CLINICAL STUDY REPORT ADDENDUM

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:	14 February 2025
Report Version:	Final v1.0

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.

SIGNATURE PAGE

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.

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

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

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 – 16.3) 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, 31 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 4.0% having stable disease as well as an OS of 2.2 to 46.5 months in resected patients, it appears that that further investigations in suitable designed studies of this combination therapy in subgroups of glioblastoma patients may yield clearer results.
- 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: 14 February, 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. 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

6. 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.

6.1 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)

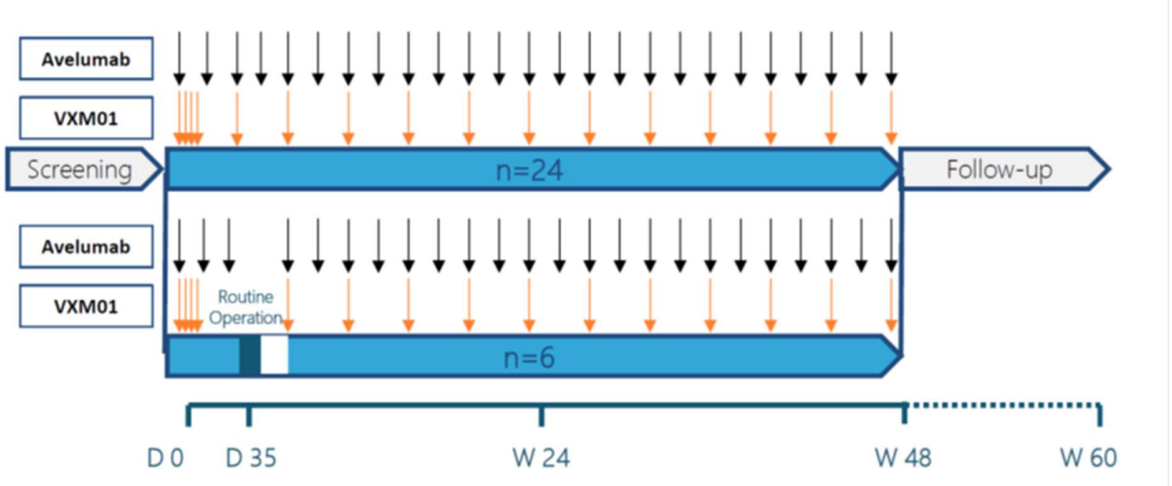
Patients who were candidates for tumor re-operation but, for any reason, did not have this routine surgical resection were allowed to enter the non-resectable cohort if this was agreed by the investigator and medical monitor.

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 6-1 and a detailed schematic of the trial design is presented in Figure 6-2.

Figure 6-1: 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.

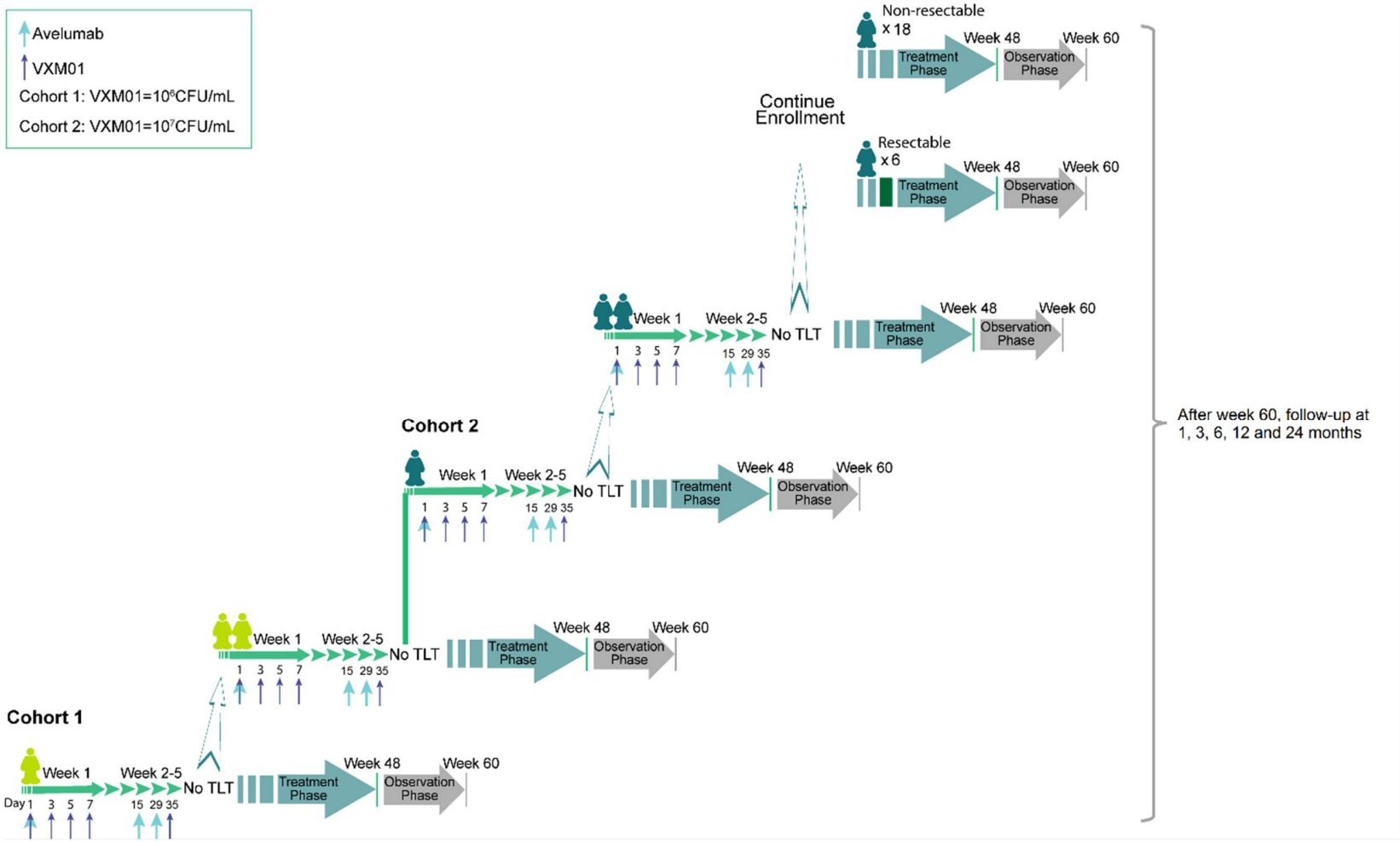
During the prolongation phase VXM01 vaccine in combination with avelumab was administered from Week 52 to Week 96 (VXM01 in a 4-weekly administration scheme and avelumab in a 2-weekly administration scheme), followed by an observation phase of 8 weeks. The end of patient-specific treatment prolongation 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.

For additional information related to protocol-specified procedures, please see the original CSR.

Figure 6-2: Trial Design Schematic



Source: Protocol Figure 3-2

6.1.1 Safety Run-in

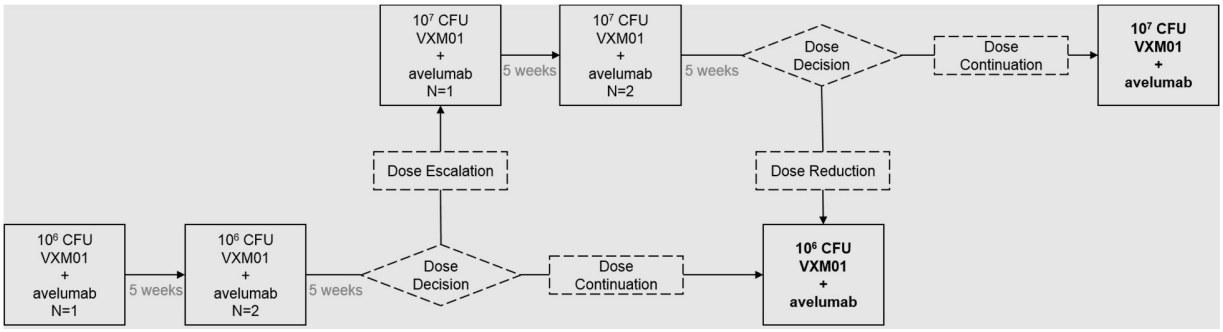
The safety run was planned to investigate 2 doses of VXM01 vaccine, 10^6 CFU/mL and 10^7 CFU/mL (Figure 6-3).

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 the original CSR.

Figure 6-3: Staggered Dosing and Dose Escalation During Safety Run-in



Source: Protocol Figure 3-3

7. STUDY PATIENTS

7.1 Disposition of Patients

The primary reasons for discontinuation of study treatment and discontinuation from the study are detailed in Table 7-1. 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 (85.7% overall). One patient (10^7 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.

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 7-1: Discontinuation from Study Treatment 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 from 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	1 (33.3)	1 (4.0)	-	1 (33.3)	1 (4.0)	2 (7.1)
Discontinued Study	2 (66.7)	24 (96.0)	22 (100)	2 (66.7)	24 (96.0)	26 (92.9)
Primary Reason for Discontinuation from Study						
Death	2 (66.7)	22 (88.0)	20 (90.9)	2 (66.7)	22 (88.0)	24 (85.7)
Progressive Disease	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)
Study Terminated by Sponsor	-	1 (4.0)	1 (4.5)	-	1 (4.0)	1 (3.6)

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

7.2 Protocol Deviations

A listing of the major protocol deviations is provided in Table 7-2. 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 4 patients assigned to receive 10^7 CFU/mL VXM01 vaccine (Listing 16.2.4.1). 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 7-2: 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

8. EFFICACY EVALUATION

The primary objective of the study was to evaluate the safety of the IMP. Safety results are presented in Section 9.

8.1 Data Sets Analyzed

Please see the original report for information about the datasets analyzed.

8.2 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.

8.2.1 Demographics and Baseline Characteristics

The demographics and baseline characteristics are summarized in Table 8-1.

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 8-1: 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

	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)		
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

8.2.2 Cancer Diagnosis and Treatment

8.2.2.1 Primary Cancer Diagnosis

Details on the primary cancer diagnosis per group are summarized in Table 8-2 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 8-2: 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[ab] (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 (11.22)	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)
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.

8.2.2.2 Previous Anti-Cancer Therapy

The previous anti-cancer therapy of patients in the SAF is summarized in Table 8-3 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).

8.2.2.3 Previous Anti-Cancer Procedures

Previous anti-cancer procedures reported for patients in the SAF are presented in Table 8-4. 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.

8.2.3 Medical History

A summary of the medical history occurring in ≥ 10% of patients overall is provided in Table 8-5 (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.

8.2.4 Prior Medications and Procedures

A summary of prior medications reported for ≥ 10% of patients overall is provided in Table 8-6 (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.

8.3 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 9.1.

Table 8-3: 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 8-4: 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 8-5: 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 8-6: 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.

8.4 Analysis of Efficacy

8.4.1 Tumor Response

8.4.1.1 Objective Response Rate

The ORR per cohort in the FAS is presented in Table 8-7. 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 (22 [78.6%]) 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 7-2). 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 8-7: 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)	3 (12.0)	3 (10.7)
SD	-	3 (12.0)	1 (4.0)	3 (10.7)
PD	2 (66.7)	20 (80.0)	21 (84.0)	22 (78.6)
ORR (%) [95% CI]	33.3 [0.8 – 90.6]	8.0 [1.0 – 26.0]	12.0 [2.5 – 31.2]	10.7 [2.3 – 28.2]
DCR (%) [95% CI]	33.3 [0.8 – 90.6]	20.0 [6.8 – 40.7]	16.0 [4.5 – 36.1]	21.4 [8.3 – 41.0]

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 response; 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.

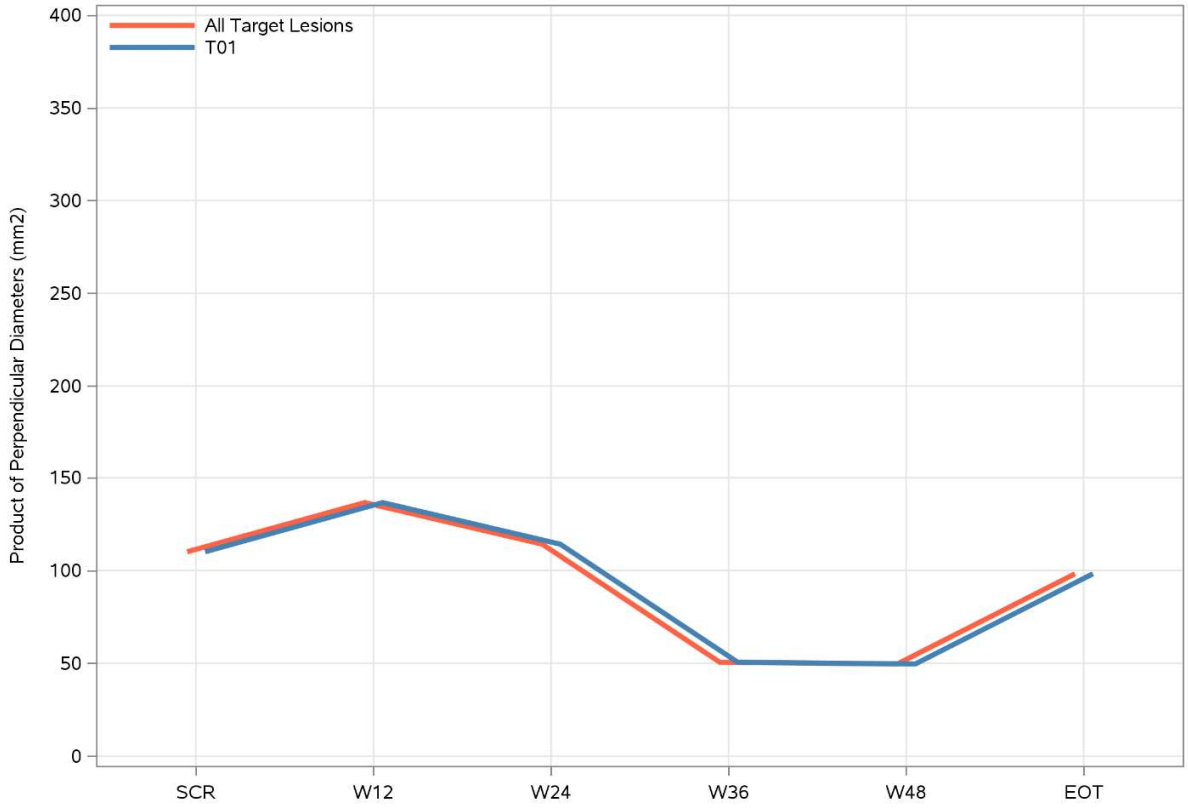
Based on the iRANO criteria, Patient 01-04 (10^6 CFU/mL group) first had stable disease in Week 12 and 24, with subsequent partial remission in Week 36 and 48. At the EoT visit,

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 8-1).

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 8-2), 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 8-3). 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.

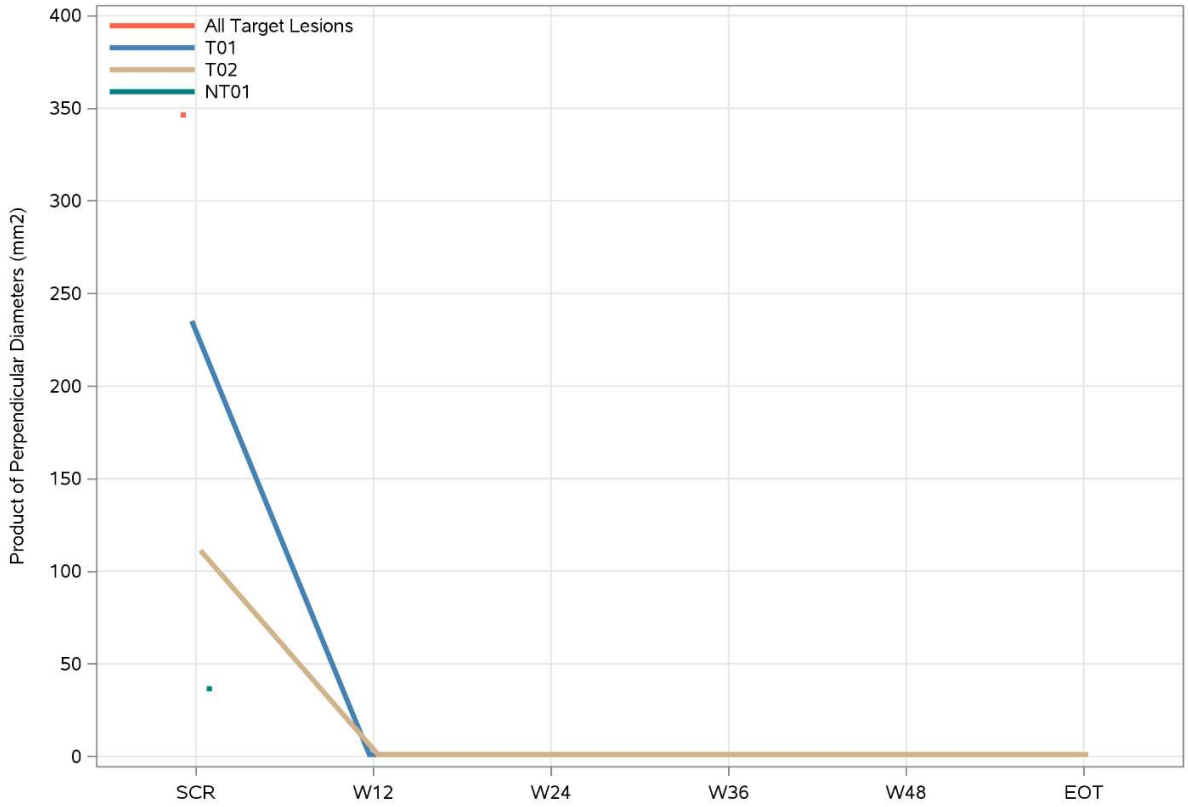
Figure 8-1: Tumor Response (Patient 01-04)



Source: Figure 14.2.2.8.1

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

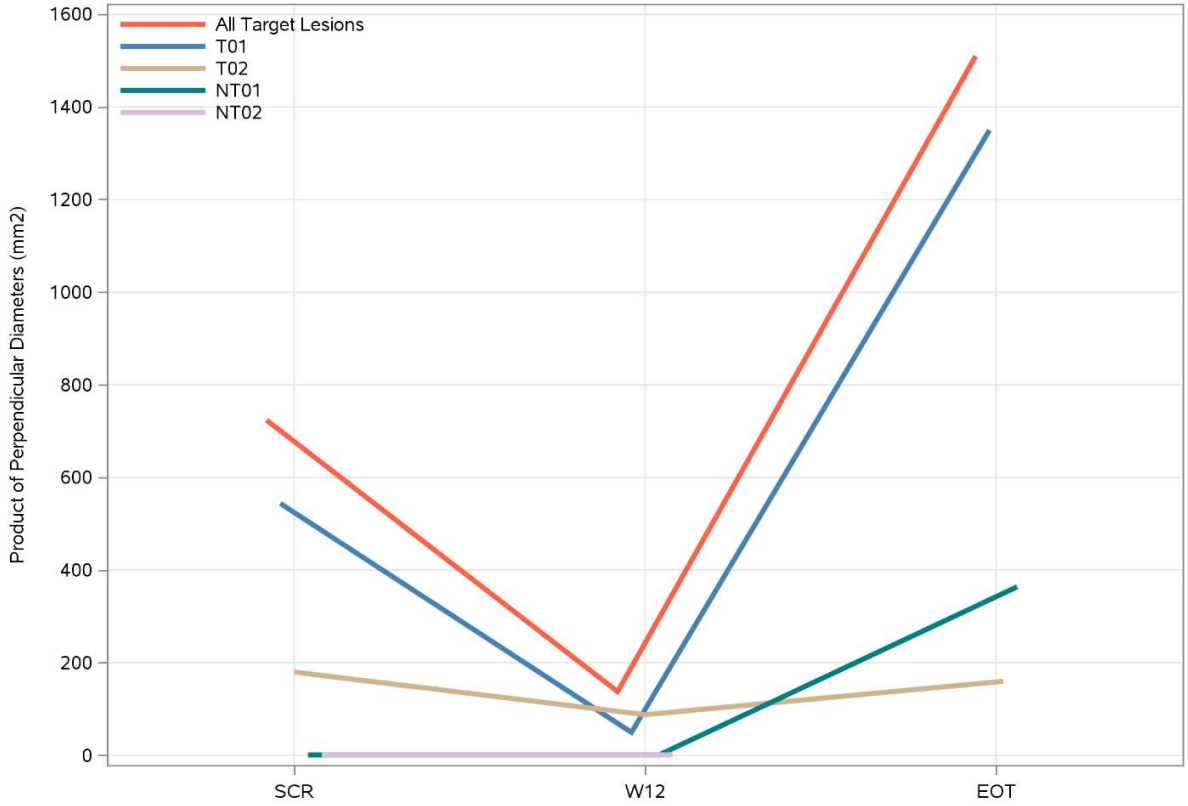
Figure 8-2: Tumor Response (Patient 01-09)



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 8-3: 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.

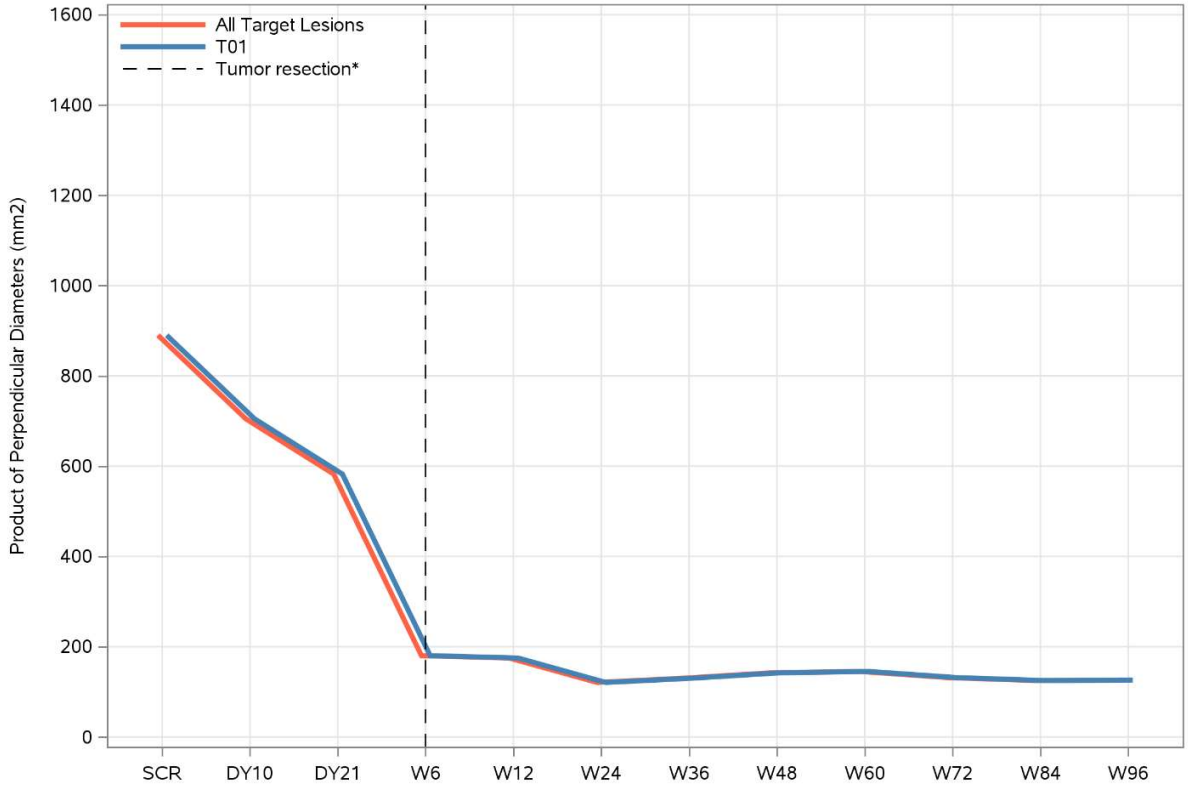
For Patient 01-14 (10^7 CFU/mL R group), the tumor did not grow significantly over 22 months until the time of database lock. The tumor response on Day 10 and Day 21, prior to tumor resection, was assessed as stable disease, with a decrease in size of 21% on Day 10 and 35% on Day 21 compared to Screening (Figure 8-4). 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 8-5). 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 8-6). During an unscheduled visit on 29 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 8-4: Tumor Response (Patient 01-14)

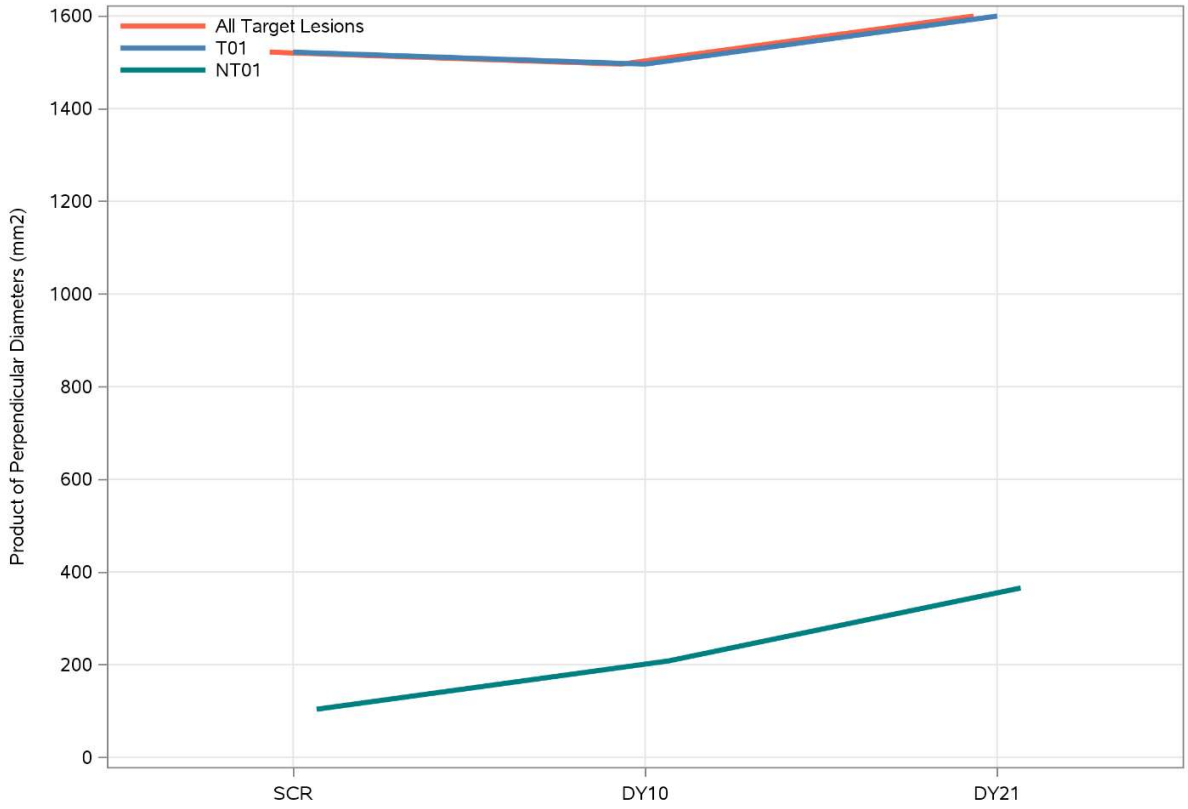


Source: Figure 14.2.2.8.1

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)

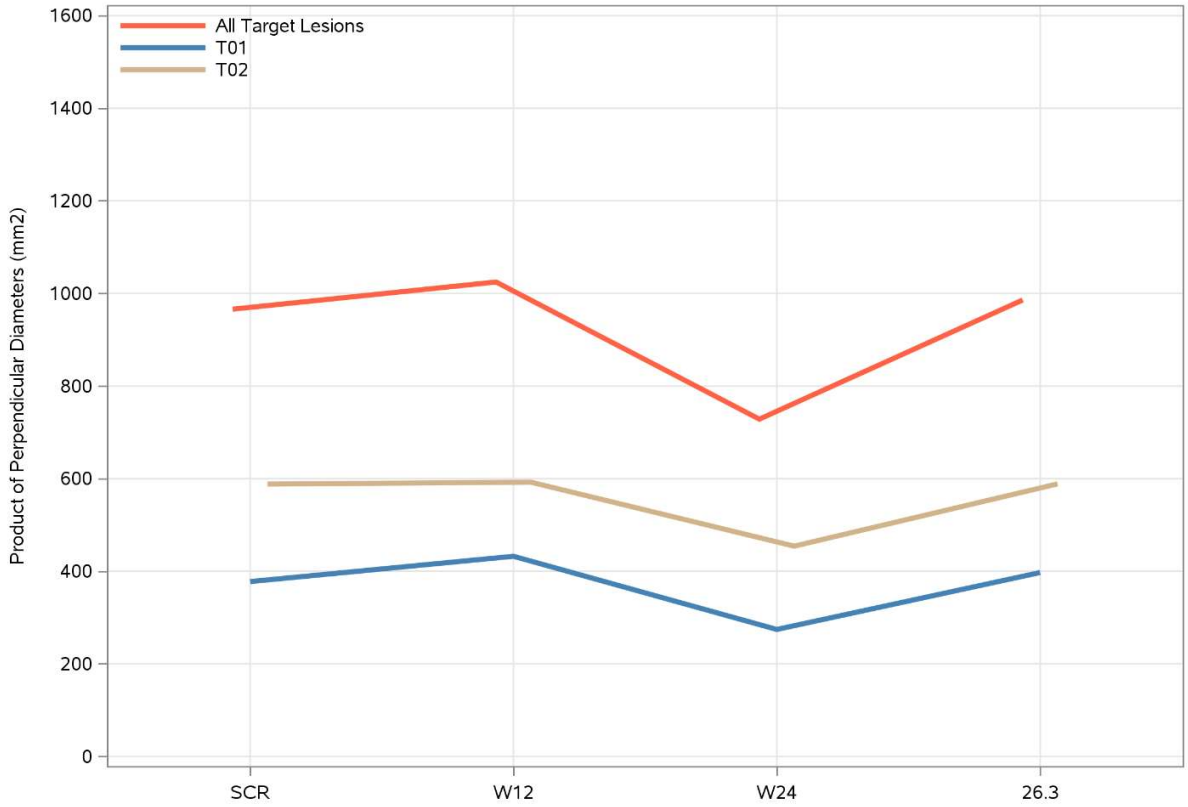
Figure 8-5: Tumor Response (Patient 01-31)



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 8-6: Tumor Response (Patient 02-29)



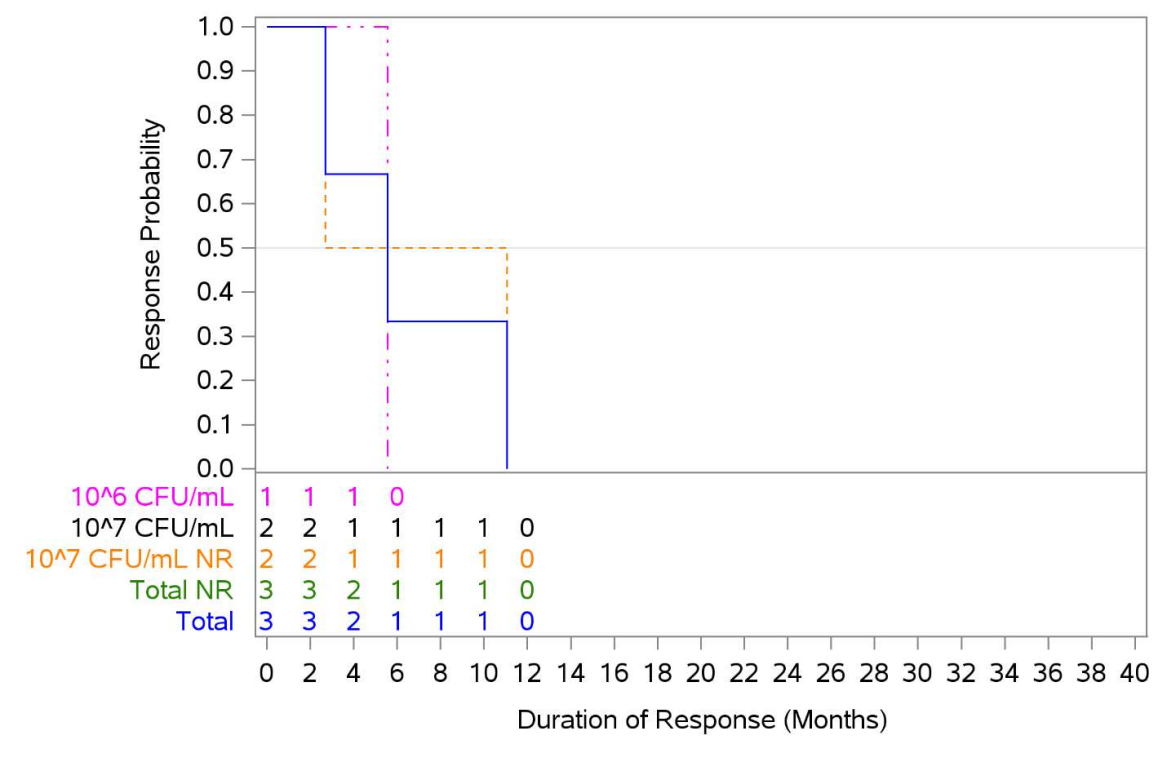
Source: Figure 14.2.2.8.1

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

8.4.1.2 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 8-8 and the Kaplan-Meier plot is shown in Figure 8-7. One patient (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 (Patient 01-09 and Patient 22-10) had a DoR of 2.7 (Patient 01-09) and 11.1 months (Patient 22-10). In the PPS, one patient in the 10^7 CFU/mL group had a response duration of 2.7 months (Patient 22-10) (Table 14.2.2.2.1, Figure 14.2.2.2.1).

Figure 8-7: 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 8-8: 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	-
	NR	2	2 (100)	-	6.9	-	2.7	11.1	-
Total NR[a]		3	3 (100)	-	5.6	-	2.7	11.1	-
Total		3	3 (100)	-	5.6	-	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.

8.4.2 Clinical Response

8.4.2.1 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.

8.4.2.2 Time-to-Progression

The time to disease progression is presented in Table 8-9. 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 (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 8-9: 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	-
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

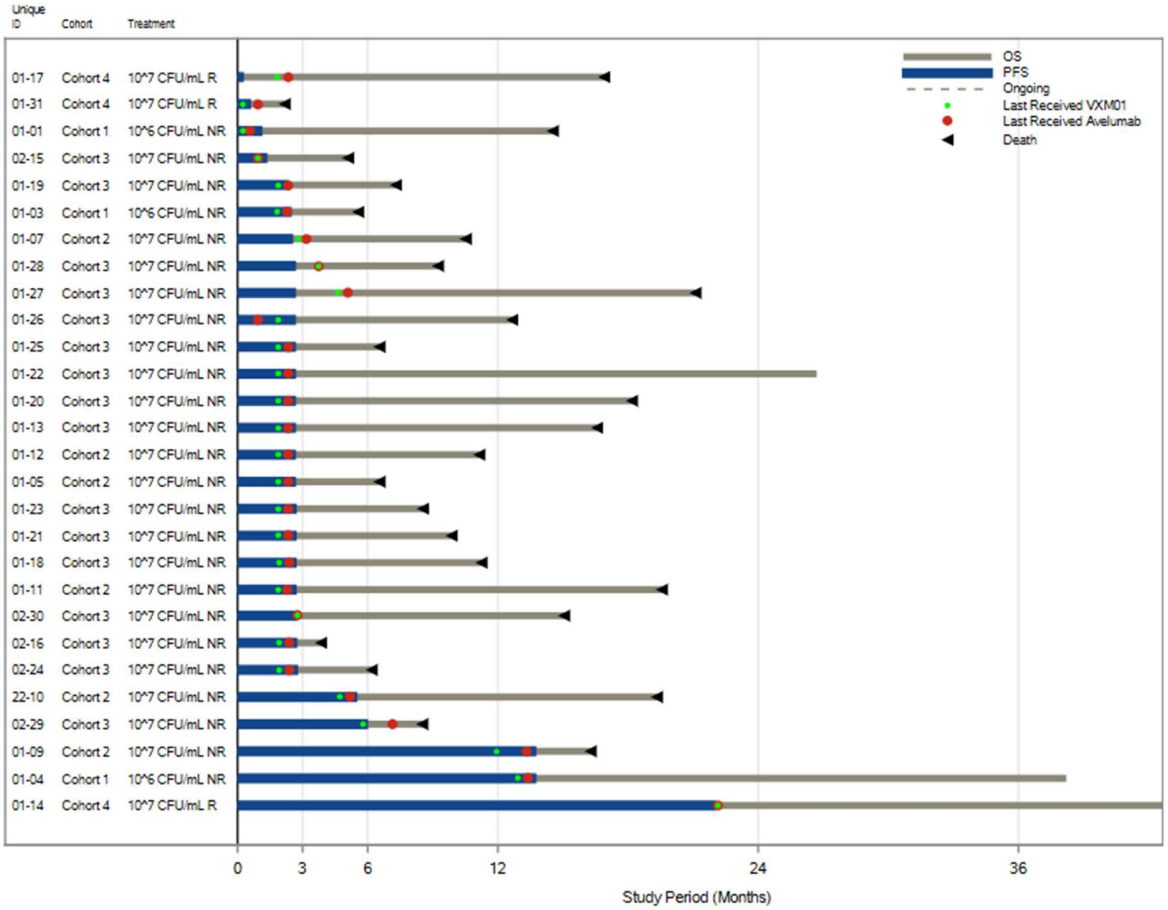
a Total NR comprises 3 patients from the 10^6 CFU/mL group and 22 patients from the 10^7 CFU/mL NR group.

8.4.2.3 Progression Free Survival

The results on PFS were identical to the results on TTP (Table 8-9) 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 8-8), 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.

Figure 8-8: 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

8.4.2.4 Overall Survival

Overall survival in the FAS is presented in Table 8-10 and Figure 8-9. The data for 3 patients were censored because they were alive at the last measured time point. The median OS in the Total NR group was 11.1 months (95% CI: 8.5 – 16.3) 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 46.5 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).

Figure 8-9: Product-Limit Survival Estimates with Number of Subjects at Risk (iRANO 2015) (FAS)

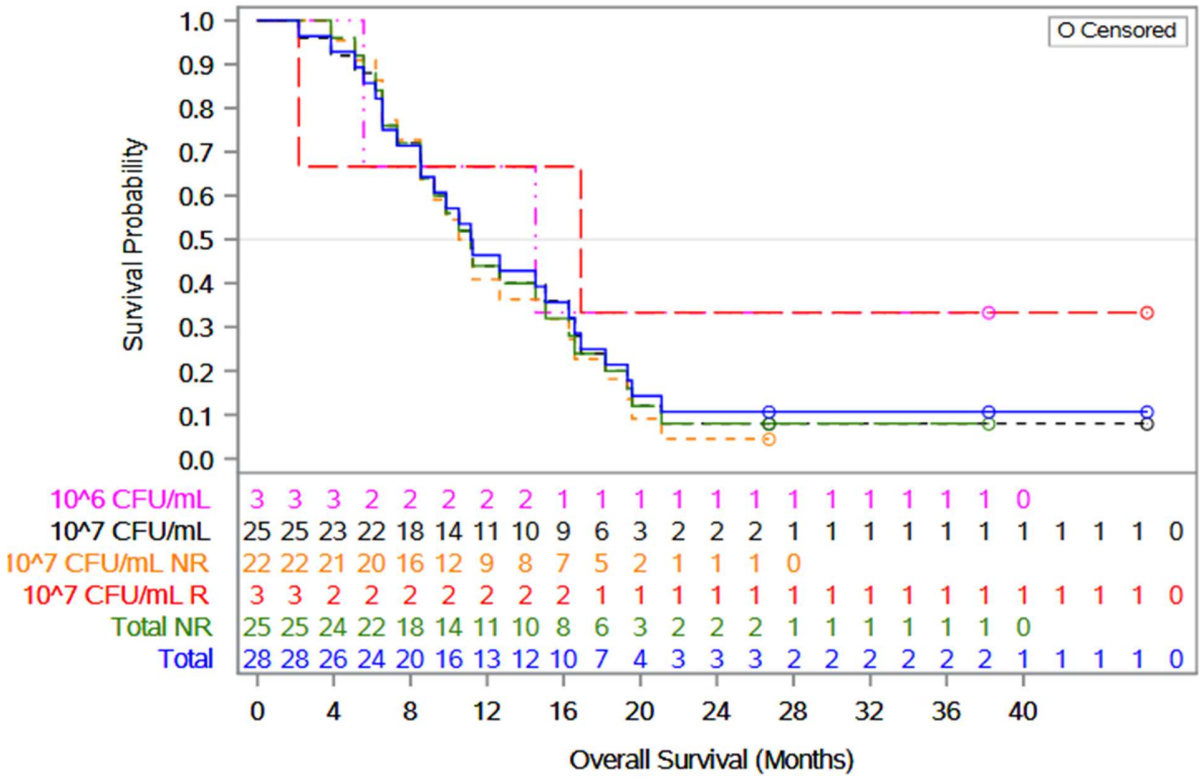


Table 8-10: Overall Survival (FAS)

		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	23 (92.0)	2 (8.0)	11.1	[8.5 – 16.6]	2.2	46.5	Alive (2 patients)
	NR	22	21 (95.5)	1 (4.5)	10.8	[7.3 – 16.3]	3.8	26.7	Alive (1 patient)
	R	3	2 (66.7)	1 (33.3)	16.9	-	2.2	46.5	Alive (1 patient)
Total NR[a]		25	23 (92.0)	2 (8.0)	11.1	[8.5 – 16.3]	3.8	38.2	Alive (2 patients)
Total		28	25 (89.3)	3 (10.7)	11.2	[8.5 – 16.3]	2.2	46.5	Alive (3 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.

8.4.3 Karnofsky Performance Status

The baseline category and post-baseline shifts in KPS in the FAS are provided in Table 8-11. 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 8-11: 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.

8.4.4 Exploratory Pharmacodynamic and Biomarker Analysis

8.4.4.1 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.

8.4.4.2 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.

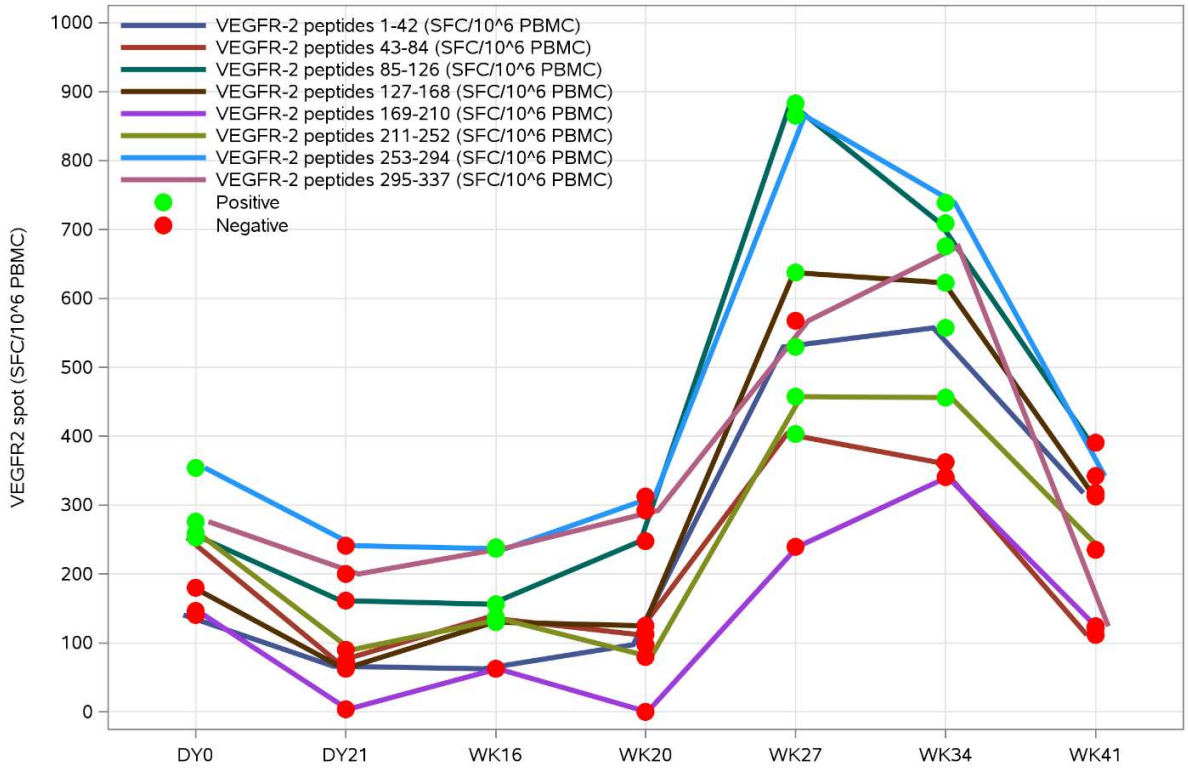
The VEGFR-2 specific T cell response was decreased on Day 21 compared with baseline in 6 patients, including all 3 patients in the 10^6 CFU/mL group, 2 patients in the 10^7 CFU/mL NR group, and 1 patient (Patient 01-17) in the 10^7 CFU/mL R group. The VEGFR-2 specific T cell response was increased on 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 8-10). Interestingly, no increase of the VEGFR-2 specific T cell response had been observed during the antibiotic 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 8-10: VEGFR-2 Specific T Cell Response (Patient 01-04)

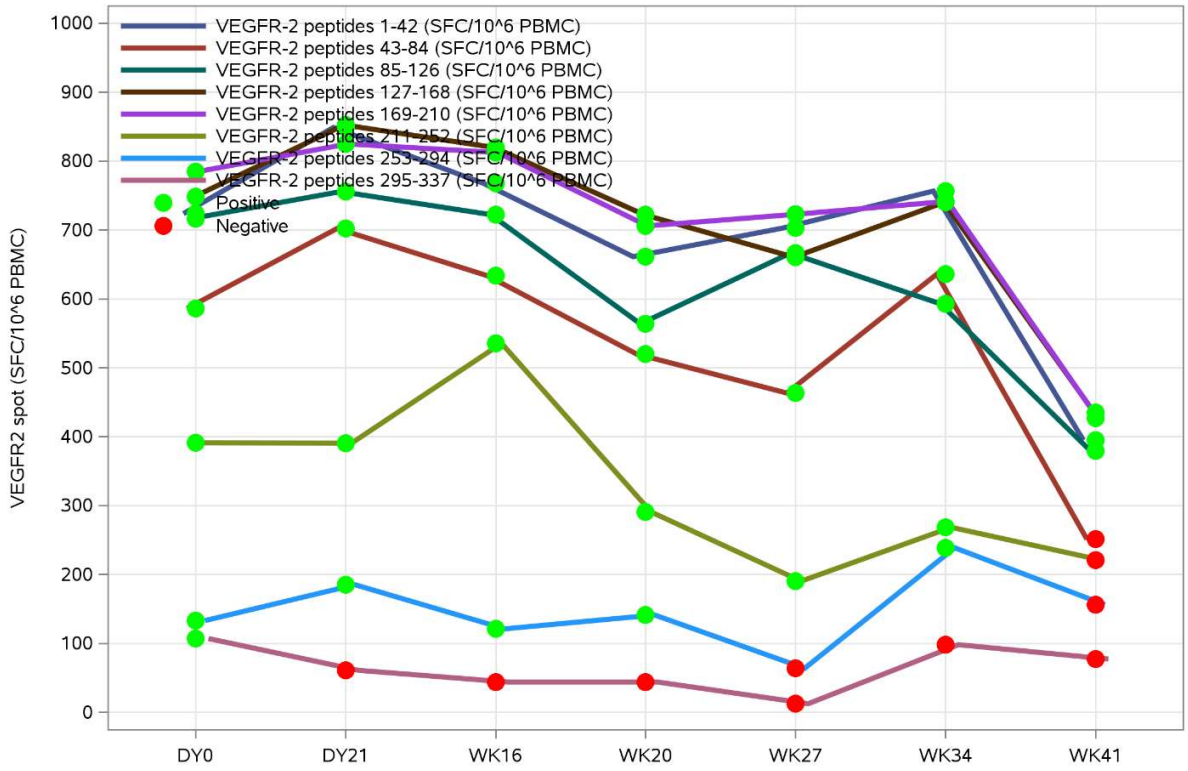


Source: Figure 14.3.2.2.8.2

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 8-11).

Figure 8-11: VEGFR-2 Specific T Cell Response (Patient 01-09)

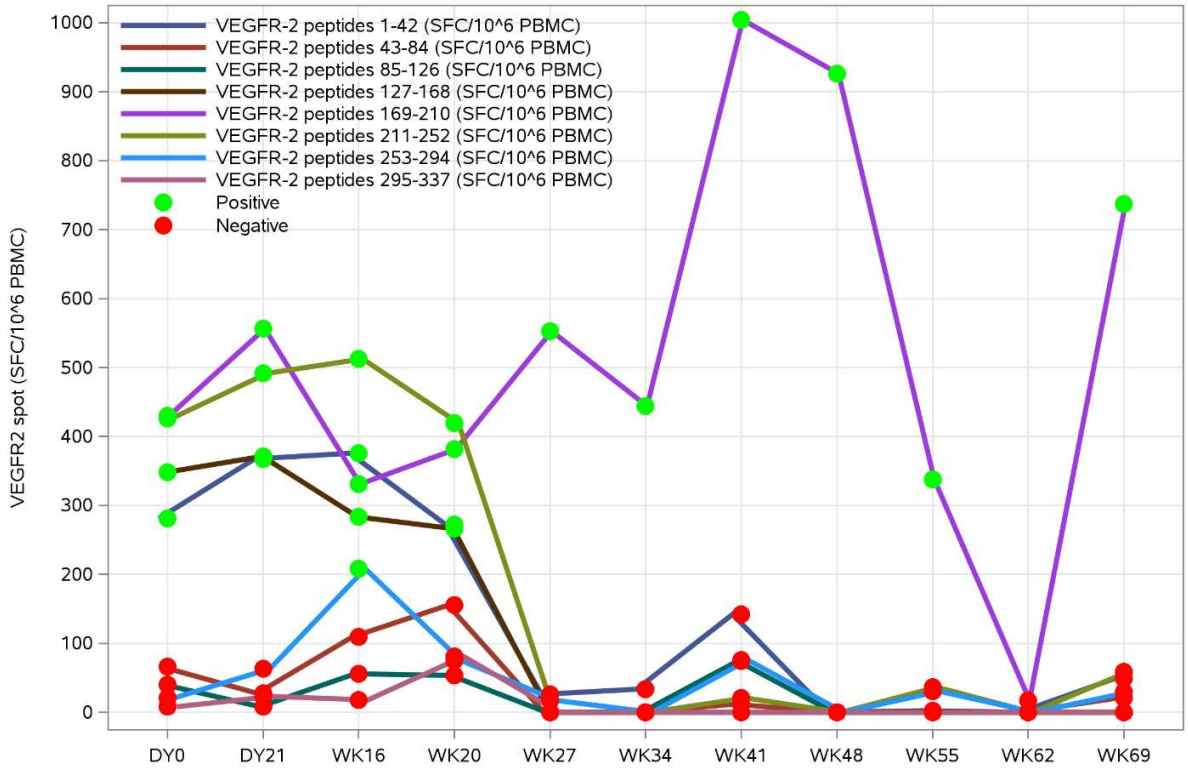


Source: Figure 14.3.2.2.8.2

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 8-12). 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 8-12: VEGFR-2 Specific T Cell Response (Patient 01-14)

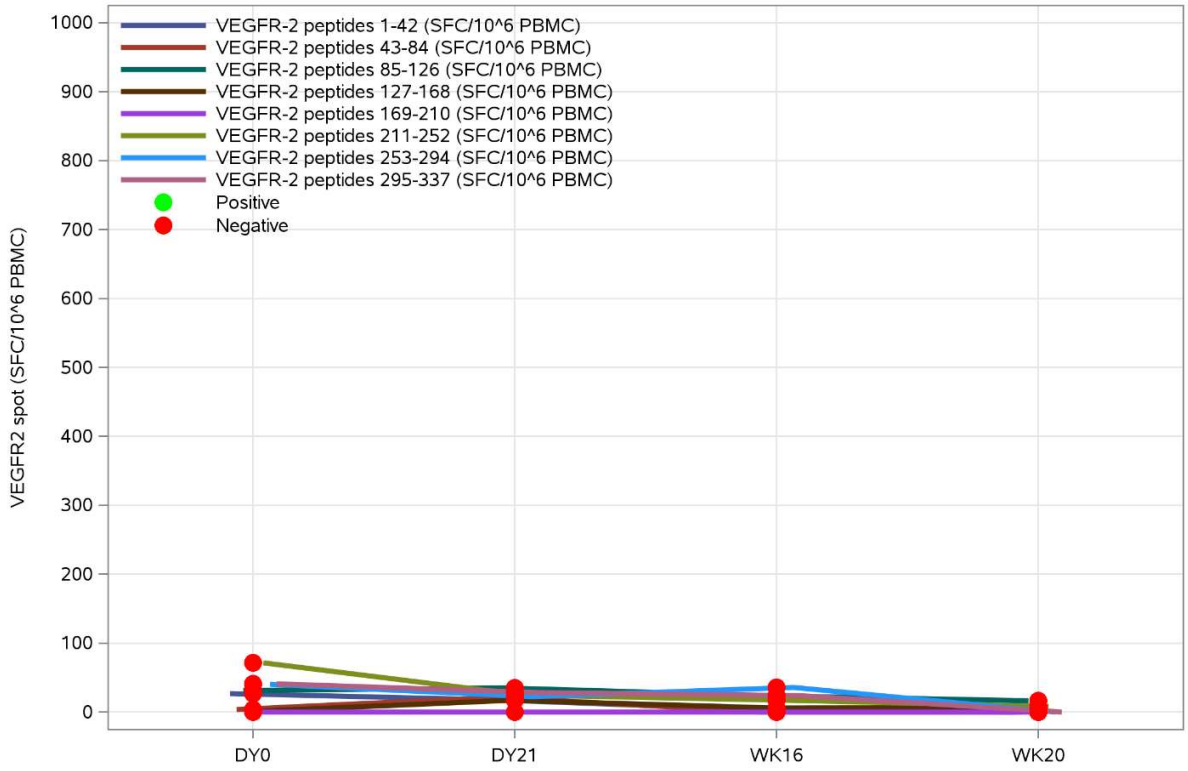


Source: Figure 14.3.2.2.8.2

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 8-13). 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 8-13: VEGFR-2 Specific T Cell Response (Patient 22-10)

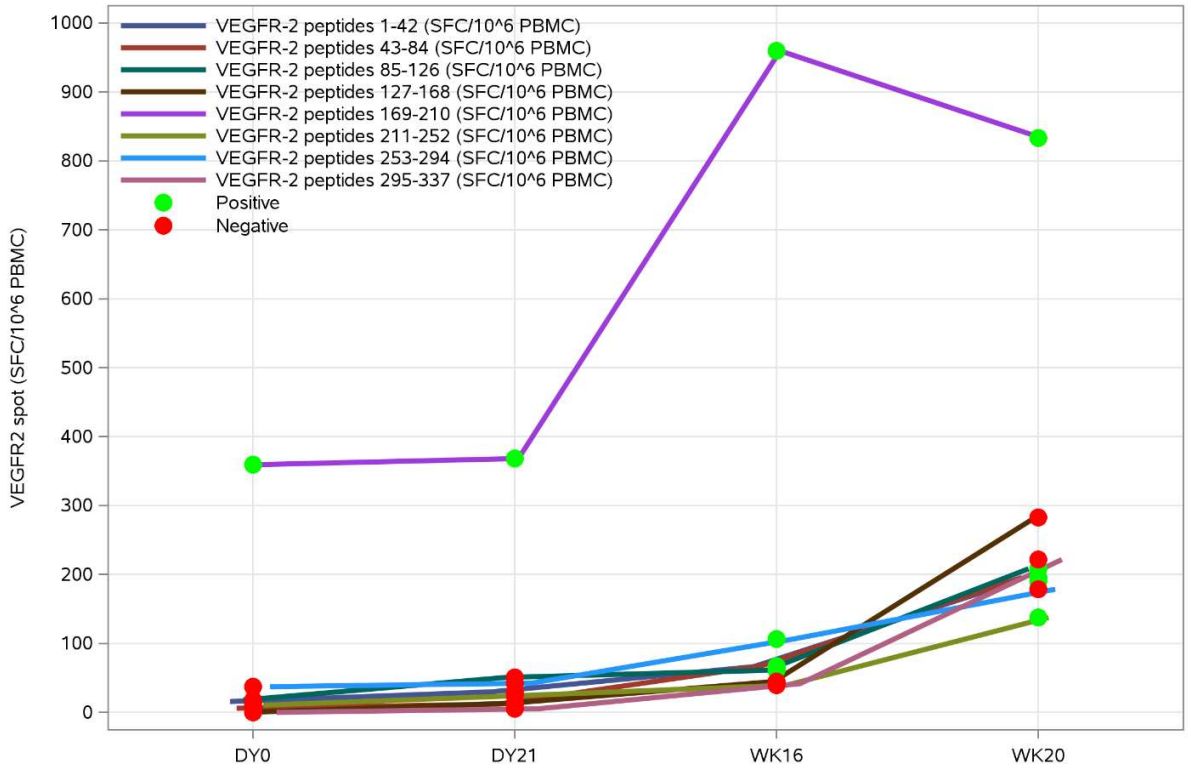


Source: Figure 14.3.2.2.8.2

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 8-14). 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 8-14: VEGFR-2 Specific T Cell Response (Patient 01-27)

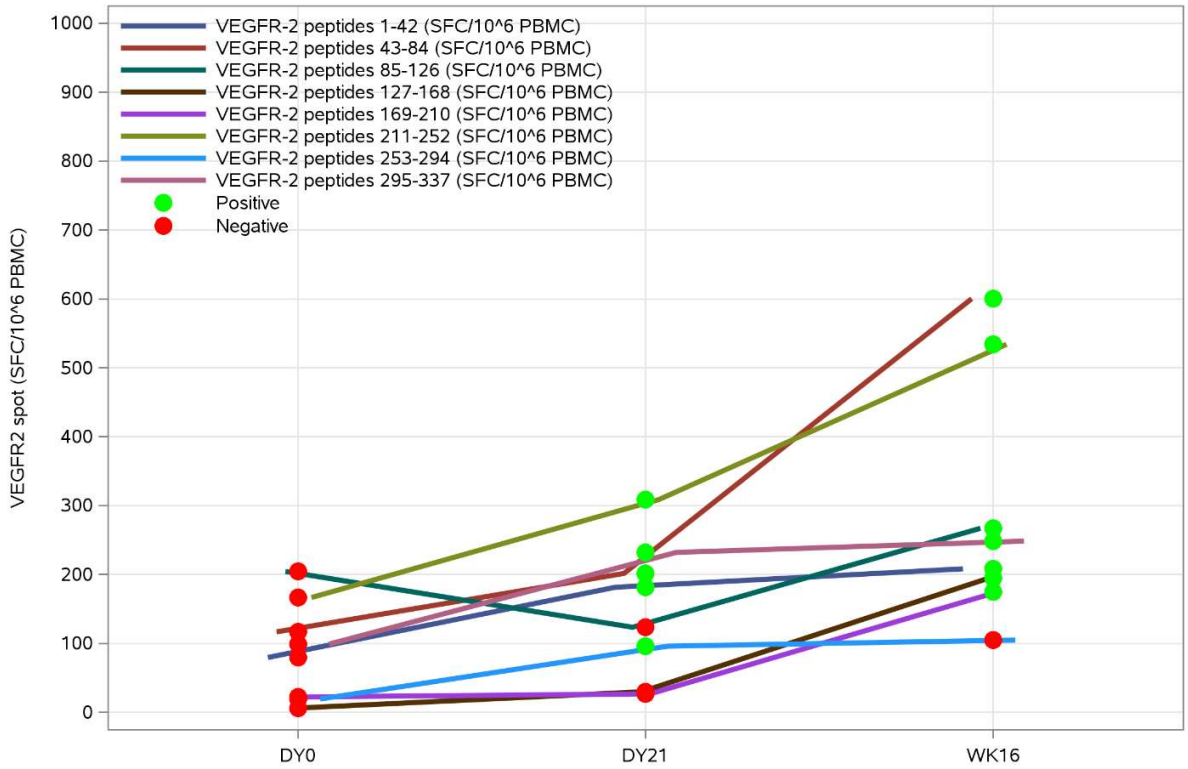


Source: Figure 14.3.2.2.8.2

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 8-15), 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 8-15: 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

8.4.4.3 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).

8.4.4.4 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 patient 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, 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.

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.

8.4.5 Statistical/Analytical Issues

Not applicable.

8.4.6 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

8.4.7 Drug Dose, Drug Concentration, and Relationship to Response

Not applicable.

8.4.8 Drug-Drug and Drug-Disease Interactions

Not applicable.

8.4.9 By-Patient Displays

Individual patient profiles are available upon request.

8.4.10 Efficacy Conclusions

8.4.10.1 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 – 16.3) 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.

8.4.10.2 Conclusions

- With the non-resected patients showing an ORR of 12.0% (partial remission) and 4.0% having stable disease as well as an OS of 2.2 to 46.5 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).

9. SAFETY EVALUATION

9.1 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 9-1. 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 9-1: 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.

9.2 Adverse Events

9.2.1 Brief Summary of Adverse Events

The AEs by group are summarized in Table 9-2. 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 9-2: 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.

9.2.2 Display of Adverse Events

Summaries of AEs are provided in the following tables:

Table 14.3.1.2.1	Adverse Events Summary
Table 14.3.1.3.1	Treatment Emergent Adverse Events
Table 14.3.1.3.2	Treatment Emergent Adverse Events by Severity
Table 14.3.1.3.3	Treatment Emergent Adverse Events by VXM01 Relationship
Table 14.3.1.3.4	Treatment Emergent Adverse Events by Avelumab Relationship
Table 14.3.1.3.5	Treatment Emergent Adverse Events by Target Disease Relationship
Table 14.3.1.4.1	Treatment Emergent Adverse Events of Grade 3 or 4
Table 14.3.1.4.2	Treatment Emergent Adverse Events of Grade 3 or 4 by Severity
Table 14.3.1.4.3	Treatment Emergent Adverse Events of Grade 3 or 4 by VXM01 Relationship
Table 14.3.1.4.4	Treatment Emergent Adverse Events of Grade 3 or 4 by Avelumab Relationship
Table 14.3.1.4.5	Treatment Emergent Adverse Events of Grade 3 or 4 by Target Disease Relationship
Table 14.3.1.5.1	Treatment Emergent Serious Adverse Events
Table 14.3.1.5.2	Treatment Emergent Serious Adverse Events by Severity
Table 14.3.1.5.3	Treatment Emergent Serious Adverse Events by VXM01 Relationship
Table 14.3.1.5.4	Treatment Emergent Serious Adverse Events by Avelumab Relationship
Table 14.3.1.5.5	Treatment Emergent Serious Adverse Events by Target Disease Relationship
Table 14.3.1.6.1	Treatment Limiting Toxicities Related to VXM01
Table 14.3.1.6.2	Treatment Limiting Toxicities Related to Avelumab
Table 14.3.1.6.3	Infusion Related Adverse Events
Table 14.3.1.6.4	Immune-related Adverse Events
Table 14.3.1.6.5	Treatment Discontinuations Due to AEs
Table 14.3.1.6.6	Study Discontinuations Due to AEs
Table 14.3.1.7.1	Treatment Emergent Adverse Events of Highest Grade
Table 14.3.1.7.2	Treatment Emergent VXM01 Related Adverse Events of Highest Grade
Table 14.3.1.7.3	Treatment Emergent Avelumab Related Adverse Events of Highest Grade
Table 14.3.1.7.4	Treatment Emergent Target Disease Related Adverse Events of Highest Grade

9.2.3 Analysis of Adverse Events

9.2.3.1 Incidence of Adverse Events

Treatment-emergent AEs occurring in ≥ 10% of patients (total SAF) are summarized in Table 9-3 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 9-3: 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.

9.2.3.2 Adverse Events by Severity

Treatment-emergent AEs by severity and TEAEs of toxicity Grades 3 and 4 are summarized in Table 9-4, 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 9-4: 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
Musculoskeletal and Connective Tissue Disorders		-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Rheumatoid arthritis	Grade 3	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
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

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**		
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
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 Grades 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.

9.2.3.3 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 9-5). 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 9-6). 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, 31 events (97.0%) 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 9-5: Treatment-Emergent Adverse Events Considered Related to VXM01 (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
Blood and Lymphatic System Disorders	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
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
Gastrointestinal Disorders	Related	-	3 (12.0) 6	3 (13.6) 6	-	3 (12.0) 6	3 (10.7) 6
Nausea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Diarrhoea	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 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
Fatigue	Related	-	5 (20.0) 6	5 (22.7) 6	-	5 (20.0) 6	5 (17.9) 6
Influenza Like Illness	Related	-	1 (4.0) 1	1 (4.5) 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
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
Lymphocyte Count Decreased	Related	-	3 (12.0) 8	3 (13.6) 8	-	3 (12.0) 8	3 (10.7) 8
White Blood Cell Count Decreased	Related	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1

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**		
Metabolism and Nutrition Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Hypertriglyceridaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Musculoskeletal and Connective Tissue Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Myalgia	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
Headache	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Skin and Subcutaneous Tissue Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Pruritus	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
Hypertension	Related	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3

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 9-6: Treatment-Emergent Adverse Events Considered Related to Avelumab (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
Blood and Lymphatic System Disorders	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
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
Endocrine Disorders	Related	-	2 (8.0) 3	1 (4.5) 1	1 (33.3) 2	1 (4.0) 1	2 (7.1) 3
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
Nausea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Diarrhoea	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
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	2 (66.7) 8	8 (32.0) 13	7 (31.8) 12	1 (33.3) 1	9 (36.0) 20	10 (35.7) 21
Fatigue	Related	-	8 (32.0) 9	7 (31.8) 8	1 (33.3) 1	7 (28.0) 8	8 (28.6) 9
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
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
Lymphocyte Count Decreased	Related	-	3 (12.0) 8	3 (13.6) 8	-	3 (12.0) 8	3 (10.7) 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**		
White Blood Cell Count Decreased	Related	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
Blood Creatine Phosphokinase Increased	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Lymphocyte Count Increased	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Metabolism and Nutrition Disorders	Related	-	2 (8.0) 3	2 (9.1) 3	-	2 (8.0) 3	2 (7.1) 3
Hypertriglyceridaemia	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
Hyponatraemia	Related	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
Musculoskeletal and Connective Tissue Disorders	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
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
Headache	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
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
Pruritus	Related	1 (33.3) 2	-	-	-	1 (4.0) 2	1 (3.6) 2
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
Hypertension	Related	-	1 (4.0) 3	1 (4.5) 3	-	1 (4.0) 3	1 (3.6) 3

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.

9.2.3.4 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 9-7). 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 9-7: Treatment-Emergent Adverse Events by Considered Related to the Target Disease (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
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
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
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
Fatigue	Related	-	6 (24.0) 7	5 (22.7) 6	1 (33.3) 1	5 (20.0) 6	6 (21.4) 7
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
Investigations	Related	-	5 (20.0) 7	3 (13.6) 5	2 (66.7) 2	3 (12.0) 5	5 (17.9) 7
Lymphocyte Count Decreased	Related	-	3 (12.0) 5	3 (13.6) 5	-	3 (12.0) 5	3 (10.7) 5
White Blood Cell Count Decreased	Related	-	2 (8.0) 2	-	2 (66.7) 2	-	2 (7.1) 2
Metabolism and Nutrition Disorders	Related	-	1 (4.0) 5	1 (4.5) 5	-	1 (4.0) 5	1 (3.6) 5
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

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**		
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
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
Headache	Related	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
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
Insomnia	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**		
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
Persistent Depressive Disorder	Related	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
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
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.

9.2.4 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

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

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

9.3.1.1 Deaths

A listing of deaths is provided in Table 14.3.2.1. All 25 patients who died in the study, died of target disease progression.

9.3.1.2 Other Serious Adverse Events

The SAEs are summarized in Table 9-8 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.

9.3.1.3 Other Significant Adverse Events

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

Table 9-8: 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 9-9: 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	10	2	VXM01: Unlikely related Avelumab: Unlikely 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	6	2	VXM01: Not related Avelumab: Not related	Not related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	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

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
01-27	Lymphocyte count decreased	14	3	VXM01: Unlikely related Avelumab: Unlikely related	Unlikely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved with sequelae
	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

Patient ID	Preferred Term	Duration (days)	Grade	Relationship to IMP	Relationship to Target Disease	Action Taken	Outcome
02-24	Diarrhoea	2	1	VXM01: Possibly related Avelumab: Possibly related	Definitely related	VXM01: Dose not changed Avelumab: Dose not changed	Resolved
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	Resolved
	Hypertension	533	3	VXM01: Probably related Avelumab: Possibly related	Not related	VXM01: Drug interrupted Avelumab: Dose not changed	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

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

Narratives for individual patients can be found in Section 11.3.3.

9.3.3 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 AEs 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.

9.4 Clinical Laboratory Evaluation

9.4.1 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

9.4.2 Evaluation of Each Laboratory Parameter

9.4.2.1 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 9-10).

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 9-10).

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 9-10).

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 9-10). 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 9-10. 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 9-10: 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.

9.4.2.2 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 9-11.

For gamma-glutamyltransferase increased and hyponatremia, the worst post-baseline category was Grade 3 (severe) and reported AEs are presented in Table 9-11. 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 9-11). 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 blood potassium increased and lipase increased (occurred in 5 patients each), and ALT increased and gamma-glutamyltransferase increased (occurred in 4 patients each).

Table 9-11: 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	-	1 (3.6) 1
Lipase increased	Grade 1	-	4 (16.0) 5	3 (13.6) 4	1 (33.3) 1	3 (12.0) 4	4 (14.3) 5
	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) 1	1 (3.6) 1
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.

9.4.2.3 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.

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

9.5.1 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 9-12.

The majority of physical examination findings were NCS, or AEs of mild or moderate severity. There was 1 patient (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 9-12: 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 (33.3) 1	4 (16.0) 5	4 (18.2) 5	-	5 (20.0) 6	5 (17.9) 6
Diarrhoea	Grade 1	1 (33.3) 2	2 (8.0) 2	2 (9.1) 2	-	3 (12.0) 4	3 (10.7) 4
Vomiting	Grade 1	-	1 (4.0) 2	1 (4.5) 2	-	1 (4.0) 2	1 (3.6) 2
	Grade 2	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
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	1 (33.3) 1	13 (52.0) 16	11 (50.0) 12	2 (66.7) 2	12 (48.0) 15	14 (50.0) 17
	Grade 2	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	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	-	2 (8.0) 2	1 (4.5) 1	1 (33.3) 1	1 (4.0)1	2 (7.1) 1
	Grade 2	2 (66.7) 2	2 (8.0) 2	2 (9.1) 2	-	4 (16.0) 4	4 (14.3) 4
Aphasia	Grade 1	-	1 (4.0) 1	1 (4.5) 1	-	1 (4.0) 1	1 (3.6) 1
	Grade 2	1 (33.3) 1	2 (8.0) 2	2 (9.1) 2	-	3 (12.0)	3 (10.7) 3
Fine motor skill dysfunction	Grade 1	-	1 (4.0) 1	-	1 (33.3) 1	-	1 (3.6) 1
	Grade 2	1 (33.3) 1	1 (4.0) 1	1 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
Headache	Grade 1	-	2 (8.0) 2	2 (9.1) 2	-	2 (8.0) 2	2 (7.1) 2
	Grade 2	-	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) 2	-	-	-	1 (4.0) 2	1 (3.6) 2

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**		
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
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 (4.5) 1	-	2 (8.0) 2	2 (7.1) 2
	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 14.3.1.3.2, 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.

9.5.2 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 (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 (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 11.3.3).

9.5.3 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.

9.5.4 Concomitant Medications and Procedures

A summary of concomitant medications reported for ≥ 10% of patients is provided in Table 9-13 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 9-14. 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 9-13: Concomitant Medications Reported for ≥ 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) 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 9-14: 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.

9.6 Safety Conclusions

9.6.1.1 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 12patients. 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, 31 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 25 patients who died during the study, died of target disease progression.
- 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.

9.6.1.2 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.

10. DISCUSSION AND OVERALL CONCLUSIONS

10.1 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 Time to Progression of 2.7 months (95% CI: 2.7 – 2.7), with a range of 0.3 to 22.1

months, and median OS of 11.1 months (95% CI: 8.5 – 16.3), with a range of 3.8to 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.

10.2 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. With the non-resected patients showing an ORR of 12.0% (partial remission) and 4.0% having stable disease as well as an OS of 2.2 to 46.52 months in resected patients, it appears that that further investigations in suitable designed studies of this combination therapy in subgroups of glioblastoma patients may yield clearer results.

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

11.1 Demographic Data

11.2 Efficacy Data

11.3 Safety Data

11.3.1 Displays of Adverse Events

11.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

11.3.3 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

11.3.3.1 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.

11.3.3.2 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.

11.3.4 Abnormal Laboratory Value Listing (each patient)

12. REFERENCE LIST

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13. 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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16.2 Subject Data Listings
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