hamid et al. 2013).

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T cells, avelumab targets tumor cells, and therefore is hypothesized to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2 / PD-1 pathway intact to promote peripheral self-tolerance (Latchman et al. 2001). For complete details of the in vitro and nonclinical studies, please refer to the current IB.

Available safety data for the avelumab program, which are summarized in the current IB, demonstrate an acceptable safety profile with 10 mg/kg of avelumab and the 800 mg flat dose (to be used in the present trial), administered intravenously (i.v.), once every 2 weeks (Q2W).

The increasing awareness of the benefits of a flat dose has resulted in a switch to flat dosing regimens for compounds that were initially approved using weight-based dosing regimens, such as pembrolizumab and atezolizumab (see also Section 9.2.2).

In Europe, avelumab (Bavencio®) is approved conditionally as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC) and, in combination with axitinib, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

In the U.S., avelumab (Bavencio®) is approved for the treatment of adults and pediatric patients 12 years and older with metastatic MCC, patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy and as first-line treatment, in combination with axitinib of patients with RCC.

Infusion-related reactions (IRR) including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related

hepatitis, immune-related endocrinopathies, thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, immune-related nephritis and renal dysfunction) and other immune-related adverse events (AEs) (including myocarditis, pancreatitis, myositis, hypopituitarism, uveitis, Guillain-Barré syndrome) have been identified as important risks for avelumab. Detailed guidelines for the management of immune-related adverse events (irAEs) and IRR have been implemented in all ongoing clinical studies with avelumab, including the current protocol.

7.4 Rationale

Based on the pharmacodynamic effects of VXM01 vaccine and avelumab, a synergistic activity of both agents can be expected. The VXM01 vaccine has been shown to induce target specific $CD8^+$ T cells in animals and cancer patients. In the clinical trial VXM01-02-DE, signals indicative for a beneficial effect of the treatment of patients suffering from recurrent glioblastoma with VXM01 have been observed. The effect was apparent particularly in patients with high expression of the target antigen VEGFR-2 in the tumor. The number of infiltrating T cells in the tumor tissue from re-operation was increased compared with the primary tumor.

Avelumab increases the number of $CD8^+PD\text{-}1^+$ T cells as well as $CD8^+$ TEM cells and releases anti-tumor T cells from immune suppression by blocking the PD-1/PD-L1 interaction. It is anticipated that the number of VEGFR-2 specific $CD8^+$ T cells induced by VXM01 vaccine can be increased by concomitant treatment with avelumab. Interim data from trial VXM01-02-DE indicate that these T cells target VEGFR-2 expressed by the tumor neovasculature or on tumor cells. Furthermore, inhibitory effects of PD-L1 expression in tumor tissue on tumor-targeting T cells as observed in tumor specimen taken from trial patients with unfavorable course of disease could be overcome by co-administration of avelumab. Both mechanisms can potentially lead to an enhanced efficacy of either combination partner.

Importantly, the VXM01 vaccine provides signs of efficacy; PD-L1 inhibition, although so far without proven efficacy may only be effective in specific scenarios; one being the DNA mismatch repair (MMR)-deficient or microsatellite instable tumor and one being a microenvironment with specific tumor-targeting T cells, e.g., elicited by a vaccination (with VXM01).

This was the second trial with VXM01 vaccine in patients with glioblastoma to further understand the patient population and biology of VXM01 therapy for future registration trial.

8. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Safety and tolerability of VXM01 vaccine in combination with avelumab	• Safety and tolerability up to 60 weeks after first IMP administration (including end of study [EoS] visit, Week 60)
Secondary	
• Efficacy of VXM01 vaccine in combination with avelumab by assessment of tumor ORR per Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria and according to (Okada 2015) (see Protocol Appendix I) in non-resected and resected patients (up to re-operation)	• Best overall response (BOR) and Duration of Response (DoR) on MRI according to iRANO in patients with or without surgery prior to trial entry (up to re-operation)
• Efficacy of VXM01 vaccine in combination with avelumab by assessment of clinical response	• Clinical response as assessed by time-to-progression (TTP), PFS, recurrence-free survival after re-operation (RFS) and overall survival (OS) up to end of trial
Exploratory	
• Effect of VXM01 vaccine plus avelumab on immune- and biomarkers in tumor tissue and blood samples pre-and post-treatment	• Patient-individual VEGFR-2 specific interferon (IFN)-gamma T cell responses pre- and post-vaccination, determined by Enzyme Linked Immuno Spot (ELISpot) using cryopreserved peripheral blood mononuclear cells (PBMCs) (all patients) • Frequency of peripheral regulatory T cells (T_{regs}) and myeloid derived suppressor cells (MDSCs) measured using flow cytometry analysis • Tumor tissue immunohistochemistry and immunofluorescent staining evaluations including, but not limited to, VEGFR-2 expression on tumor cells and tumor vasculature, effector T cell infiltration, T_{reg}, MDSCs, PD-1, PD-L1 (primary tumors of all patients and recurrent tumors of re-operated patients) • T cell receptor (TCR) sequencing of tumor-infiltrating lymphocytes (TILs) and peripheral T cells • Tumor phosphatase and tensin homolog (PTEN) mutation/deletion status (primary

Objectives	Endpoints
	tumors of all patients and recurrent tumors of re-operated patients)
• To characterize the pharmacokinetics (PK) of avelumab in combination with VXM01	• PK profile of avelumab in combination with VXM01
• To characterize the immunogenicity of avelumab in combination with VXM01	• Microsatellite instability (MSI)/ MMR status • Anti-avelumab anti-drug antibodies (ADA)
• To characterize the gut microbiome pre- and post-treatment	• Gut microbiome status

9. INVESTIGATIONAL PLAN

An assessments overview is provided in Protocol Table 11, and a detailed schedules of assessments are provided in Protocol Table 2 to 8.

9.1 Overall Study Design

This trial was conducted as a multicenter, open-label, Phase I/II trial to evaluate the efficacy and safety of VXM01 vaccine in combination with avelumab in patients with resectable and non-resectable progressive glioblastoma following at least one prior therapy regimen that had contained radiation and chemotherapy with TMZ.

The trial was performed in 28 patients with progressive glioblastoma:

- 25 patients who were not candidates for a tumor re-operation (non-resectable patients)
- 3 patients who were candidates for a tumor re-operation (resectable patients)

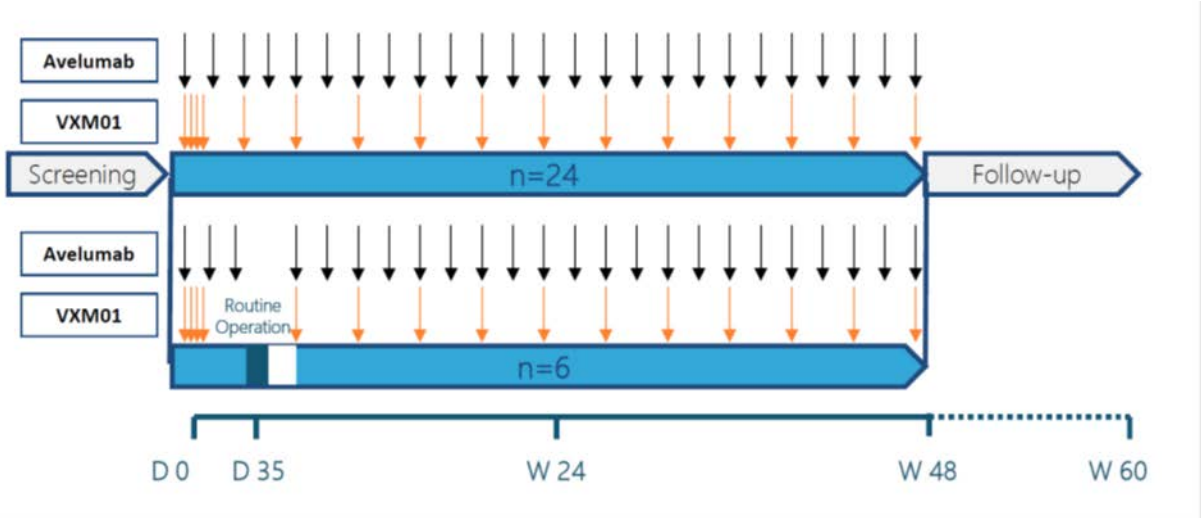
Patients who were candidates for tumor re-operation but, for any reason, did not have this routine surgical resection were allowed to enter the non-resectable cohort if this was agreed by the investigator and medical monitor.

The trial started with a safety run-in to determine which dose of VXM01 (10^6 or 10^7 colony forming units [CFU]/mL) vaccine in combination with avelumab (800 mg) to take forward. This part of the trial was performed in the patients with non-resectable glioblastoma only.

For each patient, the trial consisted of a screening period (approximately 3 weeks), a treatment period (up to 48 weeks), and an observation period (12 weeks). During the treatment period, the patient received prime and boosting administrations of VXM01 vaccine in combination with avelumab.

An overview of the trial treatment is shown in Figure 9-1 and a detailed schematic of the trial design is presented in Figure 9-2.

Figure 9-1: VXM01-AVE-04-INT Trial Treatment Overview



Source: Protocol Figure 3-1

Patients received VXM01 vaccine in combination with avelumab up to Week 48:

- VXM01 (10^6 or 10^7 CFU/mL) vaccine was administered as 4 single oral prime administrations on Day 1, 3, 5, and 7, followed by single oral boosting administrations every 4 weeks (from Week 4 to 48 in non-resectable patients and from Week 8 to 48 in resectable patients).
- Avelumab (800 mg) was administered as single i.v. administrations Q2W (in resectable patients the treatment was stopped after the third dose on Day 29 due to re-operation and continued from Week 8 to 48).

The EoS visit assessment was performed at Week 60.

Follow-up visits were performed 1, 3, 6, 12, and 24 months after the EoS examination.

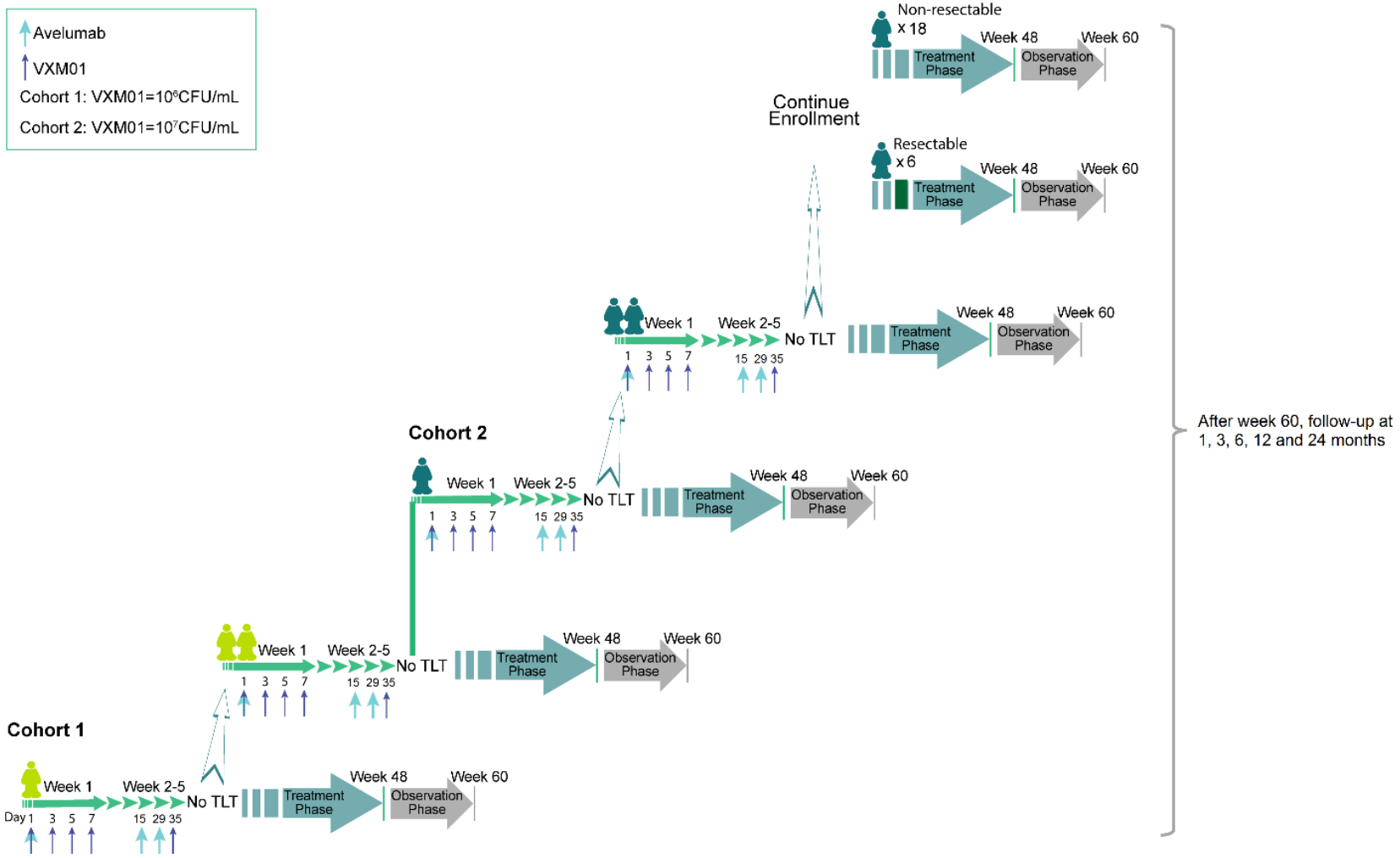
If the investigator deemed appropriate, treatment with the combination of VXM01 vaccine and avelumab could continue beyond Week 48 and under a patient-specific treatment prolongation phase. Patients could continue to receive trial treatments as long as, in the investigator's or delegate's opinion, they were benefiting from treatment and did not meet any of the protocol specific discontinuation criteria, or withdrawal of consent. VXM01/avelumab combination was not given concomitantly with other anti-cancer treatment.

During the prolongation phase VXM01 vaccine in combination with avelumab was administered from Week 52 to Week 96 (VXM01 in a 4-weekly administration scheme and avelumab in a 2-weekly administration scheme), followed by an observation phase of 8 weeks. The end of patient-specific treatment prolongation visit (EoP) was performed at Week 104. Follow-up visits were performed 1, 3, 6, 12, and 24 months after the EoP.

In case of patient-specific prolongation, the duration of the trial was approximately 107 weeks (from screening to end of prolongation). The entire trial including follow-up lasted approximately 5 years (recruitment phase of approximately 10 months, treatment phase of up to 24 months, follow-up phase of 24 months).

A Data Safety Monitoring Board (DSMB) was convened to periodically assess the trial conduct and data in terms of risk-benefit balance and provide recommendations to Vaximm regarding the trial's continuation or modification. Furthermore, the DSMB was consulted in case a Treatment-Limiting Toxicity (TLT) was classified as possibly related to either of the IMPs.

Figure 9-2: Trial Design Schematic



Source: Protocol Figure 3-2

9.1.1 Safety Run-in

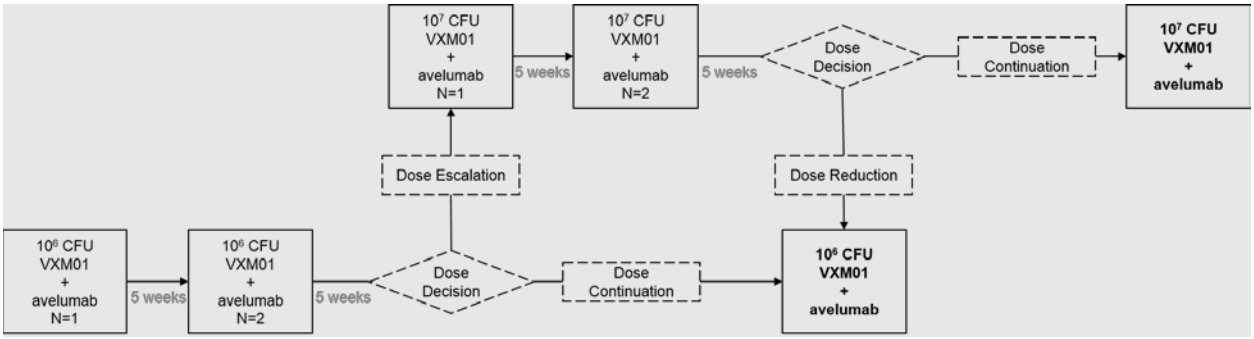
The safety run was planned to investigate 2 doses of VXM01 vaccine, 10^6 CFU/mL and 10^7 CFU/mL (Figure 9-3).

The first 3 non-resectable patients treated with the VXM01 10^6 CFU/mL dose in combination with avelumab were included in a staggered fashion (1+2). For safety reasons, there was a time interval of at least 5 weeks between dosing of the first patient and the following 2 patients (TLT observation period). If no TLTs were observed, the VXM01 vaccine dose was to be increased to 10^7 CFU/mL, after review of the safety data by the DSMB.

Similarly, also the first 3 patients treated with the VXM01 10^7 CFU/mL dose in combination with avelumab were included in a staggered fashion (1+2). If the safety and tolerability were considered acceptable for the VXM01 10^7 CFU/mL dose in combination with avelumab, all patients treated with VXM01 10^6 CFU/mL dose in combination with avelumab could be treated with the higher dose (intra-dose escalation allowed) after general approval by the DSMB, at the investigator's discretion.

The decision to dose escalate from the 10^6 CFU/mL to the 10^7 CFU/mL VXM01 dose and to proceed with the 10^7 CFU/mL beyond the run-in part of the trial, was made after mutual agreement between the investigators, Vaximm and the medical monitor, after involvement of the DSMB, and considered the "Discontinuation of Treatment" rules defined in Section 9.3.3.1.

Figure 9-3: Staggered Dosing and Dose Escalation During Safety Run-in



Source: Protocol Figure 3-3

9.2 Discussion of Study Design

9.2.1 Scientific Rationale for Trial Design

The study design was developed based on the relevant clinical trial guidelines (see Protocol Section 1.4: relevant guidelines) and was considered adequate to achieve the trial objectives.

The trial has been designed as an exploratory trial. This was the second trial with VXM01 vaccine in patients with glioblastoma to further understand the patient population and biology of VXM01 therapy for future registration trial.

The trial design followed the recommendations of the scientific advisory board meeting performed on 31 May 2017 except for the VXM01 vaccine monotherapy reference group.

The primary objective of the trial was to evaluate the safety and tolerability of the combination of VXM01 vaccine and avelumab. However, the important additional objective of the trial was to

determine whether the beneficial effects of VXM01 vaccine in glioblastoma patients observed in trial VXM01-02-DE could be enhanced by addition of avelumab to the treatment regimen.

The trial was designed as an open-label trial. Twenty-eight patients were treated with a combination of VXM01 vaccine and avelumab as described above. Trial arms each consisted of 3 patients who were candidates for a re-operation and 25 patients who did not receive a re-operation of their tumor.

With respect to safety, this trial design allowed determination of whether the additional treatment with avelumab would have an impact in the safety profile of VXM01 vaccine. In addition, the AEs observed in the combination arm could be compared to the well-established safety profile of avelumab to identify any potential additive or synergistic safety concern for the combination therapy.

Inclusion of 3 patients scheduled for a re-operation provided the opportunity to obtain tumor tissue for immunohistochemical analysis and allowed the evaluation of the effects of the combination treatments by comparing tissues of the primary tumor and recurrent tumor. As similar analyses have been conducted in the first trial VXM01-02-DE it was possible to determine whether the addition of avelumab to the treatment schedule altered the patterns of immune cell infiltration or biomarker expression in tumor tissues observed.

In summary, considering the exploratory nature of the trial the proposed trial design seemed to be appropriate for addressing the objectives stipulated in the trial protocol and providing the relevant information needed for decision-making regarding the further clinical development of VXM01+avelumab in glioblastoma.

9.2.2 Dosing Rationale

The VXM01 vaccine dosing scheme was identical to the one chosen in the VXM01-02-DE trial in patients with glioblastoma, i.e., prime administration on Day 1, Day 3, Day 5, and Day 7 and 4-weekly single boosting doses. A patient-specific prolongation of VXM01 vaccine boosting could have been introduced at the investigator's discretion.

Immunomonitoring results from trial VXM01-01-DE in patients with pancreatic cancer indicate that immune responses induced by repeated administration of VXM01 vaccine at doses of 10^7 CFU were significantly higher than those induced with the lower dose of 10^6 CFU (Schmitz-Winnenthal et al. 2018).

However, potential risks for patients in the trial could arise due to an overstimulation of the VEGFR-2 specific immune response induced by VXM01 vaccine by the concomitantly administered anti-PD-L1 monoclonal antibody avelumab leading to AEs caused by exaggerated anti-angiogenic effects. Therefore, the trial protocol included a safety-run in phase with a reduced dose of VXM01 of 10^6 CFU/administration. As outlined above data from trial VXM01-01-DE indicate that mean immune responses induced by the lower dose of 10^6 CFU of VXM01 vaccine were found to be significantly lower than values obtained after administration of the higher dose of 10^7 CFU. Therefore, the risk for immune-related AEs (irAEs) caused by a synergistic activity of VXM01 vaccine and avelumab should be lower with a lower dose of VXM01.

The protocol therefore stipulated a safety run-in in which the first 3 trial patients under VXM01/avelumab who were included in a staggered fashion (1+2) and treated with the VXM01 10^6 CFU dose in combination with avelumab. If no TLTs were observed at a dose of

10^6 CFU the VXM01 dose was to be increased to 10^7 CFU. Again, the first 3 trial patients treated with the VXM01 10^7 CFU dose in combination with avelumab were included in a staggered fashion (1+2). Details are provided in Section 9.4.

To date, avelumab has been administered at the clinically active, safe, and tolerable dose of 10 mg/kg Q2W to more than 1700 patients across multiple indications. Furthermore, this 10 mg/kg Q2W avelumab dosing regimen has been approved by the U.S. Food and Drug Administration (FDA) as the first treatment for MCC. Avelumab was originally dosed on a mg/kg basis in order to reduce inter-patient variability in drug exposure. However, emerging data for monoclonal antibodies, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (i.e., body weight independent) dosing regimens (Wang et al. 2009, Freshwater et al. 2017, Zhao et al. 2017). Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population PK analysis was conducted based on the acquired data across 3 single-agent avelumab studies in 1827 patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are less variable with 800 mg Q2W compared with 10 mg/kg Q2W; exposures were similar near the population median weight. Simulations of exposure comparing weight-based (10 mg/kg Q2W) and flat dosing (800 mg Q2W) after the first cycle (PK CYCLE) and at steady state (PK SS) suggest that the overall variability in exposures is marginally lower for the flat dosing group (27.1% versus 29.0%). Low weight patients tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when flat dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the whole population. Furthermore, the 800 mg Q2W dosing regimen was expected to result in trough concentration (C_{trough}) > 1 mg/mL required to maintain avelumab serum concentrations at > 95% TO throughout the entire Q2W dosing interval in all weight categories. Overall the exposure at 800 mg flat dosing falls within the exposure range for avelumab that was shown to be clinically efficacious with a manageable safety profile, serving as the primary evidence and providing strong support for the modification of the dose regimen from weight-based to flat dosing. Additional analysis comparing the exposure metrics (area under the concentration-time curve from 0 to 336 hours post-dose [$AUC_{0\text{-}336h}$] and minimum plasma concentration [C_{min}]) – overall response (OR) relationship between weight-based (10 mg/kg Q2W) and flat dosing (800 mg Q2W) after the first cycle (PK CYCLE) and at steady state (PK SS) suggested that the probability of OR was similar for both dosing regimens and for each tumor type of interest.

The exposure-safety simulations provided additional justification for the proposed change to a flat 800 mg Q2W dosing regimen. Simulations comparing the exposure-safety relationship for irAEs and IRRs between weight-based (10 mg/kg Q2W) and flat dosing (800 mg Q2W) suggested that the probability of experiencing an irAE (all grades) or an IRR is similar for both dosing regimens and irrespective of the underlying exposure metric. In light of the observed irAE and IRR incidences, there was no evidence that flat 800 mg dosing was expected to lead to a difference in AE incidence of clinical consequence in any body weight subset.

Therefore, in this clinical trial, a fixed dosing regimen of 800 mg administered as a 1-hour i.v. infusion Q2W was utilized for avelumab.

9.3 Selection of Study Population

The trial was performed in patients with progressive glioblastoma.

Male or female patients were included in this trial because the product is intended for use in men and women. However, as no data about reproductive toxicity of VXM01 vaccine are available, only postmenopausal (for at least 2 years) or surgically sterile women were included in the trial. Efforts were made to include similar numbers of male and female patients in this trial.

Only patients meeting all inclusion (see Section 9.3.1) and none of the exclusion criteria (see Section 9.3.2) were included into the treatment phase. The criteria were assessed at screening and a re-check was performed at the inclusion visit (Day 0). For assessment of eligibility, examinations as described in Section 9.5 were performed before drug administration.

In comparison to previous clinical VXM01 vaccine trials, the exclusion criterion "Positive for anti-typhoid IgG/IgM antibodies" including the typhoid rapid test at baseline has been deleted. The rationale for this modification was based on recently obtained in vitro data which indicate that coating of *Salmonella typhi Ty21a* with anti-LPS antibodies leads to an increased uptake of the bacteria into macrophages. Moreover, several patients in the trial VXM01-01-DE which were assessed as anti-LPS positive at the beginning of the trial were able to raise a VEGFR-2-specific immune response leading to the conclusion that potentially, anti-LPS positivity is not prohibitive for the generation of the desired immune response.

9.3.1 Inclusion Criteria

Patients who met all of the following criteria were eligible to participate in the study.

1.	Were able to understand and follow instructions during the trial
2.	Were able and willing to give written informed consent, signed and dated
3.	Were male or female patients. Female patients had to be post-menopausal for at least 2 years or surgically sterile
4.	Were age ≥18 years
5.	Had histologically diagnosed intracranial supratentorial malignant glioma (contrast-enhancing glioblastoma WHO Grade IV)
6.	Had evidence of tumor progression by Response Assessment for Neuro-Oncology (RANO) criteria following at least one prior therapy regimen that had contained radiation and chemotherapy with TMZ, as measured by MRI. Radiotherapy had been completed at least 3 months prior to the inclusion visit
7.	Were candidates for a tumor reoperation (for the resectable arm [n=6] only). Neurosurgical intervention had to be postponable for 30 days
8.	Had adequate bone marrow function including: Absolute neutrophil count (ANC) ≥1,500 /mm^3 or ≥1.5 ×10^9/L; Platelets ≥100,000 /mm^3 or ≥100 ×10^9/L; Hemoglobin ≥9 g/dL (may have been transfused); international normalized ratio (INR) <1.5× the upper limit of normal range (ULN). Patients with documented benign cyclical neutropenia were allowed if white blood cell (WBC) count was ≥ 1.5 ×10^9/L

	with ANC ≥ 1.0 $\times 10^9$/L and appropriate hematology parameters: leukocytes ≥4.0 $\times 10^9$/L, lymphocytes ≥0.6 $\times 10^9$/L
9.	Had adequate hepatic function defined by a total bilirubin level ≤1.5× ULN, an aspartate aminotransferase (AST), level ≤2.5× ULN, and an alanine aminotransferase (ALT) level ≤2.5× ULN or, for patients with documented metastatic disease to the liver, AST and ALT levels ≤5× ULN. Patients with documented Gilbert disease were allowed if total bilirubin ≤3× ULN
10.	Had adequate renal function defined by an estimated creatinine clearance ≥30 mL/min according to the Cockcroft-Gault formula
11.	Were able to undergo MRI
12.	Had no active bacterial infection requiring antibiotic treatment
13.	Had a Karnofsky performance status (KPS) ≥70
14.	Had primary (or most recently obtained available) tumor samples available for pathology review, panel sequencing, as well as central detection of T cell responses in the peripheral blood and in the tumor tissue
15.	Had no medical or social conditions that could interfere with trial outcome and follow-up

9.3.2 Exclusion Criteria

Individuals who met any of the following criteria were not eligible to participate in the study.

Medical and surgical history and diseases	
1.	Had cardiovascular disease defined as: a. Uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg) b. Arterial thromboembolic event within 6 months before trial entry including: – Myocardial infarction – Unstable angina pectoris – Cerebrovascular accident – Transient ischemic attack
2.	Had congestive heart failure New York Heart Association Grade III to IV
3.	Had serious ventricular arrhythmia requiring medication and arrhythmias requiring Implantable Cardioverter Defibrillator (ICDs)
4.	Had clinically significant peripheral artery disease > Grade 2b according to Fontaine

5.	Had a history of relevant intracranial hemorrhage (not confined to susceptibility [iron] lesions on MRI only)
6.	Had hemoptysis within 6 months before trial entry
7.	Had known esophageal varices
8.	Had upper or lower gastrointestinal bleeding within 6 months before inclusion (Day 0)
9.	Had significant traumatic injury or surgery within 4 weeks before trial entry
10.	Had a non-healing wound, incomplete wound healing, bone fracture or gastrointestinal ulcers within 3 years before inclusion, or positive gastroscopy within 3 months before inclusion
11.	Had gastrointestinal fistula
12.	Received thrombolysis therapy within 4 weeks before trial entry
13.	Had a history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that based on the investigators judgement provided a reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that might affect the interpretation of the trial results or render the patient at high risk for treatment complications
14.	Had previous malignant disease (other than the tumor disease for this trial) within the last 5 years (except adequately treated non-melanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to trial entry and the patient was deemed to have been cured with no additional therapy required or anticipated to be required
15.	Had prior organ transplantation, including allogeneic stem cell transplantation
16.	Had active autoimmune disease that might deteriorate when receiving an immunostimulatory agent: a. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment were eligible b. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) was acceptable
17.	Had a history of uncontrolled intercurrent illness including but not limited to uncontrolled diabetes (e.g., hemoglobin A1c ≥8%)
18.	Had a known prior hypersensitivity to investigational product or any component in its formulations or any other drug scheduled or likely to be given during the trial, including known severe hypersensitivity reactions to monoclonal antibodies (National

	Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.3 Grade ≥3)
19.	Experienced persisting toxicity related to prior therapy (NCI CTCAE v4.3 Grade >1); however, alopecia, sensory neuropathy Grade ≤2, or other Grade ≤2 AEs not constituting a safety risk based on investigator's judgment were acceptable
20.	Suffered from other severe acute or chronic medical conditions including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that could increase the risk associated with trial participation or trial treatment administration or could interfere with the interpretation of trial results and, in the judgment of the investigator, would make the patient inappropriate for entry into this trial
21.	Had an active infection requiring systemic therapy
22.	Had a known history of human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome or multi-drug resistant Gram-negative bacteria
23.	Had a hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
24.	Was a female patient of childbearing potential
25.	Had a history of serious ophthalmological diseases, e.g., optic neuropathy, retinal detachment, uveitis
Prior and concomitant medication	
26.	Received treatment in any other clinical trial within 30 days or within 5 half-lives of any prior treatment, before screening
27.	Had any other condition or treatment that, in the opinion of the investigator, could interfere with the trial or current drug or substance abuse
28.	Received chronic concurrent therapy within 2 weeks before and during the treatment period with: a. Corticosteroids (except steroids up to equivalent of dexamethasone 4 mg daily dose) b. Immunosuppressive agents c. Antibiotics (if required for any medical reason, antibiotics were to be avoided between 3 days before until 3 days after VXM01 vaccine administration) d. Bevacizumab or any other anti-angiogenic treatment e. Any other anti-cancer therapy or concurrent anticancer treatment (for example, cytoreductive therapy, radiotherapy [with the exception of palliative short

	course, limited field (i.e., ≤10 fractions and ≤ 30% bone marrow involvement or per institutional standard) radiotherapy, which could be administered during the study. However, dosing was to be suspended at least 14 days prior to the start of radiotherapy and was not to be resumed until at least 14 days after the last radiotherapy fraction], immune therapy, or cytokine therapy, except for erythropoietin) f. Administration of live vaccines (other than VXM01) within 30 days prior to study treatment
Other	
29.	Received a vaccination within 4 weeks of the first dose of avelumab and while on trials was prohibited except for administration of inactivated vaccines (other than VXM01)
30.	Was unable to understand the protocol requirements, instructions and trial-related restrictions, the nature, scope, and possible consequences of the trial
31.	Was unlikely to comply with the protocol requirements, instructions and trial-related restrictions, e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial
32.	Was legally incapacitated or had limited legal capacity
33.	Had any condition which resulted in an undue risk for the patient during the trial participation according to the investigator

9.3.3 Trial Discontinuation and Withdrawal

9.3.3.1 Discontinuation of Treatment

After trial enrolment, individual patients were scheduled to continue to receive the trial treatment (VXM01 vaccine in combination with avelumab) for a period of 48 weeks or until any of the following occurred:

- An AE fulfilling TLT criteria (see Section 9.4.5)
- AEs, other than TLTs that in the opinion of the investigator made continuation of the study undesirable for this patient
- Clinically significant test procedure results, which endangered the patient as determined by the investigator
- Radiological disease progression or significant clinical deterioration (clinical progression), defined as new symptoms that were deemed by the investigator to be clinically significant or significant worsening of existing symptoms
- Occurrence of pregnancy of a female trial patient
- Use of a prohibited concomitant drug which necessitated withdrawal from the trial treatment as considered by the investigator, medical monitor or Vaximm

- Withdrawal of consent
- Occurrence of an exclusion criterion, which was clinically relevant and affected the patient's safety, if trial treatment discontinuation was considered necessary by the investigator and/or Sponsor

Treatment in all patients was to be stopped in case of any of the following events:

- Two patients having an AE Grade 3 or 4 which fulfilled TLT criteria (see Section 9.4.5) and the relationship to either IMP is classified as probably or definitely related
- One patient with an AE Grade 5 (fatal) which fulfilled TLT criteria (see Section 9.4.5) and the relationship to either IMP is classified as probably or definitely related.

Under condition that the above mentioned TLTs were classified as possibly related to any of the trial drugs, the investigator was to decide on continuation of the trial after consultation of the DSMB, in mutual agreement with Vaximm.

The reason, date of discontinuation, and the particular details (nature of event) were specified in the electronic Case Report Form (eCRF). The investigator had to determine one primary reason for discontinuation (only one choice was permitted).

In case of withdrawal from treatment, the patients were to participate in the End of Treatment (EoT) visit and in follow-up visits according to the schedule of events. Additional follow-up visits could have been scheduled according to the investigator's judgment.

Patients who discontinued from treatment prematurely and in the absence of confirmed disease progression were to continue to undergo scheduled assessments until confirmed disease progression or initiation of next line anti-tumor therapy. In particular, tumor assessments were to continue to be performed according to schedule in order to assess DoR or late anti-tumor response or progression.

In case of withdrawal of consent (and withdrawal from the trial), all data collected until withdrawal of consent were to be reported. The patient was to be asked for availability for further follow-up of survival by phone.

Any decision for removal of individual patients from treatment was to be made after mutual agreement between the investigator and the Vaximm after consultation of the DSMB.

9.3.3.2 Withdrawal from the Trial

Patients were free to withdraw from participation in the trial at any time upon request. The investigator was ultimately responsible for the safety and well-being of the patient. If at any time participation in this study was detrimental to the patient's health, the patient could be taken off treatment or off trial. An investigator could discontinue or withdraw a patient from the trial for the following reasons:

- Pregnancy
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurred such that continued participation in the trial was not in the best interest of the patient
- Disease progression which required discontinuation of the IMP

- If the patient met an exclusion criterion (either newly developed or not previously recognized) that precluded further trial participation

The reason for patient discontinuation or withdrawal from the trial were recorded on the eCRF.

Based on the above, there was a differentiation between treatment withdrawal (withdraw of treatment, but continue to follow-up after performing the EoS visit) and trial drop-out (withdrawal from trial e.g., unwillingness of the patient to comply with trial procedures, withdraw consent, or lost to follow-up).

The investigator had to determine one primary reason for discontinuation and this was documented in the eCRF (only one choice was permitted).

9.3.4 Patient Replacement

Patients who discontinued the trial before first drug administration (e.g., screening failures/ patients not meeting the entry criteria at the inclusion visit) were to be replaced. Patients who discontinued participation after trial entry and prior to completion of the first week of treatment could be replaced after mutual agreement between Vaximm, medical monitor and the site investigator. Patients who discontinued the trial after completion of the first week of treatment were not replaced.

9.3.5 Contraception Method in Male Patients

As a measure of precaution, male study patients were to use condoms as contraception method during at least 7 days after each administration throughout the study.

9.4 Treatments

9.4.1 Treatments Administered

Two IMPs were administered as part of this clinical trial (Table 9-1).

Table 9-1: Identity of IMPs

Name:	VXM01	Avelumab
Active ingredient (INN):	*Salmonella Typhi* Strain Ty21a carrying plasmid pVax10-VEGFR-2	Avelumab
Formulation:	Frozen Suspension	Solution for infusion
Strength or concentration:	10^6 or 10^7 CFU/mL	20 mg/mL concentrate for solution for infusion
Dose:	10^6 or 10^7 CFU	800 mg
Mode of administration:	Oral administration	Intravenous administration
Manufacturer/Marketing Authorization Holder:	Richter-Helm BioLogics, Hannover, Germany	Merck KgaA, Darmstadt, Germany

CFU = colony forming unit; IMP = investigational medicinal product; INN = International Nonproprietary Name; VEGFR = vascular endothelial growth factor receptor

Source: Protocol Table 9

9.4.1.1 Packaging

VXM01 vaccine was packaged, labeled, and supplied by Richter-Helm BioLogics, Hannover, Germany under the existing manufacturing license. Each VXM01 vial was packed in one labeled high-density polyethylene bottle. The qualified person of the manufacturer released the finished IMP (batch numbers VXM01-14/2018-P6, VXM01-15/2018-P7, VXM01-16/2019-P7).

Powder components for the preparation of buffer solution (sodium hydrogen carbonate [sodium bicarbonate], ascorbic acid, and lactose monohydrate) were supplied in stick packs. Stick packs were filled by Catalent, Schorndorf, Germany. One stick pack of each component, distinguishable by color code, was supplied in a cardboard box. The qualified person of the manufacturer released the finished IMP (batch numbers SAL04/2018, SAL-06/2019, SAL-08/2021).

Avelumab was formulated as a 20.0 mg/mL solution and was supplied by Merck KgaA, Darmstadt, Germany in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal. Each box of IMP contained 1 vial. The qualified person of the manufacturer released the finished IMP (packaging batch AVE-01/2018 using drug product batch PD1H005/1, and packaging batch AVE-02/2019 using drug product batch PD1J002/2).

Vaximm maintained a complete record of batch numbers and expiry dates of all IMPs as well as the labels of all IMPs in the Trial Master File.

The investigator maintained, amongst other documents, a record of the batch numbers and expiry dates of all IMP received at the trial site in the Investigator site file.

9.4.1.2 Storage

VXM01

Vaccine potency is dependent upon storage under refrigeration (≤–70°C). The vaccine was stored under refrigeration at all times.

VXM01 vaccine was used as a liquid frozen formulation.

For application in this trial, VXM01 drinking solution was prepared within 30 minutes before oral administration as described in the reconstitution procedure available at site.

The drink solution containing the patient’s IMP was administered; all other material not used for administration was either autoclaved and discarded according to established procedures or discarded following local procedures for GMO waste.

Avelumab

The contents of the avelumab vials were sterile and nonpyrogenic, and did not contain bacteriostatic preservatives. Any spills that occurred were cleaned up using the facility’s standard cleanup procedures for biologic products.

Avelumab was stored at 2°C to 8°C until use, with a temperature log maintained daily. All avelumab boxes supplied to each trial site were stored carefully, safely, and separately from other drugs.

For application in this trial, avelumab was diluted with 0.9% saline solution (sodium chloride injection); alternatively, a 0.45% saline solution could have been used if needed. It was recommended that the diluted avelumab solution be used immediately. If not used immediately,

the diluted drug product could have been stored up to 8 hours at room temperature or up to 24-hours at 2°C to 8°C. Detailed information on infusion bags and medical devices used for the preparation of the dilutions and subsequent administration was provided in the Pharmacy Manual.

Avelumab was not used for any purpose other than the trial. The administration of avelumab to patients who have not been enrolled into the trial was not covered by the trial insurance.

Any unused portion of the solution was discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

Storage, handling, preparation, and disposal of IMP was according to local institutional guidelines.

9.4.1.3 Accountability

The investigators maintained records of IMP accountability in the Investigator site file for all IMP provided by the Vaximm.

After the end of the trial, the investigator returned all used and unused IMP to Vaximm or destroyed used and unused IMP according to written agreement with the Vaximm.

9.4.2 Method of Assigning Patients to Treatment Groups

Eligible, non-resectable patient and patients who were candidates for re-operation received VXM01 vaccine in combination with avelumab.

9.4.3 Selection of Doses in the Study

The treatments administered during the trial are displayed in Table 9-2.

Table 9-2: Treatment Administered

Population	Treatment	Drug and dose	Route of administration	Frequency and duration of administration	No. of patients
Non-resectable patients	VXM01 + avelumab	10^6 or 10^7 CFU VXM01 vaccine	Oral administration	4 prime single doses followed by 4-weekly single boosting doses	24
		800mg avelumab	Intravenous administration	2-weekly single dose	
Resectable patients	VXM01 + avelumab	10^6 or 10^7 CFU VXM01 vaccine	Oral administration	4 prime single doses followed by 4-weekly single boosting doses	6
		800mg avelumab	Intravenous administration	2-weekly single doses	

CFU = colony forming unit

Source: Protocol Table 10

Each non-resectable patient received a total of 4 prime doses and 12 boosting doses of VXM01 vaccine up to Week 48 and 25 doses of avelumab. In case of patient-specific prolongation, additional 12 doses of VXM01 vaccine and additional 24 doses of avelumab were to be given. Thus, a maximum dose of 28 doses VXM01 vaccine and 49 doses avelumab were given.

Each resectable patient received a total of 4 prime doses and 11 boosting doses of VXM01 vaccine up to Week 48 and 21 doses of avelumab. In case of patient-specific prolongation, additional 12 doses of VXM01 vaccine and additional 24 doses of avelumab were given. Thus, a maximum dose of 27 doses VXM01 vaccine and 45 doses avelumab were given.

A fixed dosing regimen of 800 mg administered as a 1-hour i.v. infusion Q2W was used for avelumab. Following avelumab infusions, patients were observed for 60 minutes for potential IRRs.

9.4.4 Timing of Dose for Each Patient

VXM01 vaccine was administered at a dose of 10^6 or 10^7 CFU as oral drink solution approximately 1 hour before a meal. The patients received 4 prime administrations on Days 1, 3, 5, and 7, followed by boosting doses every 4 weeks up to Week 48. A patient-specific prolongation of the boosting could have been initiated at the investigator's discretion. For dose modifications see Section 9.4.6.

Avelumab was administered at a dose of 800 mg as i.v. infusion over a duration of 1 hour (-10 minutes/+20 minutes). The patients received doses every 2 weeks up to Week 48.

In order to mitigate immune-related immediate type of reactions, all patients in the run-in phase received the avelumab infusion i.v. over 1 hour first and were monitored for another hour prior to taking the VXM01 vaccine. Having drunk the VXM01 solution, patients continued to be monitored for an additional hour. The procedure for further monitoring of patients treated with the combination VXM01 vaccine and avelumab once the TLT observation period had been completed and beyond the run-in stage was confirmed by the DSMB.

9.4.5 Treatment-Limiting Toxicities

TLTs were defined taking into account toxicities described for Avastin®, Cyramza® and Bavencio®, as well as the safety data of the studies VXM01-01-DE, VXM01-02-DE, and VXM01-03-DE.

Up to date, no TLTs have been observed for VXM01 vaccine doses 10^6 CFU/mL up to 10^{10} CFU/mL.

9.4.5.1 Treatment-Limiting Toxicities for VXM01 Vaccine

TLTs for VXM01 vaccine were defined as any AEs that were related to VXM01 vaccine reported according to the CTCAE criteria (version 4.3):

- Any related AE of Grade 4 (except epilepsy) or higher
- Any related AE Grade 3 or higher for gastrointestinal fistula, diarrhea, gastrointestinal perforation, multi-organ failure, anaphylaxis, auto-immune disorder, cytokine-release syndrome, intestinal bleeding, renal failure, proteinuria, thromboembolic events, stroke, heart failure, intracranial hemorrhage, and vasculitis.

9.4.5.2 Treatment-Limiting Toxicities for Avelumab

- Any Grade 4 adverse drug reactions (ADRs) requiring treatment discontinuation with avelumab except for single laboratory values out of normal range that did not have any clinical correlate, and resolved within 7 days with adequate medical management.

- Any Grade 3 ADRs requiring treatment discontinuation with avelumab except for any of the following:
  - Diarrhea of ≤7 days duration following adequate and optimal therapy that resolved to Grade ≤1
  - Grade 3 skin toxicity that resolved to Grade 1 or less with supportive measures within 7 days
  - Nausea and vomiting of ≤72 hours duration with adequate and optimal therapy
  - Single laboratory values out of the normal range that had no clinical correlate, and resolved to Grade ≤1 within 10 days with adequate medical management (except Grade ≥3 liver function test increase without any clinical correlate)
  - Grade 3 IRRs that resolved within 6 hours from the end of infusion and controlled with medical management
  - Transient (≤72 hours) Grade 3 fatigue, local reactions, flu-like symptoms, fever, headache that resolved to Grade ≤1 with adequate treatment
  - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
  - Asymptomatic Grade ≥3 lipase or amylase elevation not associated with clinical manifestations of pancreatitis. Medical Monitor had to be consulted for such lipase and amylase abnormalities
- Any Grade 5 ADR

9.4.6 Dose Modification in Individual Patients

9.4.6.1 Dose Modification for VXM01 Vaccine

The doses and nature of VXM01 vaccine administered for re-vaccination (boosting) were identical to the doses administered for initial vaccination (priming).

In patients taking part in the run-in stage, those at the 10^6 CFU dose could have had their dose escalated to 10^7 after the 10^7 CFU dose was shown to be safe, and according to investigator's decision. Otherwise, no other dose modification was allowed.

Administration of VXM01 vaccine (at either dose) could have continued even if avelumab administration was skipped or delayed.

9.4.6.2 Dose Modification for Avelumab

Each patient stayed on the avelumab assigned dose of 800 mg unless treatment needed to be stopped. Changes in infusion rate and dose delays could have been used. There were no dose reductions.

Treatment with avelumab could have been skipped for a delay of up to 4 weeks from the previous dose for any nonrelated AEs, laboratory abnormalities, or intercurrent illness, which in the judgment of the investigator warranted delaying the dose of study medication. If dosing was delayed more than 4 weeks, treatment could have been resumed only after consultation with the study medical monitor. Any delay in dosing in excess of 12 weeks was not permitted.

9.4.7 Blinding

This was an open-label trial and hence the combination treatment administered was not blinded.

9.4.8 Prior and Concomitant Therapy

9.4.8.1 Avelumab Premedication & Observation Period

- Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25 to 50 mg diphenhydramine and 500 to 650 mg paracetamol [acetaminophen] i.v. or oral equivalent) approximately 30 to 60 minutes prior to the first 4 doses of avelumab was mandatory. Premedication was administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reaction. This regimen could have been modified based on local treatment standards and guidelines as appropriate. However, the prophylactic use of systemic corticosteroids was not permitted.
- Following avelumab infusions, patients were observed for 60 minutes postinfusion for potential IRRs.

9.4.8.2 Concomitant Medication

Permitted Medication and Other Treatments

Mandatory premedication with antihistamine and paracetamol (acetaminophen) for the first 4 doses was required in all patients to be treated with avelumab. Premedication was administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions in accordance with the IB of avelumab.

During and following a patient's participation in the trial, the investigator ensured that adequate medical care was provided to a patient for any AE including CS laboratory values. The investigator was to inform a patient when medical care was needed for intercurrent illness(es) of which the investigator became aware.

Any medications, therapies, or procedures (other than those excluded by the clinical trial protocol) that were considered necessary for the patient's welfare and would not interfere with the trial medicinal products could be given at the investigator's discretion.

Other drugs used for prophylaxis, treatment of hypersensitivity reactions, and treatment of fever or flu-like symptoms are described in Protocol Section 7.3 (see also Section 9.5.3.1).

Rescue medications may have been administered due to anticipated adverse reactions or anticipated emergency situations (see Protocol Appendix III).

Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) were acceptable.

Prohibited Medication and Other Treatments

For restrictions on prior therapy, see Section 9.3.

The following treatments were not to be administered during the trial:

- Immunotherapy, immunosuppressive drugs (that is, chemotherapy or systemic corticosteroids except for short-term treatment (≤1 week) of allergic reactions or for the treatment of irAEs or steroids for adrenal failure or emesis prophylaxis up to 4 mg dexamethasone daily dose equivalent within 2 weeks before and during the treatment

period up to Week 48), or other experimental pharmaceutical products. Short-term (≤1 week) administration of systemic steroid (that is, for allergic reactions or the management of irAEs) was allowed. Steroids with no or minimal systemic effect (topical, inhalation) were allowed.

- Chronic concurrent therapy with antibiotics were to be avoided within 2 weeks before and during the treatment period up to Week 48. Antibiotics were not to be used between 3 days before until 3 days after VXM01 vaccine administration.
- Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin).
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) EXCEPT for erythropoietin and darbepoietin alpha.
- Bevacizumab or any other anti-angiogenic treatment
- Any other anti-cancer therapy or concurrent anticancer treatment
- Radiotherapy, with the exception of palliative short course, limited field radiotherapy (i.e., ≤0 fractions and ≤30% bone marrow involvement or per institutional standard) which could be administered during the study. However dosing had to be suspended at least 14 days prior to the start of radiotherapy and was not to be resumed until at least 14 days after the last radiotherapy fraction)
  - In case of radiotherapy scheduled after the trial, the last dose of avelumab was to be at least 6 weeks prior to the radiotherapy
- Live vaccines (other than VXM01) within 30 days prior to study treatment

9.4.9 Treatment Compliance

Treatment was administered at the study site by adequately trained medical professionals.

9.5 Efficacy and Safety Variables

An assessments overview is provided in Protocol Table 11, and a detailed Schedule of Assessments (SoA) is provided in Protocol Table 2 to 8.

9.5.1 Efficacy Assessments

9.5.1.1 Efficacy Based on Immunotherapy Response Assessment for Neuro-Oncology

All lesions radiographically identified at screening/baseline were consistently followed by MRI using the unique lesion number assigned at screening/baseline. Routine tumor follow-up by MRI was done at the time points given in the SoA.

Routine tumor follow-up included tumor assessment of the primary tumor and metastasis, e.g., determination of primary tumor size, number and size of metastasis. Tumor response or progression on MRI was determined according to the RANO criteria plus their adaption for immunotherapy trials (iRANO; Okada et al., 2015) See Protocol Appendix I for the iRANO treatment algorithm. The iRANO assessment classified patients as having progressive disease, complete remission, partial remission, or stable disease. MRI comprised the National Brain Tumor Society/European Organisation for Research and Treatment of Cancer protocol for gliomas including perfusion MRI (Ellingson 2014).

9.5.2 Pharmacodynamic and Biomarker Assessments

All relevant blood and tissue sample collection were performed at the time points given in the SoA. Sample analysis was performed according to qualified and/or Good Laboratory Practice (GLP) methods, as appropriate. Full details are provided in the trial Laboratory Manual available in the Trial Master File.

9.5.2.1 Peripheral Immune Response and T cell Immunomonitoring

Specific T cell-response against VEGFR-2 was determined by IFN-gamma ELISpot using cryopreserved PBMCs at the time points provided in the schedules of assessment.

In addition, flow cytometry analysis using PBMCs was performed to determine the frequency of T_{regs} and MDSCs.

9.5.2.2 Tumor Biopsy

Primary (archival) tumor material of all patients and recurrent tumor material of re-operated patients was used for analysis.

Tumor samples were processed according to local standards.

Tumor tissue staining was performed provided there was access to sufficient tissue (formalin-fixed paraffin-embedded [FFPE]), *post hoc*, batchwise during the study or at the end of the trial and from the most recent available tissue. Staining was performed for the following:

- Immune cell infiltrates
    - CD3, CD4, CD8, PD-L1, PD-1
    - CD68
    - T_{regs}, Forkhead box P3 (FoxP3)
- Vessels
    - VEGFR-2
- Tumor tissue characterization
    - Expression of VEGFR2 on vessels and tumor cells
    - PTEN mutation /depletion status
    - MMR/ MSI status
    - PD-L1

Additional staining for other factors based on emerging scientific understanding of the combination therapy could also be performed.

9.5.2.3 Peripheral T Cell and Tumor-Infiltrating Lymphocyte Receptor Sequencing

TCR sequencing was to be performed for primary and recurrent tumor samples and blood T cells of the respective time point (if available) to assess overlap of T cell clones of periphery and intratumoral T cells in respect to expansion as well as breadth of T cell clonality before and after vaccination. Sequencing of the samples was to be performed at DKFZ Core Facility Heidelberg, analysis of the TCR data was to be done at Adaptive Biosciences and Immunmonitoring Laboratory Heidelberg (Dr. D. Riehl).

9.5.2.4 Human Leukocyte Antigen-typing

To support the assessment of immunological parameters, e.g., ELISpot by using human leukocyte antigen (HLA)-specific peptides, the determination of patients HLA-type was to be performed. Required DNA extraction of PBMCs was to be performed in the Immunmonitoring Laboratory at NCT (Prof. Platten/Dr. Riehl). Further analysis of the HLA was to be done at the DKMS (Deutsche Knochenmarkspenderdatei), Dresden.

9.5.2.5 Anti-LPS ELISA

Peripheral blood samples were taken at the time points given in the SoA. Specific IgM and IgG antibody responses against the lipopolysaccharide (LPS) of the carrier bacterium (anti-LPS IgG and anti-LPS IgM) were determined by validated enzyme linked immunosorbent assay (ELISA) methods.

9.5.2.6 Anti-drug Antibody

For patients receiving avelumab, blood samples for human ADA analysis were collected at the time points indicated in the SoA.

Samples positive for ADAs were to be re-analyzed to determine the titer and tested for neutralizing capacity.

9.5.2.7 Gut Microbiome

Stool samples were collected at the time points given in the SoA. These should have been collected within 72 hours before the visits. Type and diversity of bacterial species were to be assessed and correlated with responsiveness to therapy.

9.5.3 Safety Assessments

9.5.3.1 Adverse Events

An AE was defined as any untoward medical occurrence in a clinical investigation patient administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptoms, or disease temporally associated with the use of an IMP, whether or not it is related to the IMP. When there were reasonable grounds for suspicion that the event was caused by the investigational product (i.e. there are facts or arguments to suggest a causal relationship), it was considered an ADR.

Worsening of the patient’s condition for which the trial treatment was being used, was not considered an AE.

AEs included:

- A CS worsening of a concomitant illness
- A clinical laboratory AE: a clinical abnormality which was CS, i.e., any abnormality that suggested a disease and/or organ toxicity and was of a severity that required active management (active management included active treatment or further investigations, e.g., change of dose or more frequent follow-up due to the abnormality.)

The following were not considered as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedure unless the condition for which the procedure was planned has worsened from the first trial-related activity after the patient signed the informed consent

When assessing an AE, the following definitions were used:

Severity:

Each AE was classified and graded according to the NCI CTCAE Version 4.3. If no CTC grading was available, the severity of an AE was graded as follows:

- **Mild (Grade 1):** the AE caused discomfort without disruption of normal daily activities
- **Moderate (Grade 2):** the AE caused discomfort that affects normal daily activities
- **Severe (Grade 3):** the AE made the patient unable to perform normal daily activities or significantly affected his/her clinical status
- **Life-threatening (Grade 4):** the patient was at risk of death at the time of the AE or the event caused disablement
- **Death (Grade 5):** death related to AE

Causality:

The relationship of an AE to either VXM01 vaccine or avelumab treatment was recorded for each medicinal product, as follows:

- **Definitely related:** There was a reasonable possibility that the event may have been caused by IMP. A certain event had a strong temporal relationship and an alternative cause was unlikely.
- **Probably related:** An AE that had a reasonable possibility that the event was likely to have been caused by IMP. The AE had a timely relationship and followed a known pattern of response, but a potential alternative cause may have been present.
- **Possibly related:** An AE that had a reasonable possibility that the event may have been caused by IMP. The AE had a timely relationship to the IMP; however, the pattern of response was untypical, and an alternative cause seemed more likely, or there was significant uncertainty about the cause of the event.
- **Unlikely related:** An AE that followed such a temporal sequence from administration of the study medication that a relationship was not likely, and was likely to be due to a cause such as (known characteristics of) the patient’s clinical state or other treatment.
- **Not related:** An AE that did not follow a reasonable temporal sequence related to IMP and was likely to have been produced by the patient’s clinical state, other modes of therapy or other known etiology.

Ultimately the relationship to the AE was categorized as either **“unrelated”** (including, unlikely or not related) or **“related”** (including definitely, probably or possibly related).

Management Procedures for Certain, Potential, Specific AEs or ADRs

It is worth noting that no ADRs have been observed for VXM01 vaccine in any of its clinical trials to date. In the event of AEs judged to be related to the immunization, treatment was given to alleviate symptoms and/or avoid their further aggravation. Symptoms like skin reactions, rash, urticaria, edema, nausea, vomiting, bronchospasm, glottis edema, coughing, dyspnea, hypotension, or tachycardia which resemble hypersensitivity (anaphylactic) reactions mediated by histamine and/or leukotrienes and/or cytokines were treated as such, i.e., depending on the condition. It should be noted, that this has not been reported when using *Salmonella TyhpiTy21a*. Appropriate rescue medication is described in Protocol Appendix III.

Considering the anti-angiogenic mode of action of the VXM01 vaccine and due to the combination treatment, certain AEs could arise including hypertension, congestive heart failure or proteinuria. Management procedures for these followed those described for other anti-angiogenic therapies, e.g., Avastin. The management procedures as well as guidelines for IRRs and irAEs are described in Protocol Section 7.3.

Adverse Drug Reaction

All noxious and unintended responses to the 2 medicinal products used in this trial, related to any dose were considered as ADR. The phrase “responses to medicinal product” means that a causal relationship between a medicinal product (in this trial 2 such products, VXM01 vaccine and avelumab) and an AE was at least a reasonable possibility, i.e., a relationship cannot be ruled out. ADRs are also referred to as **toxicity**.

Unexpected Adverse Drug Reaction

An unexpected ADR is an ADR of which the nature or severity was not consistent with the available product information, e.g., the IB for an unapproved investigational product. ADRs that were more specific or more severe than described in the IB were also considered unexpected.

Serious Adverse Event

A serious adverse event (SAE) was defined as any AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the IMP, comparator, or placebo, that fulfilled one or more of the following:

- Resulted in death
- Was immediately life-threatening
- Required inpatient hospitalization or prolongations of an existing hospitalization
- Resulted in persistent or significant disability or incapacity
- Resulted in a congenital abnormality or birth defect
- Was an important medical event that could have jeopardized the patient or required medical intervention to prevent one of the outcomes listed above

In line with the section ‘Adverse Event’ above indicating that worsening of the patient’s condition for which the study treatment was being used, was not considered an AE, death due to progression of glioma was not considered an AE. Thereby not an SAE (i.e., death due to progression of glioma did not need to be reported as an SAE). The following were also not considered (and did not need to be reported) as SAEs:

- Hospitalization due to a social indication
- Planned hospitalization aiming exclusively at diagnosis

All SAEs that occurred after any patient had been enrolled, before treatment, during treatment or before discharge, whether or not they were related to the IMP, must have been recorded on forms provided by Vaximm.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR was defined as any SAE or reaction where the nature or severity was not consistent with the product information mentioned in the IB or the trial protocol.

Collection, Recording, and Reporting of Adverse Events

All AEs, whether serious or non-serious, were reported from the time a signed and dated ICF was obtained until the end of the post-treatment follow-up period. In addition, patients were observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?” at each contact with the trial site (visit or telephone). Patients were encouraged to spontaneously report AEs occurring at any other time during the trial.

AEs occurring after the 30 days after last VXM01/avelumab administration and coming to the attention of the investigator were recorded only if they were considered, in the opinion of the medical monitor and Sponsor, unexpected and related to VXM01 vaccine and avelumab combination.

All AEs, regardless of seriousness, severity, or presumed relationship to investigational product , were recorded and evaluated by the investigator. Whenever possible, diagnoses were given when signs and symptoms were due to a common etiology. If no diagnosis could be made, the investigator was to record each sign and symptom as individual AEs. Investigators recorded their opinion concerning the relationship of the AE to the investigational product.

For a list of the information collected about each AE, please see Protocol Section 7.2.

Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of investigational product, were reported to the appropriate Sponsor contact person(s) within 24 hours after obtaining knowledge about the event, followed by a complete SAE form as soon as more information was available. For each SAE, a separate SAE form (or Additional Safety Information [ASI] form) was completed in the eCRF. In addition, for all patients with any remaining SAEs at the 30-day follow-up visit, regardless of its relationship to trial medication, AE information was collected every 3 weeks until: 1) the symptom subsided; 2) any clinically relevant abnormal laboratory value had returned to baseline; 3) there was a satisfactory explanation other than the VXM01 vaccine and avelumab combination treatment for the change(s) observed; or 4) death, in which case an autopsy report was supplied to Allucent (formerly SMS-Oncology), if performed.

Follow-up of Adverse Events

Follow-up information was reported by eCRF in a similar manner as initial AE/SAEs. The SAE follow-up information only included new (e.g., corrections or additional) information and was reported within 24 hours of the investigator’s first knowledge of the information. This was also the case for AEs initially reported as non-serious which subsequently became SAEs.

All SAEs were followed actively until resolution or stabilization. The above was also applicable to follow-up SAE information.

SAEs reporting to relevant authorities and IECs was done in the form of periodic line-listings instead of individual reports within applicable legal timelines.

Allucent (formerly SMS-Oncology), on behalf of Vaximm was required by law to report to the health authorities in a written safety report: 1) all fatal or life-threatening SUSARs within seven (7) calendar days of initial notification; and 2) all other SUSARs within fifteen (15) calendar days of initial notification.

In France, all fatal or life-threatening SUSARs were reported to health authorities in a written safety report without delay according to décret no. 2016-1537 dated November 16th, 2016.

Pregnancy

Pregnancy during the trial was to be avoided, and the patients were instructed in highly effective contraception as per local guidelines.

9.5.3.2 Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory safety tests (Table 9-3) were collected at time points outlined in the SoA.

Table 9-3: Clinical Laboratory Parameters

Clinical laboratory parameter (central laboratory)
Hematology: Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell (RBC) count, WBC differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), and platelet count.
Biochemistry: Creatinine, alkaline phosphatase, total bilirubin, ALT, AST, gamma-glutamyltransferase, total protein, uric acid, urea, sodium, potassium, calcium, chloride, glucose, lactate dehydrogenase, creatine phosphokinase, inorganic phosphate, cholesterol, triglycerides, amylase and lipase.
Urinalysis: Leukocytes, nitrite, pH, protein, glucose, ketone, urobilinogen, bilirubin, blood (hemoglobin and erythrocytes)
Coagulation: Prothrombin time, INR, and activated partial thromboplastin time (PTT)
Hormones: Thyroid Stimulating Hormone (TSH) and T4

Source: Protocol Section 6.1

9.5.3.3 Physical Examination

Patients underwent a physical examination at the time points outlined on the SoA. The physical examination included an examination of the following: head, eyes, ears, nose and throat; respiratory system/chest; cardiovascular system/heart; abdomen; skin, lymph nodes; extremities and (at the investigator's discretion) genitourinary system/pelvis.

For height and body weight measurements, preferably the same equipment was used throughout the trial. To obtain the actual body weight, patients had to be weighed lightly clothed. Body height was recorded in centimeters and body weight in kilograms.

9.5.3.4 Vital Signs

Vital signs (systolic and diastolic blood pressure [mm/Hg], heart rate [beats per minute], and temperature) were measured at times outlined in the SoA, after the patient had rested in a seated position for at least 5 minutes. Vital signs were repeated if judged necessary by the investigator (or designee).

9.5.3.5 Electrocardiograms

Twelve-lead electrocardiograms (ECGs) were recorded at times outlined on the SoA, after the patient had rested supine on a bed for at least 5 minutes. The following were recorded for each ECG: heart rate, PR/PQ interval, QRS and QT intervals, QT interval corrected for by Bazett's formula, (QTcB), QT interval corrected for heart rate by Fridericia's formula (QTcF), and an overall evaluation by the investigator.

9.5.3.6 Performance Status

The KPS scale as a measure of quality of life was determined at the time points specified in the SoA.

The KPS scale (Karnofsky and Burchenal 1949) was used to quantify the general well-being and activities of daily life in cancer patient and uses scores from 100 (for good health) to 0 (for death) as described in Table 9-4.

Table 9-4: Karnofsky Performance Status Scale

Condition	%	Comments
A: Able to carry on normal activity and to work. No special care is needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
B: Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
C: Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

Source: SAP Section 11.2.1

9.5.3.7 Concomitant Medications

Information on concomitant medication use was collected within the time period outlined in the SoA.

9.5.4 Appropriateness of Measurements

The procedures in this study were performed in accordance with clinically appropriate standard procedures that are widely used for assessing the efficacy and safety of an IMP in this population.

9.5.5 Drug Concentration Measurements

All relevant sample collection and analysis were to be performed according to qualified and/or GLP methods, as appropriate. Full details are provided in the trial Laboratory Manual.

No measurements of VXM01 concentration were performed.

Pharmacokinetics of avelumab for all the patients were to be recorded using a sparse sampling approach. Plasma concentrations from sparse PK sampling for avelumab were planned to allow population PK analyses.

9.6 Data Quality Assurance

Information about trial risks identified, evaluated, reviewed, and reported as well as risk mitigation is provided in the Risk Management Plan that is available in the Trial Master File.

9.6.1 Monitoring

Before an investigational site began enrolling patients into the trial, a representative of Vaximm visited the investigational trial site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Vaximm or its representatives

During the trial, the investigational site was regularly monitored in order to:

- Provide information and support to the investigator(s)
- Confirm that facilities remained acceptable
- Confirm that the investigational team was adhering to the protocol, that data were being accurately recorded in the eCRFs, and that investigational product accountability checks were being performed
- Perform source data verification. This included a comparison of the data in the case report forms with the patient’s medical records at the hospital or practice, and other records relevant to the trial
- Record and report any protocol deviations to Vaximm
- Confirm AEs and SAEs had been properly documented on the eCRFs and confirm any SAEs had been forwarded to Vaximm and that those SAEs that met criteria for reporting had been forwarded to the IRB/IEC

The monitor was available between visits if the investigator(s) or other staff needed information or advice.

Additionally, medical monitors reviewed the clinically relevant data points to provide independent medical and safety oversight to protect the safety of the trial patients and the integrity of data.

9.6.2 Audits and Inspections

There have been no site audits or inspections. There has been a GCP inspection of CATO Europe GmbH by Bezirksregierung Köln (Cologne Regional Government) on 06 and 07 April 2022, which included review of this study.

Copies of the audit/inspection certificates are provided in Appendix 16.1.8.

9.6.3 Quality Control and Quality Assurance

9.6.3.1 Electronic Case Report Forms

Electronic case report forms were used for data collection. Following training, trial staff were given access to the eCRF. Access to the database was restricted to staff participating in the trial, and the extent of access depended on the participants' user role in the trial.

The trial participants were identified in the database by patient numbers. The investigator or delegate was to enter patient data into the eCRF within 2 working days (if at all possible). Data recorded in the eCRFs were accessible to the trial staff throughout the trial.

After data entry, systematic data validation was performed, and data entry discrepancies were presented electronically directly to the site staff. Queries for discrepant data could be generated automatically by the software upon entry and/or generated manually by the monitor or the trial data manager. All queries, whether generated by the system or by trial staff, were in electronic format.

All sections of the eCRF were electronically approved by the investigator after the data were entered and all queries had been resolved. Changes to any eCRF page subsequent to the approval required a new approval signature.

All queries and changes/corrections to the data were documented in the eCRF.

9.6.3.2 Data Processing

The trial was run as an electronic data capture trial, i.e., all relevant data were entered by the site directly into the clinical database. The database and application were set up and managed by Allucent (formerly SMS-Oncology). The eCRF was designed to capture all required information in compliance with GCP standards. Site staff were provided with eCRF guidelines for this trial.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

The performed statistical analyses are summarized below, with full details provided in the final Statistical Analysis Plan (SAP) included in Appendix 16.1.9. Statistical analyses were in accordance with the final SAP.

9.7.1 Analysis Populations

The following analysis sets are defined for this trial:

- **Full analysis set (FAS)**: included all patients who received any trial drug after trial entry.

- **Per-protocol analysis set (PPS)**: included all patients who received trial drug in compliance with the scheduled treatment regimen, underwent re-operation if in the resectable subgroup and without any major protocol deviations.
- **Safety analysis set (SAF)**: all patients who received at least one dose of the trial drug and for which at least one post-dose safety assessment is available.

The FAS and PPS was used for efficacy analyses and the SAF was used for safety analysis.

9.7.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics of patients in the SAF were summarized for the total population, by dose level of VXM01 administered, and by patient category (NR/R). The characteristics were presented as descriptive statistics for age, height, and weight, and with frequencies for gender, ethnicity, and race. Primary cancer diagnoses were summarized including frequencies for histological type, recurrence details, and descriptive statistics for the number of months between the first primary cancer diagnosis date and the first IMP exposure, and between last recurrence date and first IMP exposure.

Medical and surgical history was listed by patient and summarized by frequency tables. Diagnoses were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 and summarized by system organ class (SOC) and preferred term (PT).

9.7.3 Interim Analysis

No interim statistical analysis was conducted.

9.7.4 Efficacy Analysis

Efficacy data included tumor and response data, KPS, and pharmacodynamics and other biomarkers, including anti-LPS, PBMC immunomonitoring, and tumor biomarkers. All identified tumor lesions will be presented in tumor identification listings, describing tumor location, location details, laterality, method, and MRI sequence data. Listings regarding evaluation of the tumor lesion will present tumor state, diameters (mm), sum of diameters, tumor or lesion presentation type, completion status, and reason for missing tumor assessments.

9.7.4.1 Secondary Efficacy Endpoints

Efficacy results were analyzed for both the FAS and the PPS.

Clinical efficacy of VXM01 vaccine was measured by CT/ MRI-scan starting at screening followed by an every 12-week interval from the first administration of VXM01 vaccine while on trial treatment. Tumor response or progression on MRI was determined according to RANO criteria plus their adaption for immunotherapy trials (iRANO; Okada et al., 2015)).

All identified tumor lesions were presented in tumor identification listings, describing tumor location, location details, laterality, method and MRI sequence data. Listings regarding evaluation of the tumor lesion present, tumor state, diameters (mm), sum of diameters, tumor or lesion presentation type, completion status and reason for missing tumor assessments.

Tumor Response

iRANO overall tumor response was determined by the Target response, Non-target response, T2/FLAIR response, metabolic response, i.e., status of corticosteroid treatment compared to baseline scan, and clinical status. All response parameters were compared to baseline. The

overall tumor response could result in complete remission, partial remission, progressive disease, stable disease or not evaluable. Best overall response was the best response recorded from the start of the study treatment until the EoT, taking into account any requirements for confirmation. The ORR was defined as the proportion of responders, patients who achieved a BOR of complete or partial remission.

The ORR summary statistics reported the frequency and proportions per response type and when informative, the ORR including the exact 95% CI.

DoR was defined as the first time a response (complete or partial remission) was observed until progression or death from any cause. The DoR summary statistics comprised the number of included patients, having a BOR of complete or partial remission, number and percentage of patients with an event, number and percentage of patients censored, the lower, upper ranges and median with exact 95% CI in months estimated using the Kaplan-Meier method. Kaplan-Meier plots were provided per response.

The response listing presents the target response, non-target response, T2/FLAIR response, metabolic response, clinical status, overall tumor response, BOR, and reason for EoT and EoS.

Derived response efficacy details, DoR, censoring (yes/no), event or censoring description, were listed per patient.

Clinical Response

Progression Free Survival (PFS) was defined as the time between the first dose of VXM01 vaccine and the first documented progression or death from any cause.

Time-to-Progression (TTP) was defined as the time between the first dose of VXM01 vaccine and the first documented progression.

Recurrence-Free Survival (RFS) was defined as the time between the reoperation and the first documented progression or death from any cause.

Overall Survival (OS) was defined as the time between the first dose of VXM01 vaccine and death from any cause.

The summary statistics included the number of included patients, number and percentages of patients with an event, number and percentages of patients censored, the lower, upper ranges and the estimated median survival with 95% CI in months estimated using the Kaplan-Meier method. Kaplan-Meier plots were provided per response.

Derived survival efficacy details, duration of survival, censoring (yes/no), event or censoring description, were listed per patient. OS and PFS were illustrated in a Swimmers' response plot, including the duration of treatment and the occurrence of death.

9.7.4.2 Karnofsky Performance Status

KPS ranged from 100 to 0% as detailed in Table 9-4.

The KPS was summarized in frequency tables by visit in change from baseline tables per time point and worst-case cross-tabulation for the whole study period.

A patient-based listing was provided presenting the analysis time point, baseline and analysis flag and the KPS.

9.7.4.3 Exploratory Pharmacodynamic and Biomarker Analyses

Biomarker data included peripheral immune response/T cell immunomonitoring and various molecules (biomarker) assessed in tumor biopsies. Outcome variables were summarized descriptively for each assessment point using summary statistics. Data was plotted by dose level of VXM01 vaccine, at baseline and over time (on semi-logarithmic scale if appropriate).

Exploratory microbiome analysis was performed before and after vaccination. The diversity and type of bacteria was assessed. Results were correlated with the overall responsiveness to the combination therapy.

Anti-LPS

Anti-LPS IgG and IgM results were summarized in frequency tables per cohort and per time point. The listings include baseline, analysis values and any related comments, if applicable.

VEGFR2 Specific T Cell Response

T cell response against VEGFR-2 was determined by IFN-gamma ELISpot using cryopreserved PBMCs.

Derived values for ELISpot were generated based on the mean of the actual values measured in triplicates corrected for any background noise (negative control). Any values reported as below the lower limit of quantification (LLOQ) were imputed with the actual LLOQ value.

An individual T effector cell response against VEGFR2 was defined positive when test peptide wells had at least two-fold higher spot counts compared to the negative control and the difference of the triplicates was significant in the unpaired 2-tailed student's t-test.

The strength of the VEGFR2-specific T cell response after vaccination was graded for each time point in patients matching the acceptance criterion of a minimum mean of 10 IFN-gamma spots/well at d0 according to the following rule:

Grade	**Response**	**Fold Change Value/Value D0**
Grade 0	Negative or positive	≤1
Grade 1	Positive	>1 and ≤3
Grade 2	Positive	>3 and ≤5
Grade 3	Positive	>5

The VEGFR2 peptide results will be illustrated in an individual line plot per patient, whereby negative results are highlighted in red and positive results are highlighted in green.

Myeloid Derived Suppressor and Regulatory T Cells

Flow cytometry analysis using PBMCs was performed to determine the frequency of MDSCs and T_{regs}, calculated from single tests with correction of background noise. Tabulation of the derived values and change from baseline was produced per cohort and per visit. The listings include baseline and derived analysis values, change from baseline and any related comments.

Tumor Biomarkers

Tumor tissue staining was performed for

- Immune cell infiltrates (CD3, CD4, CD8, PD-L1, PD-1, CD68, T_{regs}, FoxP3).
- Vessels (VEGFR2).
- Tumor tissue characterization (VEGFR2 expression on vessels and tumor cells, PTEN mutation /depletion status, MMR/MSI statis, PD-L1).

Tabulation of actual values and change from baseline was produced per cohort and per visit. The listings include baseline and analysis values, change from baseline and any related comments.

9.7.5 Safety Analyses

Results of all safety measurements were listed individually and summarized.

9.7.5.1 Exposure

Exposure to IMP was presented by patient and by cohort and included duration of exposure (days), number of doses VXM01 vaccine and avelumab administered, mean dose administered, and total dose administered. The cohort statistics were based on the mean statistics at patient level.

Additionally a summary table of IMP interruptions and modifications was presented per cohort.

The patient-based listings are provided and include:

- Day and datetime of exposure
- Dose per administration (mg for avelumab and CFU/mL for VXM01 vaccine)
- Volume administered (mL)
- Infusion (mL/h) (avelumab only)
- Duration of infusion (minutes) (avelumab only)

9.7.5.2 Adverse Events

All AEs were listed together with information on onset, duration, severity, seriousness, determination of attribution (e.g., relationship to trial drugs or underlying disease), outcome and action taken.

AEs were coded using MedDRA. Coding was performed with the dictionary version 25.1. Coding terms and investigator terms were given in the listings.

An AE occurring before the first dosing was counted as pre-treatment AE (baseline complaint) unless it increased in severity after first dosing. An event was considered as a treatment-emergent adverse event (TEAE) if the event occurred or worsened at or after first dosing.

Only TEAEs were analyzed. All percentages were calculated against the total number of patients in the SAF, per cohort and as a total. When a patient experienced the same AE twice or more during the study period the patient was counted once for the calculation of the frequency (n) and proportion (%). The total number of events was also reported.

An AE summary table summarized the numbers and percentages of patients (n) and total number of events for all AE's, subcategorized by the following:

- Grade 3, 4 and 5
- VXM01 vaccine-related
- Avelumab-related
- Target disease-related
- Drug-related with Grade 3, 4 or 5 (VXM01 vaccine or avelumab)

The above was followed by subcategorized SAEs, TEAEs and serious TEAEs.

Additionally, treatment-limiting toxicities (TLT) due to VXM01 vaccine, TLTs due to avelumab, infusion-related AEs, irAEs, treatment (VXM01 vaccine or avelumab) discontinuation due to AEs and study discontinuations due to AEs were summarized.

Further tabular safety analysis was focused on TEAEs. Tabulation of TEAEs showing numbers and percentages of patients (n) and total number of events per SOC and PT were sorted on highest frequency per table. Tables reporting TEAE by severity were subdivided at the level of PT ordered by grade. Tables reporting TEAE by relatedness were subdivided at the level of PT ordered as related or not related.

Tabulation of the highest grade TEAEs was based on the PT with the highest grade observed within each patient during the study period. These tables were presented for all TEAEs, and for TEAEs related to VXM01 vaccine, avelumab, and target disease, sorted by highest to lowest frequency.

AE listings (related and nonrelated) are provided and include:

- All AEs
- AEs leading to treatment and or study discontinuation
- Grade 3 or 4 AEs
- AEs leading to death.

Additional listings include all deaths, combined with all relevant AE data when applicable, SAEs including all non-fatal AEs, other significant AEs including all non-serious and/or non-fatal AE's for which action was taken with IMP and/or AEs for which concomitant medications were subscribed.

9.7.5.3 Clinical Laboratory Assessments

Continuous

Laboratory tabular data was analyzed per category and presented in the section Laboratory findings. All units were converted into is the International System of Units. Continuous results were categorized into Low, Normal and High based on local standard reference ranges. CTCAE grades were assigned where applicable.

Tabulation of actual values and change from baseline was produced per cohort per visit and per time point where applicable for all continuous parameters.

Cross-tabulations by worst-case abnormalities (Low, Normal, High, High/Low) and by CTCAE grades (Grade 0 through 5) were generated per cohort per total study period.

The laboratory findings listings include baseline and analysis values, change from baseline, shift from baseline, clinical significance, and local reference ranges. All records flagged as clinically significant and records flagged with comments were presented in individual listings.

Categorical

Urinalysis data were presented as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS) with cross-tabulations per cohort and for the total populations. In the categories of Serology and Pregnancy results were collected at screening only and were exclusively presented in Listings.

9.7.5.4 Physical Examination

Physical Examination tabular summaries were ordered alphabetically. Cross-tabulations by worst-case abnormalities (Normal, Abnormal NCS, Abnormal CS) were generated per cohort per total study period. Listings include abnormalities and not performed evaluations only.

9.7.5.5 Vital Signs

Repeated measurements were averaged. For discrete repeated results, as well as for the indication of clinically significant, the most frequently observed result was used. In case of a tie the worst-case scenario was applied. Continuous results were categorized into Low, Normal and High based on industry standard reference ranges. Tabulation of actual values and change from baseline was produced per cohort per visit and per time point where applicable for all continuous parameters. Cross-tabulations by worst-case abnormalities (Low, Normal, High, High/Low) were generated per cohort per total study period. The vital signs listings include baseline and analysis values, change from baseline, the shift from baseline and clinically significance, where applicable. Related comments were flagged and reported in an individual listing.

9.7.5.6 Electrocardiogram

Continuous results were categorized into Low, Normal and High based on industry standard reference ranges. Tabulation of actual values and change from baseline was produced per cohort per visit. Cross-tabulations by worst-case abnormalities (Low, Normal, High, High/Low) and worst-case interpretations (Normal, Abnormal NCS, Abnormal CS) were generated per cohort per total study period. The ECG listings include baseline and analysis values, change from baseline, shifts from baseline and clinically significance where applicable. ECG abnormalities were presented in a separate listing in which clinically significant values were flagged. Related comments were flagged and reported in an individual listing.

9.7.5.7 Concomitant Medications

Compliance to and duration (in days) of the VXM01 vaccine and avelumab combination treatment was listed and summarized by means of descriptive statistics. Concomitant medications and significant non-drug therapies prior to and after the start of the trial drug were listed by patient and summarized by the Anatomical Therapeutic Chemical (ATC) Classification System term by means of contingency tables. For analysis tables, differentiation will be made between prior and concomitant medications based on the start date of the treatment in relation to the start of the study reference period. The patient-based listings will include all relevant

information as collected on the eCRF. Prior and concomitant medications are collected on the eCRF as such and will be flagged, respectively with P or C.

9.7.6 Determination of Sample Size

As this is an exploratory trial no formal sample size calculation was performed to assess safety and tolerability of the combination of VXM01 vaccine and avelumab treatment. The chosen sample size of 30 patients was based on achievable recruitment numbers. With the current design, the probability to detect at least 1 TLT was 64% (1/30; if it is 1/20 the probability is 79%) using normal power calculations with a 95% CI 0 considered to be sufficient to fulfill the objectives.

In addition, the proposed sample size of 6 patients was chosen for the group of patients who were candidates for re-operation, in line with proposed number for proof-of concept trials, generating first data in this patient population for the combined treatment of VXM01 vaccine and avelumab.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes to the Conduct of the Study

The original protocol (version1.0, dated 30 March 2018) was amended 7 times as described in Table 9-5.

Table 9-5: Changes to the Conduct of the Study

Version Number (Date)	Changes
2.0 (05 Sep 2018)	• Update and revision based on comments from Ethics Committee and Competent Authorities in France, Germany and the Netherlands (see Protocol Appendix IV)
3.0 (21 Sep 2018)	• Update and revision based on comments from the ANSM in France (see Protocol Appendix IV)
4.0 (31 Oct 2018)	• Update based on CCMO comments (vital sign measurements defined and added reference for immune-related cardiac events treatment guidelines) • Record archiving period changed from 15 to 25 years
5.0 (11 Jun 2019)	• Introduction of gut microbiome analysis • Administrative changes
6.0 (05 Nov 2019)	• Update of the avelumab safety information regarding pancreatitis in accordance with the current version of the Investigator's brochure • Update of the approval status of avelumab • Updates of the administrative section regarding members of the study team
7.0 (28 Nov 2019)	• Alignment of the Safety information regarding pancreatitis with the current version of the SmPC for Bavencio® (INN Avelumab)

Table 9-5: Changes to the Conduct of the Study

Version Number (Date)	Changes
8.0 (04 Sep 2020)	• Update to language regarding prior and concomitant use of antibiotics • Update of SOE, Visit week 50 and avelumab treatment added • Update of adverse reactions of avelumab: myasthenia gravis /myasthenic syndrome added

Source: Protocol Summaries of Changes (Appendix 16.1.1)

9.8.2 Changes to the Planned Analyses

Upon the Sponsor's decision, PK of avelumab, TCR sequencing, HLA-typing, ADA analysis and gut microbiome analysis as mentioned in the protocol were not performed.

Therefore the following exploratory objectives were not addressed:

- To characterize the PK of avelumab in combination with VXM01
- To characterize the immunogenicity of avelumab in combination with VXM01
- To characterize the gut microbiome pre- and post-treatment

The following exploratory endpoints were not addressed:

- TCR sequencing of TILs and peripheral T cells
- Tumor PTEN mutation/deletion status (primary tumors of all patients and recurrent tumors of re-operated patients)
- PK profile of avelumab in combination with VXM01 vaccine
- MSI/ MMR status
- Anti-avelumab ADA
- Gut microbiome status

Additionally, patients could not be assigned to the avelumab PK nor the avelumab Immunogenicity analysis set. The remaining exploratory endpoints related to pharmacodynamic and other biomarkers were therefore analyzed in the FAS and PPS population.

10. STUDY PATIENTS

10.1 Disposition of Patients

The primary reasons for discontinuation of study treatment and discontinuation from the study are detailed in Table 10-1. Overall, 96.4% of patients discontinued study treatment with the primary reason being progressive disease (92.9%). Death was the primary reason for discontinuation from the study (82.1% overall). One patient (10^6 CFU/mL group) completed the study and one patient (10^7 CFU/mL NR group) discontinued from the study due to progressive disease. Incidences for discontinuation of study treatment and discontinuation from the study were similar among the groups. Listing 16.2.1.1 presents the by-patient listing of trial analysis periods and termination. Three patients are still in the long-term follow-up phase of the study and are thus excluded from Table 10-1.

Results for the PPS were similar to those seen for the FAS (Table 14.1.1.4 [treatment termination] and Table 14.1.1.5 [study termination]). Further details on the disposition of patients, including the patients by site and visit can be found in Table 14.1.1.2 and Table 14.1.1.3, respectively.

Table 10-1: Reasons for Study Treatment Discontinuation and Study Discontinuation (FAS)

	10^6 CFU/mL (N = 3) n (%)	10^7 CFU/mL			Total NR[a] (N = 25) n (%)	Total (N = 28) n (%)
		All Patients (N = 25) n (%)	NR (N = 22) n (%)	R (N = 3) n (%)		
Completed Study Treatment	-	1 (4.0)	-	1 (33.3)	-	1 (3.6)
Discontinued Study Treatment	3 (100)	24 (96.0)	22 (100)	2 (66.7)	25 (100)	27 (96.4)
Primary Reason for Discontinuation of Study Treatment						
Physician Decision	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Progressive Disease	3 (100)	23 (92.0)	21 (95.5)	2 (66.7)	24 (96.0)	26 (92.9)
Completed Study[b]	1 (33.3)	-	-	-	1 (4.0)	1 (3.6)
Discontinued Study	2 (66.7)	22 (88.0)	20 (90.9)	2 (66.7)	22 (88.0)	24 (85.7)
Primary Reason for Discontinuation from Study						
Death (Due to Progressive Disease)	2 (66.7)	22 (88.0)	20 (90.9)	2 (66.7)	22 (88.0)	24 (85.7)

Source: Table 14.1.1.4, Table 14.1.1.5

Note: A correction was made in the primary reason for discontinuation from study: Patient 22-10 died as listed in Table 14.3.2.1 and this event was incorrectly listed as progressive disease in Listing 16.2.1.1 and Table 14.1.1.5.

CFU = colony forming unit; FAS = full analysis set; N = number of patients; NR = non-resectable; R = resectable

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group

b At the time of database lock, 2 patients in the 10^7 CFU/mL NR group and 1 patient in the 10^7 CFU/mL R group were in the follow-up phase of the study

10.2 Protocol Deviations

A listing of the major protocol deviations is provided in Table 10-2. A summary of the major protocol deviations is provided in Table 14.1.2.1 with the by-patient details in Listing 16.2.2.1.

Overall, 5 patients had major protocol deviations during the study. Most of the major protocol deviations concerned exclusion criteria being met (which occurred in all 5 patients), with half of the deviations being concomitant administration of an antibiotic (co-trimoxazole; which occurred in 4 patients). All of the patients treated with an antibiotic were part of the safety run-in cohorts, with 1 patient assigned to receive 10^6 CFU/mL VXM01 vaccine and 3 patients assigned to receive 10^7 CFU/mL VXM01 vaccine. As decided by the Sponsor, in agreement with the Principal Investigator, 3 additional patients were enrolled into the study for completion of the safety assessment in the safety run-in cohort, all assigned to receive 10^7 CFU/mL VXM01 vaccine.

Table 10-2: Listing of Major Protocol Deviations

Patient ID	Study Period	Protocol Deviation (Coded)	Protocol Deviation Subcategory	Protocol Deviation
01-04	Screening	Exclusion criteria met	Eligibility assessment	Patient met exclusion criterion 19 (persisting toxicity related to prior therapy)
	Treatment	Exclusion criteria met	Prior and concomitant medication	Patient was treated with antibiotic (co-trimoxazole) for a longer period
01-05	Screening	Inclusion criteria not met	Lab – hematology	Inclusion criterion 8 not met (platelet count too low)
	Treatment	Exclusion criteria met	Prior and concomitant medication	Patient was treated with antibiotic (co-trimoxazole) for a longer period
01-07	Treatment	Exclusion criteria met	Prior and concomitant medication	Patient was treated with antibiotic (co-trimoxazole) for a longer period
01-09	Treatment	Exclusion criteria met	Prior and concomitant medication	Patient was treated with antibiotic (co-trimoxazole) for a longer period
01-12	Screening	Exclusion criteria met	-	Patient met exclusion criterion 28 (chronic concurrent therapy)
	Treatment	Disallowed treatment	-	Disallowed treatment

Source: Listing 16.2.2.1

11. EFFICACY EVALUATION

The primary objective of the study was to evaluate the safety of the IMP. Safety results are presented in Section 12.

11.1 Data Sets Analyzed

The number of patients by population is presented per group in Table 11-1. The FAS and SAF analysis sets were identical (Table 14.1.1.1). A listing of patients excluded from the PPS efficacy analysis is provided in Listing 16.2.3.1.

Table 11-1: Patients by Population

Treatment Group	FAS n (%)	SAF n (%)	PPS n (%)
VXM01 10^6 CFU/mL	3 (100)	3 (100)	2 (66.7)
VXM01 10^7 CFU/mL	25 (100)	25 (100)	21 (84.0)
VXM01 10^7 CFU/mL Non-resectable	22 (100)	22 (100)	18 (81.8)
VXM01 10^7 CFU/mL Resectable	3 (100)	3 (100)	3 (100)
All Non-resectable Patients (Total NR[a])	25 (100)	25 (100)	20 (80.0)
All Patients (Total)	28 (100)	28 (100)	23 (82.1)

Source: Table 14.1.1.1

FAS = full analysis set; n = number of patients; NR = non-resectable; PPS = per-protocol analysis set; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group

11.2 Demographics and Other Baseline Characteristics

The number of patients in the FAS and SAF was the same; therefore, the safety population (SAF) will be presented in the tables below.

11.2.1 Demographics and Baseline Characteristics

The demographics and baseline characteristics are summarized in Table 11-2.

Overall, the mean age (standard deviation [StD]) was 58.0 (9.5). The majority of patients included in the study was male (22 [78.6%]), with 6 (21.4%) female patients included. The demographics and baseline characteristics were comparable between the groups and similar to the PPS (Table 14.1.3.1).

The by-patient listing of demographics and baseline characteristics is provided in Listing 16.2.4.1.

Table 11-2: Demographics and Baseline Characteristics (SAF)

	10^6 CFU/mL (N = 3)	10^7 CFU/mL			Total NR[a] (N = 25)	Total (N = 28)
		All Patients (N = 25)	NR (N = 22)	R (N = 3)		
Age (years)						
Mean (StD)	60.3 (6.4)	57.8 (9.9)	58.6 (9.3)	51.7 (13.6)	58.8 (9.0)	58.0 (9.5)
Median	63	59	58	59	60	60
Min, Max	53, 65	36, 78	37, 78	36, 60	37, 78	36, 78
Gender (n [%])						
Male	3 (100)	19 (76.0)	17 (77.3)	2 (66.7)	20 (80.0)	22 (78.6)
Female	-	6 (24.0)	5 (22.7)	1 (33.3)	5 (20.0)	6 (21.4)
Height (cm)						
Mean (StD)	180.7 (5.5)	177.2 (8.4)	177.2 (7.6)	177.0 (15.7)	177.6 (7.4)	177.5 (8.2)
Median	181	180	180	180	180	180
Min, Max	175, 186	155, 191	155, 187	160, 191	155, 187	155, 191
Weight (kg)						
Mean (StD)	81.7 (5.5)	79.2 (12.4)	79.7 (12.2)	76.0 (16.4)	79.9 (11.5)	79.5 (11.8)
Median	79	80	79	80	79	80
Min, Max	78, 88	58, 102	58, 102	58, 90	58, 102	58, 102
Karnofsky Performance Status						
Mean (StD)	83.3 (15.3)	85.6 (7.1)	85.0 (7.4)	90.0 (0.0)	84.8 (8.2)	85.4 (7.9)
Median	80	90	90	90	90	90
Min, Max	70, 100	70, 100	70, 100	90, 90	70, 100	70, 100

Source: Table 14.1.3.1

Note: Ethnicity and race were not reported for any patients in this table.

CFU = colony forming unit; N = number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set; StD = standard deviation

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group

11.2.2 Cancer Diagnosis and Treatment

11.2.2.1 Primary Cancer Diagnosis

Details on the primary cancer diagnosis per group are summarized in Table 11-3 and the by-patient listing is provided in Listing 16.2.4.2.

All patients were diagnosed with recurrent malignant glioma. The majority of patients (25 [89.3%)]) had 1 recurrence, 2 patients (7.1%) had 2 recurrences, and 1 patient (3.6%) had 3 recurrences. Recurrence of glioma was local in the majority of patients (27 [96.4%]) and the recurrence location varied between the groups. Overall, the mean time (StD) of primary cancer diagnosis to the first study drug exposure was 21.76 months (24.23). The 10^6 CFU/mL group had a longer time from primary cancer diagnosis to the first study drug exposure (57.00 months [63.17]). The mean time (StD) from last recurrence to the first study drug exposure was overall

4.32 months (16.50), in the 10^6 CFU/mL group 30.13 months (49.86), and in the 10^7 CFU/mL group 1.22 months (2.40).

Characteristics of the primary cancer diagnosis were mostly similar in the PPS compared to the SAF, with exception of the time from last recurrence to the first study drug exposure, which was shorter in the PPS (1.30 months; Table 14.1.3.2). None of the patients included in the PPS experienced three recurrences of malignant glioma.

Table 11-3: Primary Cancer Diagnosis (SAF)

	10^6 CFU/mL (N = 3)	10^7 CFU/mL			Total NR[a] (N = 25)	Total (N = 28)
		All Patients (N = 25)	NR (N = 22)	R (N = 3)		
Histological Type (n [%])						
Malignant glioma	3 (100)	25 (100)	22 (100)	3 (100)	25 (100)	28 (100)
Recurrence Re-confirmed (n [%])						
Yes	3 (100)	25 (100)	22 (100)	3 (100)	25 (100)	28 (100)
Number of Recurrences (n [%])						
1	2 (66.7)	23 (92.0)	20 (90.9)	3 (100)	22 (88.0)	25 (89.3)
2	1 (33.3)	1 (4.0)	1 (4.5)	-	2 (8.0)	2 (7.1)
3	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Recurrence Location[b] (n [%])						
Brain	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Frontal Lobe	-	7 (28.0)	5 (22.7)	2 (66.7)	5 (20.0)	7 (25.0)
Occipital Lobe	-	2 (8.0)	2 (9.1)	-	2 (8.0)	2 (7.1)
Parietal Lobe	1 (33.3)	6 (24.0)	6 (27.3)	-	7 (28.0)	7 (25.0)
Precentral Gyrus	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Temporal Lobe	2 (66.7)	9 (36.0)	8 (36.4)	1 (33.3)	10 (40.0)	11 (39.3)
Recurrence Specification[a] (n [%])						
Local	3 (100)	24 (96.0)	21 (95.5)	3 (100)	24 (96.0)	27 (96.4)
Regional	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Metastasis	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Time from Primary Cancer Diagnosis to First Study Drug Exposure (Months)						
Mean (StD)	57.00 (63.17)	17.53 (12.41)	17.05 (11.33)	21.07 (22.45)	21.84 (24.87)	21.76 (24.23)
Median	37.2	11.7	12.0	10.0	12.2	12.0
Min, Max	6.1, 127.7	6.3, 47.7	6.4, 47.7	6.3, 46.9	6.1, 127.7	6.1, 127.7
Time from Last Recurrence to First Study Drug Exposure (Months)						
Mean (StD)	30.13 (49.86)	1.22 (2.40)	0.78 (0.39)	4.50 (7.01)	4.30 (17.38)	4.32 (16.50)

	10^6 CFU/mL (N = 3)	10^7 CFU/mL			Total NR[a] (N = 25)	Total (N = 28)
		All Patients (N = 25)	NR (N = 22)	R (N = 3)		
Median	2.0	0.7	0.7	0.5	0.7	0.7
Min, Max	0.7, 87.7	0.3, 12.6	0.3, 1.9	0.4, 12.6	0.3, 87.7	0.3, 87.7

Source: Table 14.1.3.2

CFU = colony forming unit; N = number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

b Can be multiple per patient. Percentages are based on the total number of included patients per group.

11.2.2.2 Previous Anti-Cancer Therapy

The previous anti-cancer therapy of patients in the SAF is summarized in Table 11-4 and by-patient details are provided in Listing 16.2.4.4. All patients received anti-cancer therapy before this study and there were no distinct differences in previous therapy between the groups (Table 14.1.3.3).

11.2.2.3 Previous Anti-Cancer Procedures

Previous anti-cancer procedures reported for patients in the SAF are presented in Table 11-5. All patients underwent anti-cancer procedures before this study (Table 14.1.3.4). All patients received radiotherapy to the brain and the majority of patients underwent a brain tumor operation (21 [75.0%]). The reported procedures were similar between the groups. The by-patient previous anti-cancer procedures are provided in Listing 16.2.4.5.

11.2.3 Medical History

A summary of the medical history occurring in ≥ 10% of patients overall is provided in Table 11-6 (SAF) and a summary of all medical history is provided in Table 14.1.3.5. Overall, the most commonly reported medical histories (occurring in > 25% of patients overall) were hypertension (13 patients [46.4%]) and epilepsy (11 patients [39.3%]). There were no notable differences in the medical history of the different groups. A by-patient listing of medical history is provided in Listing 16.2.4.3.

11.2.4 Prior Medications and Procedures

A summary of prior medications reported for ≥ 10% of patients overall is provided in Table 11-7 (SAF) and a summary of all prior medications is provided in Table 14.1.3.6. The majority of patients received a prior medication (25 [89.3%]) and approximately half of the patients (15 [53.6%]) received antiepileptics. None of the patients in the 10^6 CFU/mL group received antiepileptics. The number of any prior medications (events) reported was comparable between the groups.

A summary of prior procedures is provided in Table 14.1.3.8. Only 2 patients in the 10^7 CFU/mL NR group reported any prior procedures. None of the prior procedures were related to a cancer diagnosis or treatment.

11.3 Measurements of Treatment Compliance

Treatment was administered at the study site by adequately trained medical professionals who monitored compliance. Further details on IMP exposure are discussed in Section 12.1.

Table 11-4: Previous Anti-Cancer Therapy (SAF)

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Therapy	3 (100) 31	25 (100) 88	22 (100) 81	3 (100) 7	25 (100) 112	28 (100) 119
Other Alkylating Agents	3 (100) 25	25 (100) 66	22 (100) 61	3 (100) 5	25 (100) 86	28 (100) 91
Temozolomide	3 (100) 25	25 (100) 66	22 (100) 61	3 (100) 5	25 (100) 86	28 (100) 91
Nitrosoureas	2 (66.7) 4	6 (24.0) 12	5 (22.7) 10	1 (33.3) 2	7 (28.0) 14	8 (28.6) 16
Lomustine	2 (66.7) 4	6 (24.0) 12	5 (22.7) 10	1 (33.3) 2	7 (28.0) 14	8 (28.6) 16
Podophyllotoxin Derivatives	-	3 (12.0) 6	3 (13.6) 6	-	3 (12.0) 6	3 (10.7) 6
Etoposide	-	3 (12.0) 6	3 (13.6) 6	-	3 (12.0) 6	3 (10.7) 6
EGFR Inhibitors	1 (33.3) 2	-	-	-	1 (4.0) 2	1 (3.6) 2
Cetuximab	1 (33.3) 2	-	-	-	1 (4.0) 2	1 (3.6) 2
PD-1/PDL-1 Inhibitors		1 (4.0) 2	1 (4.5) 2		1 (4.0) 2	1 (3.6) 2
Nivolumab	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Antineoplastic Agents	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Antineoplastic Agents	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
CDK Inhibitors	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Abemaciclib	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

Source: Table 14.1.3.3

Note: Percentages are based on the number (N) of patients in the SAF.

CDK = cyclin-dependent kinase; CFU = colony forming unit; E = number of events; EGFR = epidermal growth factor receptor; n = number of patients with an event; N = total number of patients; NR = non-resectable; PD-1 = programmed cell death protein 1; PDL-1 = programmed cell death ligand 1; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

Table 11-5: Previous Anti-Cancer Procedures (SAF)

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Procedure	3 (100) 9	25 (100) 63	22 (100) 54	3 (100) 9	25 (100) 63	28 (100) 72
Surgical and Medical Procedures	3 (100) 8	25 (100) 59	22 (100) 50	3 (100) 9	25 (100) 58	28 (100) 67
Radiotherapy to Brain	3 (100) 4	25 (100) 27	22 (100) 23	3 (100) 4	25 (100) 27	28 (100) 31
Brain Tumour Operation	3 (100) 4	18 (72.0) 18	17 (77.3) 17	1 (33.3) 1	20 (80.0) 21	21 (75.0) 22
Craniotomy	-	5 (20.0) 6	2 (9.1) 2	3 (100) 4	2 (8.0) 2	5 (17.9) 6
Tumour Treating Fields Therapy	-	5 (20.0) 5	5 (22.7) 5	-	5 (20.0) 5	5 (17.9) 5
Brain Operation	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Investigations	1 (33.3) 1	3 (12.0) 4	3 (13.6) 4	-	4 (16.0) 5	4 (14.3) 5
Biopsy Brain	1 (33.3) 1	3 (12.0) 4	3 (13.6) 4	-	4 (16.0) 5	4 (14.3) 5

Source: Table 14.1.3.4

Note: Percentages are based on the number (N) of patients in the SAF.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

Table 11-6: Summary of Medical History Occurring in >10% of Patients Overall (SAF)

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Medical History	3 (100) 18	25 (100) 134	22 (100) 124	3 (100) 10	25 (100) 142	28 (100) 152
Nervous System Disorders	3 (100) 6	21 (84.0) 29	18 (81.8) 25	3 (100) 4	21 (84.0) 31	24 (85.7) 35
Epilepsy	1 (33.3) 1	10 (40.0) 10	9 (40.9) 9	1 (33.3) 1	10 (40.0) 10	11 (39.3) 11
Seizure	-	6 (24.0) 6	4 (18.2) 4	2 (66.7) 2	4 (16.0) 4	6 (21.4) 6
Headache	2 (66.7) 2	1 (4.0) 1	1 (4.5) 1	-	3 (12.0) 3	3 (10.7) 3
Hypoaesthesia	1 (33.3) 1	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	2 (8.0) 2	3 (10.7) 3
Vascular Disorders	2 (66.7) 2	11 (44.0) 13	10 (45.5) 12	1 (33.3) 1	12 (48.0) 14	13 (46.4) 15
Hypertension	2 (66.7) 2	11 (44.0) 11	10 (45.5) 10	1 (33.3) 1	12 (48.0) 12	13 (46.4) 13
Investigations	1 (33.3) 2	8 (32.0) 9	6 (27.3) 7	2 (66.7) 2	7 (28.0) 9	9 (32.1) 11
Lymphocyte Count Decreased	1 (33.3) 1	6 (24.0) 6	5 (22.7) 5	1 (33.3) 1	6 (24.0) 6	7 (25.0) 7
Gastrointestinal Disorders	-	8 (32.0) 11	8 (36.4) 11	-	8 (32.0) 11	8 (28.6) 11
Gastrooesophageal Reflux Disease	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Inguinal Hernia	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Endocrine Disorders	-	7 (28.0) 7	7 (31.8) 7	-	7 (28.0) 7	7 (25.0) 7
Hypothyroidism	-	5 (20.0) 5	5 (22.7) (5)	-	5 (20.0) 5	5 (17.9) 5
Psychiatric Disorders	1 (33.3) 1	5 (20.0) 5	5 (22.7) 5	-	6 (24.0) 6	6 (21.4) 6
Depression	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4

Source: Table 14.1.3.5

Note: Percentages are based on the number (N) of patients in the SAF. Only events occurring in ≥ 10% of patients (Total SAF) are presented.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

Table 11-7: Summary of Prior Medications Reported by >10% of Patients Overall (SAF)

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Medication	3 (100) 11	22 (88.0) 85	19 (86.4) 75	3 (100) 10	22 (88.0) 86	25 (89.3) 96
Other Antiepileptics	-	15 (60.0) 20	12 (54.5) 15	3 (100) 5	12 (48.0) 15	15 (53.6) 20
Levetiracetam	-	12 (48.0) 12	9 (40.9) 9	3 (100) 3	9 (36.0) 9	12 (42.9) 12
Lacosamide	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4
Proton Pump Inhibitors	-	7 (28.0) 7	5 (22.7) 5	2 (66.7) 2	5 (20.0) 5	7 (25.0) 7
Pantoprazole	-	6 (24.0) 6	4 (18.2) 4	2 (66.7) 2	4 (16.0) 4	6 (21.4) 6
Ace Inhibitors, Plain	2 (66.7) 2	3 (12.0) 4	3 (13.6) 4	-	5 (20.0) 6	5 (17.9) 6
Ramipril	2 (66.7) 2	3 (12.0) 4	3 (13.6) 4	-	5 (20.0) 6	5 (17.9) 6
Thyroid Hormones	-	5 (20.0) 6	5 (22.7) 6	-	5 (20.0) 6	5 (17.9) 6
Levothyroxine	-	3 (12.0) 4	3 (13.6) 4	-	3 (12.0) 4	3 (10.7) 4
Dihydropyridine Derivatives	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4
Amlodipine	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4
Benzodiazepine Derivatives	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Lorazepam	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Combinations of Sulfonamides and Trimethoprim, Incl. Derivatives	1 (33.3) 1	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 3	3 (10.7) 3
Sulfamethoxazole;trimethoprim	1 (33.3) 1	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 3	3 (10.7) 3

Source: Table 14.1.3.6

Note: Percentages are based on the number (N) of patients in the SAF. Only events occurring in ≥ 10% of patients (Total SAF) are presented.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

11.4 Analysis of Efficacy

11.4.1 Tumor Response

11.4.1.1 Objective Response Rate

The ORR per cohort in the FAS is presented in Table 11-8. In the Total NR group, 3 patients (12.0%) had a partial remission and 1 patient (4.0%) maintained stable disease. The majority of patients (21 [84.0%]) had progressive disease as BOR. Overall, the ORR in the Total NR group (all resected patients) was 12.0% (95% CI: 2.5 – 31.2) and the disease control rate (DCR) in the Total NR group was 16.0% (95% CI: 4.5 – 36.1). For the 10^7 CFU/mL group, the ORR and DCR were comparable. The ORR and DCR showed no trends between the groups, and should be interpreted with caution due to the small sample size of the 10^6 CFU/mL group (N = 3). It should be noted that 2 out of 3 patients with partial remission (Patients 01-04 and 01-09) received concomitant treatment with antibiotics (Table 10-2). Both patients were excluded from the PPS.

With the exclusion of Patients 01-04 and 01-09 from the PPS, in the Total NR group 1 patient (5.0%) had a partial remission and 1 patient (5.0%) had stable disease (Table 14.2.2.1.1). The majority of NR patients (18 [90.0%]) had progressive disease as BOR which was similar to the results seen in the FAS. In the Total NR group, the overall ORR (5.0% [95% CI: 0.1 – 24.9])) and overall DCR (10.0% [95% CI: 1.2 – 31.7]) were lower in the PPS than in the FAS due to the exclusion of 2 patients with partial remission.

Table 11-8: Objective Response Rate (FAS)

Best Overall Response	10^6 CFU/mL (N = 3) n (%)	10^7 CFU/mL		Total NR[a] (N = 25) n (%)
		All Patients (N = 25) n (%)	NR (N = 22) n (%)	
PR	1 (33.3)	2 (8.0)	2 (9.1)	3 (12.0)
SD	-	3 (12.0)	1 (4.5)	1 (4.0)
PD	2 (66.7)	20 (80.0)	19 (86.4)	21 (84.0)
ORR (%) [95% CI]	33.3 [0.8 – 90.6]	8.0 [1.0 – 26.0]	9.1 [1.1 – 29.2]	12.0 [2.5 – 31.2]
DCR (%) [95% CI]	33.3 [0.8 – 90.6]	20.0 [6.8 – 40.7]	13.6 [2.9 – 34.9]	16.0 [4.5 – 36.1]

Source: Table 14.2.2.1.1

Note: Percentages were calculated using the number (N) of included patients as the denominator. 95% CI was calculated using the Exact Clopper-Pearson method. ORR (CR and PR) and DCR (CR, PR, and SD) were based on best overall responses (BOR) derived using iRANO 2015 guidelines.

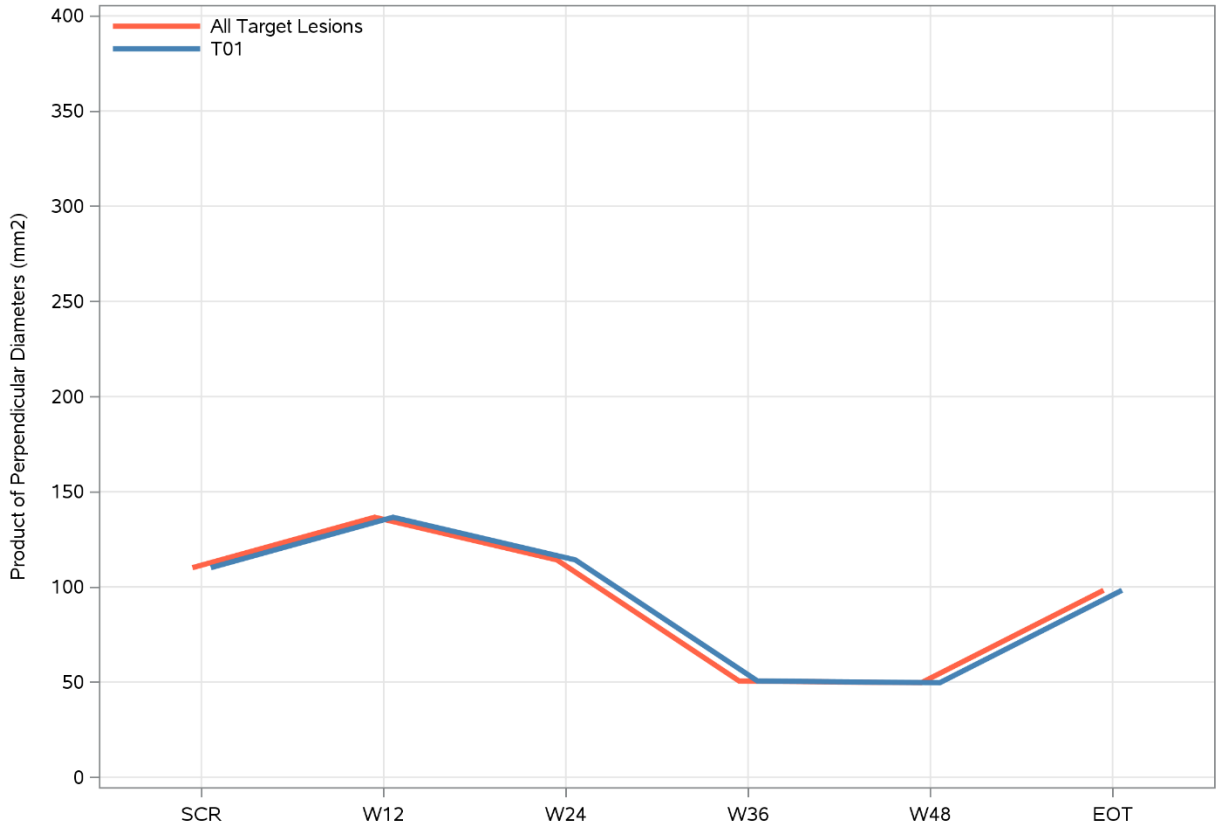
BOR = best objective responses; CFU = colony forming unit; CR = complete response; DCR = disease control rate; FAS = full analysis set; iRANO = immunotherapy Response Assessment for Neuro-Oncology; n = number of patients with response; N = total number of patients; NR = non-resectable; ORR = objective response rate; PD = progressive disease; PR = partial remission; R = resectable; SD = stable disease

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

Based on the iRANO criteria, Patient 01-04 (10^6 CFU/mL group) first had stable disease in Week 12 and 24, with subsequent partial remission in Week 36 and 48. At the EoT visit,

Patient 01-04 had progressive disease. During the partial remission, the tumor size decreased with 54% from 10.67 × 10.32 mm (110.11 mm^2) at Screening to 5.09 × 9.94 mm (50.59 mm^2) in Week 36 (Figure 11-1). Patient 01-09 (10^7 CFU/mL NR group) had 2 target lesions and 1 non-target lesion at Screening. During the study (Week 12 to Week 48), both target lesions were too small to measure and the non-target lesion was non-measurable (Figure 11-2), thus scored as partial remission. With the EOT visit, the target lesions and non-target lesion present at Screening remained the same, however, 4 new lesions were identified indicating progressive disease. Patient 22-10 (10^7 CFU/mL NR group) had a partial remission in Week 12, with 81% reduction of target lesion size from 724 mm^2 (sum of products of perpendicular diameter target lesion 1 and 2) at Screening to 138 mm^2 in Week 12 (Figure 11-3). However, by the next visit the combined target lesions had grown to approximately twice the size at Screening (1510 mm^2) and the patient discontinued study treatment due to progressive disease.

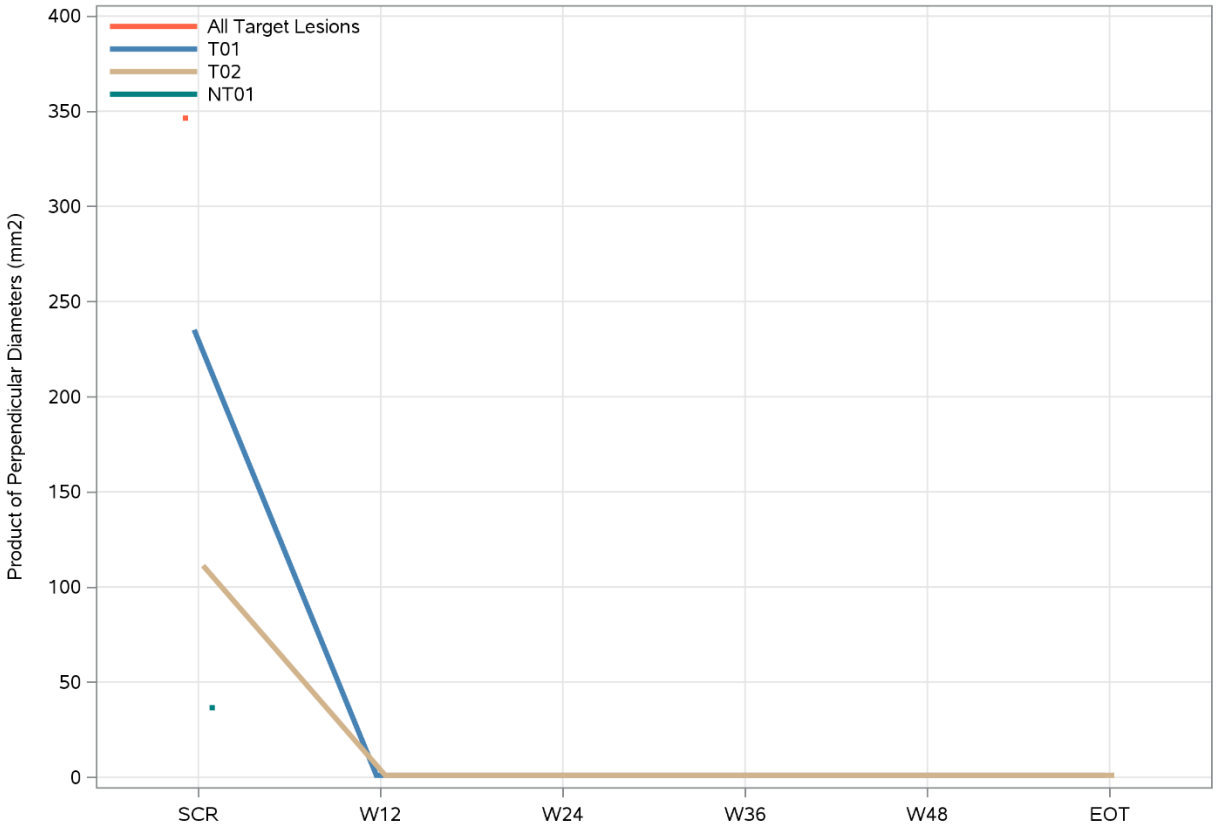
Figure 11-1: Tumor Response (Patient 01-04)



Source: Figure 14.2.2.8.1

Note: Evaluable lesions that were reported as Too Small To Measure were imputed with 1 mm^2.

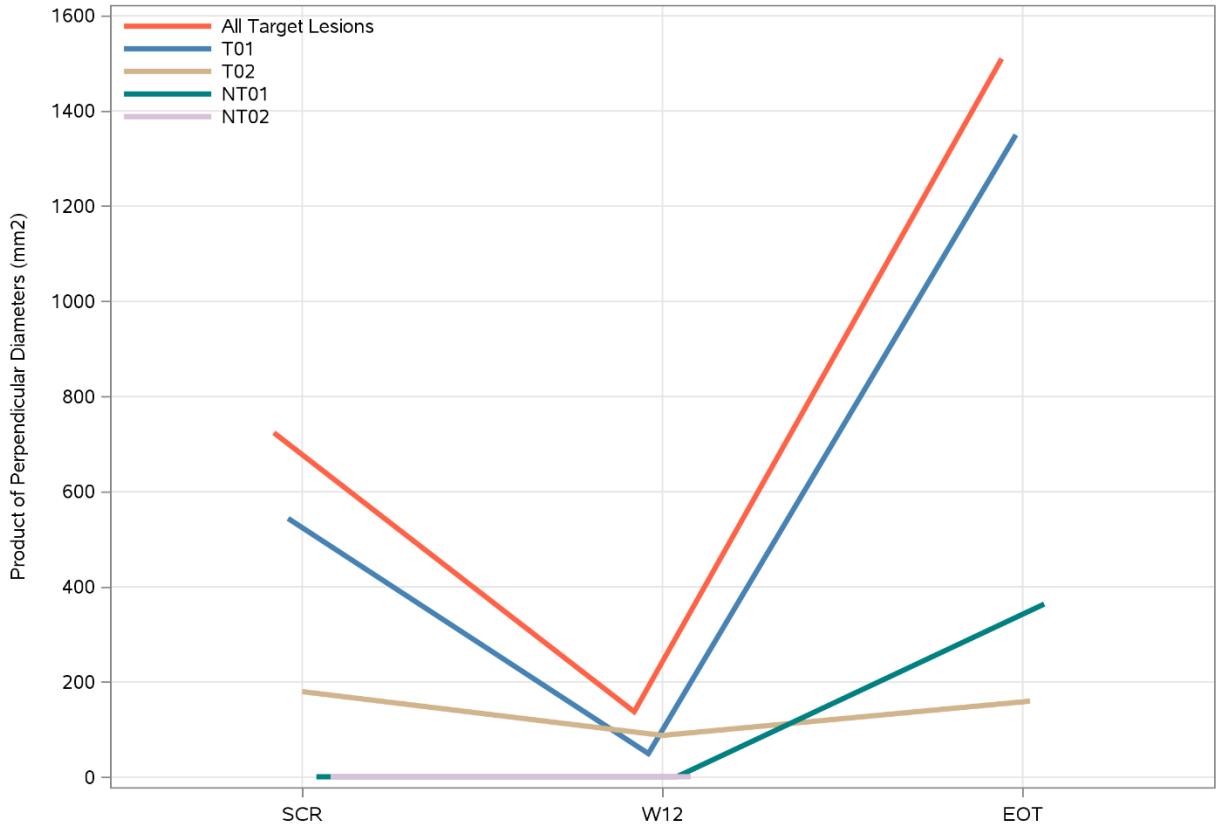
Figure 11-2: Tumor Response (Patient 01-09)



Source: Figure 14.2.2.8.1

Note: Evaluable lesions that were reported as Too Small To Measure were imputed with 1 mm^2.

Figure 11-3: Tumor Response (Patient 22-10)

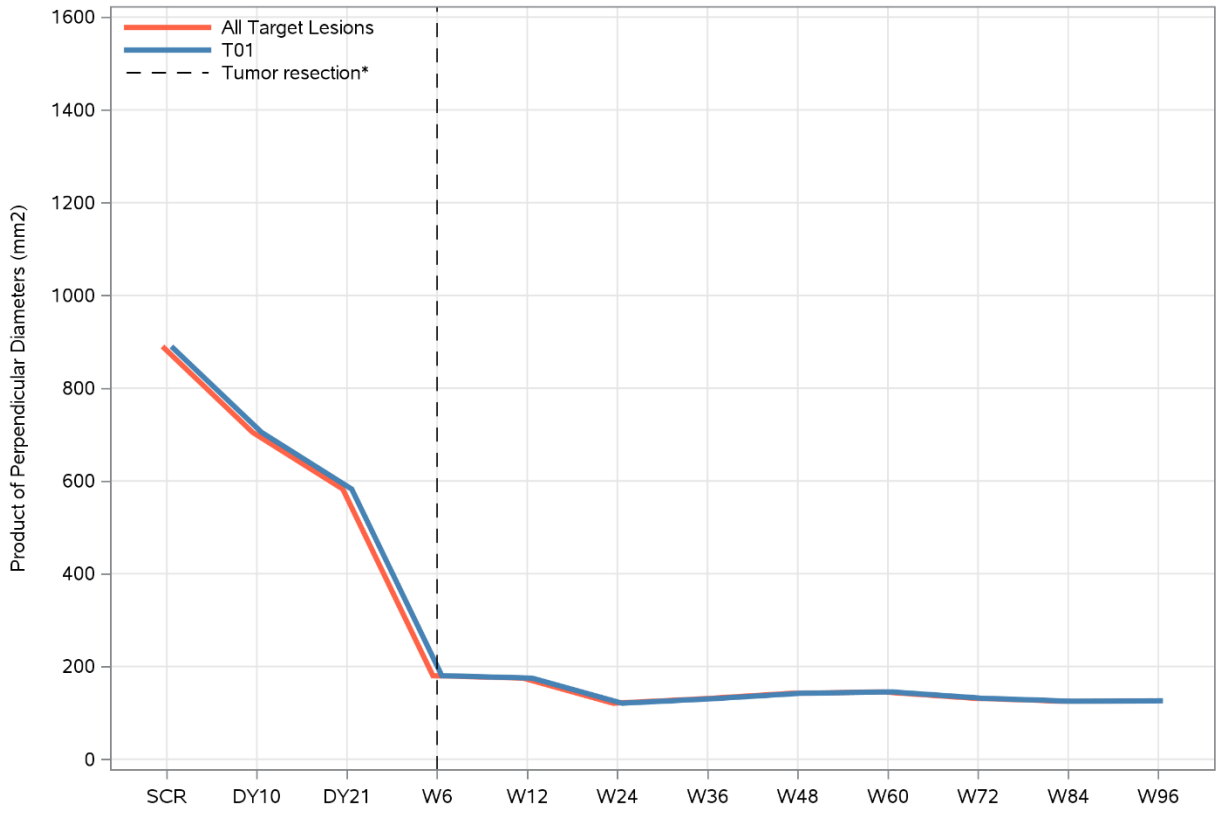


Source: Figure 14.2.2.8.1

Note: Evaluable lesions that were reported as Too Small To Measure were imputed with 1 mm^2.

For Patient 01-14 (10^7 CFU/mL R group), the tumor did not grow significantly over 22 months until the time of database lock. The tumor response on Day 10 and Day 21, prior to tumor resection, was assessed as stable disease, with a decrease in size of 21% on Day 10 and 35% on Day 21 compared to Screening (Figure 11-4). After tumor resection, the tumor size decreased from 180.35 mm^2 (13.55 × 13.31 mm) to 125.22 mm^2 (16.22 × 7.72 mm) . Patient 01-31, who was included in the 10^7 CFU/mL R group but did not undergo tumor resection, had stable disease on Day 10 which declined to progressive disease due to unequivocal progression of non-target lesions on Day 21 (Figure 11-5). After examination, the treating neurologist concluded that no tumor resection could be performed and the patient discontinued the study treatment. Patient 02-29 (10^7 CFU/mL NR group) started out with 2 target lesions at Screening and had stable disease in Week 12 and 24, with a combined target lesion size of 106% (1024.8 mm^2, sum of products of perpendicular diameter target lesion 1 and 2) in Week 12 and 75% (728.6 mm^2) in Week 24, both compared with the size of 966.12 mm^2 at Screening (Figure 11-6). During an unscheduled visit on 09 Dec 2021, it was not clear whether the patient had progressive disease and in line with iRANO the patient continued study treatment until progressive disease was confirmed in February 2022.

Figure 11-4: Tumor Response (Patient 01-14)

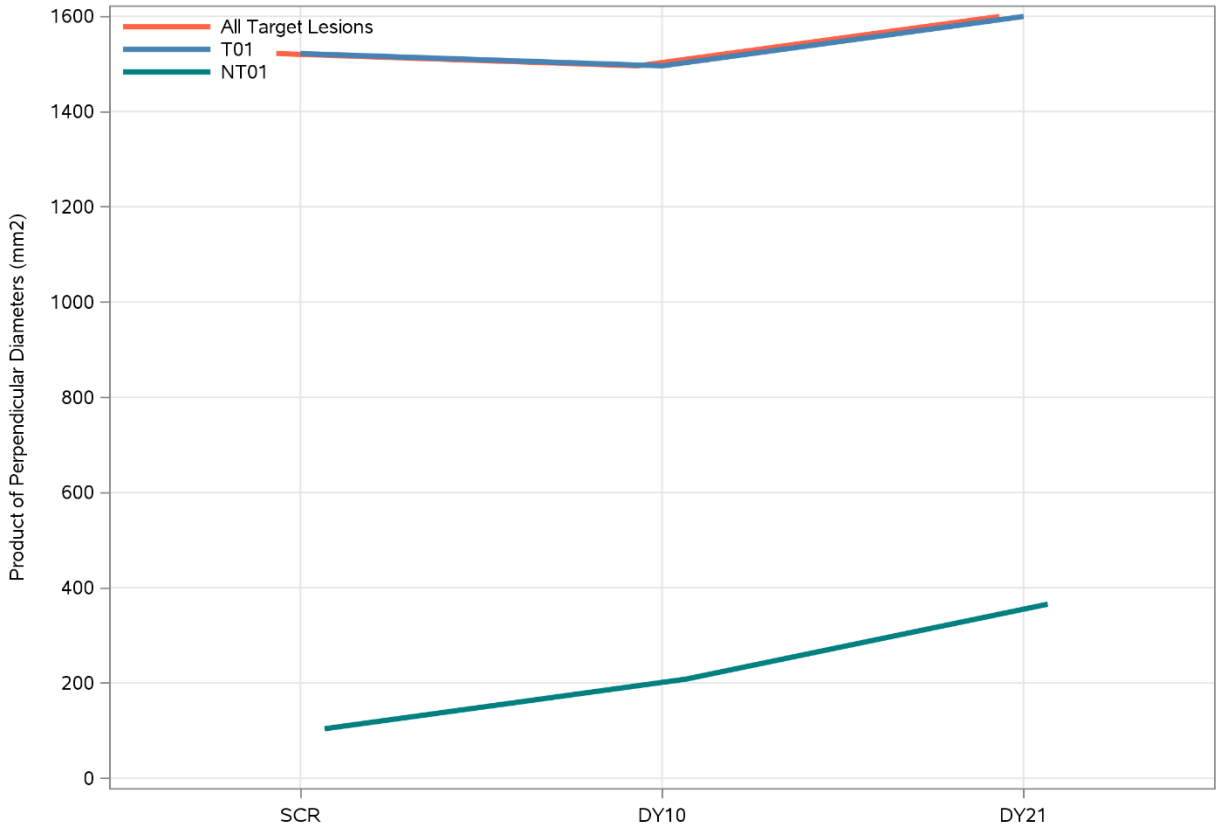


Source: Figure 14.2.2.8.1

Note: Evaluable lesions that were reported as Too Small To Measure were imputed with 1 mm^2.

* Tumor resection was done 1 day before radiological scan at Week 6 (W6)

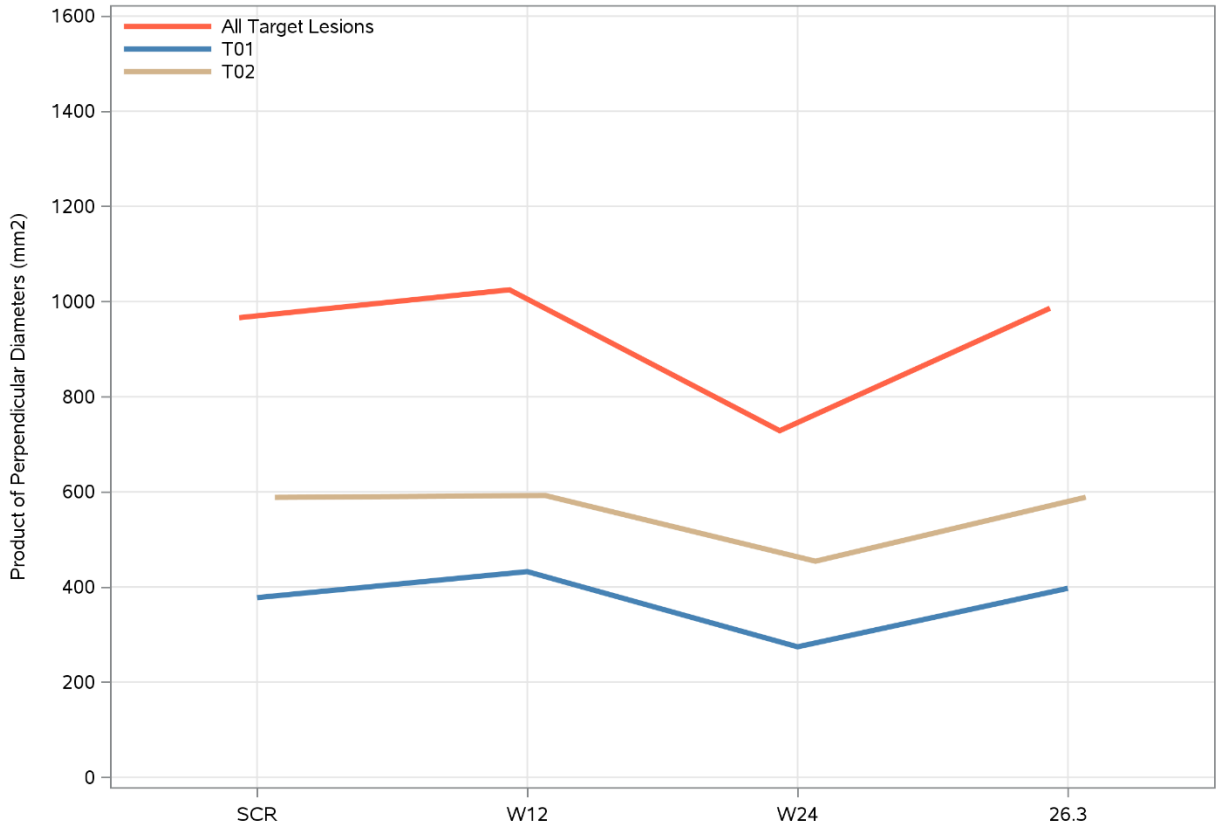
Figure 11-5: Tumor Response (Patient 01-31)



Source: Figure 14.2.2.8.1

Note: Evaluable lesions that were reported as Too Small To Measure were imputed with 1 mm^2.

Figure 11-6: Tumor Response (Patient 02-29)



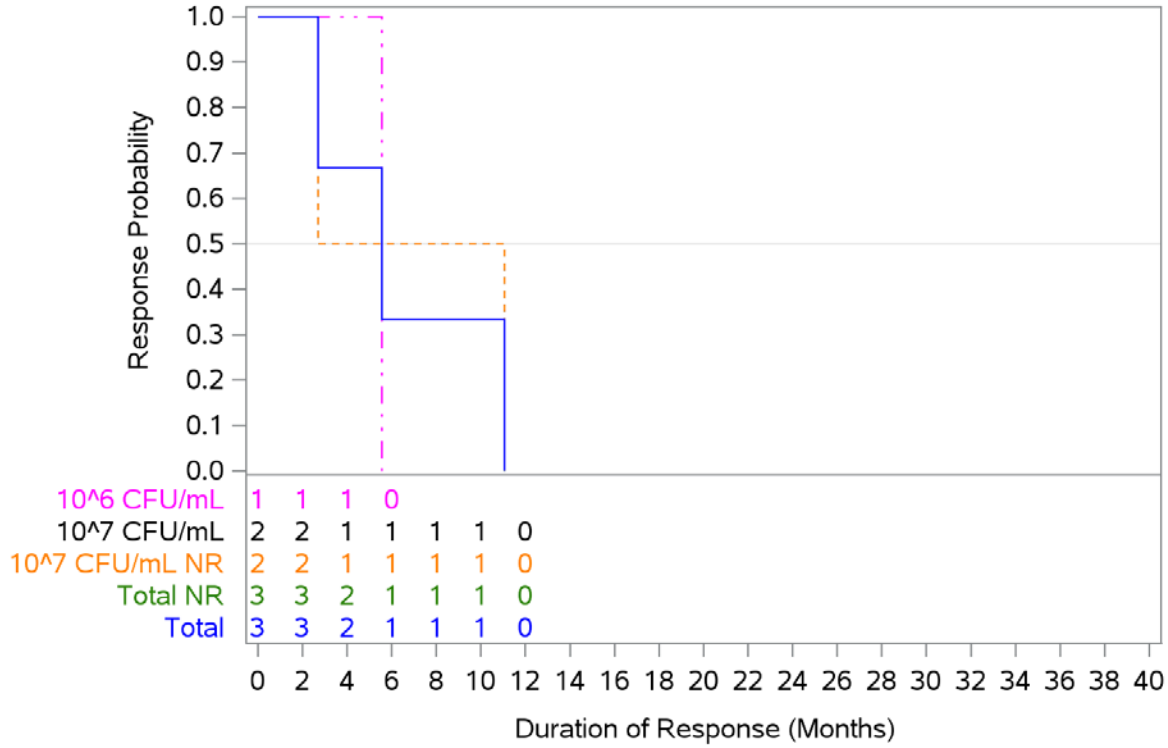
Source: Figure 14.2.2.8.1

Note: Evaluable lesions that were reported as Too Small To Measure were imputed with 1 mm^2.

11.4.1.2 Duration of Response

Three NR patients in the trial (Patient 01-04, Patient 01-09, and Patient 22-10) experienced a partial remission. The DoR for the FAS for these 3 patients is presented in Table 11-9 and the Kaplan-Meier plot is shown in Figure 11-7. One patient (01-04) in the 10^6 CFU/mL group had a DoR of 5.6 months, while the 2 patients in the high-dose VXM01 (10^7 CFU/mL) group (01-09 and 22-10) had a DoR of 2.7 and 11.1 months. In the PPS, one patient in the 10^7 CFU/mL group had a response duration of 2.7 months (Table 14.2.2.2.1, Figure 14.2.2.2.1).

Figure 11-7: Kaplan-Meier Plot of Duration of Response (FAS)



Source: Figure 14.2.2.2.1

Note: Product-limit survival estimates with number of patients at risk, according to iRANO 2015

CFU = colony forming unit; FAS = full analysis set; NR = non-resectable; R = resectable

Table 11-9: Duration of Response (FAS)

		N	Event n (%)	Censored n (%)	Median (Months)	95% CI	Min	Max	Reason for Censoring
10^6 CFU/mL		1	1 (100)	-	5.6	-	5.6	5.6	-
10^7 CFU/mL	All Patients	2	2 (100)	-	6.9	[2.7 – 11.1]	2.7	11.1	-
	NR	2	2 (100)	-	6.9	[2.7 – 11.1]	2.7	11.1	-
Total NR[a]		3	3 (100)	-	5.6	[2.7 – 11.1]	2.7	11.1	-
Total		3	3 (100)	-	5.6	[2.7 – 11.1]	2.7	11.1	-

Source: Table 14.2.2.2.1

Note: Percentages were calculated using the number (N) of responders as the denominator. The median of the duration of response in months was calculated using the Kaplan-Meier method. For the Kaplan-Meier plot see Figure 14.2.2.2.1. The duration of response (CR or PR) assessed by iRANO 2015, was measured from the start of response until recurrent disease or death of any cause was documented.

CFU = colony forming unit; CR = complete response; FAS = full analysis set; iRANO = immunotherapy Response Assessment for Neuro-Oncology; n = number of patients with response; N = total number of patients; NR = non-resectable; PR = partial remission

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

11.4.2 Clinical Response

11.4.2.1 Recurrence-Free Survival

The RFS for the 2 resected patients in the FAS (10^7 CFU/mL R group) is provided in Table 14.2.2.3.1, with a corresponding Kaplan-Meier plot in Figure 14.2.2.3.1. Patient 01-17 had an RFS of 1.8 months and Patient 01-14 was censored because no recurrence of disease was reported (RFS listed as 20.9 months). The same patients were included in the PPS.

11.4.2.2 Time-to-progression

The time to disease progression is presented in Table 11-10. In the Total NR group, the median TTP was 2.7 months (95% CI: 2.7 – 2.7) with a range of 1.2 to 13.8 months. The TTP was comparable between the 10^6 CFU/mL and 10^7 CFU/mL NR groups and the results in the PPS were comparable to the FAS (Table 14.2.2.4.1). A Kaplan-Meier plot is provided in Figure 14.2.2.4.1.

In the 10^7 CFU/mL R group, 1 patient (01-14) did not experience disease progression at the time of database lock (duration 22.1 months). The other patients in the 10^7 CFU/mL R group had a TTP of 0.3 months (Patient 01-17) and 0.6 months (Patient 01-31). It should be noted that Patient 01-31 did not undergo tumor resection due to a clinical decision.

Table 11-10: Time-To-Progression (FAS)

		N	Event n (%)	Censored n (%)	Median (Months)	95% CI	Min	Max	Reason for Censoring
10^6 CFU/mL		3	3 (100)	-	2.5	[1.2 – 13.8]	1.2	13.8	-
10^7 CFU/mL	All Patients	25	24 (96.0)	1 (4.0)	2.7	[2.7 – 2.7]	0.3	22.1	NP (1 patient)
	NR	22	22 (100)	-	2.7	[2.7 – 2.7]	1.4	13.8	-
	R	3	2 (66.7)	1 (33.3)	0.6	-	0.3	22.1	NP (1 patient)
Total NR[a]		25	25 (100)	-	2.7	[2.7 – 2.7]	1.2	13.8	-
Total		28	27 (96.4)	1 (3.6)	2.7	[2.7 – 2.7]	0.3	22.1	NP (1 patient)

Source: Table 14.2.2.4.1

Note: Percentages were calculated using the number (N) of included patients as the denominator. The median of TTP in months was calculated using the Kaplan-Meier method. For the Kaplan-Meier plot see Figure 14.2.2.4.1. TTP, assessed by iRANO 2015, was measured from the start of treatment until recurrent disease was documented.

CFU = colony forming unit; iRANO = immunotherapy Response Assessment for Neuro-Oncology; N = number of patients; NP = no progression; NR = non-resectable; R = resectable; TTP = time-to-progression

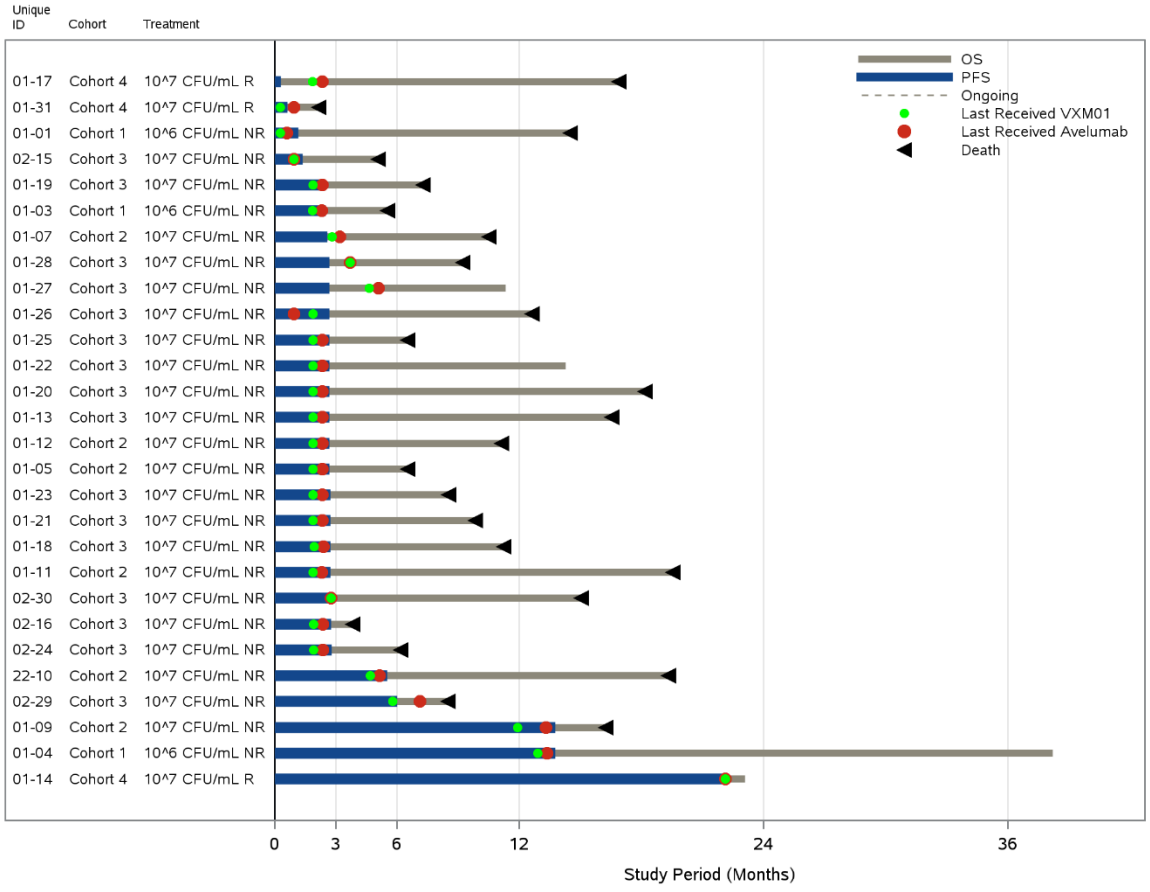
a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

11.4.2.3 Progression Free Survival

The results on PFS were identical to the results on TTP (Table 11-10) as all deaths occurred due to progression of the target disease (Table 14.2.2.5.1, Figure 14.2.2.5.1).

The PFS and OS are presented in a Swimmers plot (Figure 11-8), together with the timing of the last VXM01 and avelumab administrations. Patient 01-04 in the 10^6 CFU/mL group had the longest OS and completed the study. Patient 01-14 in the 10^7 CFU/mL R group did not experience disease progression at the time of database lock and completed the prolongation phase. The last radiologic assessment for Patient 01-14 was completed at 22 months, while the last assessment on survival was completed at 23 months. It should be noted that 3 patients are still in the follow-up phase of the study (Patients 01-14, 01-22, and 01-27).

Figure 11-8: Swimmers Plot of Response Analysis (FAS)



Source: Figure 14.2.2.7.1

CFU = colony forming unit; FAS = full analysis set; NR = non-resectable; OS = overall survival; PFS = progression free survival; R = resectable

11.4.2.4 Overall Survival

Overall survival in the FAS is presented in Table 11-11 and Figure 11-8. The data for 4 patients were censored because they were alive at the last measured time point, including 1 patient who completed the study and 3 patients who were still in the long-term follow-up phase at the time of database lock. The median OS in the Total NR group was 11.1 months (95% CI: 8.5 – 15.1) with a minimum of 3.8 months and maximum of 38.2 months. The median OS in the 10^7 CFU/mL R group was higher with 16.9 months and a range of 2.2 to 23.1 months. The median OS was higher in the 10^6 CFU/mL (3 patients) and 10^7 CFU/mL R groups (3 patients) compared with the 10^7 CFU/mL NR group, however, due to the low sample size these results should be interpreted with caution. Results in the PPS were similar to the FAS results (Table 14.2.2.6.1, Figure 14.2.2.6.1).

Table 11-11: Overall Survival (FAS)

		N	Event n (%)	Censored n (%)	Median (Months)	95% CI	Min	Max	Reason for Censoring
10^6 CFU/mL		3	2 (66.7)	1 (33.3)	14.5	-	5.6	38.2	Alive (1 patient)
10^7 CFU/mL	All Patients	25	22 (88.0)	3 (12.0)	11.1	[8.5 – 16.3]	2.2	23.1	Alive (3 patients)
	NR	22	20 (90.9)	2 (9.1)	10.8	[7.3 – 15.1]	3.8	19.6	Alive (2 patients)
	R	3	2 (66.7)	1 (33.3)	16.9	-	2.2	23.1	Alive (1 patient)
Total NR[a]		25	22 (88.0)	3 (12.0)	11.1	[8.5 – 15.1]	3.8	38.2	Alive (3 patients)
Total		28	24 (85.7)	4 (14.3)	11.2	[8.5 – 16.3]	2.2	38.2	Alive (4 patients)

Source: Table 14.2.2.6.1

Note: Percentages were calculated using the number (N) of included patients. The median of overall survival in months was calculated using the Kaplan-Meier method. For the Kaplan-Meier plot see Figure 14.2.2.6.1.

CFU = colony forming unit; FAS = full analysis set; N = number of patients; NR = non-resectable; R = resectable

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

11.4.3 Karnofsky Performance Status

The baseline category and post-baseline shifts in KPS in the FAS are provided in Table 11-12. The KPS shifts are also summarized in Table 14.2.2.7.1. Overall, 16 patients (57.1%) had a baseline KPS of > 80% and 12 patients (42.9%) had a baseline KPS of 70 to 80%. Of the 16 patients with a baseline KPS of > 80%, 11 patients had a post-baseline decline in KPS. The majority of these patients (10) had a decline from > 80% to 70 to 80%. One patient's KPS changed to < 70%. Of the 12 patients with a baseline KPS of 70 to 80%, 1 had a post-baseline decline in KPS to < 70%.

There were no notable differences between the groups in post-baseline shifts in KPS. KPS results in the PPS were comparable to the results in the FAS shown below (Table 14.2.2.7.2).

Table 11-12: Karnofsky Performance Status (FAS)

Cohort		Baseline Category	Total n (%)	N' n (%)	Worst Post-Baseline Category[a]		
					> 80 n (%)	70 – 80 n (%)	< 70 n (%)
10^6 CFU/mL (N = 3)		> 80	1 (33.3)	1 (33.3)	-	**1 (33.3)**	-
		70 – 80	2 (66.7)	2 (66.7)	-	1 (33.3)	**1 (33.3)**
		Total	3 (100)	3 (100)	-	2 (66.7)	1 (33.3)
10^7 CFU/mL	All Patients (N = 25)	> 80	15 (60.0)	10 (40.0)	5 (20.0)	**9 (36.0)**	**1 (4.0)**
		70 – 80	10 (40.0)	10 (40.0)	-	10 (40.0)	-
		Total	25 (100)	20 (80.0)	5 (20.0)	19 (76.0)	1 (4.0)
	NR (N = 22)	> 80	12 (54.5)	7 (31.8)	5 (22.7)	**6 (27.3)**	**1 (4.5)**
		70 – 80	10 (45.5)	10 (45.5)	-	10 (45.5)	-
		Total	22 (100)	17 (77.3)	5 (22.7)	16 (72.7)	1 (4.5)
	R (N = 3)	> 80	3 (100)	3 (100)	-	**3 (100)**	-
		Total	3 (100)	3 (100)	-	3 (100)	-
Total NR[b] (N = 25)		> 80	13 (52.0)	8 (32.0)	5 (20.0)	**7 (28.0)**	**1 (4.0)**
		70 – 80	12 (48.0)	12 (48.0)	-	11 (44.0)	**1 (4.0)**
		Total	25 (100)	20 (80.0)	5 (20.0)	18 (72.0)	2 (8.0)
Total (N = 28)		> 80	16 (57.1)	11 (39.3)	5 (17.9)	**10 (35.7)**	**1 (3.6)**
		70 – 80	12 (42.9)	12 (42.9)	-	11 (39.3)	**1 (3.6)**
		Total	28 (100)	23 (82.1)	5 (17.9)	21 (75.0)	2 (7.1)

Source: Table 14.2.2.7.2

Note: Percentages were calculated using the number (N) of included patients per cohort. N' = number of abnormalities (KPS ≤ 80).

CFU = colony forming unit; KPS = Karnofsky performance status; NR = non-resectable; R = resectable

a Shown in **bold** are the numbers of patients (%) who shifted to a lower KPS category post-baseline.

b Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

11.4.4 Exploratory Pharmacodynamic and Biomarker Analysis

11.4.4.1 Anti-LPS

The results on anti-LPS IgG and IgM presence in patients per visit are provided in Table 14.2.2.8.1. The majority of patients in the FAS tested negative for anti-LPS IgG (27 patients [96.4%]) at baseline. The one patient who tested positive for anti-LPS IgG remained positive for all visits tested. In the PPS, all patients tested negative for anti-LPS IgG at all visits.

All patients tested negative for anti-LPS IgM at all visits, in the FAS and in the PPS.

11.4.4.2 VEGFR-2 Specific T Cell Responses

The change from baseline in VEGFR-2 peptide pools is provided in Table 14.2.2.8.2 and individual line plots of VEGFR-2 peptides per patients over time are presented in Figure 14.3.2.2.8.2. VEGFR-2 specific ELISpot counts were calculated as the ELISpot count per peptide pool minus the negative control. The VEGFR-2 specific T cell response was defined positive when the test peptide pool had at least two-fold higher spot counts compared to the negative control and the difference of the triplicates was significant in an unpaired two-tailed student's t-test.

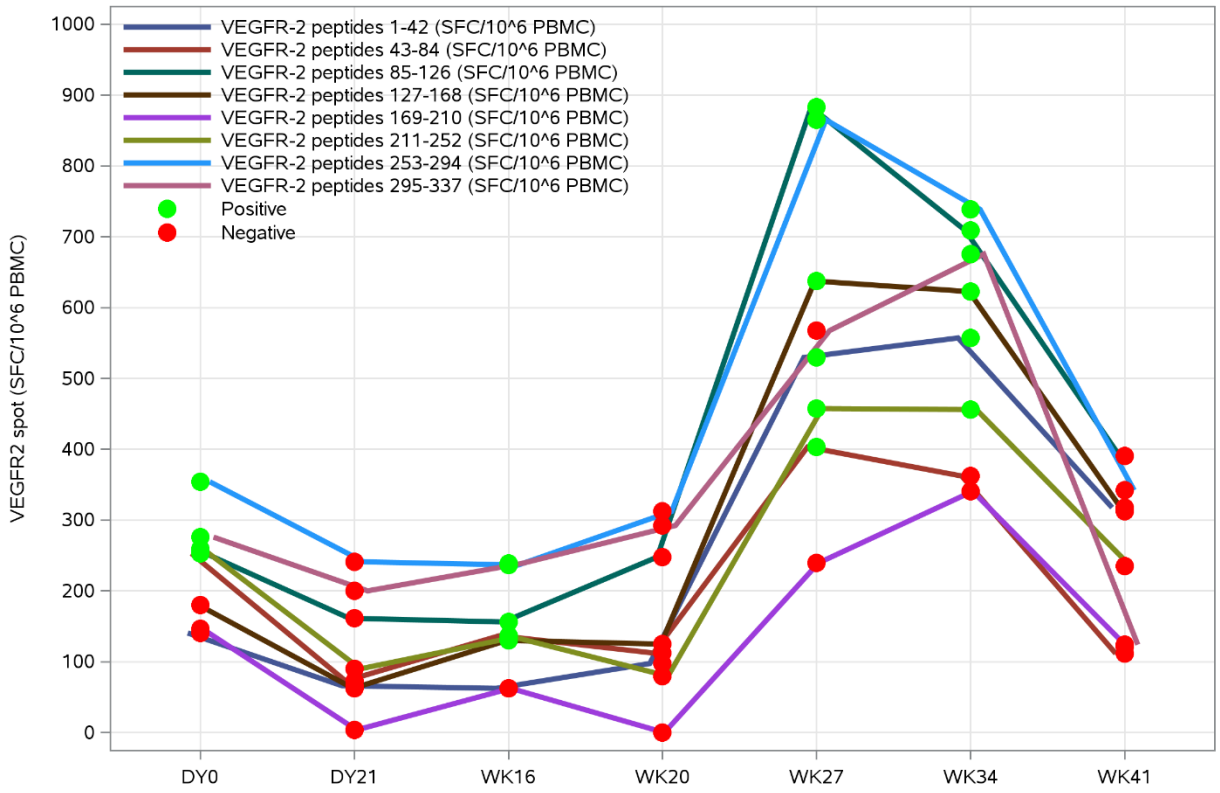
The VEGFR-2 specific T cell response was decreased on Day 21 compared with baseline in 6 patients, including all 3 patients in the 10^6 CFU/mL group, 2 patients in the 10^7 CFU/mL NR group, and 1 patient (01-17) in the 10^7 CFU/mL R group. The VEGFR-2 specific T cell response was increased on Day 21 in 4 patients (all 10^7 CFU/mL NR group). The VEGFR-2 specific T cell response remained at the same level compared with baseline in 5 patients (all 10^7 CFU/mL group, 2 patients in R group, 3 patients in NR group).

At Week 16, the VEGFR-2 specific T cell response was increased compared with baseline in 7 patients (1 patient in 10^6 CFU/mL group, 6 patients in 10^7 CFU/mL group), decreased in 5 patients (all 10^7 CFU/mL group), and remained the same in 3 patients (1 patient in 10^6 CFU/mL group, 2 patients in 10^7 CFU/mL group).

No clear trend could be observed in the VEGFR-2 specific T cell responses. Of the 3 patients with a partial remission as BOR, 2 patients (01-04 and 01-09) had a VEGFR-2 specific T cell response classified as positive at times, while 1 patient (22-10) had a response classified as negative at all time points. Of the 3 patients who had stable disease as BOR, 1 patient (01-14) had a VEGFR-2 specific T cell response classified as positive at times, while 2 patients (01-31 and 02-29) had a response mostly classified as negative at all time points.In 4 patients, the VEGFR-2 specific T cell response was recorded on additional time points after Week 16.

Patient 01-04 (10^6 CFU/mL group), who had been treated with antibiotics during the first 4.5 months, had a partial remission starting in Week 36 and a peak in VEGFR-2 specific T cell response from Week 27 to Week 34, with subsequent decline for all peptide pools to levels similar to baseline at Week 41 (Figure 11-9). Interestingly, no increase of the VEGFR-2 specific T cell response had been observed during the antibiotics treatment administration period (10 July 2018 – 10 July 2019). After the peak of VEGFR-2 specific T cell response from Week 27 to Week 34, tumor shrinkage was observed with a partial remission at Week 36.

Figure 11-9: VEGFR-2 Specific T Cell Response (Patient 01-04)

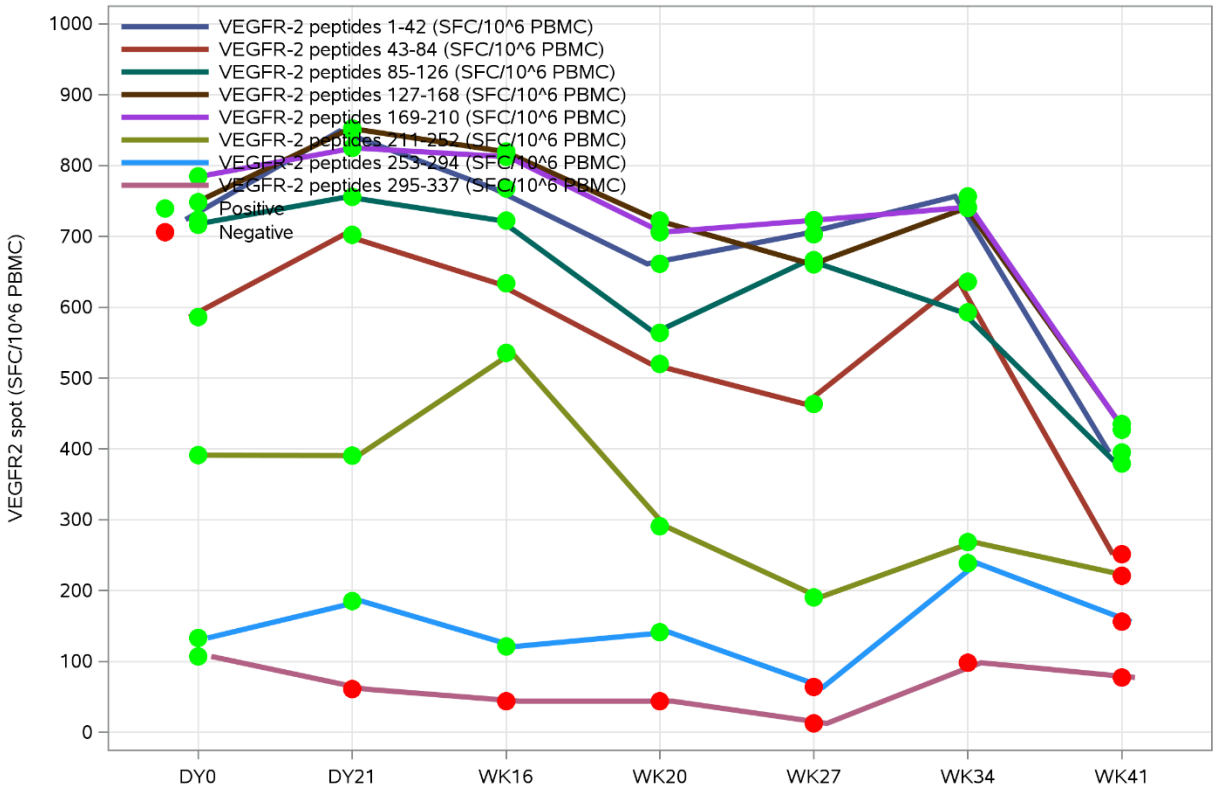


Source: Figure 14.3.2.2.8.2

DY = Day; PBMC = peripheral blood mononuclear cell; SFC = spot-forming cells; VEGFR = vascular endothelial growth factor receptor; WK = Week

Patient 01-09 (10^7 CFU/mL NR group), who had a PFS of 13.8 months, had pre-existing VEGFR-2 specific immune responses and a somewhat stable VEGFR-2 specific T cell response up to Week 34, with subsequent decline to negative for half of the tested peptide pools at Week 41 (Figure 11-10).

Figure 11-10: VEGFR-2 Specific T Cell Response (Patient 01-09)

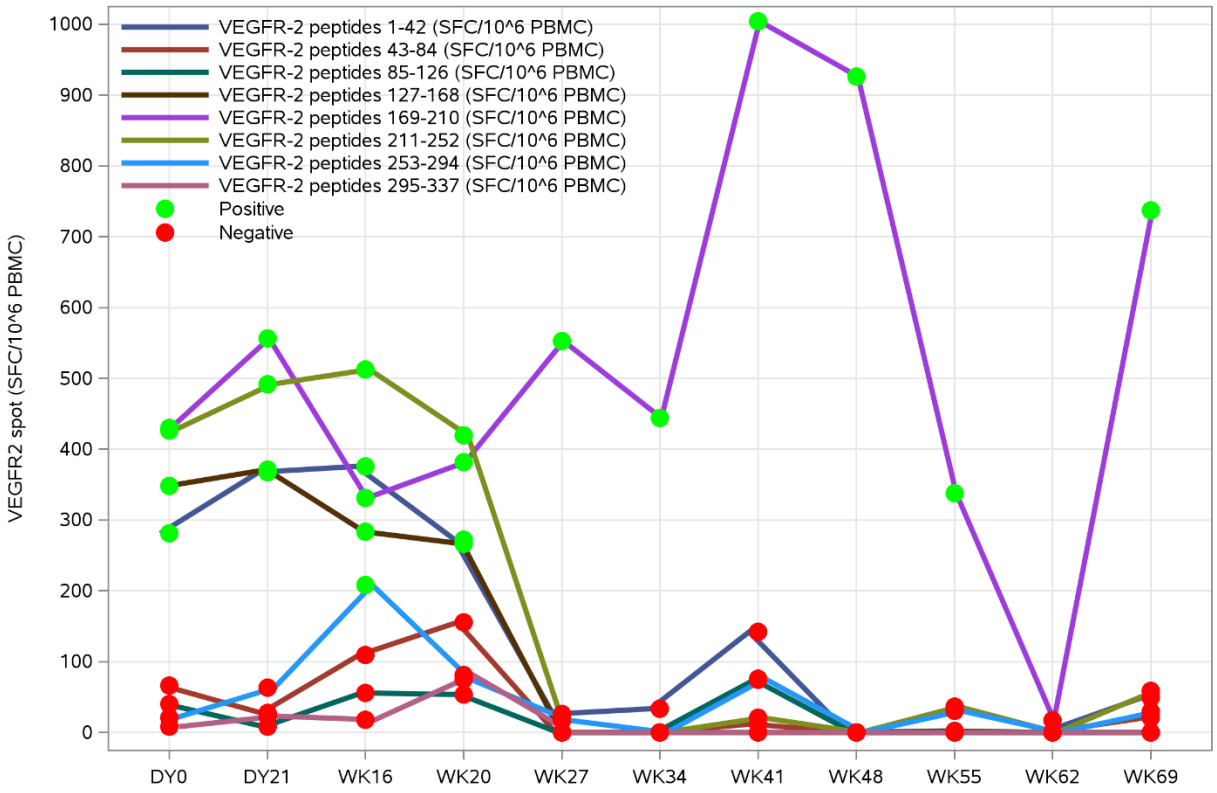


Source: Figure 14.3.2.2.8.2

DY = Day; PBMC = peripheral blood mononuclear cell; SFC = spot-forming cells; VEGFR = vascular endothelial growth factor receptor; WK = Week

Patient 01-14, a resected patient who did not experience disease progression at the time of database lock after completion of the prolongation phase of the study, had a somewhat stable VEGFR-2 specific T cell response up to Week 20 with subsequent decline of all tested peptide pools except one (Figure 11-11). For peptide pool 169 – 210, a strong increase of ELISpot signal compared to the already pre-existing signal at baseline to maximum spot counts up 1000 were observed beyond Week 27 including a drop to 0 at Week 62 and an increase to ELISpot counts around 700 at the last time point of Week 69.

Figure 11-11: VEGFR-2 Specific T Cell Response (Patient 01-14)

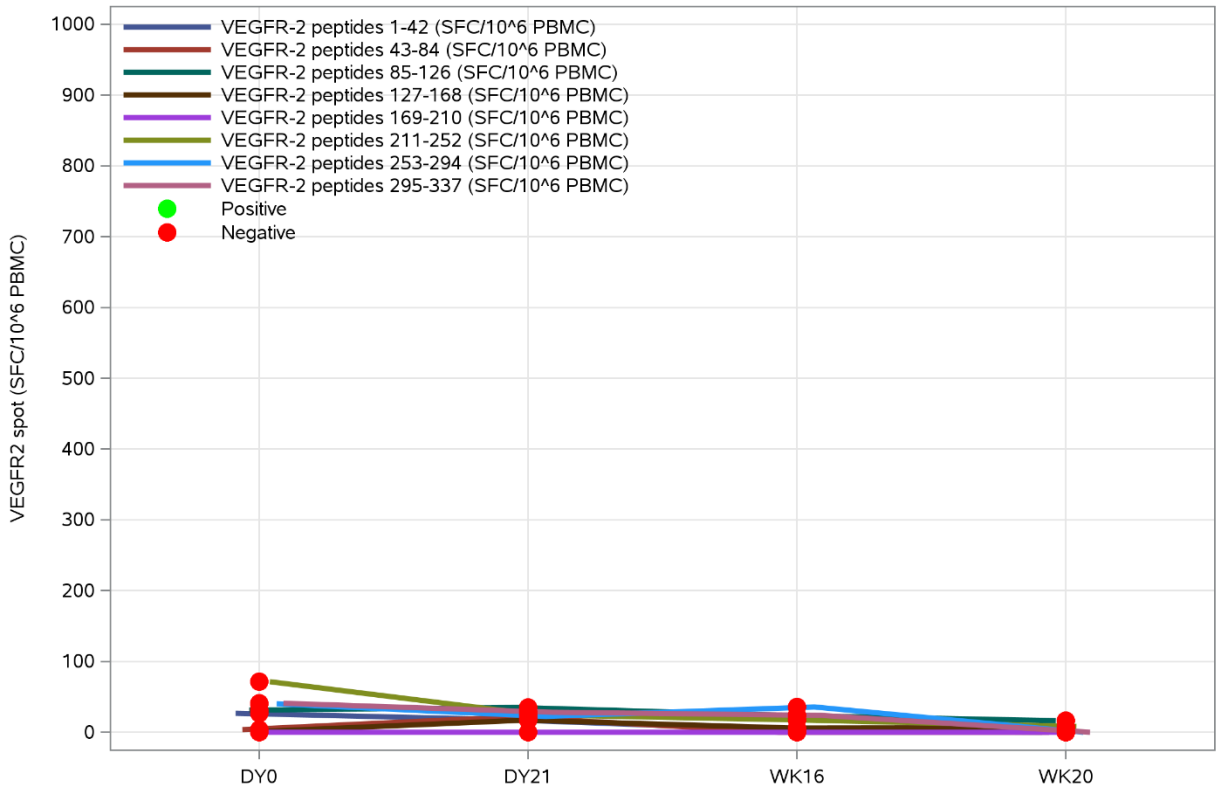


Source: Figure 14.3.2.2.8.2

DY = Day; PBMC = peripheral blood mononuclear cell; SFC = spot-forming cells; VEGFR = vascular endothelial growth factor receptor; WK = Week

In Patient 22-10, who had experienced an early decrease of tumor size resulting in a partial remission, no increase in the VEGFR-2 specific immune response was observed (Figure 11-12). It might be speculated that the tumor shrinkage of this patient was associated with an elevated tumor mutational burden and a corresponding checkpoint inhibitor effect.

Figure 11-12: VEGFR-2 Specific T Cell Response (Patient 22-10)

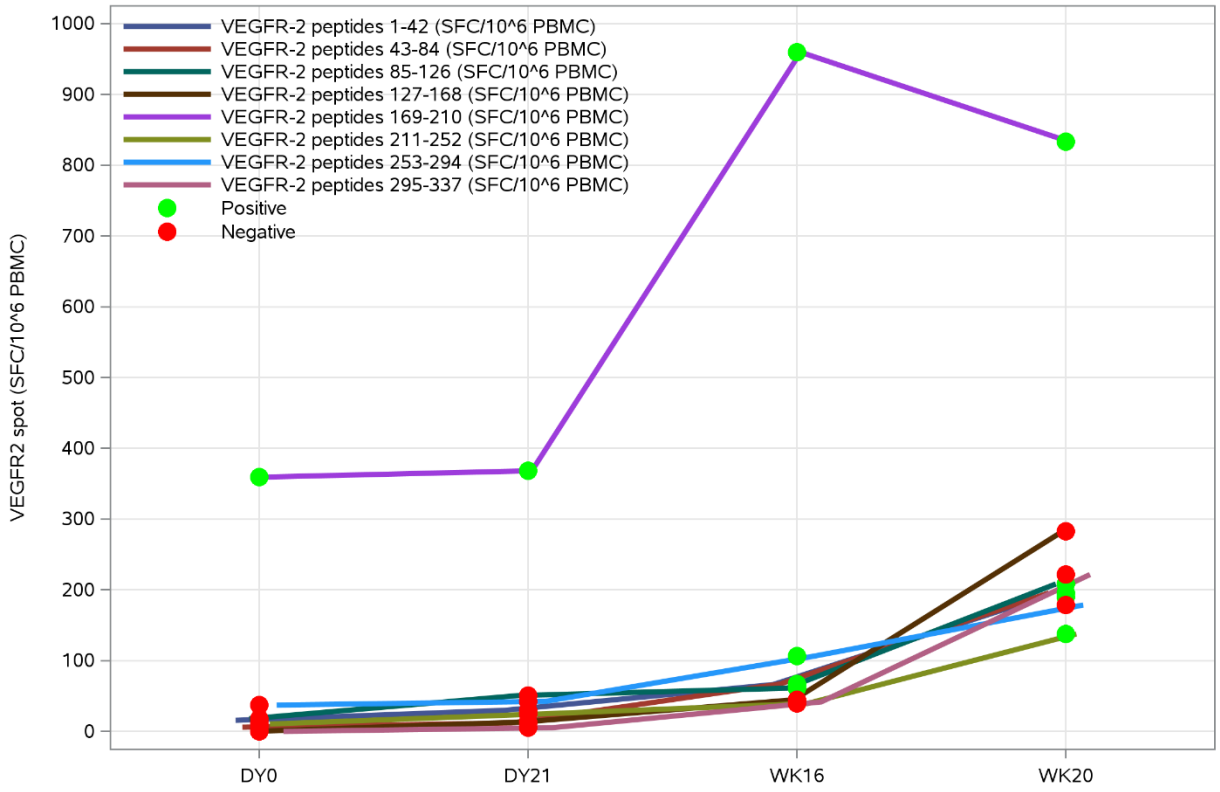


Source: Figure 14.3.2.2.8.2

DY = Day; PBMC = peripheral blood mononuclear cell; SFC = spot-forming cells; VEGFR = vascular endothelial growth factor receptor; WK = Week

In Patient 01-27, an increase of the VEGFR-2 specific T cell response was observed (Figure 11-13). Similar to Patient 01-14, a clear increase compared to the already pre-existing signal at baseline was found in peptide pool 169 – 210. It is worth noting that despite the progression of disease already experienced at Month 3, this patient is one of the long-term survivors in the study and still in the safety follow-up phase of the study.

Figure 11-13: VEGFR-2 Specific T Cell Response (Patient 01-27)

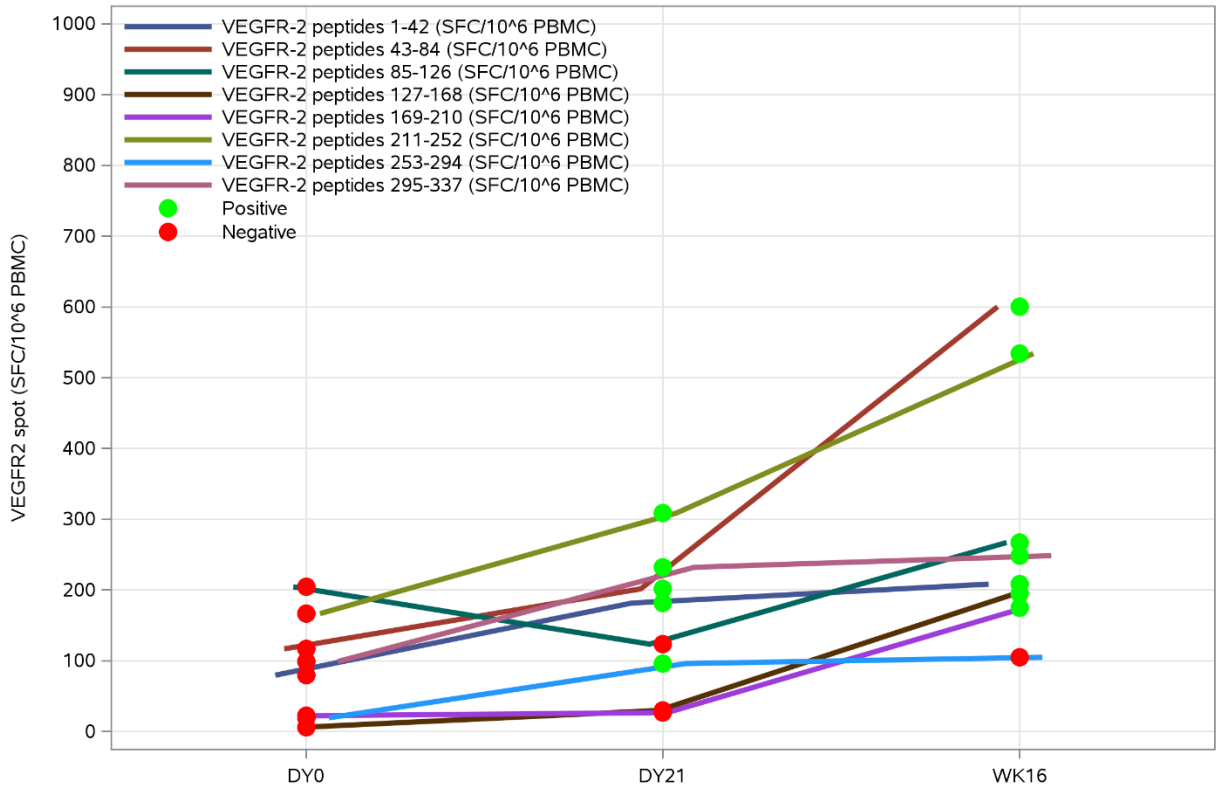


Source: Figure 14.3.2.2.8.2

DY = Day; PBMC = peripheral blood mononuclear cell; SFC = spot-forming cells; VEGFR = vascular endothelial growth factor receptor; WK = Week

In Patient 01–11, a clear increase of the VEGFR-2 specific immune response in several peptide pools up to Week 16 was observed (Figure 11-14), which did not result in shrinkage of the patient's tumor. In this patient, who was not pre-treated with antibiotics, an increase of tumor size from 10.64 mm × 14.95 mm (159.07 mm^2) at baseline to 12.41 mm × 18.82 mm (233.56 mm^2) at Week 12 (46.8%) was observed.

Figure 11-14: VEGFR-2 Specific T Cell Response (Patient 01-11)



Source: Figure 14.3.2.2.8.2

DY = Day; PBMC = peripheral blood mononuclear cell; SFC = spot-forming cells; VEGFR = vascular endothelial growth factor receptor; WK = Week

11.4.4.3 Myeloid Derived Suppressor and Regulatory T Cells

The actual and change from baseline values for myeloid derived suppressor and T_{regs} are provided in Table 14.2.2.8.3 and listed by-patient in Listing 16.2.6.3.3. No clear trend could be observed in change from baseline for MDSCs (% of living cells), MDSCs (% of Lin– cells), T_{regs} (% of living cells), and T_{regs} (% of CD4+ cells).

11.4.4.4 Tumor Biomarkers

The actual and change from baseline values for the investigated tumor biomarkers are provided in Table 14.2.2.8.4 and listed by-patient in Listing 16.2.6.3.4. Results should be interpreted with caution, since the post-baseline assessment was reported for only 2 patients (10^7 CFU/mL R group, Patient 01-14 and Patient 1-17) based on the tumor material obtained during resection. The same 2 patients were included in the FAS and the PPS. Both of the included patients were, in line with the clinical study protocol, in the resected patients cohort (10^7 CFU/mL R group).

For the CD3 and CD8 infiltrating lymphocytes, the change from baseline in cell count (/mm) was positive in Patient 01-14, increasing from 40 to 600 CD8+ T cells and 280 to > 800 CD3+ T cells. This resected patient completed the prolongation phase of the study and was in the follow-up phase at the time of database lock. In Patient 01-17 no such effect could be observed. For the

CD4 infiltrating lymphocytes, the change from baseline in cell count (/mm) was negative in both patients (–64 and –168). For the FoxP3 infiltrating lymphocytes, the changes from baseline in cell count (/mm) were 0 (Patient 01-17) and 144 (Patient 01-14). The change from baseline in PD-1 score was positive in Patient 01-14 and negative in Patient 01-17. The change from baseline in PD-L1 score was negative in both patients (–1 and –90). No post-baseline results were reported for CD68 infiltrating lymphocytes.

For non-resected patients who experienced a partial remission, Patients 01-04, 01-09, and 22-10, the intratumoral CD8+ T cell count pre-treatment was 288, 416, 560 per mm^2, respectively. It is important to note that for Patient 01-04 a second tumor sample (2011) taken 3 years after the first sample (2008) had an intratumoral CD8+ T cell count of 32 per mm^2.

In the patients who had shown a positive VEGFR-2 specific T cell response, Patients 01-11 and 01-27, the intratumoral CD8+ T cell count pre-treatment was > 800 or 256 cells/mm^2.

11.4.5 Statistical/Analytical Issues

Not applicable.

11.4.6 Tabulation of Individual Response Data

By-patient displays of efficacy results are provided in the following listings:

Listing 16.2.6.1.1	iRANO Tumor Lesion Identification
Listing 16.2.6.1.2	iRANO Tumor Lesion Results
Listing 16.2.6.1.3	iRANO Tumor Response
Listing 16.2.6.1.4	Derived Efficacy Results
Listing 16.2.6.2.1	Karnofsky Performance Status
Listing 16.2.6.3.1	Anti-LPS
Listing 16.2.6.3.2	VEGFR-2 Specific T Cell Responses
Listing 16.2.6.3.3	Myeloid Derived Suppressor and Regulatory T Cells
Listing 16.2.6.3.4	Tumor Biomarkers

11.4.7 Drug Dose, Drug Concentration, and Relationship to Response

Not applicable.

11.4.8 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.9 By-Patient Displays

Individual patient profiles are available upon request.

11.4.10 Efficacy Conclusions

11.4.10.1 Summary of Efficacy Results

- The tumor response was assessed by ORR and DoR according to iRANO (2015). Overall, in the NR patients the ORR was 12.0% (95% CI: 2.5 – 31.2), with 3 responders out of 25 patients (12.0%) who had a partial remission. In addition, overall 1 of 25 NR patients (4.0%) had stable disease. Of the patients with a partial remission, 1 patient in the 10^6 CFU/mL group had a DoR of 5.6 months, while the patients in the 10^7 CFU/mL group had a DoR of 2.7 and 11.1 months. All patients who had stable disease received 10^7 CFU/mL VXM01.
- The clinical response was assessed by RFS (in the 10^7 CFU/mL R group), TTP, PFS, and OS. In the patients who underwent tumor resection (10^7 CFU/mL R group), disease progression occurred only in Patient 01-17 with an RFS of 1.8. Patient 01-14 was censored with an RFS of 20.9 months. The results for TTP and PFS were identical, with an overall median of 2.7 months (95% CI: 2.7 – 2.7) and range of 1.2 to 13.8 months in the non-resected patients (Total NR group). The median OS in the Total NR group was 11.1 months (95% CI: 8.5 – 15.1) with a range of 3.8 to 38.2 months. At the time of database lock, 1 patient in the 10^7 CFU/mL R group was alive and had stable disease without post-resection recurrence, while 3 patients in the 10^7 CFU/mL NR group were alive with progressive disease in long-term follow-up.
- The effect of VXM01 plus avelumab was explored by evaluating the VEGFR-2 specific T cell response and frequency of immune cells in peripheral blood, and by staining of immune- and biomarkers in tumor tissue obtained during resection. Overall, 12 of 28 patients (42.9%, all in the 10^7 CFU/mL NR group) had a VEGFR-2 specific T cell response classified as negative for all peptides at all time points tested. Two of the long-term survivors in the study (Patient 01-14 and Patient 01-27) had an increase found in peptide pool 169 – 210, indicating an increased VEGFR-2 specific T cell response. However, overall no clear trend could be observed in the VEGFR-2 specific T cell response classified as positive. Similarly, no clear trends could be observed in the change from baseline in peripheral MDSCs and T_{regs}, and in the tumor biomarkers evaluated in localized tumor tissue.

11.4.10.2 Conclusions

- With the non-resected patients showing an ORR of 12.0% (partial remission) and 10.7% having stable disease as well as an OS of 2.2 to 23.1 months in resected patients, it appears that this combination therapy may be suitable for some patients with recurrent glioblastoma.
- Additionally, increases in peptide pool 169-210 may serve as potential biomarker for a VEGFR-2 specific T cell response in these patients.
- Due to the study design being an uncontrolled trial, no conclusion can be made regarding the extent of VXM01 treatment efficacy compared with the standard of care treatment for patients with recurrent glioblastoma, although a threshold of 20% with objective responses is usually regarded to be of interest (Galanis et al. 2012).

12. SAFETY EVALUATION

12.1 Extent of Exposure

The individual exposure to IMP by patient is provided in Table 14.3.1.1.1 and Listing 16.2.5.1. The exposure to IMP by cohort is presented in Table 12-1. Only 3 patients, all in the 10^7 CFU/mL NR group, required an interruption of avelumab infusion (Table 14.3.1.1.3). Of those 3 patients, one patient also required a modification of avelumab infusion. A complete list of IMP exposure interruptions and modifications for VXM01 and avelumab is provided in Listing 16.2.5.2.

The treatment duration and number of doses were comparable between the groups, except for the 10^7 CFU/mL R group that included a patient who received the maximum number of VXM01 administrations (26). This was notably higher than the overall maximum number of VXM01 administrations (18 for 10^6 CFU/mL and 17 for the 10^7 CFU/mL NR group), however, the median number of doses and median cumulative dose for the 10^7 CFU/mL R group were similar to those for the other groups.

Table 12-1: Exposure to IMP by Cohort (SAF)

		Treatment (Units)	Duration (Days)		Number of Doses		Mean Dose	Cumulative Doses	
			Median	Min, Max	Median	Min, Max		Median	Min, Max
10^6 CFU/mL (N = 3)		Avelumab (mg)	70	18, 407	6	2, 30	800.0	4800	1600, 24000
		VXM01 (10^6 CFU/mL)	56	8, 393	6	4, 18	1.0	6	4, 18
10^7 CFU/mL	All Patients (N = 25)	Avelumab (mg)	71	29, 673	6	3, 48	799.1	4800	2400, 38400
		VXM01 (10^7 CFU/mL)	57	8, 673	6	4, 26	1.0	6	4, 26
	NR (N = 22)	Avelumab (mg)	71	29, 405	6	3, 30	799.0	4800	2400, 23334.4
		VXM01 (10^7 CFU/mL)	57	29, 363	6	5, 17	1.0	6	5, 17
	R (N = 3)	Avelumab (mg)	71	29, 673	4	3, 48	800.0	3200	2400, 38400
		VXM01 (10^7 CFU/mL)	56	8, 673	5	4, 26	1.0	5	4, 26
Total NR[a] (N = 25)		Avelumab (mg)	71	18, 407	6	2, 30	799.1	4800	1600, 24000
		VXM01 (10^6 CFU/mL)	56	8, 393	6	4, 18	1.0	6	4, 18
		VXM01 (10^7 CFU/mL)	57	29, 363	6	5, 17	1.0	6	5, 17
Total (N = 28)		Avelumab (mg)	71	18, 673	6	2, 48	799.2	4800	1600, 38400
		VXM01 (10^6 CFU/mL)	56	8, 393	6	4, 18	1.0	6	4, 18
		VXM01 (10^7 CFU/mL)	57	8, 673	6	4, 26	1.0	6	4, 26

Source: Table 14.3.1.1.2

CFU = colony forming unit; N = number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

The AEs by group are summarized in Table 12-2. All patients experienced multiple AEs. No treatment-limiting toxicities related to VXM01 or avelumab, infusion-related AEs, or AEs leading to study discontinuation were recorded for any group. No SAEs and no treatment-emergent SAEs were recorded for the 10^6 CFU/mL and 10^7 CFU/mL R groups. No VXM01- or avelumab-related SAEs or treatment-emergent SAEs were recorded for any group. There was 1 AE reported as leading to discontinuation of the study treatment, and 4 patients experienced a total of 5 irAEs. Generally, the incidence of AEs and TEAEs was comparable between groups.

Table 12-2: Adverse Events Summary (SAF)

	10^6 CFU/mL (N = 3) n (%) E	10^7 CFU/mL			Total NR[a] (N = 25) n (%) E	Total (N = 28) n (%) E
		All Patients (N = 25) n (%) E	NR (N = 22) n (%) E	R (N = 3) n (%) E		
Adverse Events	3 (100) 30	25 (100) 247	22 (100) 218	3 (100) 29	25 (100) 248	28 (100) 277
Grade 3, 4, or 5	2 (66.7) 2	12 (48.0) 30	12 (54.5) 30	-	14 (56.0) 32	14 (50.0) 32
VXM01-related	-	12 (48.0) 32	11 (50.0) 31	1 (33.3) 1	11 (44.0) 31	12 (42.9) 32
Avelumab-related	2 (66.7) 11	14 (56.0) 45	12 (54.5) 41	2 (66.7) 4	14 (56.0) 52	16 (57.1) 56
Target disease-related	3 (100) 12	18 (72.0) 67	15 (68.2) 61	3 (100) 6	18 (72.0) 73	21 (75.0) 79
Drug related Grade 3, 4, or 5	-	3 (12.0) 4	3 (13.6) 4	-	3 (12.0) 4	3 (10.7) 4
Serious Adverse Events	-	7 (28.0) 11	7 (31.8) 11	-	7 (28.0) 11	7 (25.0) 11
Grade 3, 4, or 5	-	7 (28.0) 10	7 (31.8) 10	-	7 (28.0) 10	7 (25.0) 10
VXM01-related	-	-	-	-	-	-
Avelumab-related	-	-	-	-	-	-
Target disease-related	-	6 (24.0) 9	6 (27.3) 9	-	6 (24.0) 9	6 (21.4) 9
Drug related Grade 3, 4, or 5	-	-	-	-	-	-
Treatment-Emergent Adverse Events	3 (100) 30	25 (100) 226	22 (100) 198	3 (100) 28	25 (100) 228	28 (100) 256
Grade 3, 4, or 5	2 (66.7) 2	12 (48.0) 26	12 (54.5) 26	-	14 (56.0) 28	14 (50.0) 28
VXM01-related	-	12 (48.0) 32	11 (50.0) 31	1 (33.3) 1	11 (44.0) 31	12 (42.9) 32
Avelumab-related	2 (66.7) 11	14 (56.0) 45	12 (54.5) 41	2 (66.7) 4	14 (56.0) 52	16 (57.1) 56
Target disease-related	3 (100) 12	18 (72.0) 65	15 (68.2) 59	3 (100) 6	18 (72.0) 71	21 (75.0) 77
Drug related Grade 3, 4, or 5	-	3 (12.0) 4	3 (13.6) 4	-	3 (12.0) 4	3 (10.7) 4
Treatment-Emergent Serious Adverse Events	-	6 (24.0) 9	6 (27.3) 9	-	6 (24.0) 9	6 (21.4) 9
Grade 3, 4, or 5	-	6 (24.0) 8	6 (27.3) 8	-	6 (24.0) 8	6 (21.4) 8
VXM01-related	-	-	-	-	-	-
Avelumab-related	-	-	-	-	-	-
Target disease-related	-	5 (20.0) 7	5 (22.7) 7	-	5 (20.0) 7	5 (17.9) 7
Drug related Grade 3, 4, or 5	-	-	-	-	-	-

	10^6 CFU/mL (N = 3) n (%) E	10^7 CFU/mL			Total NR[a] (N = 25) n (%) E	Total (N = 28) n (%) E
		All Patients (N = 25) n (%) E	NR (N = 22) n (%) E	R (N = 3) n (%) E		
Treatment-Limiting Toxicities Related to VXM01	-	-	-	-	-	-
Treatment-Limiting Toxicities Related to Avelumab	-	-	-	-	-	-
Infusion-related Adverse Events	-	-	-	-	-	-
Immune-related Adverse Events	-	4 (16.0) 5	2 (9.1) 2	2 (66.7) 3	2 (8.0) 2	4 (14.3) 5
Treatment Discontinuations Due to AEs	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Study Discontinuations Due to AEs	-	-	-	-	-	-

Source: Table 14.3.1.2.1

Note: Percentages are based on the number (N) of patients in the SAF. A hyphen (-) indicates no events were reported.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.2.2 Display of Adverse Events

Summaries of AEs are provided in the following tables:

12.2.3 Analysis of Adverse Events

12.2.3.1 Incidence of Adverse Events

Treatment-emergent AEs occurring in ≥ 10% of patients (total SAF) are summarized in Table 12-3 and all TEAEs are summarized in Table 14.3.1.3.1.

Overall, the most frequently reported TEAEs were a decreased lymphocyte count in 16 patients (57.1%, 46 events), fatigue in 14 patients (50.0%, 19 events), and decreased WBC count in 8 patients (28.6%, 20 events). The SOC with most reported TEAEs was investigations (21 patients [75.0%] with 116 events), followed by nervous system disorders (17 patients [60.7%] with 38 events), and general disorders and administration site conditions (15 patients [53.6%] with 34 events).

Gastrointestinal disorders occurred in approximately one-third of the patients (9 [32.1%] with 18 events). The most commonly reported gastrointestinal TEAEs included nausea (5 patients [17.9%] with 6 events), diarrhea, and vomiting (both in 3 patients [10.7%] with 4 events). Oral dysesthesia, gastroesophageal reflux disease, and mouth ulceration each occurred in only one patient. Viral gastroenteritis occurred in one patient who received 10^6 CFU/mL of the VXM01 vaccine.

Table 12-3: Treatment-Emergent Adverse Events in ≥ 10% of Patients (SAF)

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Adverse Event	3 (100) 30	25 (100) 226	22 (100) 198	3 (100) 28	25 (100) 228	28 (100) 256
Gastrointestinal Disorders	2 (66.7) 3	7 (28.0) 15	7 (31.8) 15	-	9 (36.0) 18	9 (32.1) 18
Nausea	1 (33.3) 1	4 (16.0) 5	4 (18.2) 5	-	5 (20.0) 6	5 (17.9) 6
Diarrhoea	1 (33.3) 2	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 4	3 (10.7) 4
Vomiting	-	3 (12.0) 4	3 (13.6) 4	-	3 (12.0) 4	3 (10.7) 4
General Disorders and Administration Site Conditions	2 (66.7) 10	13 (52.0) 24	11 (50.0) 22	2 (66.7) 2	13 (52.0) 32	15 (53.6) 34
Fatigue	1 (33.3) 1	13 (52.0) 18	11 (50.0) 16	2 (66.7) 2	12 (48.0) 17	14 (50.0) 19
Influenza Like Illness	2 (66.7) 7	2 (8.0) 4	2 (9.1) 4	-	4 (16.0) 11	4 (14.3) 11
Investigations	1 (33.3) 3	20 (80.0) 113	17 (77.3) 92	3 (100) 21	18 (72.0) 95	21 (75.0) 116
Lymphocyte Count Decreased	-	16 (64.0) 46	13 (59.1) 40	3 (100) 6	13 (52.0) 40	16 (57.1) 46
White Blood Cell Count Decreased	-	8 (32.0) 20	6 (27.3) 13	2 (66.7) 7	6 (24.0) 13	8 (28.6) 20
Lipase Increased	-	5 (20.0) 6	4 (18.2) 5	1 (33.3) 1	4 (16.0) 5	5 (17.9) 6
Alanine Aminotransferase Increased	-	4 (16.0) 6	3 (13.6) 5	1 (33.3) 1	3 (12.0) 5	4 (14.3) 6
Blood Potassium Decreased	-	4 (16.0) 6	2 (9.1) 2	2 (66.7) 4	2 (8.0) 2	4 (14.3) 6
Gamma-glutamyltransferase Increased	-	3 (12.0) 6	3 (13.6) 6	-	3 (12.0) 6	3 (10.7) 6
Blood Creatine Phosphokinase Increased	1 (33.3) 3	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 5	3 (10.7) 5
Nervous System Disorders	2 (66.7) 9	15 (60.0) 29	14 (63.6) 27	1 (33.3) 2	16 (64.0) 36	17 (60.7) 38
Hemiparesis	2 (66.7) 2	4 (16.0) 4	3 (13.6) 3	1 (33.3) 1	5 (20.0) 5	6 (21.4) 6
Aphasia	1 (33.3) 1	3 (12.0) 3	3 (13.6) 3	-	4 (16.0) 4	4 (14.3) 4

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Brain Oedema	2 (66.7) 2	2 (8.0) 2	2 (9.1) 2	-	4 (16.0) 4	4 (14.3) 4
Fine Motor Skill Dysfunction	1 (33.3) 1	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	2 (8.0) 2	3 (10.7) 3
Headache	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3

Source: Table 14.3.1.3.1

Note: Percentages are based on the number (N) of patients in the SAF. Only events occurring in ≥ 10% of patients (Total SAF) are presented.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.2.3.2 Adverse Events by Severity

Treatment-emergent AEs by severity and TEAEs of toxicity Grade 3 and 4 are summarized in Table 12-4, and all TEAEs by severity are provided in Table 14.3.1.3.2. The majority of TEAEs, (228 of 256 events [89.1%]) was mild or moderate (Grade 1 or Grade 2). No TEAEs of Grade 5 (AEs leading to death) were reported. Overall, Grade 3 (severe) TEAEs occurred in 13 patients (46.4%) with 27 events (10.5%) and one patient in the 10^7 CFU/mL NR group had one Grade 4 (life-threatening) TEAE of pulmonary embolism in Patient 01-28 which was not related to either VXM01 or avelumab according to the investigator.

Two of 3 patients (66.7%) in the 10^6 CFU/mL group and 11 of 25 patients (44.0%) in the 10^7 CFU/mL group had a Grade 3 TEAE. The most frequently occurring Grade 3 TEAE was decreased lymphocyte count with 5 events in 4 of 25 patients (16.0%) in the 10^7 CFU/mL group. All other Grade 3 TEAEs occurred in less than 3 patients. One patient (01-28) in the 10^7 CFU/mL NR group experienced a pulmonary embolism classified as Grade 4 TEAE. No TEAEs above Grade 2 were reported for the 10^7 CFU/mL R group.

Table 12-4: Treatment-Emergent Adverse Events of Grade 3 and 4 by Severity (SAF)

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Adverse Event	Grade 1	3 (100) 15	25 (100) 135	22 (100) 113	3 (100) 22	25 (100) 128	28 (100) 150
	Grade 2	3 (100) 13	22 (88.0) 65	19 (86.4) 59	3 (100) 6	22 (88.0) 72	25 (89.3) 78
	Grade 3	2 (66.7) 2	11 (44.0) 25	11 (50.0) 25	-	13 (52.0) 27	13 (46.4) 27
	Grade 4	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Blood and Lymphatic System Disorders		-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Lymphopenia	Grade 3	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Investigations		1 (33.3) 1	6 (24.0) 7	6 (27.3) 7	-	7 (28.0) 8	7 (25.0) 8
Lymphocyte Count Decreased	Grade 3	-	4 (16.0) 5	4 (18.2) 5	-	4 (16.0) 5	4 (14.3) 5
Blood Creatine Phosphokinase Increased	Grade 3	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Gamma-glutamyltransferase Increased	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Platelet Count Decreased	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Metabolism and Nutrition Disorders		-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
Hyponatraemia	Grade 3	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
Nervous System Disorders		1 (33.3) 1	3 (12.0) 4	3 (13.6) 4	-	4 (16.0) 5	4 (14.3) 5
Brain Oedema	Grade 3	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Cerebrovascular Accident	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Status Epilepticus	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Syncope	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Psychiatric Disorders		-	2 (8.0) 5	2 (9.1) 5	-	2 (8.0) 5	2 (7.1) 5
Insomnia	Grade 3	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Confusional State	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Depression	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Personality Change	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Respiratory, Thoracic, and Mediastinal Disorders		-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Pulmonary Embolism	Grade 4	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Vascular Disorders		-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
Hypertension	Grade 3	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3

Source: Table 14.3.1.3.2 and Table 14.3.1.4.2

Note: Percentages are based on the number (N) of patients in the SAF. For the SOCs and PTs, only events of toxicity Grade 3 or 4 are presented.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.2.3.3 Adverse Events by Relationship

All TEAEs related to VXM01 occurred in the 10^7 CFU/mL group (N = 25), with 31 events in 11 of 22 patients (50.0%) in the NR group and 1 event in 1 of 3 patients (33.3%) in the R group (Table 12-5). The following events that were considered related to VXM01 vaccine treatment occurred in 2 or more patients: fatigue in 5 patients, lymphocyte count decreased in 3 patients, and diarrhea in 2 patients. A complete overview of TEAEs by VXM01 relationship is provided in Table 14.3.1.3.3. Of the TEAEs considered related to VXM01, all events were Grade 1 (mild) or Grade 2 (moderate) severity, with exception of lymphopenia and hypertension, both Grade 3 (severe), each occurring in one patient in the 10^7 CFU/mL NR group (Table 14.3.1.4.3).

Treatment-emergent AEs related to avelumab occurred at both VXM01 vaccine dose levels, with 11 events in 2 of 3 patients in the 10^6 CFU/mL group and 45 events in 14 of 25 patients in the 10^7 CFU/mL group (Table 12-6). A complete overview of TEAEs by avelumab relationship is provided in Table 14.3.1.3.4. Of the TEAEs considered related to avelumab, all events were Grade 1 or Grade 2 severity, with exception of lymphopenia, rheumatoid arthritis, and hypertension. Each Grade 3 event occurred in a different patient in the 10^7 CFU/mL NR group (Table 14.3.1.4.4).

Of the 32 events considered related to VXM01 treatment, 29 events (90.6%) were also considered related to avelumab treatment. The 3 events considered only related to VXM01 treatment were diarrhea, myalgia, and pruritus. The majority of events were considered not related to VXM01 treatment (224 of 256 events [87.5%]).

Table 12-5: Treatment-Emergent Adverse Events by VXM01 Relationship (SAF)

System Organ Class **Preferred Term**	**VXM01 Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Adverse Event	Related	-	12 (48.0) 32	11 (50.0) 31	1 (33.3) 1	11 (44.0) 31	12 (42.9) 32
	Not Related	3 (100) 30	23 (92.0) 194	20 (90.9) 167	3 (100) 27	23 (92.0) 197	26 (92.9) 224
Blood and Lymphatic System Disorders	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Anaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Lymphopenia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Gastrointestinal Disorders	Related	-	3 (12.0) 6	3 (13.6) 6	-	3 (12.0) 6	3 (10.7) 6
	Not Related	2 (66.7) 3	4 (16.0) 9	4 (18.2) 9	-	6 (24.0) 12	6 (21.4) 12
Nausea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	3 (12.0) 4	3 (13.6) 4	-	4 (16.0) 5	4 (14.3) 5
Diarrhoea	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
	Not Related	1 (33.3) 2	-	-	-	1 (4.0) 2	1 (3.6) 2
Oral Dysaesthesia	Related	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Gastrooesophageal Reflux Disease	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
General Disorders and Administration Site Conditions	Related	-	5 (20.0) 7	5 (22.7) 7	-	5 (20.0) 7	5 (17.9) 7
	Not Related	2 (66.7) 10	9 (36.0) 17	7 (31.8) 15	2 (66.7) 2	9 (36.0) 25	11 (39.3) 27
Fatigue	Related	-	5 (20.0) 6	5 (22.7) 6	-	5 (20.0) 6	5 (17.9) 6
	Not Related	1 (33.3) 1	9 (36.0) 12	7 (31.8) 10	2 (66.7) 2	8 (32.0) 11	10 (35.7) 13

System Organ Class **Preferred Term**	**VXM01 Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Influenza Like Illness	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	2 (66.7) 7	1 (4.0) 3	1 (4.5) 3	-	3 (12.0) 10	3 (10.7) 10
Infections and Infestations	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Urinary Tract Infection	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Investigations	Related	-	4 (16.0) 9	3 (13.6) 8	1 (33.3) 1	3 (12.0) 8	4 (14.3) 9
	Not Related	1 (33.3) 3	19 (76.0) 104	16 (72.7) 84	3 (100) 20	17 (68.0) 87	20 (71.4) 107
Lymphocyte Count Decreased	Related	-	3 (12.0) 8	3 (13.6) 8	-	3 (12.0) 8	3 (10.7) 8
	Not Related	-	15 (60.0) 38	12 (54.5) 32	3 (100) 6	12 (48.0) 32	15 (53.6) 38
White Blood Cell Count Decreased	Related	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
	Not Related	-	8 (32.0) 19	6 (27.3) 13	2 (66.7) 6	6 (24.0) 13	8 (28.6) 19
Metabolism and Nutrition Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	3 (12.0) 9	3 (13.6) 9	-	4 (16.0) 10	4 (14.3) 10
Hypertriglyceridaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
Musculoskeletal and Connective Tissue Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	3 (12.0) 3	3 (13.6) 3	-	4 (16.0) 4	4 (14.3) 4
Myalgia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Nervous System Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	2 (66.7) 9	14 (56.0) 28	13 (59.1) 26	1 (33.3) 2	15 (60.0) 35	16 (57.1) 37

System Organ Class **Preferred Term**	**VXM01 Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Headache	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Skin and Subcutaneous Tissue Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 2	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 4	3 (10.7) 4
Pruritus	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 2	-	-	-	1 (4.0) 2	1 (3.6) 2
Vascular Disorders	Related	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3	1 (4.0) 3
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Hypertension	Related	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

Source: Table 14.3.1.3.3

Note: Percentages are based on the number (N) of patients in the SAF. Only SOCs with related events are included in this table and only PTs with related events are listed.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

Table 12-6: Treatment-Emergent Adverse Events by Avelumab Relationship (SAF)

System Organ Class **Preferred Term**	**Avelumab Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Adverse Event	Related	2 (66.7) 11	14 (56.0) 45	12 (54.5) 41	2 (66.7) 4	14 (56.0) 52	16 (57.1) 56
	Not Related	3 (100) 19	24 (96.0) 181	21 (95.5) 157	3 (100) 24	24 (96.0) 176	27 (96.4) 200
Blood and Lymphatic System Disorders	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Anaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Lymphopenia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Endocrine Disorders	Related	-	2 (8.0) 3	1 (4.5) 1	1 (33.3) 2	1 (4.0) 1	2 (7.1) 3
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Hypothyroidism	Related	-	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	1 (4.0) 1	2 (7.1) 2
Autoimmune Thyroiditis	Related	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
Gastrointestinal Disorders	Related	-	2 (8.0) 5	2 (9.1) 5	-	2 (8.0) 5	2 (7.1) 5
	Not Related	2 (66.7) 3	5 (20.0) 10	5 (22.7) 10	-	7 (28.0) 13	7 (25.0) 13
Nausea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	3 (12.0) 4	3 (13.6) 4	-	4 (16.0) 5	4 (14.3) 5
Diarrhoea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 2	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 3	2 (7.1) 3
Oral Dysaesthesia	Related	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Gastrooesophageal Reflux Disease	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Avelumab Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
General Disorders and Administration Site Conditions	Related	2 (66.7) 8	8 (32.0) 13	7 (31.8) 12	1 (33.3) 1	9 (36.0) 20	10 (35.7) 21
	Not Related	2 (66.7) 2	7 (28.0) 11	6 (27.3) 10	1 (33.3) 1	8 (32.0) 12	9 (32.1) 13
Fatigue	Related	-	8 (32.0) 9	7 (31.8) 8	1 (33.3) 1	7 (28.0) 8	8 (28.6) 9
	Not Related	1 (33.3) 1	6 (24.0) 9	5 (22.7) 8	1 (33.3) 1	6 (24.0) 9	7 (25.0) 10
Influenza Like Illness	Related	2 (66.7) 7	2 (8.0) 4	2 (9.1) 4	-	4 (16.0) 11	4 (14.3) 11
Malaise	Related	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Infections and Infestations	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Urinary Tract Infection	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Investigations	Related	-	6 (24.0) 11	5 (22.7) 10	1 (33.3) 1	5 (20.0) 10	6 (21.4) 11
	Not Related	1 (33.3) 3	19 (76.0) 102	16 (72.7) 82	3 (100) 20	17 (68.0) 85	20 (71.4) 105
Lymphocyte Count Decreased	Related	-	3 (12.0) 8	3 (13.6) 8	-	3 (12.0) 8	3 (10.7) 8
	Not Related	-	15 (60.0) 38	12 (54.5) 32	3 (100) 6	12 (48.0) 32	15 (53.6) 38
White Blood Cell Count Decreased	Related	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
	Not Related	-	8 (32.0) 19	6 (27.3) 13	2 (66.7) 6	6 (24.0) 13	8 (28.6) 19
Blood Creatine Phosphokinase Increased	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 3	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 4	2 (7.1) 4
Lymphocyte Count Increased	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Metabolism and Nutrition Disorders	Related	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
	Not Related	1 (33.3) 1	3 (12.0) 7	3 (13.6) 7	-	4 (16.0) 8	4 (14.3) 8

System Organ Class **Preferred Term**	**Avelumab Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Hypertriglyceridaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
Hyponatraemia	Related	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
	Not Related	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
Musculoskeletal and Connective Tissue Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 1	3 (12.0) 3	3 (13.6) 3	-	4 (16.0) 4	4 (14.3) 4
Rheumatoid Arthritis	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Nervous System Disorders	Related	1 (33.3) 1	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 3	3 (10.7) 3
	Not Related	2 (66.7) 8	13 (52.0) 27	12 (54.5) 25	1 (33.3) 2	14 (56.0) 33	15 (53.6) 35
Headache	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Dizziness	Related	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Seizure	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Skin and Subcutaneous Tissue Disorders	Related	1 (33.3) 2	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 3	2 (7.1) 3
	Not Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Pruritus	Related	1 (33.3) 2	-	-	-	1 (4.0) 2	1 (3.6) 2
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Rash	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Vascular Disorders	Related	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Avelumab Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Hypertension	Related	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

Source: Table 14.3.1.3.4

Note: Percentages are based on the number (N) of patients in the SAF. Only SOCs with related events are included in this table and only PTs with related events are listed.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.2.3.4 Adverse Events Related to Target Disease

A summary of TEAEs by target disease relationship is provided in Table 14.3.1.3.5. Treatment-emergent AEs related to the target disease occurred in the majority of patients (21 of 28 [75.0%]) (Table 12-7). The following events that were considered related to the target disease occurred in 3 or more patients (≥ 10%): fatigue in 6 patients (21.4%), nausea in 5 patients (17.9%), vomiting in 3 patients (10.7%), and lymphocyte count decreased in 3 patients (10.7%). In the SOC nervous system disorders, approximately half of the patients (15 [53.6%]) experienced TEAEs considered related to the target disease, corresponding to the majority of events (33 of 38 events [86.8%]). Target disease-related nervous system disorders occurring in 3 or more patients (≥ 10%) included hemiparesis in 6 patients (21.4%), aphasia in 4 patients (14.3%), brain oedema in 4 patients (14.3%), and fine motor skill dysfunction in 3 patients (10.7%). The occurrence of TEAEs related to the target disease was similar between groups.

Table 12-7: Treatment-Emergent Adverse Events by Target Disease Relationship (SAF)

System Organ Class **Preferred Term**	**Target Disease Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Adverse Event	Related	3 (100) 12	18 (72.0) 65	15 (68.2) 59	3 (100) 6	18 (72.0) 71	21 (75.0) 77
	Not Related	3 (100) 18	24 (96.0) 161	21 (95.5) 139	3 (100) 22	24 (96.0) 157	27 (96.4) 179
Blood and Lymphatic System Disorders	Related	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
Lymphopenia	Related	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Anaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Gastrointestinal Disorders	Related	1 (33.3) 1	5 (20.0) 10	5 (22.7) 10	-	6 (24.0) 11	6 (21.4) 11
	Not Related	1 (33.3) 2	3 (12.0) 5	3 (13.6) 5	-	4 (16.0) 7	4 (14.3) 7
Nausea	Related	1 (33.3) 1	4 (16.0) 5	4 (18.2) 5	-	5 (20.0) 6	5 (17.9) 6
Vomiting	Related	-	3 (12.0) 4	3 (13.6) 4	-	3 (12.0) 4	3 (10.7) 4
Diarrhoea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	1 (33.3) 2	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 3	2 (7.1) 3
General Disorders and Administration Site Conditions	Related	1 (33.3) 2	7 (28.0) 8	6 (27.3) 7	1 (33.3) 1	7 (28.0) 9	8 (28.6) 10
	Not Related	2 (66.7) 8	9 (36.0) 16	8 (36.4) 15	1 (33.3) 1	10 (40.0) 23	11 (39.3) 24
Fatigue	Related	-	6 (24.0) 7	5 (22.7) 6	1 (33.3) 1	5 (20.0) 6	6 (21.4) 7
	Not Related	1 (33.3) 1	8 (32.0) 11	7 (31.8) 10	1 (33.3) 1	8 (32.0) 11	9 (32.1) 12
Gait Disturbance	Related	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Malaise	Related	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Target Disease Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Investigations	Related	-	5 (20.0) 7	3 (13.6) 5	2 (66.7) 2	3 (12.0) 5	5 (17.9) 7
	Not Related	1 (33.3) 3	20 (80.0) 106	17 (77.3) 87	3 (100) 19	18 (72.0) 90	21 (75.0) 109
Lymphocyte Count Decreased	Related	-	3 (12.0) 5	3 (13.6) 5	-	3 (12.0) 5	3 (10.7) 5
	Not Related	-	16 (64.0) 41	13 (59.1) 35	3 (100) 6	13 (52.0) 35	16 (57.1) 41
White Blood Cell Count Decreased	Related	-	2 (8.0) 2	-	2 (66.7) 2	-	2 (7.1) 2
	Not Related	-	8 (32.0) 18	6 (27.3) 13	2 (66.7) 5	6 (24.0) 13	8 (28.6) 18
Metabolism and Nutrition Disorders	Related	-	1 (4.0) 5	1 (4.5) 5	-	1 (4.0) 5	1 (3.6) 5
	Not Related	1 (33.3) 1	3 (12.0) 5	3 (13.6) 5	-	4 (16.0) 6	4 (14.3) 6
Hyponatraemia	Related	-	1 (4.0) 5	1 (4.5) 5	-	1 (4.0) 5	1 (3.6) 5
Musculoskeletal and Connective Tissue Disorders	Related	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4
Trigger Finger	Related	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Nervous System Disorders	Related	2 (66.7) 8	13 (52.0) 25	12 (54.5) 23	1 (33.3) 2	14 (56.0) 31	15 (53.6) 33
	Not Related	1 (33.3) 1	4 (16.0) 4	4 (18.2) 4	-	5 (20.0) 5	5 (17.9) 5
Hemiparesis	Related	2 (66.7) 2	4 (16.0) 4	3 (13.6) 3	1 (33.3) 1	5 (20.0) 5	6 (21.4) 6
Aphasia	Related	1 (33.3) 1	3 (12.0) 3	3 (13.6) 3	-	4 (16.0) 4	4 (14.3) 4
Brain Oedema	Related	2 (66.7) 2	2 (8.0) 2	2 (9.1) 2	-	4 (16.0) 4	4 (14.3) 4
Fine Motor Skill Dysfunction	Related	1 (33.3) 1	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	2 (8.0) 2	3 (10.7) 3
Cognitive Disorder	Related	1 (33.3) 2	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 3	2 (7.1) 3

System Organ Class **Preferred Term**	**Target Disease Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Headache	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Hypoaesthesia	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Ataxia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Cerebrovascular Accident	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Dysarthria	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Dysdiadochokinesis	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Epilepsy	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Facial Paralysis	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Paresis	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Seizure	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Status Epilepticus	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Psychiatric Disorders	Related	-	5 (20.0) 6	4 (18.2) 5	1 (33.3) 1	4 (16.0) 5	5 (17.9) 6
	Not Related	-	2 (8.0) 7	2 (9.1) 7	-	2 (8.0) 7	2 (7.1) 7
Insomnia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 4	1 (4.5) 4	-	1 (4.0) 4	1 (3.6) 4
Confusional State	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Depression	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Persistent Depressive Disorder	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Target Disease Relationship**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Personality Change	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Psychomotor Retardation	Related	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
Respiratory, Thoracic and Mediastinal Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Not Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Pulmonary Embolism	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

Source: Table 14.3.1.3.5

Note: Percentages are based on the number (N) of patients in the SAF. Only SOCs with related events are included in this table and only PTs with related events are listed.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.2.4 Listing of Adverse Events by Patient

Details on the AEs by patient are provided in the following listings:

Listing 16.2.7.1 Adverse Events

Listing 16.2.7.2 Adverse Events Leading to Discontinuation

Listing 16.2.7.3 Adverse Events of Grade 3 or 4

Listing 16.2.7.4 Adverse Events Leading to Death

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listings of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

12.3.1.1 Deaths

A listing of deaths is provided in Table 14.3.2.1. All 24 patients who died in the study, died of target disease progression.

12.3.1.2 Other Serious Adverse Events

The SAEs are summarized in Table 12-8 and the complete listing is provided in Table 14.3.2.2. The investigator did not consider any of the SAEs to be related to IMP treatment (VXM01 vaccine or avelumab). The majority of SAEs (9 of 11 [81.8%]) was considered related to the target disease and approximately half (5 of 11 [45.5%]) belonged to the SOC nervous system disorders. The IMP dose remained unchanged for all recorded SAEs and all events resolved, with or without sequelae.

12.3.1.3 Other Significant Adverse Events

Other significant AEs are summarized in Table 12-9 and the complete listing is provided in Table 14.3.2.3.

Table 12-8: Listing of Serious Adverse Events

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-05	Brain oedema	4	3	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-19	Epilepsy	6	3	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-26	Status epilepticus	10	3	VXM01: Not related Avelumab: Not related	Probably related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
01-28	Gait disturbance	2	3	VXM01: Not related Avelumab: Not related	Probably related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Pulmonary embolism	8	4	VXM01: Not related Avelumab: Not related	Probably related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
02-29	Hyponatraemia	2	3	VXM01: Unlikely related Avelumab: Unlikely related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Hyponatraemia	5	3	VXM01: Unlikely related Avelumab: Unlikely related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Hyponatraemia	4	3	VXM01: Unlikely related Avelumab: Unlikely related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
02-30	Cerebrovascular accident	12	3	VXM01: Unlikely related Avelumab: Unlikely related	Probably related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
22-10	Headache	3	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Insomnia	5	3	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved

Source: Table 14.3.2.2

IMP = investigational medicinal product

Table 12-9: Listing of Other Significant Adverse Events

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-01	Influenza like illness	4	2	VXM01: Not related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Nausea	20	2	VXM01: Unlikely related Avelumab: Unlikely related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Malaise	9	2	VXM01: Not related Avelumab: Possibly related	Definitely related	VXM01: Drug interrupted Avelumab: Drug interrupted	Resolved
	Cognitive disorder	8	2	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Drug interrupted Avelumab: Drug interrupted	Resolved
	Brain oedema	8	3	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Drug interrupted Avelumab: Drug interrupted	Resolved
	Fine motor skill dysfunction	8	2	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Drug interrupted Avelumab: Drug interrupted	Resolved
	Gait disturbance	8	1	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Drug interrupted Avelumab: Drug interrupted	Resolved
	Hemiparesis	8	2	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Drug interrupted Avelumab: Drug interrupted	Resolved
01-03	Brain oedema	118	2	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolving
	Hemiparesis	94	2	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-05	Lymphocyte count decreased	1	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	28	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	14	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Syncope[a]	1	3	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Nausea	120	2	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-05	Vomiting	120	2	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-07	Lymphocyte count decreased	19	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	36	1	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	23	2	VXM01: Not related Avelumab: Not related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Blood creatine phosphokinase increased	11	1	VXM01: Not related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	225	2	VXM01: Unlikely related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Hypothyroidism	176	2	VXM01: Not related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-09	Lymphocyte count decreased	4	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Alanine aminotransferase increased	7	2	VXM01: Unlikely related Avelumab: Unlikely related	Not related	VXM01: Dose not changed Avelumab: Dose reduced	Resolved
	Blood alkaline phosphatase increased	15	2	VXM01: Unlikely related Avelumab: Unlikely related	Not related	VXM01: Dose not changed Avelumab: Dose reduced	Resolved with sequelae
	Gamma-glutamyltransferase increased	14	3	VXM01: Unlikely related Avelumab: Unlikely related	Not related	VXM01: Dose not changed Avelumab: Dose reduced	Resolved with sequelae
01-12	Adrenal insufficiency	340	1	VXM01: Not related Avelumab: Not related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Facial paralysis	301	1	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Brain oedema	294	2	VXM01: Unlikely related Avelumab: Unlikely related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-13	Influenza like illness	2	1	VXM01: Possibly related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-13	Hypertension	15	3	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Drug interrupted	Resolved
	Platelet count decreased	6	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Drug interrupted	Resolved
	Blood potassium increased	15	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Rash	29	1	VXM01: Unlikely related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-14	Blood potassium decreased	2	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Blood potassium decreased	15	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Autoimmune thyroiditis	-	2	VXM01: Not related Avelumab: Probably related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Hypothyroidism	-	2	VXM01: Not related Avelumab: Probably related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Blood potassium decreased	15	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	15	1	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-17	Lymphocyte count decreased	41	1	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Fine motor skill dysfunction	487	1	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Hemiparesis	487	1	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Lymphocyte count decreased	28	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	45	1	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	387	2	VXM01: Unlikely related Avelumab: Unlikely related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	No resolved

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-18	Lymphocyte count decreased	27	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	13	1	VXM01: Not related Avelumab: Not related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-19	Lymphocyte count decreased	2	1	VXM01: Not related Avelumab: Not related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Blood sodium decreased	22	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	2	3	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	5	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	2	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	31	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	14	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Dysdiadochokinesis	153	1	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-20	Lymphocyte count decreased	5	3	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	14	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	8	3	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	15	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	13	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-25	Lymphocyte count decreased	6	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-25	Lymphocyte count decreased	65	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
01-26	Influenza like illness	2	1	VXM01: Not related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	3	3	VXM01: Unlikely related Avelumab: Unlikely related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	8	2	VXM01: Possibly related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Persistent depressive disorder	382	1	VXM01: Not related Avelumab: Not related	Probably related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Blood potassium decreased	3	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Epilepsy	373	1	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Lymphocyte count decreased	7	1	VXM01: Possibly related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Rheumatoid arthritis	346	3	VXM01: Not related Avelumab: Probably related	Not related	VXM01: Dose not changed Avelumab: Drug withdrawn	Not resolved
	Lymphocyte count decreased	318	1	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-27	Lymphocyte count decreased	3	4	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	6	3	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count decreased	1	1	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	113	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	Lymphocyte count decreased	14	3	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-27	Lymphocyte count decreased	-	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-28	Depression	230	1	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Insomnia	230	1	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Lymphocyte count increased	17	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Lymphocyte count increased	157	1	VXM01: Not related Avelumab: Not related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
01-31	Lymphocyte count increased	3	2	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
02-15	Headache	118	1	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Nausea	118	2	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Personality change	7	3	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Vomiting	118	2	VXM01: Not related Avelumab: Not related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
02-16	Headache	108	1	VXM01: Possibly related Avelumab: Possibly related	Probably related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Nausea	3	2	VXM01: Possibly related Avelumab: Possibly related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Urinary tract infection	34	2	VXM01: Probably related Avelumab: Probably related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolving
02-24	Gastrooesophageal reflux disease	67	2	VXM01: Possibly related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Diarrhoea	2	1	VXM01: Possibly related Avelumab: Possibly related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
02-29	Hyponatraemia	19	1	VXM01: Unlikely related Avelumab: Possibly related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
22-10	Insomnia	31	2	VXM01: Unlikely related Avelumab: Unlikely related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Hypertension	10	3	VXM01: Probably related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Anxiety	559	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Hypertension	26	2	VXM01: Probably related Avelumab: Possibly related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Confusional state	~34	3	VXM01: Not related Avelumab: Not related	Possibly related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
	Depression	545	3	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Insomnia	29	3	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Hypertension	533	3	VXM01: Probably related Avelumab: Possibly related	Not related	VXM01: Drug interrupted Avelumab: Not related	Not resolved
	Back pain	524	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved
	Insomnia	511	1	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Not resolved

Source: Table 14.3.2.3

IMP = investigational medicinal product

a Other action taken: application infusion

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

Narratives for individual patients can be found in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study were due to progressive disease. None of the SAEs were considered to be related to IMP treatment (VXM01 vaccine or avelumab) and the majority of SAEs were considered related to the target disease. All SAEs resolved, with or without sequelae and without IMP dose adjustment. Other significant adverse events were defined as all non-serious and/or non-fatal AEs for which either action was taken with regard to the IMP or for which concomitant medication was administered.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Patient

The following listings of laboratory measurements are presented in Appendix 16.2.8:

Listing 16.2.8.1.1	Clinical Chemistry
Listing 16.2.8.1.2	Hematology
Listing 16.2.8.1.3	Coagulation
Listing 16.2.8.1.4	Urinalysis
Listing 16.2.8.1.5	Serology
Listing 16.2.8.1.6	Pregnancy
Listing 16.2.8.2.1	Hormones
Listing 16.2.8.3.1	Clinically Significant Abnormalities
Listing 16.2.8.3.2	Comments

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Hematology

Actual and change from baseline values for hematology are provided in Table 14.3.4.2.1. Cross-tabulations of the worst-case abnormalities post-baseline and by CTCAE grades are provided in Table 14.3.4.2.2 and Table 14.3.4.2.3, respectively. Details on the coagulation laboratory results are provided in Table 14.3.4.3.1, Table 14.3.4.3.2, and Table 14.3.4.3.3.

The majority of patients overall (20 [71.4%]) had WBC counts within the normal range at baseline. Of those patients, 8 patients had a worst post-baseline category of Grade 1. Six patients (21.4%) had a decreased WBC count of Grade 1 at baseline. Of those patients, 4 patients declined to a worst post-baseline category of Grade 2. Two patients (7.1%) had a decreased WBC count of Grade 2 at baseline. Of those patients, one patient declined to a worst post-baseline category of Grade 3. In total, 7 patients (25.0%) reported 17 Grade 1 AEs and 2 patients (7.1%) reported 3 Grade 2 AEs of decreased WBC count (Table 12-10).

Overall, the majority of patients (23 [82.1%]) had a platelet count within the normal range at baseline. From that group, 10 patients declined to a worst post-baseline category of Grade 1 and 1 patient declined to Grade 2. Five patients (17.9%) had a decreased platelet count of Grade 1 at baseline. Of those patients, only 1 patient declined to a worst post-baseline category of Grade 3. One patient (3.6%) reported one Grade 2 and one Grade 3 AE, while another patient reported one Grade 2 AE of decreased platelet count (Table 12-10).

The majority of patients overall (20 [71.4%]) had RBC counts in the normal range at baseline. From those patients, approximately half (8 patients) declined to a worst post-baseline category of Grade 1 anemia. Eight patients (28.6%) started off with Grade 1 anemia at baseline. Of those patients, one declined to a worst post-baseline category of Grade 2 anemia which was reported as AE (Table 12-10).

Overall, 39.3% of patients had a lymphocyte count in the normal range at baseline. Of those, the worst post-baseline category was Grade 1 for 5 patients, Grade 2 for 4 patients, Grade 3 for 1 patient, and Grade 4 for 1 patient. Nine patients (32.1%) had a Grade 1 decreased lymphocyte count at baseline. Of those, the worst post-baseline category was Grade 2 for 5 patients and Grade 3 for 4 patients. Seven patients (25.0%) had a Grade 2 decreased lymphocyte count at baseline. Of those, the worst post-baseline category was Grade 2 for 4 patients and Grade 3 for 3 patients. One patient (3.6%) had a Grade 3 decreased lymphocyte count at baseline and declined to a worst post-baseline category of Grade 4 (Table 14.3.4.2.3). Decreased lymphocyte count was reported as AE in a total of 16 patients with 46 events with severity ranging from Grade 1 to Grade 3 (Table 12-10). Lymphopenia was reported as Grade 3 AE in one patient with 2 events.

All reported hematology AEs are presented by severity and by cohort in Table 12-10. No abnormal laboratory values were reported for PTs of Haemoglobin decreased and Lymphocyte count increased. For PTs of Eosinophilia, Haemoglobin increased, Leukocytosis, Neutrophil count decreased, Activated PTT prolonged, and INR increased, the majority of patients had a baseline value in the normal range and all patients had a worst post-baseline category of Grade 2 (mild) or lower, with no AEs reported. All of the reported hematology AEs occurred in the 10^7 CFU/mL group.

Table 12-10: Hematology Reported Adverse Events (SAF)

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Blood and lymphatic system disorders							
Anemia	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Eosinophilia	-	-	-	-	-	-	-
Lymphopenia	Grade 3	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Investigations							
Haemoglobin increased	-	-	-	-	-	-	-
Haemoglobin decreased	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Lymphocyte count decreased	Grade 1	-	14 (56.0) 19	12 (54.5) 16	2 (66.7) 3	12 (48.0) 16	14 (50.0) 19
	Grade 2	-	12 (48.0) 22	10 (45.5) 19	2 (66.7) 3	10 (40.0) 19	12 (42.9) 22
	Grade 3	-	4 (16.0) 5	4 (18.2) 5	-	4 (16.0) 5	4 (14.3) 5
Lymphocyte count increased	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Grade 2	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Leukocytosis	-	-	-	-	-	-	-
Neutrophil count decreased	-	-	-	-	-	-	-
Platelet count decreased	Grade 2	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
White blood cell count decreased	Grade 1	-	7 (28.0) 17	5 (22.7) 10	2 (66.7) 7	5 (20.0) 10	7 (25.0) 17
	Grade 2	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
Activated partial thromboplastin time prolonged	-	-	-	-	-	-	-
INR increased	-	-	-	-	-	-	-

Source: Table 14.3.1.3.2, Table 14.3.4.2.3. Note: a hyphen (-) indicates no events were reported.

CFU = colony forming unit; E = number of events; INR = international normalized ratio; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.4.2.2 Chemistry

The actual and change from baseline values for the investigated clinical chemistry parameters are provided in Table 14.3.4.1.1, with cross-tabulations of the worst-case abnormalities in Table 14.3.4.1.2 and worst-case CTCAE grades in Table 14.3.4.1.3. In addition, actual and change from baseline values and cross-tabulations for the investigated hormones (thyrotropin and thyroxine) are provided in Table 14.3.4.5.1, Table 14.3.4.5.2 and Table 14.3.4.5.3.

There were only mild to moderate changes in lactate dehydrogenase, cholesterol, calcium, chloride, glucose, sodium, urate, and urea. Only mild to moderate changes were noted with regard to chronic kidney disease. No AEs were reported for these parameters.

There were only mild to moderate changes in ALT, alkaline phosphatase, amylase, AST, bilirubin, creatinine, potassium, triglycerides, lipase, and TSH. The reported AEs are presented by severity in Table 12-11.

For gamma-glutamyltransferase increased and hyponatremia, the worst post-baseline category was Grade 3 (severe) and reported AEs are presented in Table 12-11. For blood creatine phosphokinase increased, the worst post-baseline category was Grade 2 in Table 14.3.4.1.3, however, the reported AEs were Grade 1, 2, and 3.

A number of mild and moderate AEs were reported for PTs of blood potassium decreased, blood potassium increased, gamma-glutamyltransferase decreased, and ALT decreased (Table 12-11). For blood potassium decreased and increased, the laboratory values are provided in Table 14.3.4.1.2, however, the post-baseline category by CTCAE grade was not included in Table 14.3.4.1.3. No laboratory values below the normal range were reported for gamma-glutamyltransferase and ALT in Table 14.3.4.1.2.

The majority of AEs occurred in the 10^7 CFU/mL group, with only blood creatine phosphokinase increased reported for both groups. Additionally, the majority of AEs occurred in 3 or fewer patients, except for lipase increased (occurred in 5 patients), ALT increased (occurred in 4 patients), and blood potassium decreased (occurred in 4 patients).

Table 12-11: Chemistry Reported Adverse Events (SAF)

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Investigations							
Blood potassium decreased	Grade 1	-	4 (16.0) 5	2 (9.1) 2	2 (66.7) 3	2 (8.0) 2	4 (14.3) 5
	Grade 2	-	1 (4.0) 1	-	1 (33.3) 1	3 (12.0) 4	4 (14.3) 5
Lipase increased	Grade 1	-	4 (16.0) 5	3 (13.6) 4	1 (33.3) 1	2 (8.0) 3	3 (10.7) 4
	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Alanine aminotransferase increased	Grade 1	-	3 (12.0) 4	2 (9.1) 3	1 (33.3) 1	2 (8.0) 3	3 (10.7) 4
	Grade 2	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Gamma-glutamyltransferase increased	Grade 1	-	3 (12.0) 4	3 (13.6) 4	-	3 (12.0) 4	3 (10.7) 4
	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Blood creatine phosphokinase increased	Grade 1	1 (33.3) 1	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 3	3 (10.7) 3
	Grade 2	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
	Grade 3	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Blood potassium increased	Grade 1	-	2 (8.0) 3	1 (4.5) 2	1 (33.3) 1	1 (4.0) 2	2 (7.1) 3
Amylase increased	Grade 1	-	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	1 (4.0) 1	2 (7.1) 2
Aspartate aminotransferase increased	Grade 1	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Gamma-glutamyltransferase decreased	Grade 1	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Alanine aminotransferase decreased	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 2	1 (3.6) 2
Blood alkaline phosphatase increased	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Blood bilirubin increased	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Blood creatinine increased	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Blood thyroid stimulating hormone increased	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Metabolism and nutrition disorders							
Hypertriglyceridaemia	Grade 1	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Hyponatraemia	Grade 1	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
	Grade 3	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3
Hypokalaemia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

Source: Table 14.3.1.3.2, Table 14.3.4.1.3

Note: a hyphen (-) indicates no events were reported.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.4.2.3 Urinalysis

Cross-tabulations of all worst-case abnormalities found by urinalysis are provided in Table 14.3.4.4.1 for the following parameters: bacteria, bilirubin in urine, crystals, epithelial cells, erythrocytes in urine, glucose in urine, ketones, leukocyte esterase, leukocytes in urine, nitrite, occult blood, protein in urine, urobilinogen, and pH.

In general, the urinalysis data included no clinically meaningful laboratory abnormalities except for one patient (02-16) in the 10^7 CFU/mL NR group who experienced a urine tract infection, which was reported as AE probably related to VXM01 and avelumab treatment.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Physical Examination

A cross-tabulation of the worst-case abnormalities reported based on physical examination is provided in Table 14.3.5.2.1 and all AEs reported based on physical examination findings are summarized in Table 12-12.

The majority of physical examination findings were NCS, or AEs of mild or moderate severity. There was 1 patient (01-12) in the 10^7 CFU/mL NR group with a CS abnormal finding (inguinal hernia right) that was not reported as AE. In addition, there were 6 CS findings of abnormalities of the neurological system which were not reported as AEs, for 1 patient in the 10^6 CFU/mL group (1 event) and for 3 patients in the 10^7 CFU/mL NR group (5 events). The majority of CS abnormalities were reported for the neurological system, with 22 of 25 reported events related to the target disease. Of all physical examination findings, 1 event of personality change was reported as Grade 3 (severe) AE. Due to 1 event of cognitive disorder (Grade 2, 10^6 CFU/mL group), VXM01 and avelumab administrations were interrupted. Overall, the majority of AEs (31 of 36 events [86.1%]) were reported for the 10^7 CFU/mL group.

Table 12-12: Physical Examinations Reported Adverse Events (SAF)

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Gastrointestinal disorders							
Nausea	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Mouth ulceration	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Oral dysesthesia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
General disorders and administration site conditions							
Fatigue	Grade 1	-	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	1 (4.0) 1	2 (7.1) 2
Infections and infestations							
Urinary tract infection	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Nervous system disorders							
Hemiparesis	Grade 1	-	4 (16.0) 4	3 (13.6) 3	1 (33.3) 1	3 (12.0) 3	4 (14.3) 4
	Grade 2	2 (66.7) 2	-	-	-	2 (8.0) 2	2 (7.1) 2
Aphasia	Grade 2	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
Fine motor skill dysfunction	Grade 1	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Headache	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Cognitive disorder	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Grade 2	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Ataxia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Dysarthria	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Dysdiadochokinesis	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Dysgeusia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Facial paralysis	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

System Organ Class **Preferred Term**	**Toxicity Grade**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
			All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Hypoaesthesia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Grade 2	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Paraesthesia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Paresis	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Psychiatric disorders							
Persistent depressive disorder	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Personality change	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Psychomotor retardation	Grade 1	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
Respiratory, thoracic and mediastinal disorders							
Cough	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Skin and subcutaneous tissue disorders							
Pruritus	Grade 1	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
	Grade 2	1 (33.3) 1	-	-	-	1 (4.0) 1	1 (3.6) 1
Rash	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1

Source: Table 14.3.5.2.1, Listing 16.2.7.1, Listing 16.2.9.2.1

Note: only AEs reported based on physical examination findings are included in this table. A hyphen (-) indicates no events were reported.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.5.2 Vital Signs

A summary of the recorded vital signs (actual and change from baseline) is provided in Table 14.3.5.1.1, with cross-tabulations of the worst-case abnormalities, by CTCAE grades, and interpretations in Table 14.3.5.1.2, Table 14.3.5.1.3, and Table 14.3.5.1.4, respectively. The investigated parameters included weight, systolic blood pressure, diastolic blood pressure, pulse rate, and temperature.

In general, changes from baseline were small and not clinically meaningful. One patient (01-13) in the 10^7 CFU/mL NR group experienced hypertension, which was reported as AE not related to study treatment. Avelumab administration was interrupted due to the event. One patient (22-10) in the 10^7 CFU/mL NR group experienced hypertension, which was reported as AE on three occasions, all probably related to VXM01 and possibly related to avelumab treatment. VXM01 administration was interrupted once because of the third reported AE. The event of hypertension was not resolved at the time of database lock, as described further in the narrative of Patient 22-10 (Section 14.3.3).

12.5.3 Electrocardiograms

Results from the ECGs (actual and change from baseline) are summarized in Table 14.3.5.3.1, with cross-tabulations of the worst-case abnormalities in Table 14.3.5.3.2 and interpretations in Table 14.3.5.3.3. All changes from baseline were small and not clinically meaningful. No ECG abnormalities were reported as AEs.

12.5.4 Concomitant Medications and Procedures

A summary of concomitant medications reported for ≥ 10% of patients is provided in Table 12-13 and a summary of all concomitant medications is provided in Table 14.1.3.7. All patients received paracetamol during the study and the majority of patients received aminoalkyl ethers (clemastine fumarate and/or clemastine) (27 patients [96.4%]). Approximately half of the patients received pentamidine (13 patients [46.4%]), which was introduced as prophylaxis for pneumonia instead of antibiotics treatment with co-trimoxazol. The number of any concomitant medications (events) reported was comparable between the groups. Finally, none of the patients in the 10^6 CFU/mL group received concomitant medications in the following SOCs, where 3 or more patients (≥ 10%) in the 10^7 CFU/mL group did receive concomitant medications: other antiepileptics, nitrosoureas, thyroid hormones, dihydropyridine derivatives, plain ace inhibitors, combinations of sulfonamides and trimethoprim (including derivatives), and podophyllotoxin derivatives.

An overview of all concomitant procedures is presented in Table 12-14. Overall, approximately half of the patients (15 [53.6%]) underwent any concomitant procedures, including investigations and surgical procedures. The number of procedures and proportion of patients undergoing procedures were similar between the groups.

The prior and concomitant medications and procedures for individual patients are provided in Listing 16.2.4.6 and Listing 16.2.4.7, respectively.

Table 12-13: Concomitant Medications (SAF)

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Any Medication	3 (100) 110	25 (100) 628	22 (100) 503	3 (100) 125	25 (100) 613	28 (100) 738
Anilides	3 (100) 39	25 (100) 235	22 (100) 180	3 (100) 55	25 (100) 219	28 (100) 274
Paracetamol	3 (100) 39	25 (100) 235	22 (100) 180	3 (100) 55	25 (100) 219	28 (100) 274
Aminoalkyl Ethers	3 (100) 39	24 (96.0) 219	21 (95.5) 164	3 (100) 55	24 (96.0) 203	27 (96.4) 258
Clemastine Fumarate	3 (100) 39	19 (76.0) 181	16 (72.7) 126	3 (100) 55	19 (76.0) 165	22 (78.6) 220
Clemastine	-	6 (24.0) 38	6 (27.3) 38	-	6 (24.0) 38	6 (21.4) 38
Other Agents Against Leishmaniasis and Trypanosomiasis	1 (33.3) 1	12 (48.0) 13	9 (40.9) 10	3 (100) 3	10 (40.0) 11	13 (46.4) 14
Pentamidine	1 (33.3) 1	12 (48.0) 13	9 (40.9) 10	3 (100) 3	10 (40.0) 11	13 (46.4) 14
Glucocorticoids	2 (66.7) 9	9 (36.0) 23	8 (36.4) 22	1 (33.3) 1	10 (40.0) 31	11 (39.3) 32
Dexamethasone	2 (66.7) 9	7 (28.0) 19	6 (27.3) 18	1 (33.3) 1	8 (32.0) 27	9 (32.1) 28
Proton Pump Inhibitors	2 (66.7) 3	6 (24.0) 8	5 (22.7) 7	1 (33.3) 1	7 (28.0) 10	8 (28.6) 11
Pantoprazole	2 (66.7) 3	5 (20.0) 5	4 (18.2) 4	1 (33.3) 1	6 (24.0) 7	7 (25.0) 8
Other Antiepileptics	-	6 (24.0) 22	5 (22.7) 18	1 (33.3) 4	5 (20.0) 18	6 (21.4) 22
Levetiracetam	-	3 (12.0) 8	3 (13.6) 8	-	3 (12.0) 8	3 (10.7) 8
Lamotrigine	-	3 (12.0) 6	2 (9.1) 2	1 (33.3) 4	2 (8.0) 2	3 (10.7) 6
Lacosamide	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Nitrosoureas	-	5 (20.0) 5	4 (18.2) 4	1 (33.3) 1	4 (16.0) 4	5 (17.9) 5
Lomustine	-	5 (20.0) 5	4 (18.2) 4	1 (33.3) 1	4 (16.0) 4	5 (17.9) 5
Benzodiazepine Derivatives	1 (33.3) 1	3 (12.0) 10	3 (13.6) 10	-	4 (16.0) 11	4 (14.3) 11
Clobazam	-	3 (12.0) 8	3 (13.6) 8	-	3 (12.0) 8	3 (10.7) 8
Thyroid Hormones	-	4 (16.0) 11	3 (13.6) 9	1 (33.3) 2	3 (12.0) 9	4 (14.3) 11
Levothyroxine	-	4 (16.0) 11	3 (13.6) 9	1 (33.3) 2	3 (12.0) 9	4 (14.3) 11
Dihydropyridine Derivatives	-	4 (16.0) 8	4 (18.2) 8	-	4 (16.0) 8	4 (14.3) 8

System Organ Class **Preferred Term**	**10^6 CFU/mL (N = 3) n (%) E**	**10^7 CFU/mL**			**Total NR[a] (N = 25) n (%) E**	**Total (N = 28) n (%) E**
		All Patients (N = 25) n (%) E	**NR (N = 22) n (%) E**	**R (N = 3) n (%) E**		
Amlodipine	-	3 (12.0) 6	3 (13.6) 6	-	3 (12.0) 6	3 (10.7) 6
Other Antidepressants	1 (33.3) 1	3 (12.0) 5	3 (13.6) 5	-	4 (16.0) 6	4 (14.3) 6
Mirtazapine	1 (33.3) 1	3 (12.0) 4	3 (13.6) 4	-	4 (16.0) 5	4 (14.3) 5
Ace Inhibitors, Plain	-	4 (16.0) 5	4 (18.2) 5	-	4 (16.0) 5	4 (14.3) 5
Ramipril	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Combinations of Sulfonamides and Trimethoprim, Incl. Derivatives	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4
Sulfamethoxazole;trimethoprim	-	4 (16.0) 4	4 (18.2) 4	-	4 (16.0) 4	4 (14.3) 4
Podophyllotoxin Derivatives	-	4 (16.0) 4	3 (13.6) 3	1 (33.3) 1	3 (12.0) 3	4 (14.3) 4
Etoposide	-	4 (16.0) 4	3 (13.6) 3	1 (33.3) 1	3 (12.0) 3	4 (14.3) 4

Source: Table 14.1.3.7

Note: Percentages are based on the number (N) of patients in the SAF. Only events occurring in ≥ 10% of patients (Total SAF) are presented. A hyphen (-) indicates no events were reported.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

Table 12-14: Concomitant Procedures (SAF)

System Organ Class **Preferred Term**	10^6 CFU/mL (N = 3) n (%) E	10^7 CFU/mL			Total NR[a] (N = 25) n (%) E	Total (N = 28) n (%) E
		All Patients (N = 25) n (%) E	NR (N = 22) n (%) E	R (N = 3) n (%) E		
Any Procedure	1 (33.3) 3	14 (56.0) 20	12 (54.5) 17	2 (66.7) 3	13 (52.0) 20	15 (53.6) 23
Investigations	1 (33.3) 1	10 (40.0) 15	10 (45.5) 15	-	11 (44.0) 16	11 (39.3) 16
Computerised Tomogram Head	1 (33.3) 1	5 (20.0) 6	5 (22.7) 6	-	6 (24.0) 7	6 (21.4) 7
Magnetic Resonance Imaging Head	-	3 (12.0) 3	3 (13.6) 3	-	3 (12.0) 3	3 (10.7) 3
Electroencephalogram	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Electrocardiogram	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Serology Test	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Troponin T	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Ultrasound Liver	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Surgical and Medical Procedures	1 (33.3) 2	4 (16.0) 5	2 (9.1) 2	2 (66.7) 3	3 (12.0) 4	5 (17.9) 7
Brain Tumour Operation	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Craniotomy	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Tumour Excision	-	2 (8.0) 2	-	2 (66.7) 2	-	2 (7.1) 2
Physiotherapy	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1

Source: Table 14.1.3.9

Note: Percentages are based on the number (N) of patients in the SAF. A hyphen (-) indicates no events were reported.

CFU = colony forming unit; E = number of events; n = number of patients with an event; N = total number of patients; NR = non-resectable; R = resectable; SAF = safety analysis set

a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

12.6 Safety Conclusions

12.6.1.1 Summary of Safety Results

- Overall, 277 AEs were reported for 28 patients and 11 SAEs in 7 patients.
- No TLTs related to VXM01 or avelumab, infusion-related AEs, or AEs leading to study discontinuation were recorded for any group. No SAEs and no treatment-emergent SAEs were recorded for the 10^6 CFU/mL and 10^7 CFU/mL R groups. No VXM01- or avelumab-related SAEs or treatment-emergent SAEs were recorded for any group. There was one AE reported as leading to discontinuation of the study treatment, which was recorded after the first 5 weeks of treatment and thus not reported as TLT. Four patients experienced a total of 5 irAEs.
- Overall, the most frequently reported TEAEs were a decreased lymphocyte count in 16 patients (57.1%, 46 events), fatigue in 14 patients (50.0%, 19 events), and decreased WBC count in 8 patients (28.6%, 20 events). The SOC with most reported TEAEs was investigations (21 patients [75.0%] with 116 events), followed by nervous system disorders (17 patients [60.7%] with 38 events), and general disorders and administration site conditions (15 patients [53.6%] with 34 events).
- The majority of TEAEs, 228 of 256 events (89.1%), were mild or moderate (Grade 1 or Grade 2). No TEAEs of Grade 5 (AEs leading to death) were reported.
- All TEAEs related to VXM01 occurred in the 10^7 CFU/mL group, in total 32 events in 12 patients. Treatment-emergent AEs related to avelumab occurred at both VXM01 vaccine dose levels, with 56 events in 16 patients. Of the 32 events considered related to VXM01 treatment, 29 events were also considered related to avelumab treatment. The 3 events considered only related to VXM01 treatment were diarrhea, myalgia, and pruritus. The majority of events were considered not related to VXM01 treatment (224 of 256 events [87.5%]) and none of the reported SAEs were considered related to study treatment.
- Treatment-emergent AEs related to the target disease (77 events [90.6%]) were reported for the majority of patients (21 of 28 [75.0%]).
- All 24 patients who died during the study, died of target disease progression. Three patients (01-14, 01-22, and 01-27) were alive and in the long-term follow-up phase at the time of database lock and 1 patient (01-04) completed the study (Figure 11-8).
- The majority of laboratory findings, including hematology, chemistry, and urinalysis, were in the normal range or of mild to moderate severity. For vital signs and ECGs, changes from baseline were small and not clinically meaningful. The majority of physical examination findings were NCS or of mild to moderate severity, with most findings reported for the neurological system related to the target disease.

12.6.1.2 Conclusions

- VXM01 treatment in combination with avelumab was generally safe and well-tolerated.
- The majority of safety events were of mild to moderate severity. Of the SAEs, 9 of 11 events (81.8%) were target disease-related and no SAEs were considered related to the study treatment.

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The VXM01-AVE-04-INT study was a Phase I/II, open-label, multicenter trial in 28 patients with progressive glioblastoma following standard treatment, to evaluate the treatment of VXM01 vaccine in combination with avelumab. In total, 3 patients received 10^6 CFU/mL VXM01 vaccine and 25 patients received 10^7 CFU/mL VXM01 vaccine, of whom 2 patients underwent tumor resection during the study.

The main objective of the study was to evaluate the safety and tolerability of VXM01 vaccine treatment in combination with avelumab. VXM01 had a favorable safety profile with the majority of reported events being mild to moderate severity. The majority of SAEs were target disease-related and all patients who died during the study, died of target disease progression. One patient discontinued the study due to disease progression and 3 patients were alive in the long-term follow-up phase at the time of database lock.

One event of rheumatoid arthritis led to discontinuation of the study treatment. This event was considered not related to VXM01 vaccine treatment or target disease, but probably related to avelumab treatment. Four patients experienced immune-related AEs, including hypothyroidism, autoimmune thyroiditis, fatigue, and the before mentioned rheumatoid arthritis.

A study on angiogenesis inhibitor bevacizumab in newly diagnosed glioblastoma patients reported a higher incidence of arterial thromboembolic events and cerebral hemorrhage in the bevacizumab-treated group compared with the placebo group (Saran et al. 2016). In the present study on VXM01 vaccine, the relationship of safety events to IMP treatment and target disease was assessed by the investigators. As such, events of pulmonary embolism and cerebrovascular accident were considered not or unlikely related to IMP treatment, and probably related to the target disease. To gain more insight into the potential relatedness of this type of events to VXM01 vaccine treatment in future clinical trials, an independent reviewer could be used to determine relatedness. In addition, a randomized blinded study design with a control group can provide results where the incidence of safety events can be compared between groups for more explicit conclusions.

The majority of laboratory findings, including hematology, chemistry, and urinalysis, were in the normal range or of mild to moderate severity. For vital signs and ECGs, changes from baseline were small and not clinically meaningful. The majority of physical examination findings were NCS or of mild to moderate severity, with most findings reported for the neurological system related to the target disease. The reported concomitant medications were typical for the target patient population.

The secondary objective of the study was to evaluate the efficacy of VXM01 vaccine in combination with avelumab by assessment of tumor response per iRANO criteria and by assessment of the clinical response. Overall, 3 non-resected patients had a partial remission corresponding to an ORR of 12.0% (95% CI: 2.5 – 31.2). One of the three patients undergoing tumor resection had stable disease without post-resection recurrence at the time of database lock.

The VXM01-AVE-04-INT study was an open-label study with focus on demonstrating the safety and tolerability of VXM01 vaccine treatment in combination with avelumab. Despite this design, the median PFS of 2.7 months (95% CI: 2.7 – 2.7), with a range of 0.3 to 22.1 months, and

median OS of 11.2 months (95% CI: 8.5 – 16.3), with a range of 2.2 to 38.2 months, are promising results in the context of prognosis for patients with recurrent malignant glioblastoma, which has been reported to have a median PFS of 1.5 to 6 months and median OS of 2 to 9 months (Birzu et al. 2020).

Finally, the effects of VXM01 vaccine in combination with avelumab were evaluated using immune- and biomarkers in peripheral blood samples from all patients and tumor tissue obtained during resection from the patients in the 10^7 CFU/mL R group. All patients tested negative for anti-LPS IgM at all visits and all patients but one tested negative for anti-LPS IgG at all visits, indicating that the desired immune response was not affected by anti-LPS positivity.

In total, 3 patients had a partial response during the study. For Patient 01-04 from the 10^6 CFU/mL group, PFS of 13.8 months was reported with a partial response in the target lesion. This patient had high levels of tumor-infiltrating CD8+ T cells and low levels of T_{regs} and MDSCs at baseline, together with an increase in the VEGFR-2 specific T cell response after IMP treatment. Together, these results support the contribution of VXM01 vaccine therapy to the partial response of the target lesion. Patient 01-09 (10^7 CFU/mL NR group) had a partial response of 11.1 months and PFS of 13.8 months. This patient started out with high levels of tumor-infiltrating CD8+ T cells, MDSCs, and PD-L1, and without T_{regs} at baseline. In addition, the VEGFR-2 specific T cell response was somewhat stable up to Week 34. Patient 22-10 (10^7 CFU/mL NR group) first had a partial response in Week 12 and subsequent progressive disease in Week 24. Similar to the other patients with partial remission, this patient had high levels of tumor-infiltrating CD8+ T cells and low levels of T_{regs} and MDSCs at baseline. In contrast, no positive VEGFR-2 specific T cell response was reported for Patient 22-10 at any timepoint.

Besides the patients described above, 3 patients had stable disease during the study. Patient 01-14 (10^7 CFU/mL R group) had stable disease both before and after tumor resection, up until the time of database lock (22.1 months). A decrease in tumor size was noted both before and after the incomplete tumor resection. The level of tumor-infiltrating CD8+ T cells was low at baseline but increased in the resected tumor tissue after VXM01 vaccine treatment. The VEGFR-2 specific T cell response of Patient 01-14 was somewhat stable up to Week 20, further supporting the contribution of VXM01 vaccine therapy to disease control in this patient. Patient 01-31 was in the 10^7 CFU/mL R group but discontinued study treatment before the tumor resection procedure was performed. This patient had stable disease on Day 10 which declined to progressive disease on Day 21 due to unequivocal progression of a non-target lesion. At baseline, Patient 01-31 did not have particularly high levels of tumor-infiltrating CD8+ T cells and the VEGFR-2 specific T cell response was mostly negative. Finally, Patient 02-29 (10^7 CFU/mL NR group) had stable disease for 6.0 months until progressive disease was established due to worsening of T2/FLAIR results, while the tumor size was still comparable to baseline. This patient had relatively low levels of tumor-infiltrating CD8+ T cells at baseline and high levels of PD-L1. The levels of T_{regs} and MDSCs were close to the median (10^7 CFU/mL NR group) at baseline, while the number of T_{regs} increased and the number of MDSCs decreased over time.

As described above, decrease in tumor size was observed both in patients with relatively small tumors (Patient 01-04 and 01-09) and relatively large tumors (Patient 22-10 and 01-14). This further supports the expectation that VXM01 vaccine treatment is effective in patients with larger sized tumors as well as patients with early stage cancer or very small tumors.

13.2 Overall Conclusions

The overall results of Study VXM01-AVE-04-INT demonstrate a positive safety profile of VXM01 vaccine treatment in combination with avelumab in patients with recurrent glioblastoma. The majority of related AEs was of mild or moderate severity. The only safety event leading to discontinuation of study treatment was not considered related to VXM01, but related to avelumab. Efficacy of VXM01 treatment is difficult to assess based on the sample size. This was additionally confounded by the use of VXM01 in combination with avelumab. When looking at the exploratory pharmacodynamic biomarkers, the results suggest contribution of VXM01 vaccine therapy to the tumor response based on the levels of TILs and VEGFR-2 specific T cell response. Pre-treatment levels of CD8+ T cells could be investigated as predictive biomarker in future trials.

14. TABLES AND FIGURES REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

14.2 Efficacy Data

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events.

The following table describes the information included in each narrative. A particular narrative is placed in the section with the most severe outcome. Other significant adverse events were defined as all non-serious and/or non-fatal AEs for which either action was taken with regard to the IMP or for which concomitant medication was administered.

Patient ID	SAE	Other Significant AE	Discontinuation
01-01		8 events	
01-03		2 events	
01-05	1 event	6 events	
01-07		6 events	
01-09		4 events	
01-12		3 events	
01-13		5 events	
01-14		6 events	
01-17		6 events	
01-18		2 events	
01-19	1 event	8 events	
01-20		5 events	
01-25		2 events	
01-26	1 event	9 events	1 event
01-27		6 events	
01-28	2 events	4 events	
01-31		1 event	
02-15		4 events	
02-16		3 events	
02-24		2 events	
02-29	3 events	1 event	
02-30	1 event		
22-10	2 events	10 events	

Source: Table 14.3.2.2, Table 14.3.2.3

14.3.3.1 Serious Adverse Events Narratives

Narrative for Patient 01-05

Study number:	VXM01-AVE-04-INT	
Patient number:	01-05	
Reason for narrative:	SAE and Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 10 Apr 2019 / 05 Jun 2019 Avelumab: 10 Apr 2019 / 19 Jun 2019	
Event preferred term (verbatim term):	Serious: 1. Brain oedema (brain edema) Significant: 2. Lymphocyte count decreased (lymphocyte count decreased) 3. Lymphocyte count decreased (lymphocyte count decreased) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Syncope (syncope) 6. Nausea (nausea) 7. Vomiting (vomiting)	
Start/stop dates:	1. 29 Jun 2019 / 02 Jul 2019 2. 26 Apr 2019 / 26 Apr 2019 3. 22 May 2019 / 18 Jun 2019 4. 19 Jun 2019 / 02 Jul 2019 5. 26 Jun 2019 / 26 Jun 2019 6. 29 Jun 2019 / 26 Oct 2019 7. 29 Jun 2019 / 26 Oct 2019	
Action taken with study drug:	VXM01 vaccine: 1-7. Dose not changed	Avelumab: 1-7. Dose not changed
Intensity:	1. Severe 2-3. Moderate 4. Mild 5. Severe 6-7. Moderate	
Study medication relationship:	VXM01 vaccine: 1-7. Not related	Avelumab: 1-7. Not related
Target disease relationship:	1. Possibly related 2-5. Not related 6. Definitely related 7. Possibly related	
Outcome:	1-2. Recovered / resolved 3-4. Recovered / resolved with sequelae	

Study number:	VXM01-AVE-04-INT
Patient number:	01-05
Reason for narrative:	SAE and Significant AEs
	5-7. Recovered / resolved

Patient 01-05 was a 62-year-old man who was diagnosed with primary malignant glioma on 28 Dec 2017 and recurrence on 04 Mar 2019. Prior cancer treatment included resection and radiotherapy. Additionally, anti-cancer medications included temozolomide, lomustine, etoposide, and nivolumab. Relevant medical history included platelet count decreased (2018 – 10 Apr 2019) and lymphocyte count decreased (05 Apr 2019 – 21 Apr 2019). Ongoing conditions included rosacea (since 2008), coronary artery disease (since 2015), hypercholesterolemia (since 2015), hypertension (since 2015), and facial paresis (since 30 Dec 2017). Ongoing medications for these medical history conditions included metoprolol and simvastatin (since 2015).

Patient 01-05 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and intravenous (i.v.) administration of avelumab 800 mg. The patient received 4 priming doses starting on 10 Apr 2019 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 5 doses of avelumab starting on 10 Apr 2019. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 05 Jun 2019 and the last dose of avelumab on 19 Jun 2019.

On 29 Jun 2019, 24 days after the last dose of VXM01 and 10 days after the last dose of avelumab, the patient experienced severe brain oedema. On the same day, computed tomography (computerized tomogram head) was performed. Treatment included i.v. dexamethasone (29 Jun 2019). The event of brain oedema resolved by 02 Jul 2019.

The investigator considered the event of brain oedema unrelated to the study drugs and possibly related to the target disease.

Additionally, 6 significant adverse events (AEs) (3 events of lymphocyte count decreased, and 1 event each of syncope, nausea, and vomiting) were reported by this patient during the study. The onset of the 3 events of lymphocyte count decreased (2 moderate events and 1 mild event) occurred while the patient was still taking study drug. However, the onset dates of severe syncope (26 Jun 2019), moderate nausea (29 Jun 2019), and moderate vomiting (29 Jun 2019) occurred after the last doses of study drugs. All 6 events were considered not related to VXM01 or avelumab. The nausea was considered definitely related, and the vomiting was possibly related to the target disease, while the other 4 events were not related to the target disease. An electrolyte solution (electrolytes NOS) was administered to treat the event of syncope (26 Jun 2019), while an anti-emetic solution of doxylamine succinate, folic acid, and pyridoxine hydrochloride were administered intravenously to treat the events of nausea and vomiting (29 Jun 2019). Additionally, a combination of sulfamethoxazole and trimethoprim was given as treatment 3 times/week for medical history conditions, events of lymphocyte count decreased, and prophylaxis (01 Apr 2019 – 02 May 2019, ongoing since 22 May 2019).

The outcomes of 1 event of lymphocyte count decreased, syncope, nausea, and vomiting were resolved, while the outcome for the other 2 events of lymphocyte count decreased was resolved with sequelae. None of the events caused discontinuation of study drug.

Progressive disease was reported on 02 Jul 2019. On 26 October 2019, the patient died due to target disease progression.

Narrative for Patient 01-19

Study number:	VXM01-AVE-04-INT	
Patient number:	01-19	
Reason for narrative:	SAE and Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 25 Nov 2020 / 20 Jan 2021 Avelumab: 25 Nov 2020 / 03 Feb 2021	
Event preferred term (verbatim term):	Serious: 1. Epilepsy (epilepsia) Significant: 2. Lymphocyte count decreased (lymphocyte count decreased) 3. Blood sodium decreased (blood sodium decreased) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Lymphocyte count decreased (lymphocyte count decreased) 6. Lymphocyte count decreased (lymphocyte count decreased) 7. Lymphocyte count decreased (lymphocyte count decreased) 8. Lymphocyte count decreased (lymphocyte count decreased) 9. Dysdiadochokinesis (dysdiadocho kinesis of the right leg)	
Start/stop dates:	1. 22 Nov 2020 / 27 Nov 2020 2. 24 Nov 2020 / 26 Nov 2020 3. 24 Nov 2020 / 16 Dec 2020 4. 26 Nov 2020 / 27 Nov 2020 5. 28 Nov 2020 / 02 Dec 2020 6. 03 Dec 2020 / 04 Dec 2020 7. 05 Dec 2020 / 04 Jan 2021 8. 20 Jan 2021 / 02 Feb 2021 9. 03 Feb 2021 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-9. Dose not changed	Avelumab: 1-9. Dose not changed
Intensity:	1. Severe 2-3. Mild 4. Severe 5. Mild 6. Moderate 7-9. Mild	
Study medication relationship:	VXM01 vaccine: 1-3. Not related 4. Unlikely related 5-9. Not related	Avelumab: 1-3. Not related 4. Unlikely related 5-9. Not related

Study number:	VXM01-AVE-04-INT
Patient number:	01-19
Reason for narrative:	SAE and Significant AEs
Target disease relationship:	1. Definitely related 2. Unlikely related 3. Not related 4. Unlikely related 5-8. Not related 9. Definitely related
Outcome:	1. Recovered / resolved 2. Recovered / resolved with sequelae 3. Recovered / resolved 4-8. Recovered / resolved with sequelae 9. Not recovered / not resolved

Patient 01-19 was a 52-year-old man who was diagnosed with primary malignant glioma on 16 Mar 2020 and recurrence 09 Nov 2020. Prior cancer treatment included tumor resection and radiotherapy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included epilepsy (since Feb 2020). Ongoing medications for this medical history condition included lacosamide (since Mar 2020), levetiracetam (since Mar 2020), and lorazepam (since 12 Nov 2020), and perampanel (23 Nov 2020 – 30 Nov 2020, 01 Dec 2020 – 08 Dec 2020, 09 Dec 2020 – 15 Dec 2020, 16 Dec 2020 – 22 Dec 2020, since 23 Dec 2020). Other concomitant medications taken for this medical history condition included eslicarbazepine acetate (23 Nov 2020 – 06 Dec 2020, 07 Dec 2020 – 14 Dec 2020).

The patient underwent magnetic resonance imaging of the brain 2 days after the final dose of avelumab and 16 days after the final dose of VXM01 on 05 February 2021.

Patient 01-19 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 25 Nov 2020 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of avelumab also starting on 25 Nov 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 20 Jan 2021 and the last dose of avelumab on 03 Feb 2021.

On 22 Nov 2020, 3 days before the first dose of VXM01 and avelumab, the patient experienced severe epilepsy and was hospitalized. Treatment included oral perampanel (23 Nov 2020 – 30 Nov 2020) and clobazam (23 Nov 2020 – 23 Dec 2020). The event of epilepsy resolved by 27 Nov 2020.

The investigator considered the event of epilepsy unrelated to the study drugs and definitely related to the target disease.

Additionally, 8 significant AEs (6 events of lymphocyte count decreased, and 1 event each of blood sodium decreased and dysdiadochokinesis) were reported by this patient during the study. The onset of 1 event each of lymphocyte count decreased and blood sodium decreased (both mild events) occurred prior to the patient receiving study drug (24 Nov 2020). The other 5 events of lymphocyte count decreased (1 severe, 1 moderate, and 2 mild events) and 1 event of mild

dysdiadochokinesis occurred while the patient was taking study drug. All 8 events were considered not related or unlikely related to VXM01 or avelumab. However, the dysdiadochokinesis was considered definitely related to the target disease, while the other 7 events were not related or unlikely related to the target disease. Sodium chloride was administered to treat the event of blood sodium decreased (24 Nov 2020 – 22 Dec 2020, since 23 Dec 2020). Additionally, respiratory pentamidine was given as a treatment every 4 weeks for the events of lymphocyte count decreased and as prophylaxis (since 26 Nov 2020).

The outcome of all 6 events of lymphocyte count decreased resolved with sequelae, while the outcome of blood sodium decreased resolved. The event of dysdiadochokinesis was not resolved at the time of database lock. None of the events caused discontinuation of study drug.

Progressive disease was reported on 05 Feb 2021. On 05 Jul 2021, the patient died due to target disease progression.

Narrative for Patient 01-26

Study number:	VXM01-AVE-04-INT	
Patient number:	01-26	
Reason for narrative:	SAE and Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 07 Apr 2021 / 02 Jun 2021 Avelumab: 07 Apr 2021 / 05 May 2021	
Event preferred term (verbatim term):	Serious: 1. Status epilepticus (non convulsive status epilepticus) Significant: 2. Influenza like illness (flu like symptoms) 3. Lymphocyte count decreased (lymphocyte count decreased) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Persistent depressive disorder (dysthymia) 6. Blood potassium decreased (potassium count decreased) 7. Epilepsy (symptomatic epilepsia) 8. Lymphocyte count decreased (lymphocyte count decreased) 9. Rheumatoid arthritis (acute rheumatoid arthitis) 10. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 10 Apr 2021 / 19 Apr 2021 2. 07 Apr 2021 / 08 Apr 2021 3. 08 Apr 2021 / 10 Apr 2021 4. 10 Apr 2021 / 17 Apr 2021 5. 11 Apr 2021 / Ongoing 6. 13 Apr 2021 / 15 Apr 2021 7. 20 Apr 2021 / Ongoing 8. 21 Apr 2021 / 27 Apr 2021 9. 17 May 2021 / Ongoing 10. 14 Jun 2021 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-10. Dose not changed	Avelumab: 1-8. Dose not changed 9. Drug withdrawn 10. Dose not changed
Intensity:	1. Severe 2. Mild 3. Severe 4. Moderate 5-8. Mild 9. Severe 10. Mild	

Study number:	VXM01-AVE-04-INT	
Patient number:	01-26	
Reason for narrative:	SAE and Significant AEs	
Study medication relationship:	VXM01 vaccine: 1-2. Not related 3. Unlikely related 4. Possibly related 5-7. Not related 8. Possibly related 9. Not related 10. Unlikely related	Avelumab: 1. Not related 2. Possibly related 3. Unlikely related 4. Possibly related 5-7. Not related 8. Possibly related 9. Probably related 10. Unlikely related
Target disease relationship:	1. Probably related 2-4. Not related 5. Probably related 6. Not related 7. Definitely related 8-9. Not related 10. Unlikely related	
Outcome:	1. Recovered / resolved with sequelae 2. Recovered / resolved 3. Recovered / resolved with sequelae 4. Recovered / resolved 5. Not recovered /not resolved 6. Recovered / resolved 7. Not recovered / not resolved 8. Recovered / resolved 9-10. Not recovered / not resolved	

Patient 01-26 was a 69-year-old man who was diagnosed with primary malignant glioma on 14 Sep 2020 and recurrence on 23 Mar 2021. Prior cancer treatment included complete resection, radiotherapy, and novo TTF (tumor treating fields therapy). Additionally, anti-cancer medications included temozolomide. Relevant medical history included hemorrhoids (1980 – 1980), intervertebral disc protrusion (Dec 1990 – Dec 1990), gastroesophageal reflux disease (2009 – 2016), dyslipidemia atherogene (since 2011), dental prosthesis use (in 2015), tendon rupture (tendon tear right shoulder, since 2016), tendon rupture (torn tendon left shoulder, since 2016), hypertension (since 2018), large intestine polyp (Feb 2020 – Feb 2020), pruritus (Dec 2020 – 09 Apr 2021), rash (Dec 2020 – 10 Apr 2021), hypoesthesia (since Dec 2020), and arthralgia (since Jan 2021). Ongoing medications for these medical history conditions included metamizole (since 09 Apr 2021), candesartan (since 16 Apr 2021).

In addition to treatment for recurrent malignant glioma, concomitant medications included calcium carbonate;colecalciferol for prophylaxis (since 17 May 2021).

Patient 01-26 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 07 Apr 2021 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 3 doses of avelumab also starting on 07 Apr 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 02 Jun 2021 and the last dose of avelumab on 05 May 2021.

On 10 Apr 2021, 3 days after the first dose of avelumab and VXM01 and 1 day after the second dose of VXM01, the patient experienced severe status epilepticus and was hospitalized. On the same day, computed tomography (computerized tomogram head) was performed. Additionally, electroencephalograms (EEGs) were performed on 12 Apr 2021 and 14 Apr 2021. Treatment included oral administration of levetiracetam (13 Apr 2021 – 19 Apr 2021, since 20 Apr 2021), lacosamide (since 13 Apr 2021), mirtazapine (11 Apr 2021 – 18 Apr 2021, since 19 Apr 2021), pantoprazole (since 15 Apr 2021), and clobazam (12 Apr 2021 – 18 Apr 2021, since 19 Apr 2021). The event of status epilepticus resolved with sequelae by 19 Apr 2021. No action was taken with regard to the study drugs because of this event.

The investigator considered the event of status epilepticus unrelated to VXM01 and avelumab and probably related to the target disease.

Additionally, 9 significant AEs (4 events of lymphocyte count decreased, and 1 event each of influenza-like illness, persistent depressive disorder, blood potassium decreased, epilepsy, and rheumatoid arthritis) were reported by this patient during the study. The onset of 1 event of mild lymphocyte count decreased occurred after the patient received the last dose VXM01 and avelumab (14 Jun 2021). Onset of the other 3 events of lymphocyte count decreased (1 severe, 1 moderate, and 1 mild event) and events of mild influenza-like illness, mild persistent depressive disorder, mild blood potassium decreased, mild epilepsy, and severe rheumatoid arthritis occurred while the patient was taking VXM01.

Two events of lymphocyte count decreased were considered possibly related to both VXM01 and avelumab but not related to target disease. The other 2 events of lymphocyte count decreased were unlikely related to VXM01 and avelumab and unlikely related or not related to target disease. The event of rheumatoid arthritis was considered probably related to avelumab but not related to VXM01 or target disease. Similarly, the event of influenza-like illness was also considered possibly related to avelumab but not related to VXM01 or target disease. The events of epilepsy and persistent depressive disorder was not related to VXM01 or avelumab but were definitely related and probably related to target disease, respectively. The event of blood potassium decreased was not related to the study drugs or target disease.

Respiratory pentamidine was given as a treatment every 4 weeks for the event of lymphocyte count decreased and prophylaxis (since 08 Apr 2021). Potassium citrate was administered to treat the event of blood potassium decreased (since 13 April 2021). Lamotrigine was given as treatment treat for the event of epilepsy (since 29 Apr 2021), and prednisolone was administered as treatment for the event of rheumatoid arthritis (since 18 May 2021). Avelumab was withdrawn following the onset of rheumatoid arthritis. None of the events caused discontinuation of VXM01.

The outcome of 2 events of lymphocyte count decreased, 1 event of influenza-like illness, and 1 event of blood potassium decreased was resolved, while the outcome of another event of lymphocyte count decreased was resolved with sequelae. The outcome of 1 event each of

persistent depressive disorder, epilepsy, rheumatoid arthritis, and lymphocyte count decreased was ongoing at the time of database lock.

Progressive disease was reported on 28 Jun 2021. On 27 Apr 2022, the patient died due to target disease progression.

Narrative for Patient 01-28

Study number:	VXM01-AVE-04-INT	
Patient number:	01-28	
Reason for narrative:	SAEs and Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 07 Jul 2021 / 27 Oct 2021 Avelumab: 07 Jul 2021 / 27 Oct 2021	
Event preferred term (verbatim term):	Serious: 1. Gait disturbance (worsening of gait stability) 2. Pulmonary embolism (pulmonary artery embolism) Significant: 3. Depression (depression) 4. Insomnia (insomnia) 5. Lymphocyte count increased (lymphocyte count increased) 6. Lymphocyte count increased (lymphocyte count increased)	
Start/stop dates:	1. 05 Jul 2021 / 06 Jul 2021 2. 28 Oct 2021 / 04 Nov 2021 3. 28 Aug 2021 / Ongoing 4. 28 Aug 2021 / Ongoing 5. 27 Sep 2021 / 13 October 2021 6. 09 Nov 2021 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-6. Dose not changed	Avelumab: 1-6. Dose not changed
Intensity:	1. Severe 2. Life-threatening 3-4. Mild 5. Moderate 6. Mild	
Study medication relationship:	VXM01 vaccine: 1-6. Not related	Avelumab: 1-6. Not related
Target disease relationship:	1-2. Probably related 3-4. Possibly related 5. Not related 6. Unlikely related	
Outcome:	1-2. Recovered / resolved with sequelae 3-4. Not recovered / not resolved 5. Recovered / resolved 6. Not recovered / not resolved	

Patient 01-28 was a 51-year-old man who was diagnosed with primary malignant glioma on 17 Nov 2020 and recurrence on 02 Jun 2021. Prior cancer treatment included biopsy and radiotherapy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included hypertension (since 2001) and epilepsy (since December 2020). Ongoing medications for these medical history conditions included ramipril (2001 – 06 Jul 2021, since 07 July 2021), lacosamide (Dec 2020 – 28 Jun 2021, since 29 Jun 2021), levetiracetam (since Dec 2020), and amlodipine (12 Jul 2021 – 14 Jul 2021, 15 Jul 2021 – 27 Jul 2021, since 28 Jul 2021).

In addition to treatment for recurrent malignant glioma, concomitant medications included calcium carbonate;vitamin D NOS (since 07 Jun 2021), pantoprazole (since 15 Jun 2021), apixaban (since 06 Nov 2021) for prophylaxis. Dexamethasone was administered for other reasons and for prophylaxis (12 Jun 2021 – 23 Jun 2021, 24 Jun 2021 – 05 Jul 2021, 19 Aug 2021 – 22 Aug 2021, 23 Aug 2021 – 27 Aug 2021, since 28 Aug 2021). Additional concomitant medications included lomustine (07 Nov 2021 – 07 Nov 2021) and etoposide (07 Nov 2021 – 09 Nov 2021).

Patient 01-28 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 07 Jul 2021 followed by 4 boosting doses of 10^7 CFU/mL VXM01, in combination with 9 doses of avelumab also starting on 07 Jul 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 and avelumab on 27 Oct 2021.

On 05 Jul 2021, 2 days before the first dose of VXM01 and avelumab, the patient experienced severe gait disturbance and was hospitalized. Treatment included twice daily oral administration of dexamethasone (05 Jul 2021 – 18 Aug 2021). The event of gait disturbance resolved with sequelae by 06 Jul 2021.

The investigator considered the event of gait disturbance unrelated to VXM01 and avelumab and probably related to target disease.

On 28 Oct 2021, 1 day after the last dose of VXM01 and avelumab, the patient experienced life-threatening pulmonary embolism and was hospitalized. Treatment included twice daily subcutaneous injections of enoxaparin (28 Oct 2021 – 05 Nov 2021). The event of pulmonary embolism resolved with sequelae by 04 Nov 2021.

The investigator considered the event of pulmonary embolism unrelated to VXM01 and avelumab and probably related to target disease.

Additionally, 4 significant AEs (2 events of lymphocyte count increased, and 1 event each of depression and insomnia) were reported by this patient during the study. The onset of 1 event of mild lymphocyte count increased occurred after the patient received the last dose of VXM01 and avelumab (09 Nov 2021). Onset of the other events of moderate lymphocyte count decreased, mild depression, and mild insomnia occurred while the patient was taking VXM01 and avelumab.

All 4 significant AEs were considered not related to VXM01 and avelumab. Two events of lymphocyte count decreased were considered not related and unlikely related to target disease. The other 2 events of depression and insomnia were possibly related to target disease.

Mirtazapine was administered to treat the event of depression (since 28 Aug 2021). Respiratory pentamidine was given as a treatment every 4 weeks for the event of lymphocyte count decreased and prophylaxis (27 Sep 2021 – 13 Oct 2021, since 09 Nov 2021). None of the events caused discontinuation of VXM01 or avelumab.

The outcome of 1 event each of lymphocyte count decreased was resolved. The outcome of 1 event each of lymphocyte count decreased, depression, and insomnia was not resolved.

Progressive disease was reported on 05 Nov 2021. On 14 Apr 2022, the patient died due to target disease progression.

Narrative for Patient 02-29

Study number:	VXM01-AVE-04-INT	
Patient number:	02-29	
Reason for narrative:	SAEs and Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 29 Jun 2021 / 21 Dec 2021 Avelumab: 29 Jun 2021 / 31 Jan 2022	
Event preferred term (verbatim term):	Serious: 1. Hyponatraemia (Hyponatremia) 2. Hyponatraemia (Hyponatremia) 3. Hyponatraemia (Hyponatremia) Significant: 4. Hyponatraemia (Hyponatremia)	
Start/stop dates:	1. 21 Dec 2021 / 22 Dec 2021 2. 28 Dec 2021 / 01 Jan 2022 3. 23 Jan 2022 / 26 Jan 2022 4. 04 Jan 2022 / 22 Jan 2022	
Action taken with study drug:	VXM01 vaccine: 1-4. Dose not changed	Avelumab: 1-4. Dose not changed
Intensity:	1-3. Severe 4. Mild	
Study medication relationship:	VXM01 vaccine: 1-4. Unlikely related	Avelumab: 1-3. Unlikely related 4. Possibly related
Target disease relationship:	1-4. Possibly related	
Outcome:	1-4. Recovered / resolved	

Patient 02-29 was a 54-year-old woman who was diagnosed with primary malignant glioma on 14 Oct 2020 and recurrence on 07 Jun 2021. Prior cancer treatment included resection and radiotherapy. Additionally, anti-cancer medications included antineoplastic agents and temozolomide. Relevant medical history included hypothyroidism (since 01 Jan 1990) and epilepsy (since 16 Oct 2020). Ongoing medications for these medical history conditions included levothyroxine (since 01 Jan 1990) and brivaracetam (since 16 Oct 2020).

In addition to treatment for recurrent malignant glioma, concomitant medications included a single i.v. administration of antihistamines for prophylaxis (23 Aug 2021). The patient underwent 2 CT scans (computerized tomogram head) on 15 Feb 2022 and 16 Feb 2022 to confirm tumor progression.

Patient 02-29 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 29 Jun 2021 followed by 6 boosting doses of 10^7 CFU/mL VXM01, in combination with 16 doses of

avelumab starting on 29 Jun 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 21 Dec 2021 and the last dose of avelumab on 31 Jan 2022.

On 21 Dec 2021, on the same day as the last dose of VXM01 and the 13th dose of avelumab (176 days after the first dose of study drug), the patient experienced severe hyponatremia and was hospitalized. During this time, the patients also experienced nonserious AEs of nausea and fatigue (19 Dec 2021 – 22 Dec 2021), as well as hypokalemia (21 Dec 2021 – 22 Dec 2021). Treatment included 0.9% sodium chloride i.v. (21 Dec 2021 – 21 Dec 2021). The event of severe hyponatremia resolved by 22 Dec 2021. No action was taken with regard to the study drug because of this event.

On 28 Dec 2021, 8 days after the last dose of VXM01 and the 13th dose of avelumab (183 days after the first dose of study drug), the patient experienced a second event of severe hyponatremia and was hospitalized. During this time, the patient also experienced nonserious AEs of nausea and fatigue (26 Dec 2021 – 30 Dec 2021), as well as vomiting (26 Dec 2021 – 28 Dec 2021). Treatment included 0.9% sodium chloride i.v. (28 Dec 2021 – 01 Jan 2022), and dexamethasone was administered orally for nausea and fatigue (30 Dec 2021 – 04 Jan 2022). The event of severe hyponatremia resolved by 01 Jan 2022. No action was taken with regard to the study drug because of this event.

On 23 Jan 2022, 34 days after the last dose of VXM01 and 6 days after the 15th dose of avelumab (209 days after the first dose of study drug), the patient experienced a third event of severe hyponatremia and was hospitalized. Treatment included 0.9% sodium chloride i.v. (23 Jan 2022 – 26 Jan 2022). The event of hyponatremia resolved by 26 Jan 2022. No action was taken with regard to the study drug because of this event.

The investigator considered all 3 events of hyponatremia as unlikely related to VXM01 and avelumab and possibly related to target disease.

One significant AE of mild hyponatremia was reported by this patient during the study. Onset of this event occurred after the final dose of VXM01 but before the final dose of avelumab (04 Jan 2022). This event was considered unlikely related to VXM01 and possibly related to avelumab and target disease. Treatment included oral dexamethasone (05 Jan 2022 – 08 Jan 2022, 09 Jan 2022 – 12 Jan 2022, 13 Jan 2022 – 16 Jan 2022). This event did not cause discontinuation of avelumab. The outcome of this event was resolved by 22 Jan 2022.

Progressive disease was reported on 16 Feb 2022. On 15 Mar 2022, the patient died due to target disease progression.

Narrative for Patient 02-30

Study number:	VXM01-AVE-04-INT	
Patient number:	02-30	
Reason for narrative:	SAE	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 29 Jun 2021 / 20 Sep 2021 Avelumab: 29 Jun 2021 / 20 Sep 2021	
Event preferred term (verbatim term):	Cerebrovascular accident (stroke)	
Start/stop dates:	30 Sep 2021 / 11 Oct 2021	
Action taken with study drug:	VXM01 vaccine: Dose not changed	Avelumab: Dose not changed
Intensity:	Severe	
Study medication relationship:	VXM01 vaccine: Unlikely related	Avelumab: Unlikely related
Target disease relationship:	Probably related	
Outcome:	Recovered / resolved with sequelae	

Patient 02-30 was a 67-year-old woman who was diagnosed with primary malignant glioma on 27 Jun 2019 and recurrence on 31 May 2021. Prior cancer treatment included resection and radiotherapy. Additionally, anti-cancer medications included lomustine and temozolomide. Relevant medical history included salpingectomy (on 01 January 1987) and hypertension (since January 1999). Medications for these medical history conditions included ramipril (Jan 1999 – 30 Sep 2021).

Patient 02-30 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 29 Jun 2021 followed by 3 boosting doses of 10^7 CFU/mL VXM01, in combination with 7 doses of avelumab also starting on 29 Jun 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of both VXM01 and avelumab on 20 Sep 2021. The physician decided not to continue study drug treatment on 21 Sep 2021.

On 30 Sep 2021, 10 days after the last dose of study drugs, the patient experienced severe cerebrovascular accident and was hospitalized. The patient also underwent magnetic resonance imaging (MRI) of the brain (magnetic resonance imaging brain) on 30 Sep 2021. Treatment included acetylsalicylic, atorvastatin, and ramipril (since 30 Sep 2021). The event of cerebrovascular accident resolved with sequelae by 11 Oct 2021.

The investigator considered the event of cerebrovascular accident as unlikely related to VXM01 or avelumab and probably related to target disease

On 30 Sep 2022, the patient died due to target disease progression.

Narrative for Patient 22-10

Study number:	VXM01-AVE-04-INT	
Patient number:	22-10	
Reason for narrative:	SAEs and Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 24 Jul 2019 / 13 Dec 2019 Avelumab: 24 Jul 2019 / 27 Dec 2019	
Event preferred term (verbatim term):	Serious: 1. Headache (headache) 2. Insomnia (insomnia) Significant: 3. Insomnia (insomnia) 4. Hypertension (hypertension) 5. Anxiety (anxiety) 6. Hypertension (hypertension) 7. Confusional state (confusion) 8. Depression (depression) 9. Insomnia (insomnia) 10. Hypertension (hypertension) 11. Back pain (lombar pain) 12. Insomnia (incomnia)	
Start/stop dates:	1. 19 Aug 2019 / 21 Aug 2019 2. 06 Sep 2019 / 10 Sep 2019 3. 06 Aug 2019 / 05 Sep 2019 4. 13 Aug 2019 / 22 Aug 2019 5. 23 Aug 2019 / Ongoing 6. 23 Aug 2019 / 17 Sep 2019 7. Sep 2019 / 04 Oct 2019 8. 06 Sep 2019 / Ongoing 9. 11 Sep 2019 / 09 Oct 2019 10. 18 Sep 2019 / Ongoing 11. 27 Sep 2019 / Ongoing 12. 10 Oct 2019 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-9. Dose not changed 10. Drug interrupted 11-12. Dose not changed	Avelumab: 1-12. Dose not changed

Study number:	VXM01-AVE-04-INT	
Patient number:	22-10	
Reason for narrative:	SAEs and Significant AEs	
Intensity:	1. Moderate 2. Severe 3. Moderate 4. Severe 5-6. Moderate 7-10. Severe 11. Moderate 12. Mild	
Study medication relationship:	VXM01 vaccine: 1-3. Unlikely related 4. Probably related 5. Not related 6. Probably related 7-8. Not related 9. Unlikely related 10. Probably related 11. Not related 12. Unlikely related	Avelumab: 1-3. Unlikely related 4. Probably related 5. Not related 6. Probably related 7-8. Not related 9. Unlikely related 10. Probably related 11. Not related 12. Unlikely related
Target disease relationship:	1-2. Unlikely related 3-6. Not related 7. Possibly related 8. Not related 9. Unlikely related 10-11. Not related 12. Unlikely related	
Outcome:	1-4. Recovered / resolved 5. Not recovered / not resolved 6-7. Recovered / resolved 8. Not recovered / not resolved 9. Recovered / resolved 10-12. Not recovered / not resolved	

Patient 22-10 was a 53-year-old man who was diagnosed with primary malignant glioma on 28 Sep 2018 and recurrence on 15 Jul 2019. Prior cancer treatment included biopsy, radiotherapy, and tumor operation. Additionally, anti-cancer medications included temozolomide. Relevant medical history included migraine (since 2006), gastroesophageal reflux disease (since 2009), hiatus hernia (since 2009), renal colic (in 2011), shoulder arthroplasty (in 2012), gout (since 2014), epilepsy (since 28 Aug 2018), hypertension (since Sep 2018), depression (since Oct 2018), and headache (since 23 Apr 2019). Concomitant medications for these medical history conditions included omeprazole (2009 – 22 Aug 2019, ongoing since 28 Sep 2019), allopurinol (since 2014), levetiracetam (15 Oct 2018 – 05 Sep 2019), escilatopram

oxalate (since 17 Oct 2018), lacosamide (12 Mar 2019 – 05 Sep 2019), and paracetamol (since Apr 2019). No anti-hypertensive medication was given before study start.

Patient 22-10 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 24 Jul 2019 followed by 4 boosting doses of 10^7 CFU/mL VXM01, in combination with 12 doses of avelumab starting on 24 Jul 2019. Premedication with paracetamol and dexchlorpheniramine maleate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 13 Dec 2019 and the last dose of avelumab on 27 Dec 2019.

On 19 Aug 2019, 26 days after the first dose of study drugs, the patient experienced moderate headache. Treatment included paracetamol (20 Aug 2019 – 21 Aug 2019) and perindopril arginine (21 Aug 2019 – 09 Sep 2019), in addition to ongoing treatment with amlodipine besilate (13 Aug 2019 – 09 Sep 2019) for hypertension. The patient underwent MRI of the head on 20 Aug 2019. The event of headache was resolved by 21 Aug 2019. No action was taken with regard to the study drugs because of this event. The investigator considered the event unlikely related to the study drugs and the target disease.

On 06 Sep 2019, 44 days after the first dose of study drug, the patient experienced severe insomnia. At the same time, the patient experienced severe depression. Treatment included levetiracetam (06 Sep 2019 – 14 Sep 2019), clobazam (06 Sep 2019 – 14 Nov 2019), lacosamide (since 06 Sep 2019), lamotrigine (since 06 Sep 2019), risperidone (since 09 Sep 2019), and amlodipine besilate (since 10 Sep 2019). The event of insomnia was resolved by 10 Sep 2019 and was considered unlikely related to the study drugs and target disease. The event of depression was ongoing at the time of database lock and was considered not related to the study drugs and target disease.

In addition, Patient 22-10 experienced 8 significant AEs (3 events of mild to severe insomnia, 3 events of moderate to severe hypertension, and 1 event each of moderate anxiety, severe confusional state, and moderate back pain). The onset of all events occurred while VXM01 and avelumab treatment was ongoing.

Treatment for insomnia included zopiclone (13 Aug 2019 – 05 Sep 2019) and clobazam (ongoing since 15 Nov 2019). Treatment for hypertension included amlodipine besilate (13 Aug 2019 – 09 Sep 2019), telmisartan (14 Sep 2019 – 11 Oct 2019), and hydrochlorothiazide;telmisartan (ongoing since 12 Oct 2019). Treatment for the event of anxiety included alprazolam (23 Aug 2019 – 09 Sep 2019), pantoprazole sodium sesquihydrate (23 Aug 2019 – 27 Sep 2019), and bromazepam (03 Sep 2019 – 05 Sep 2019). Treatment for the event of back pain included arnica montana extract (27 Sep 2019 –19 Nov 2019).

The events of anxiety, hypertension, insomnia, and back pain were ongoing at the time of database lock. The event of confusional state was resolved by 04 Oct 2019.

VXM01 treatment was interrupted once on 18 Sep 2019 due to the event of hypertension, no action was taken with regard to the study drugs for all other events.

The 3 significant AEs of insomnia were considered not or unlikely related to the study drugs and the target disease. The 3 events of hypertension were considered probably related to VXM01 and avelumab, and not related to the target disease. The events of anxiety, confusional state, depression, and back pain were considered not related to the study drugs. The event of

confusional state was considered possibly related to the target disease, while the events of anxiety, depression, and back pain were considered not related to the target disease.

Progressive disease was reported on 10 Jan 2020. On 03 Mar 2021, the patient died due to target disease progression.

14.3.3.2 Other Significant Adverse Events

Narrative for Patient 01-01

Study number:	VXM01-AVE-04-INT	
Patient number:	01-01	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^6 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 23 Nov 2018 / 30 Nov 2018 Avelumab: 23 Nov 2018 / 10 Dec 2018	
Event preferred term (verbatim term):	1. Influenza like illness (flu like symptoms) 2. Nausea (nausea) 3. Malaise (malaise) 4. Cognitive disorder (coordination disorder – slight cognitive impairment) 5. Brain oedema (edema cerebral) 6. Fine motor skill dysfunction (fine motor skills disorder left hand) 7. Gait disturbance (gait disturbance) 8. Hemiparesis (coordination disorder – slight paresis left side)	
Start/stop dates:	1. 14 Dec 2018 / 17 Dec 2018 2. 14 Dec 2018 / 02 Jan 2019 3. 20 Dec 2018 / 28 Dec 2018 4. 21 Dec 2018 / 28 Dec 2018 5. 21 Dec 2018 / 28 Dec 2018 6. 21 Dec 2018 / 28 Dec 2018 7. 21 Dec 2018 / 28 Dec 2018 8. 21 Dec 2018 / 28 Dec 2018	
Action taken with study drug:	VXM01 vaccine: 1-2. Dose not changed 3-8. Dose interrupted	Avelumab: 1-2. Dose not changed 3-8. Drug interrupted
Intensity:	1-4. Moderate 5. Severe 6. Moderate 7. Mild 8. Moderate	
Study medication relationship:	VXM01 vaccine: 1. Not related 2. Unlikely related 3-8. Not related	Avelumab: 1. Possibly related 2. Unlikely related 3. Possibly related 4-8. Not related

Study number:	VXM01-AVE-04-INT
Patient number:	01-01
Reason for narrative:	Significant AEs
Target disease relationship:	Target disease: 1. Not related 2-3. Definitely related 4. Possibly related 5. Definitely related 6-7. Possibly related 8. Definitely related
Outcome:	1-8. Recovered / resolved

Patient 01-01 was a 63-year-old man who was diagnosed with primary malignant glioma on 19 Oct 2015 and recurrence on 05 Dec 2017 and 02 Nov 2018. Prior cancer treatment included tumor excision, brain biopsy, and radiotherapy. Additionally, anti-cancer medications included temozolomide and lomustine. Relevant medical history included hypertension (since 17 Oct 2006), headaches (since Oct 2015), and tachycardia (since 29 Dec 2017). Ongoing medications taken for these medical history conditions included ramipril (since 17 Oct 2006), metamizole (since 19 Oct 2015), and bisoprolol (since 29 Dec 2017).

Patient 01-01 was assigned to receive oral administration of 10^6 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses of VXM01 starting on 23 Nov 2018; no boosting doses were given. The patient received 2 doses of avelumab starting on 23 Nov 2018. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 30 Nov 2018 and the last dose of avelumab on 10 Dec 2018.

A total of 8 significant AEs were reported by this patient during the study. However, all events had start dates after the last doses of study drug were taken. On 14 Dec 2018, events of moderate influenza-like illness and nausea were reported. On 20 Dec 2018, the patient reported moderate malaise, and on 21 Dec 2018, events of severe brain oedema, moderate cognitive disorder, fine motor skill dysfunction, hemiparesis, and mild gait disturbance were reported. All events were unlikely related or not related to VXM01. The events of influenza-like illness and malaise were noted as possibly related to avelumab; all others were noted as unlikely or not related to avelumab. Additionally, all events were noted as possibly or definitely related to the target disease, with the exception of influenza-like illness which was not related to the target disease. Dexamethasone was administered to treat the brain oedema.

The patient recovered from all events.

Progressive disease was reported on 28 Dec 2018. On 02 Jan 2019, the patient underwent a brain tumor operation (microsurgical resection) and craniotomy. On 08 Feb 2020, the patient died due to target disease progression.

Narrative for Patient 01-03

Study number:	VXM01-AVE-04-INT	
Patient number:	01-03	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^6 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 01 Feb 2019 / 28 Mar 2019 Avelumab: 01 Feb 2019 / 11 Apr 2019	
Event preferred term (verbatim term):	1. Brain oedema (edema cerebral) 2. Hemiparesis (hemiparesis right)	
Start/stop dates:	1. 25 Mar 2019 / Ongoing 2. 18 Apr 2019 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-2 Dose not changed	Avelumab: 1-2 Dose not changed
Intensity:	1. Moderate 2. Moderate	
Relationship	VXM01 vaccine: 1-2. Not related	Avelumab: 1-2. Not related
	Target disease: 1. Possibly related 2. Definitely related	
Outcome:	1. Recovering / resolving 2. Not recovered / not resolved	

Patient 01-03 was a 65-year-old man who was diagnosed with primary malignant glioma on 31 Jul 2018 and recurrence 03 Dec 2018. Prior cancer treatment included tumor excision, radiotherapy. Additionally, anti-cancer medication included temozolomide. Relevant medical history included diabetes mellitus, headaches, restlessness, retinitis pigmentosa (all no start date available), hyperuricemia (since 2011), and rheumatoid arthritis (since 2011). Medications taken for these medical history conditions included allopurinol (since 2011), metamizole sodium (since 14 Aug 2018), mirtazapine (since 24 Aug 2018), metformin (since 11 Oct 2018), dapagliflozin (17 Oct 2018 – 12 Mar 2019), clonidine (since 27 Feb 2019), and diazepam (since 12 Mar 2019).

Patient 01-03 was assigned to receive oral administration of 10^6 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 01 Feb 2019 followed by 2 boosting doses of 10^6 CFU/mL VXM01, in combination with 5 doses of avelumab starting on 01 Feb 2019. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 28 Mar 2019 and the last dose of avelumab on 11 Apr 2019.

Two significant AEs (brain oedema and hemiparesis) were reported by this patient during the study. The onset of moderate brain oedema (25 Mar 2019) occurred while the patient was still taking study drug. The onset date of moderate hemiparesis (18 Apr 2019) was after the last dose of study drugs. Both events were considered not related to VXM01 or avelumab, however, the

brain oedema was considered possibly related and the hemiparesis definitely related to the target disease. Dexamethasone was administered to treat the brain oedema and hemiparesis.

The outcome of the brain oedema was resolving at the time of database lock, and the outcome of the hemiparesis was not resolved. Neither of the events caused discontinuation of study drug.

Progressive disease was reported on 18 Apr 2019. On 20 Jul 2019, the patient died due to target disease progression.

Narrative for Patient 01-07

Study number:	VXM01-AVE-04-INT	
Patient number:	01-07	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 22 May 2019 / 15 Aug 2019 Avelumab: 22 May 2019 / 26 Aug 2019	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Lymphocyte count decreased (lymphocyte count decreased) 3. Blood creatine phosphokinase increased (CPK increased) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Hypothyroidism (hypothyreosis)	
Start/stop dates:	1. 23 May 2019 / 10 June 2019 2. 17 Jul 2019 / 08 Aug 2019 3. 26 Aug 2019 / 05 Sep 2019 4. 26 Aug 2019 / Ongoing 5. 14 Oct 2019 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-5 Dose not changed	Avelumab: 1-5: Dose not changed
Intensity:	1-2. Moderate 3. Mild 4-5. Moderate	
Relationship:	VXM01 vaccine: 1-3. Not related 4. Unlikely related 5. Not related	Avelumab: 1-2. Not related 3. Possibly related 4. Not related 5. Possibly related
	Target disease: 1. Not related 2. Unlikely related 3-5. Not related	
Outcome:	1-2. Recovered / resolved with sequelae 3. Recovered / resolved 4-5. Not recovered / not resolved	

Patient 01-07 was a 55-year-old man who was diagnosed with primary malignant glioma on 30 May 2018 and recurrence occurred on 12 Apr 2019. Prior cancer treatment included tumor excision and radiotherapy. Additionally, anti-cancer medications included temozolomide, lomustine, and etoposide. Relevant medical history included epilepsy (since 24 May 2018) and decreased lymphocyte count (16 May 2019 – 21 May 2019).Ongoing concomitant medications

included ondansetron (since 2018), levetiracetam (since 16 May 2018), and lorazepam (since 24 May 2018).

Patient 01-07 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 22 May 2019 followed by 3 boosting doses of 10^7 CFU/mL VXM01, in combination with 8 doses of avelumab starting on 22 May 2019. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 15 Aug 2019 and the last dose of avelumab on 26 Aug 2019.

A total of 5 significant AEs were reported for this patient during the study. No action was taken with regard to the study drugs because of these events.

On 23 May 2019, 1 day after the first dose of study drug, the patient experienced moderate decreased lymphocyte count. Treatment included sulfamethoxazole;trimethoprim (23 May 2019 – 03 July 2019). The event of decreased lymphocyte count was resolved with sequelae by 10 Jun 2019. The investigator considered the event of decreased lymphocyte count not related to the study drugs and not related to the target disease.

On 17 Jul 2019, 56 days after the first dose of study drug, the patient experienced moderate decreased lymphocyte count. Ongoing treatment included pentamidine (since 17 Jul 2019). The event of decreased lymphocyte count was resolved with sequelae by 08 Aug 2019. The investigator considered the event of decreased lymphocyte count not related to the study drugs and unlikely to the target disease.

On 26 Aug 2019, the same day as the last administration of study drug (avelumab), the patient experienced mild increased blood creatine phosphokinase and moderate decreased lymphocyte count. The patient underwent an electrocardiogram and received troponin T for the increased blood creatine phosphokinase on the same day and the event resolved by 05 Sep 2019. The patient did not receive treatment for the decreased lymphocyte count besides the ongoing pentamidine (since 17 Jul 2019) and the event was not resolved. The investigator considered the event of increased blood creatine phosphokinase not related to VXM01, possibly related to avelumab, and not related to the target disease. The investigator considered the event of decreased lymphocyte count unlikely related to VXM01 and not related to avelumab and the target disease.

On 14 Oct 2019, 49 days after the last dose of avelumab and 60 days after the last dose of VXM01, the patient experienced moderate hypothyroidism. Treatment included levothyroxine on 07 Oct 2019, 14 Oct 2019, 31 Oct 2019, and 19 Nov 2019. The event of hypothyroidism was not resolved. The investigator considered the event of hypothyroidism possibly related to avelumab and not related to VXM01 and the target disease.

Progressive disease was reported on 05 Sep 2019. On 06 Apr 2020, the patient died due to target disease progression.

Narrative for Patient 01-09

Study number:	VXM01-AVE-04-INT	
Patient number:	01-09	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 14 Jun 2019 / 10 Jun 2020 Avelumab: 14 Jun 2019 / 22 Jul 2020	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Alanine aminotransferase increased (ALT increased) 3. Gamma-glutamyltransferase increased (GGT increased) 4. Blood alkaline phosphatase increased (Alkaline phosphatase increased)	
Start/stop dates:	1. 15 Jun 2019 / 18 Jun 2019 2. 08 Jul 2020 / 14 Jul 2020 3. 08 Jul 2020 / 21 Jul 2020 4. 08 Jul 2020 / 22 Jul 2020	
Action taken with study drug:	VXM01 vaccine: 1-4. Dose not changed	Avelumab: 1. Dose not changed 2-4. Dose reduced
Intensity:	1-2. Moderate 4. Severe 5. Moderate	
Relationship	VXM01 vaccine: 1. Not related 2-4. Unlikely related	Avelumab: 1. Not related 2-4. Unlikely related
	Target disease: 1-4. Not related	
Outcome:	1. Recovered / Resolved with sequelae 2. Recovered / Resolved 3-4. Recovered / resolved with sequelae	

Patient 01-09 was a 70-year-old man who was diagnosed with primary malignant glioma on 28 May 2018 and recurrence on 10 Jul 2018, 04 Feb 2019, and 24 May 2019. Prior cancer treatment included tumor biopsy, tumor excision, and radiotherapy. Additionally, anti-cancer medications included temozolomide, lomustine, and etoposide. Relevant medical history included a first degree atrioventricular block (since 1964), prostatic obstruction (since 2008), gastroesophageal reflux disease (since Feb 2018), and a history of seizures (since Feb 2018). Concomitant medications for these medical history conditions included serenoa repens extract;urtica dioica extract (since 2008), pantoprazole (Feb 2018 – 08 Jul 2020), levetiracetam (since Feb 2018), and sodium alginate;sodium bicarbonate (since 10 Jul 2020).

Patient 01-09 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 14 Jun 2019 followed by 13 boosting doses of 10^7 CFU/mL VXM01, in combination with 30 doses of avelumab starting on 14 Jun 2019. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 10 Jun 2020 and the last dose of avelumab on 22 Jul 2020.

On 15 Jun 2019, 1 day after the first dose of study drugs, the patient experienced moderate decreased lymphocyte count. Treatment included sulfamethoxazole;trimethoprim (17 Jun 2019 – 21 Jun 2019). The event of decreased lymphocyte count was resolved with sequelae by 18 Jun 2019. No action was taken with regard to the study drugs because of this event.

On 08 Jul 2020, 28 days after the last dose of VXM01 and on the day of avelumab administration, the patient experienced moderate increased alanine aminotransferase, severe increased gamma-glutamyltransferase, and moderate increased blood alkaline phosphatase. The avelumab dose was reduced to 134.4 mg because of this event. The patient underwent a serology test (08 Jul 2020) and ultrasound of the liver (15 Jul 2020). No treatment was reported. The event of increased alanine aminotransferase was resolved by 14 Jul 2020. The events of increased gamma-glutamyltransferase and increased blood alkaline phosphatase were resolved with sequelae by 21 Jul 2020 and 22 Jul 2020, respectively.

The investigator considered all events as not related or unlikely related to the study drugs, and not related to the target disease.

Progressive disease was reported on 06 Aug 2020. On 21 Oct 2020, the patient died due to target disease progression.

Narrative for Patient 01-12

Study number:	VXM01-AVE-04-INT	
Patient number:	01-12	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 18 Oct 2019 / 13 Dec 2019 Avelumab: 18 Oct 2019 / 27 Dec 2019	
Event preferred term (verbatim term):	1. Adrenal insufficiency (adrenal insufficiency) 2. Facial paralysis (light central facial palsy left side) 3. Brain oedema (brain edema right)	
Start/stop dates:	1. 18 Oct 2019 / Ongoing 2. 26 Nov 2019 / Ongoing 3. 03 Dec 2019 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-3. Dose not changed	Avelumab: 1-3. Dose not changed
Intensity:	1-2. Mild 3. Moderate	
Relationship	VXM01 vaccine: 1-2. Not related 3. Unlikely related	Avelumab: 1-2. Not related 3. Unlikely related
	Target disease: 1. Unlikely related 2-3. Possibly related	
Outcome:	1-3. Not recovered / not resolved	

Patient 01-12 was a 56-year-old man who was diagnosed with primary malignant glioma on 11 Oct 2018 and recurrence on 09 Oct 2019. Prior cancer treatment included a craniotomy, radiotherapy, and tumor treating fields therapy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included monoparesis (since 2019), inguinal hernia (since Jul 2019), epilepsy (since 08 Aug 2019), and decreased lymphocyte (since 09 Oct 2019). Concomitant medications for these medical history conditions included levetiracetam (since 08 Aug 2019) and pentamidine (18 Oct 2019 – 23 Jan 2020).

In addition to treatment for recurrent malignant glioma, concomitant medications included calcium carbonate;colecalciferol (since 2019), pantoprazole (15 Oct 2019 – 18 Oct 2019), lomustine (21 Jan 2020), etoposide (21 Jan 2020 – 23 Jan 2020), and sulfamethoxazole;trimethoprim (since 28 Feb 2020).

Patient 01-12 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 18 Oct 2019 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of avelumab starting on 18 Oct 2019. Premedication with paracetamol and clemastine fumarate was

administered before the avelumab treatment. The patient received the last dose of VXM01 on 13 Dec 2019 and the last dose of avelumab on 27 Dec 2019.

On 18 Oct 2019, on the same day as the first administration of study drugs, the patient experienced mild adrenal insufficiency. Ongoing treatment included hydrocortisone (since 18 Oct 2019). On 26 Nov 2019, 39 days after the first dose of study drugs, the patient experienced mild facial paralysis. On 03 Dec 2019, 46 days after the first dose of study drugs, the patient experienced moderate brain oedema. A computerized tomogram of the head was done, and the treatment included dexamethasone (03 Dec 2019 – 23 Jan 2020) and pantoprazole (03 Dec 2019 – 23 Jan 2020). No action was taken with regard to the study drugs for any of the events. All 3 events were ongoing at the time of database lock.

The investigator considered all 3 events not related or unlikely related to the study drugs. The investigator considered the event of adrenal insufficiency unlikely related to the target disease, and the events of facial paralysis and brain oedema as possibly related to the target disease.

Progressive disease was reported on 10 Jan 2020. On 21 Sep 2020, the patient died due to target disease progression.

Narrative for Patient 01-13

Study number:	VXM01-AVE-04-INT	
Patient number:	01-13	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 23 Sep 2020 / 18 Nov 2020 Avelumab: 23 Sep 2020 / 02 Dec 2020	
Event preferred term (verbatim term):	1. Influenza like illness (flu like symptoms) 2. Platelet count decreased (platelet count decreased) 3. Blood potassium increased (potassium increased) 4. Hypertension (hypertension) 5. Rash (rash neck and face)	
Start/stop dates:	1. 23 Sep 2020 / 24 Sep 2020 2. 04 Nov 2020 / 09 Nov 2020 3. 04 Nov 2020 / 18 Nov 2020 4. 04 Nov 2020 / 18 Nov 2020 5. 04 Nov 2020 / 02 Dec 2020	
Action taken with study drug:	VXM01 vaccine: 1-5. Dose not changed	Avelumab: 1. Dose not changed 2. Drug interrupted 3. Dose not changed 4. Drug interrupted 5. Dose not changed
Intensity:	1. Mild 2. Moderate 3. Mild 4. Severe 5. Mild	
Relationship	VXM01 vaccine: 1. Possibly related 2. Unlikely related 3-4. Not related 5. Unlikely related	Avelumab: 1. Possibly related 2. Unlikely related 3-4. Not related 5. Possibly related
	Target disease: 1. Not related 2. Unlikely related 3-5. Not related	
Outcome:	1-5. Recovered / resolved	

Patient 01-13 was a 78-year-old woman who was diagnosed with primary malignant glioma on 22 Jan 2019 and recurrence on 10 Sep 2020. Prior cancer treatment included tumor resection and

radiotherapy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included a thyroidectomy (in 1965), hypothyroidism (since 1965), a hysterectomy (in 1990), an oophorectomy (in 1990), a cholecystectomy (in 2000), fructose intolerance (since 2000), hypertension (since 2000), cataract (in 2016), and aphthous ulcer (since 2019). Concomitant medications for these medical history conditions included levothyroxine (since 1965), bisoprolol (2000 – 03 Nov 2020), chlorhexidine gluconate;macrogol;saccharin sodium;sodium bicarbonate;sodium edetate (since 2019), chlorhexidine gluconate (since 11 Nov 2020), and amlodipine (19 Nov 2020 – 02 Dec 2020).

In addition to treatment for recurrent malignant glioma, concomitant medications included pantoprazole (since 2019) and ramipril (since 22 Sep 2020).

Patient 01-13 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 23 Sep 2020 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 5 doses of avelumab starting on 23 Sep 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 18 Nov 2020 and the last dose of avelumab on 02 Dec 2020.

On 23 Sep 2020, on the same day as the first administration of study drugs, the patient experienced mild influenza-like illness. Treatment included paracetamol (23 Sep 2020). The event of influenza-like illness was resolved by 24 Sep 2020. No action was taken with regard to the study drugs because of this event. The investigator considered the event of influenza-like illness possibly related to VXM01 and avelumab, and not related to the target disease.

On 04 Nov 2020, 42 days after the first dose of study drugs, the patient experienced moderate decreased platelet count, mild increased blood potassium, severe hypertension, and mild rash. Treatment included bisoprolol (since 04 Nov 2020), amlodipine (05 Nov 2020 – 10 Nov 2020), dimetindene maleate (09 Nov 2020 – 02 Dec 2020), and hydrochlorothiazide (10 Nov 2020 – 02 Dec 2020). The event of decreased platelet count was resolved by 09 Nov 2020 and considered unlikely related to the study drugs and the target disease. The events of increased blood potassium and hypertension were resolved by 18 Nov 2020 and considered not related to study drugs and target disease. The event of rash was resolved by 02 Dec 2020 and considered unlikely related to VXM01, possibly related to avelumab, and not related to the target disease. No action was taken with regard to VXM01 for any of the events and the avelumab administration was interrupted because of the events of decreased platelet count and hypertension.

Progressive disease was reported on 14 Dec 2020. On 09 Feb 2022, the patient died due to target disease progression.

Narrative for Patient 01-14

Study number:	VXM01-AVE-04-INT	
Patient number:	01-14	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg Procedure: Tumor excision	
Date of first/last dose:	VXM01 vaccine: 30 Sep 2020 / 03 Aug 2022 Avelumab: 30 Sep 2020 / 03 Aug 2022 Procedure: 03 Nov 2020	
Event preferred term (verbatim term):	1. Blood potassium decreased (potassium decreased) 2. Blood potassium decreased (potassium decreased) 3. Autoimmune thyroiditis (immune thyreoditis) 4. Hypothyroidism (hypothyreosis) 5. White blood cell count decreased (while blood cell decreased) 6. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 30 Sep 2020 / 01 Oct 2020 2. 09 Dec 2020 / 23 Dec 2020 3. 23 Dec 2020 / Ongoing 4. 23 Dec 2020 / Ongoing 5. 07 Jan 2021 / 17 Feb 2021 6. 26 May 2021 / 09 Jun 2021	
Action taken with study drug:	VXM01 vaccine: 1-6. Dose not changed	Avelumab: 1-6. Dose not changed
Intensity:	1. Moderate 2. Mild 3-4. Moderate 5-6. Mild	
Relationship	VXM01 vaccine: 1-4. Not related 5-6. Unlikely related	Avelumab: 1-2. Not related 3-4. Probably related 5-6. Unlikely related
	Target disease: 1-4. Not related 5-6. Unlikely related	
Outcome:	1-2. Recovered / resolved 3-4. Not recovered / not resolved 5-6. Recovered / resolved	

Patient 01-14 was a 60-year-old woman who was diagnosed with primary malignant glioma on 23 Mar 2020 and recurrence on 16 Sep 2020. Prior cancer treatment included tumor resection, craniotomy, and radiotherapy. Additionally, anti-cancer medications included lomustine and

temozolomide. Relevant medical history included a history of seizures (since 11 Mar 2020). Ongoing medications for this medical history condition included levetiracetam (since 11 Mar 2020) and pantoprazole (since 11 Mar 2020).

Patient 01-14 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 30 Sep 2020 followed by 22 boosting doses of 10^7 CFU/mL VXM01, in combination with 48 doses of avelumab starting on 30 Sep 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. On 03 Nov 2020, the patient underwent tumor excision. She received the last dose of VXM01 and avelumab on 03 Aug 2022.

On 30 Sep 2020, on the same day as the first dose of study drugs, the patient experienced moderate decreased blood potassium. Treatment included potassium carbonate;potassium citrate (since 30 Sep 2020). The event of decreased blood potassium was resolved by 01 Oct 2020.

On 09 Dec 2020, 70 days after the first dose of study drugs, the patient experienced mild decreased blood potassium. Apart from the ongoing concomitant medication potassium carbonate;potassium citrate (since 30 Sep 2020), no treatment was reported. The event of decreased blood potassium was resolved by 23 Dec 2020.

On 23 Dec 2020, 84 days after the first dose of study drugs, the patient experienced moderate autoimmune thyroiditis and moderate hypothyroidism. Treatment included levothyroxine (since 23 Dec 2020). Both events were ongoing at the time of database lock.

On 07 Jan 2021, 99 days after the first dose of study drugs, the patient experienced moderate decreased white blood cell count. No treatment was reported. The event of decreased white blood cell count was resolved by 17 Feb 2021.

On 26 May 2021, 238 days after the first dose of study drugs, the patient experienced mild decreased lymphocyte count. Treatment included pentamidine (26 May 2021 – 09 Jun 2021). The event was resolved by 09 Jun 2021.

All events were considered not related or unlikely related to VXM01 and the target disease. The events of autoimmune thyroiditis and hypothyroidism were considered probably related to avelumab, all other events were considered not related or unlikely related to avelumab.

No action was taken with regard to the study drugs for any of the events. No progressive disease was reported at the time of database lock.

Narrative for Patient 01-17

Study number:	VXM01-AVE-04-INT	
Patient number:	01-17	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7CFU/mL Avelumab: 800 mg Procedure: Tumor excision	
Date of first/last dose:	VXM01 vaccine: 11 Nov 2020 / 05 Jan 2021 Avelumab: 11 Nov 2020 / 20 Jan 2021 Procedure: 08 Dec 2020	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Fine motor skill dysfunction (fine motor skills left impaired) 3. Hemiparesis (hemiparesis left) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Lymphocyte count decreased (lymphocyte count decreased) 6. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 25 Nov 2020 / 04 Jan 2021 2. 09 Dec 2020 / Ongoing 3. 09 Dec 2020 / Ongoing 4. 05 Jan 2021 / 01 Feb 2021 5. 02 Feb 2021 / 18 Mar 2021 6. 19 Mar 2021 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-6. Dose not changed	Avelumab: 1-6. Dose not changed
Intensity:	1-3. Mild 4. Moderate 5. Mild 6. Moderate	
Relationship	VXM01 vaccine: 1. Unlikely related 2-3. Not related 4-6. Unlikely related	Avelumab: 1. Unlikely related 2-3. Not related 4-6. Unlikely related
	Target disease: 1. Unlikely related 2-3. Definitely related 4-5. Unlikely related 6. Not related	
Outcome:	1. Recovered with sequelae 2-3. Not recovered / not resolved 4-5. Recovered with sequelae 6. Not recovered / not resolved	

Patient 01-17 was a 36-year-old man who was diagnosed with primary malignant glioma on 15 Dec 2016 and recurrence on 25 Oct 2019. Prior cancer treatment included a craniotomy and radiotherapy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included a history of seizures (since 03 Feb 2017), decreased lymphocyte count (26 Apr 2019 – 24 Nov 2020), and hypoaesthesia (since 02 Nov 2020). Ongoing medications for these medical history conditions included levetiracetam (since 03 Feb 2017).

In addition to treatment for recurrent malignant glioma, the patient underwent physiotherapy from 05 Jan 2021 to 14 Jul 2021.

Patient 01-17 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 11 Nov 2020 followed by 1 boosting dose of 10^7 CFU/mL VXM01, in combination with 4 doses of avelumab starting on 11 Nov 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. On 08 Dec 2020, Patient 01-17 underwent tumor excision. The patient received the last dose of VXM01 on 05 Jan 2021 and the last dose of avelumab on 20 Jan 2021.

On 25 Nov 2020, 14 days after the first dose of study drugs, the patient experienced mild decreased lymphocyte count. Treatment included pentamidine (since 11 Nov 2020). The event of decreased lymphocyte count was resolved by 04 Jan 2021.

On 09 Dec 2020, 28 days after the first dose of study drugs, the patient experienced mild fine motor skill dysfunction and mild hemiparesis. Treatment included metamizole (since 09 Dec 2020) and pantoprazole (since 09 Dec 2020). The events of fine motor skill dysfunction and hemiparesis were ongoing at the time of database lock.

On 05 Jan 2020, on the day of the last dose of VXM01, the patient experienced moderate decreased lymphocyte count. The event was resolved with sequelae by 01 Feb 2021. On 02 Feb 2021, 28 days after the last dose of VXM01 and 13 days after the last dose of avelumab, the patient experienced mild decreased lymphocyte count. The event was resolved with sequelae by 18 Mar 2021. On 19 Mar 2021, 73 days after the last dose of VXM01 and 58 days after the last dose of avelumab, the patient experienced moderate decreased lymphocyte count. The event was ongoing at the time of database lock. No treatment was reported other than the ongoing concomitant medications listed above.

No action was taken with regard to the study drugs because the events. All events were considered not related or unlikely related to the study drugs. The events of fine motor skill dysfunction and hemiparesis were considered definitely related to the target disease, all other events were considered not related or unlikely related to the target disease.

Progressive disease was reported on 02 Feb 2021. On 09 Apr 2022, the patient died due to target disease progression.

Narrative for Patient 01-18

Study number:	VXM01-AVE-04-INT	
Patient number:	01-18	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 11 Nov 2020 / 08 Jan 2021 Avelumab: 11 Nov 2020 / 22 Jan 2021	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 05 Nov 2020 / 01 Dec 2020 2. 09 Dec 2020 / 21 Dec 2020	
Action taken with study drug:	VXM01 vaccine: 1-2. Dose not changed	Avelumab: 1-2. Dose not changed
Intensity:	1-2. Mild	
Relationship	VXM01 vaccine: 1-2. Not related	Avelumab: 1-2. Not related
	Target disease: 1. Not related 2. Unlikely related	
Outcome:	1-2. Recovered / resolved	

Patient 01-18 was a 49-year-old man who was diagnosed with primary malignant glioma on 16 Dec 2019 and recurrence on 21 Oct 2020. Prior cancer treatment included tumor excision, radiotherapy, and tumor treating fields therapy. Additionally, anti-cancer medications included temozolomide and abemaciclib. Relevant medical history included a history of seizures (since Dec 2019) and prostate enlargement (since 2018).

Patient 01-18 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 11 Nov 2020 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of avelumab starting on 11 Nov 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 08 Jan 2021 and the last dose of avelumab on 22 Jan 2021.

Patient 01-18 experienced 2 events of decreased lymphocyte count, with 1 of them occurring before starting study drug. On 05 Nov 2021, 6 days before the first dose of study drugs, the patient experienced mild decreased lymphocyte count. Ongoing treatment included pentamidine (since 12 Nov 2020). The event was resolved by 01 Dec 2020 and considered not related to the study drugs or to the target disease. On 09 Dec 2020, 29 days after the first dose of study drugs, the patient again experienced mild decreased lymphocyte count. The event was resolved by 21 Dec 2021 and considered not related to the study drugs and unlikely related to the target disease.

No action was taken with regard to the study drugs for either of the events.

Progressive disease was reported on 02 Feb 2021. On 19 Oct 2021, the patient died due to target disease progression.

Narrative for Patient 01-20

Study number:	VXM01-AVE-04-INT	
Patient number:	01-20	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 16 Dec 2020 / 10 Feb 2021 Avelumab: 16 Dec 2020 / 24 Feb 2021	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Lymphocyte count decreased (lymphocyte count decreased) 3. Lymphocyte count decreased (lymphocyte count decreased) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 17 Dec 2020 / 21 Dec 2020 2. 22 Dec 2020 / 04 Jan 2021 3. 05 Jan 2021 / 12 Jan 2021 4. 13 Jan 2021 / 27 Jan 2021 5. 24 Feb 2021 / 08 Mar 2021	
Action taken with study drug:	VXM01 vaccine: 1-5. Dose not changed	Avelumab: 1-5. Dose not changed
Intensity:	1. Severe 2. Moderate 3. Severe 4. Mild 5. Moderate	
Relationship	VXM01 vaccine: 1. Not related 2-3. Unlikely related 4. Not related 5. Unlikely related	Avelumab: 1. Not related 2-3. Unlikely related 4. Not related 5. Unlikely related
	Target disease: 1. Possibly related 2-3. Unlikely related 4. Not related 5. Unlikely related	
Outcome:	1. Recovered / resolved 2-3. Recovered / resolved with sequelae 4-5. Recovered / resolved	

Patient 01-20 was a 63-year-old man who was diagnosed with primary malignant glioma on 25 Jul 2018 and recurrence on 24 Nov 2020. Prior cancer treatment included radiotherapy and craniotomy. Additionally, anti-cancer medications included temozolomide. Relevant medical

history included mixed testicular germ cell tumor (Feb 1996 – Mar 1996), renal neoplasm (Feb 2005 – Mar 2005), hypertonia (since 2011), abdominal hernia (since 2014), lumbar spinal stenosis (since 2014), benign prostatic hyperplasia (since 2016), intervertebral disc protrusion (since Feb 2018), pulmonary embolism (Jul 2018 – Aug 2018), increased coagulation Factor VII level (since Sep 2018), pneumonia klebsiella (since Sep 2018). Ongoing medications for these medical history conditions included metoprolol (since 2011), sativa cannabis (since 2014), tamsulosin (since 2016), and apixaban (since Jul 2018).

Patient 01-20 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 16 Dec 2020 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of avelumab starting on 16 Dec 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 10 Feb 2021 and the last dose of avelumab on 24 Feb 2021.

Patient 01-20 experienced 5 events of decreased lymphocyte count of different severity. On 17 Dec 2021, 1 day after the first dose of study drugs, the patient experienced severe decreased lymphocyte count. Ongoing treatment included pentamidine (since 17 Dec 2020). The event was resolved by 21 Dec 2020 and considered not related to the study drugs and possibly related to the target disease.

On 22 Dec 2020, 6 days after the first dose of study drugs, the patient experienced moderate decreased lymphocyte count. The event was resolved with sequelae by 04 Jan 2021. On 05 Jan 2021, 20 days after the first dose of study drugs, the patient experienced severe decreased lymphocyte count. The event was resolved with sequelae by 12 Jan 2021. On 13 Jan 2021, 28 days after the first dose of study drugs, the patient experienced mild decreased lymphocyte count. The event was resolved by 27 Jan 2021. On 24 Feb 2021, on the day of the last dose of avelumab, the patient experienced moderate decreased lymphocyte count. The event was resolved by 08 Mar 2021. All events from 22 Dec 2020 and after were considered not or unlikely related to the study drugs and the target disease.

No action was taken with regard to the study drugs for any of the events.

Progressive disease was reported on 08 Mar 2021. On 22 Jun 2022, the patient died due to target disease progression.

Narrative for Patient 01-25

Study number:	VXM01-AVE-04-INT	
Patient number:	01-25	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 17 Mar 2021 / 12 May 2021 Avelumab: 17 Mar 2021 / 26 May 2021	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Lymphocyte count decreased (lymphocyte count decreased) 3. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 18 Mar 2021 / 27 Mar 2021 2. 31 Mar 2021 / 05 Apr 2021 3. 06 Apr 2021 / 09 Jun 2021	
Action taken with study drug:	VXM01 vaccine: 1-3. Dose not changed	Avelumab: 1-3. Dose not changed
Intensity:	1-2. Moderate 3. Mild	
Relationship	VXM01 vaccine: 1. Unlikely related 2-3. Not related	Avelumab: 1. Unlikely related 2-3. Not related
	Target disease: 1-3. Not related	
Outcome:	1-2. Recovered / resolved with sequelae 3. Recovered / resolved	

Patient 01-25 was a 53-year-old man who was diagnosed with primary malignant glioma on 04 Sep 2020 and recurrence on 23 Feb 2021. Prior cancer treatment included radiotherapy and brain lobectomy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included epilepsy (since Sep 2020), and medication for epilepsy was levetiracetam (since Sep 2020).

Patient 01-25 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 17 Mar 2021 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of avelumab starting on 17 Mar 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 12 May 2021 and the last dose of avelumab on 26 May 2021.

Patient 01-25 experienced 3 events of decreased lymphocyte count of mild or moderate severity. On 18 Mar 2021, 2 days after the first dose of study drugs, the patient experienced moderate decreased lymphocyte count. Ongoing treatment included pentamidine (since 18 Mar 2021). The event was resolved with sequelae by 27 Mar 2021 and considered unlikely related to the study drugs and not related to the target disease.

On 31 Mar 2021, 15 days after the first dose of study drugs, the patient again experienced moderate decreased lymphocyte count. The event was resolved with sequelae by 05 Apr 2021. On 06 Apr 2021, 21 days after the first dose of study drugs, the decreased lymphocyte count improved to mild severity. The event was resolved by 09 Jun 2021. Both events were considered not related to the study drugs and the target disease.

No action was taken with regard to the study drugs for any of the events.

Progressive disease was reported on 07 Jun 2021. On 02 Oct 2021, the patient died due to target disease progression.

Narrative for Patient 01-27

Study number:	VXM01-AVE-04-INT	
Patient number:	01-27	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 26 May 2021 /13 Oct 2021 Avelumab: 26 May 2021 / 27 Oct 2021	
Event preferred term (verbatim term):	1. Lymphocyte count decreased (lymphocyte count decreased) 2. Lymphocyte count decreased (lymphocyte count decreased) 3. Lymphocyte count decreased (lymphocyte count decreased) 4. Lymphocyte count decreased (lymphocyte count decreased) 5. Lymphocyte count decreased (lymphocyte count decreased) 6. Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	1. 12 May 2021 /14 May 2021 2. 14 May 2021 / 19 May 2021 3. 25 May 2021 / 25 May 2021 4. 26 May 2021 / 15 Sep 2021 5. 29 Sep 2021 / 12 Oct 2021 6. 13 Oct 2021 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-6. Dose not changed	Avelumab: 1-6. Dose not changed
Intensity:	1. Life-threatening 2. Severe 3. Mild 4. Moderate 5. Severe 6. Moderate	
Relationship	VXM01 vaccine: 1-4. Not related 5-6. Unlikely related	Avelumab: 1-4. Not related 5-6. Unlikely related
	Target disease: 1-4. Not related 5-6. Unlikely related	
Outcome:	1. Recovered / resolved with sequelae 2. Recovered / resolved 3-5. Recovered / resolved with sequelae 6. Not recovered / resolved	

Patient 01-27 was a 71-year-old man who was diagnosed with primary malignant glioma on 29 Sep 2020 and recurrence on 29 Apr 2021. Prior cancer treatment included radiotherapy and a brain operation. Additionally, anti-cancer medications included temozolomide. Relevant medical history included migraine with aura (since 2000), lumbar spinal stenosis (2016 – 2016), hypertension (since 2017), inguinal hernia (2019 – 2019), depression (since 15 Sep 2020), fine motor skill dysfunction and hemianopia homonymous (since Oct 2020), and lymphocyte count decreased (Apr 2021 – 12 May 2021). Ongoing medications for these medical history conditions included trimipramine maleate (15 Sep 2020 – 23 Jun 2021) and pregabalin (since 07 Jul 2021).

Patient 01-27 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 26 May 2021 followed by 5 boosting doses of 10^7 CFU/mL VXM01, in combination with 12 doses of avelumab starting on 26 May 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 13 Oct 2021 and the last dose of avelumab on 27 Oct 2021.

Patient 01-27 experienced 6 events of decreased lymphocyte count of different severity, of which 3 events occurred before the start of study drugs. On 12 May 2021, 14 days before the first dose of study drugs, the patient experienced life-threatening decreased lymphocyte count that lasted for 3 days and had resolved by 15 May 2021. The event improved to severe and then to mild before the start of study drugs. Ongoing treatment included pentamidine (since 14 May 2021).

On 26 May 2021, 1 day after the first dose of study drugs, the patient experienced moderate decreased lymphocyte count. The event was resolved with sequelae by 15 Sep 2021. On 29 Sep 2021, 127 days after the first dose of study drugs, the severity of the decreased lymphocyte count increased to severe. The severity returned to moderate again on 13 Oct 2021, 141 days after the first dose of study drugs and remained ongoing. All 6 events of decreased lymphocyte count were considered not or unlikely related to the study drugs and the target disease.

No action was taken with regard to the study drugs for any of the events.

Progressive disease was reported on 09 Nov 2021.

Narrative for Patient 01-31

Study number:	VXM01-AVE-04-INT	
Patient number:	01-31	
Reason for narrative:	Significant AE	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 28 Jul 2021 / 04 Aug 2021 Avelumab: 28 Jul 2021 / 25 Aug 2021	
Event preferred term (verbatim term):	Lymphocyte count decreased (lymphocyte count decreased)	
Start/stop dates:	29 Jul 2021 / 31 Jul 2021	
Action taken with study drug:	VXM01 vaccine: Dose not changed	Avelumab: Dose not changed
Intensity:	Moderate	
Relationship	VXM01 vaccine: Unlikely related	Avelumab: Unlikely related
	Target disease: Unlikely related	
Outcome:	Recovered / resolved	

Patient 01-31 was a 59-year-old man who was diagnosed with primary malignant glioma on 28 Sep 2020 and recurrence on 15 Jul 2021. Prior cancer treatment included radiotherapy and a craniotomy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included hypertension (no dates provided), vitamin B12 decreased (since 2021), and epilepsy (since 21 Feb 2021). Ongoing medications for these medical history conditions included vitamin B12 (since 2021), levetiracetam (since 21 Feb 2021), and lamotrigine (since 21 Jul 2021).

Patient 01-31 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 28 Jul 2021 and no boosting doses of 10^7 CFU/mL VXM01, in combination with 3 doses of avelumab starting on 28 Jul 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 04 Aug 2021 and the last dose of avelumab on 25 Aug2021.

Patient 01-31 experienced 1 event of moderate decreased lymphocyte count. On 29 Jul 2021, 1 day after the first dose of study drugs, the patient experienced decreased lymphocyte count that lasted for 3 days and had resolved by 31 Jul 2021. The event was considered unlikely related to the study drugs and the target disease. No action was taken with regard to the study drugs.

Progressive disease was reported on 26 Aug 2021. On 02 Oct 2021, the patient died due to target disease progression.

Narrative for Patient 02-15

Study number:	VXM01-AVE-04-INT	
Patient number:	02-15	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 07 Oct 2020 / 04 Nov 2020 Avelumab: 07 Oct 2020 / 04 Nov 2020	
Event preferred term (verbatim term):	1. Personality change (personality changes) 2. Headache (headache) 3. Nausea (nausea) 4. Vomiting (vomiting)	
Start/stop dates:	1. 14 Nov 2020 / 20 Nov 2020 2. 14 Nov 2020 / Ongoing 3. 14 Nov 2020 / Ongoing 4. 14 Nov 2020 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-4. Dose not changed	Avelumab: 1-4. Dose not changed
Intensity:	1. Severe 2. Mild 3-4. Moderate	
Relationship	VXM01 vaccine: 1-4. Not related	Avelumab: 1-4. Not related
	Target disease: 1-4. Definitely related	
Outcome:	1. Recovered / resolved 2-4. Not recovered / not resolved	

Patient 02-15 was a 37-year-old man who was diagnosed with primary malignant glioma on 23 Oct 2019 and recurrence on 11 Aug 2020. Prior cancer treatment included radiotherapy, brain operation, and tumor treating fields therapy. Additionally, anti-cancer medications included temozolomide. Relevant medical history included hypertriglyceridemia (no dates reported), hypertension (since Sep 2019), and lymphopenia (since 27 Aug 2020). Ongoing medications for these medical history conditions included amlodipine and candesartan (both Sep 2019 – Aug 2020 and restarting on 16 Nov 2020).

Patient 02-15 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 07 Oct 2020 followed by 1 boosting dose of 10^7 CFU/mL VXM01, in combination with 3 doses of avelumab starting on 07 Oct 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of both VXM01 and avelumab on 04 Nov 2020.

On 14 Nov 2020, 10 days after the last dose of study drugs, the patient experienced severe personality change, mild headache, moderate nausea, and moderate vomiting. Treatment included dimenhydrinate, metamizole sodium, and dexamethasone (all since 16 Nov 2020). The event of personality change resolved by 20 Nov 2020, while the other events were ongoing at the time of database lock. All events were considered not related to the study drugs and definitely related to the target disease.

No action was taken with regard to the study drugs for any of the events.

Progressive disease was reported on 17 Nov 2020. On 11 Mar 2021, the patient died due to target disease progression.

Narrative for Patient 02-16

Study number:	VXM01-AVE-04-INT	
Patient number:	02-16	
Reason for narrative:	Significant AE(s)	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 20 Oct 2020 / 16 Dec 2020 Avelumab: 20 Oct 2020 / 30 Dec 2020	
Event preferred term (verbatim term):	1. Headache (headache) 2. Nausea (nausea) 3. Urinary tract infection (urinary tract infection)	
Start/stop dates:	1. 30 Oct 2020 / Ongoing 2. 07 Dec 2020 / 09 Dec 2020 3. 12 Jan 2021 / Ongoing	
Action taken with study drug:	VXM01 vaccine: 1-3. Dose not changed	Avelumab: 1-3. Dose not changed
Intensity:	1. Mild 2-3. Moderate	
Relationship	VXM01 vaccine: 1-2. Possibly related 3. Probably related	Avelumab: 1-2. Possibly related 3. Probably related
	Target disease: 1. Probably related 2. Possibly related 3. Not related	
Outcome:	1. Not recovered / not resolved 2. Recovered / resolved 3. Recovering / resolving	

Patient 02-16 was a 60-year-old man who was diagnosed with primary malignant glioma on 04 Jan 2019 and recurrence on 06 Oct 2020. Prior cancer treatment included radiotherapy and brain operation. Additionally, anti-cancer medications included temozolomide. Relevant medical history included hypothyroidism (since 2004), sciatica (since 2015), depression (since 2019), and epilepsy (since Jan 2019). Ongoing medications for these medical history conditions included levothyroxine sodium (since 2004), levetiracetam (since Dec 2018), lorazepam (since 2019), and paroxetine (since Jan 2019).

Patient 02-16 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 20 Oct 2020 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of

avelumab starting on 20 Oct 2020. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 16 Dec 2020 and the last dose of avelumab on 30 Dec 2020.

On 30 Oct 2020, 10 days after the first dose of study drugs, the patient experienced a mild headache. Treatment included ibuprofen (since 25 Oct 2020). The event was ongoing at the time of database lock.

On 07 Dec 2020, 48 days after the first dose of study drugs, the patient experienced moderate nausea. Treatment included dexamethasone (07 Dec 2020 – 09 Dec 2020). The event was resolved by 09 Dec 2020.

On 12 Jan 2021, 27 days after the last dose of VXM01 and 13 days after the last dose of avelumab, the patient experienced a moderate urinary tract infection. Treatment included cefpodoxime (12 Jan 2021 – 19 Jan 2021). The event was ongoing at the time of database lock.

The events of headache and nausea were considered possibly related to both study drugs; the headache was considered probably related to the target disease, and the nausea possibly related to the target disease. Finally, the urinary tract infection was considered probably related to both study drugs and not related to the target disease.

Progressive disease was reported on 12 Jan 2021. On 14 Feb 2021, the patient died due to target disease progression.

Narrative for Patient 02-24

Study number:	VXM01-AVE-04-INT	
Patient number:	02-24	
Reason for narrative:	Significant AEs	
Study medication:	VXM01 vaccine: 10^7 CFU/mL Avelumab: 800 mg	
Date of first/last dose:	VXM01 vaccine: 05 Jan 2021 / 03 March 2021 Avelumab: 05 Jan 2021 / 17 Mar 2021	
Event preferred term (verbatim term):	1. Gastrooesophageal reflux disease (gastroesophageal reflux disease) 2. Diarrhoea (diarrhea)	
Start/stop dates:	1. 07 Jan 2021 / 14 Mar 2021 2. 12 Jan 2021 / 13 Jan 2021	
Action taken with study drug:	VXM01 vaccine: 1-2. Dose not changed	Avelumab: 1-2. Dose not changed
Intensity:	1. Moderate 2. Mild	
Relationship	VXM01 vaccine: 1-2. Possibly related	Avelumab: 1-2. Possibly related
	Target disease: 1. Not related 2. Definitely related	
Outcome:	1-2. Recovered / resolved	

Patient 02-24 was a 65-year-old woman who was diagnosed with primary malignant glioma on 16 Jan 2017 and recurrence on 15 Dec 2020. Prior cancer treatment included radiotherapy, brain operation, tumor treating fields therapy, and tumor excision. Additionally, anti-cancer medications included temozolomide and lomustine. Relevant medical history included drug intolerance to beta blockers (since 2005), hypothyroidism (since 2016), epilepsy (since Jan 2017), depression (since 2018), hypertension (since 2018), and numerous environmental and substance allergies. Ongoing medications for these medical history conditions included levothyroxine sodium (since 2016), lamotrigine (since 2017), amlodipine (since 2018), irbesartan (since 2018), duloxetine (since 2018), pipamperone hydrochloride (Jan 2020 – 30 Mar 2021), and mirtazapine (31 Mar 2021 – ongoing).

Patient 02-24 was assigned to receive oral administration of 10^7 CFU/mL VXM01 and i.v. administration of avelumab 800 mg. The patient received 4 priming doses starting on 05 Jan 2021 followed by 2 boosting doses of 10^7 CFU/mL VXM01, in combination with 6 doses of avelumab starting on 05 Jan 2021. Premedication with paracetamol and clemastine fumarate was administered before the avelumab treatment. The patient received the last dose of VXM01 on 03 Mar 2021 and avelumab on 17 Mar 2021.

On 07 Jan 2021, 2 days after the first dose of study drugs, the patient experienced moderate gastroesophageal reflux disease. Treatment included pantoprazole (ongoing since 07 Jan 2021). On 12 Jan 2021, 7 days after the first dose of study drugs, the patient experienced mild diarrhea. Treatment included loperamide hydrochloride (12 Jan 2021 – 26 Feb 2021). The event of diarrhea resolved by 13 Jan 2021, while the gastroesophageal reflux disease resolved by 14 Mar 2021. Both events were considered possibly related to the study drugs. The gastroesophageal reflux disease was considered not related to the target disease, whereas the diarrhea was considered definitely related to the target disease.

No action was taken with regard to the study drugs for any of the events.

Progressive disease was reported on 31 Mar 2021. On 12 Jul 2021, the patient died due to target disease progression.

14.3.4 Abnormal Laboratory Value Listing (each patient)

15. REFERENCE LIST

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16. APPENDICES

The following appendices are included as separate files.

16.1 Trial Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form

16.1.3 List of Independent Ethics Committees or Institutional Review Boards

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