# Statistical Analysis Plan

# Enterome

# EOGBM1-18

**"A MulticenteR, Open-Label, First-in-Human, PhaSe Ib/IIa Trial of EO2401, a Novel Multipeptide Therapeutic VAccine, with and without PD-1 Check Point Inhibitor, FoLlowing Standard Treatment in PatIents with ProgrEssive Glioblastoma (Rosalie study)"**

[redacted]

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# Reviewers

The following reviews of the SAP were conducted:

[redacted]

# Glossary of Abbreviations

| Abbreviation | Term |
|---|---|
| ACTH | Adreno CorticoTrophic Hormone |
| AE | Adverse event |
| ATC | Anatomical Therapeutic Chemical |
| BIRC5 | Baculoviral inhibitor of apoptosis repeat-containing 5 |
| BP | Blood Pressure |
| CI | Confidence Interval |
| COVID-19 | Coronavirus Disease of 2019 |
| CR | Complete response |
| CRF | Case report form |
| DoR | Duration of Response |
| DTH | Delayed Type Hypersensitivity |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ELISA | Enzyme-linked immunosorbent assay |
| ELISpot | Enzyme-linked immunospot |
| FAS | Full Analysis Set |
| FIH | First-in-Human |
| FOXM1 | Forkhead box M1 |
| GB | Glioblastoma |
| HR | Heart rate |
| iCPD | immune Confirmed Progressive Disease |
| ICS | Intra Cellular Staining |
| IFN-γ | Interferon-gamma |
| IHC | Immunohistochemistry |
| IL-13Rα2 | interleukin 13 receptor alpha-2 |
| IVS | in vitro stimulation |
| iRANO | Immunotherapy Response Assessment in Neuro-Oncology |
| iUPD | immune Unconfirmed Progressive Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGMT | Methylguanine-DNA-methyltransferase |
| MHC | Major histocompatibility complex |
| MRI | Magnetic resonance imaging |
| NANO | Neurologic Assessment in Neuro-Oncology |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PBMC | Peripheral blood mononuclear cells |
| PD(L)-1 | Programmed death (ligand)-1 |
| PFS | Progression Free Survival |
| PMEL | Pre-melanosome protein |
| PP | Per-protocol |
| PR | Partial Response |
| PsR | Pseudo Response |
| PT | Preferred term |

| | |
|---|---|
| PTHrP | Parathyroid hormone-related protein |
| QTcB | Bazett corrected QT interval |
| QTcF | Fridericia corrected QT interval |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TAA(s) | Tumor-associated antigen(s) |
| TEAE | Treatment-emergent Adverse Event |
| TFLs | Tables, Figures and Listings |
| TSH | Thyroid-stimulating hormone |
| UCP2 | Universal cancer peptide 2 |

# 1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Protocol | 27Apr2022 | 4.0 |
| CRF | 13Jan2023 | 9.0 |
| IDMC Charter | 04Mar2020 | 2.0 |
| Protocol Deviation Management Plan | 19Mar2020 | 1.0 |

# 2. Protocol Details

## 2.1 Study Objectives

### 2.1.1 Primary Objective

The primary objective of this first-in-human (FIH) trial of EO2401 is to evaluate the safety and tolerability of EO2401 as monotherapy and in combination with nivolumab, and nivolumab/bevacizumab in patients with progressive glioblastoma (GB). The safety and tolerability evaluation include assessments of different patient populations within the group of patients with recurrent GB: i) Cohorts 1a, 2a, and 3 evaluate patients with measurable disease, ii) Cohort 2b evaluates patients with non-measurable disease (after surgery of recurrent disease, i.e. adjuvant treatment), and iii) Cohort 2c evaluates a neoadjuvant/surgery/adjuvant treatment concept.

### 2.1.2 Secondary Objectives

The secondary objectives are:

- The evaluation of survival
- The evaluation of tumor progression and response by magnetic resonance imaging (MRI) assessment using the Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria
- To assess the immunogenicity of EO2316, EO2317, EO2318, and Universal cancer peptide 2 (UCP2) that compose EO2401 [redacted] Cross reactivities with the human Tumor-associated antigens (TAAs) interleukin 13 receptor alpha-2 (IL-13Rα2) and Baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) (survivin) will also be tested.

### 2.1.3 Exploratory Objectives

- To assess the neurologic function assessed by the Neurologic Assessment in Neuro-Oncology (NANO) scale
- To explore the correlation between immunogenicity of EO2316, EO2317, EO2318, and UCP2 that compose the EO2401 and tumor progression and response outcome parameters
- [redacted]
- [redacted]

[redacted]

## 2.2 Overall Study Design

This is a multicenter, Phase Ib/IIa, FIH study to assess the safety, tolerability, immunogenicity, and preliminary efficacy of EO2401 in patients with unequivocal evidence of progressive or first recurrent GB confirmed by MRI as defined by the Response Assessment in Neuro-Oncology criteria [redacted]

The FIH protocol is an open-label, multi-cohort study intended to recruit a maximum of approximately 100 evaluable patients in total. The design builds on a 3-by-3 approach for Cohort 1 (as study safety lead-in, before global amendment 2) and then by the global amendment 2 (leading to EOGBM1-18 version 3) the planned patient numbers per cohort are:

- Cohort 1 (as study safety lead-in, before global amendment 2) includes an evaluation by a 3-by-3 design of EO2401 monotherapy (2 administrations of EO2401 each followed by a 2-weeks observation period) planned to be followed in the same individual patients by continued EO2401 in combination with nivolumab; 3 to 12 evaluable patients will be included depending on the safety profile of the administered treatments

    - In the safety lead-in part (3-by-3 design) of the trial, 3 evaluable patients started treatment in Cohort 1a (sub-cohort referred to as C1a/1), after which the safety lead-in was closed after a recommendation from the IDMC, and Cohorts 2a and 2b opened.
    - In global amendment 2 (EOGBM1-18 version 3), plus via re-distribution of patients from Cohort 2b, 18 evaluable patients were added to Cohort 1a for further evaluation of the treatment schedule with a 4-weeks

delayed start of nivolumab also with inclusion of extended patient management measures (sub-cohort referred to as C1a/2); safety precautions for the added patients will follow the same principles as for Cohorts 2a, 2b, 2c, and 3, since Cohort 1a is no longer a safety lead-in part of the trial) (recruitment finalized before global amendment 3

- Cohorts 2a and 2b are an evaluation of EO2401 in combination with nivolumab (both compounds started at the same time) planned to include approximately 48 evaluable patients in total (patients in Cohort 2a with at least one measurable lesion and patients in Cohort 2b with no measurable enhancing disease).
    - Before global amendment 2 (EOGBM1-18 version 3), 23 evaluable patients (sub-cohort referred to as C2a/1) started treatment in Cohort 2a (after re-distribution of patients between Cohort 1 and Cohort 2a to keep a relevant safety database; see protocol Section 1.2.3)
    - In global amendment 2 (EOGBM1-18 version 3), plus via re-distribution of patients from Cohort 2b, 15 evaluable patients (sub-cohort referred to as C2a/2) were added to Cohort 2a for further evaluation of the treatment schedule with simultaneous start of EO2401 and nivolumab, but with inclusion of extended patient management measures (recruitment finalized before global amendment 3)
    - Cohort 2b was planned to include 15 evaluable patients both before and after global amendment 2 (EOGBM1-18 version 3), but number of patients lowered to 6 (no sub-cohorts, cohort referred to as C2b) by re-distribution of patients to Cohorts 1a and 2a (recruitment finalized before global amendment 3)
- Cohort 2c is a cohort introduced by global amendment 2 (EOGBM1-18 version 3), to include 6 evaluable patients to assess safety and feasibility of a neoadjuvant/adjuvant treatment strategy including EO2401/nivolumab (both compounds started at the same time); actual end recruitment 9 patients (no sub-cohort, cohort referred to as C2c)
- Cohort 3 is an evaluation of EO2401 in combination with nivolumab and bevacizumab planned to include 10 evaluable patients before global amendment 3, which increased the target recruitment to 26 patients (no sub-cohorts, cohort referred to as C3). [redacted]

Generally, patients evaluable for safety will include all patients who have received at least 1 dose of EO2401. Patients who are not considered evaluable for safety will be replaced (reasons for nonevaluability and pretreatment safety will be reported). [redacted]

[redacted]

Eligible patients who meet the inclusion criteria and do not meet any of the exclusion criteria and have provided informed consent will be enrolled in the study in Europe and/or the United States. Each patient will participate in the study for a maximum of 24 months from the time of informed consent through final study contact. It is planned for all patients to be followed for survival for 24 months after last patient enrollment, if possible, via hospital records or other registers. The actual recruitment period for the study was 28 months.

The study treatments will be administered until confirmed tumor progression, intolerable toxicity, death, Investigator or patient decision, or early termination of the study at the request from the Sponsor. At the time of stopping study treatment, appropriate standard of care will be initiated by the Investigator. The patient should continue study follow-up measures as long as the individual patient consent for follow-up is not withdrawn, the site is open, and the study not terminated per plan or by the Sponsor.

The clinically critical "extended patient management measures" introduced in global amendment 2 (EOGBM1-18 version 3), included a treatment algorithm for neurological symptoms:

1. At neurological symptoms, judgement on which type of supportive treatment is needed to be made by the treating physician:

    a. No added concomitant medications, observation and general supportive measures is deemed to be adequate.

    b. In situations where added supportive medication is judged as medically appropriate by the treating physician due to patient brain edema with symptoms:

        i. low-dose bevacizumab (7.5 mg/kg every 3 weeks, alternatively 5 mg/kg every 2 weeks, whichever is more logistically advantageous considering patient management and hospital visits) may be added for up to three months unless medically contra-indicated (see Section 4.2, exclusion criterion #8). The number of bevacizumab doses to be administered during the three-month window will be determined by the treating physician based on her/his assessment of the best interest of the patient. Subsequent bevacizumab may be administered for symptomatic cerebral edema based on the judgement of the treating physician. When bevacizumab is administered for symptomatic cerebral edema, study therapy may be continued at the discretion of the treating physician. Patients will be counselled

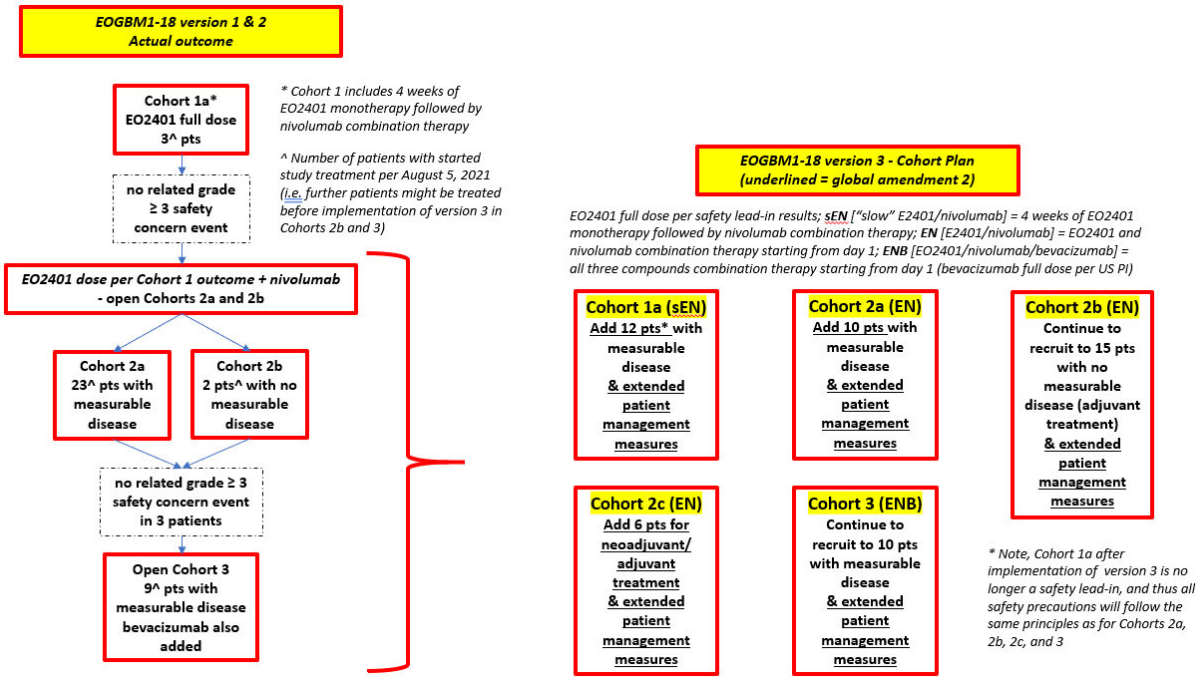
by the treating physician separately on this treatment in countries, where it is not part of the standard procedure.

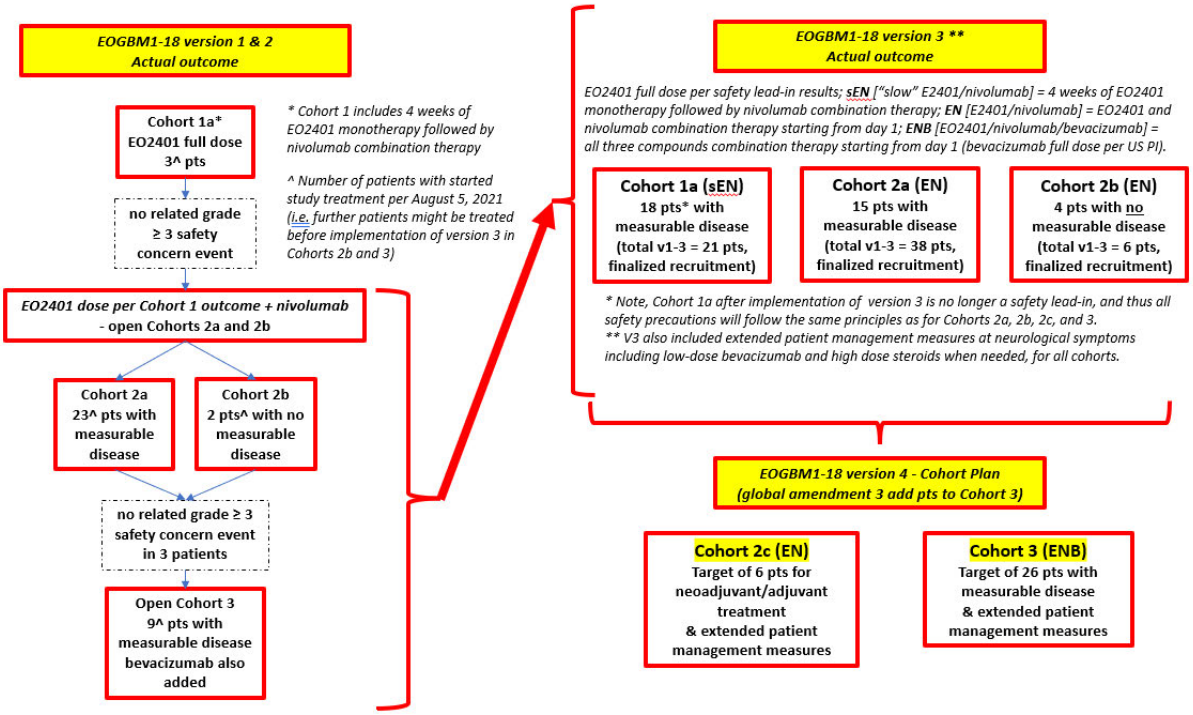
c. In situations where symptomatic cerebral edema is more significant or anticipated to evolve to become more significant, the treating physician may also (i.e. in addition to, or before, low-dose bevacizumab) prescribe a high dose of dexamethasone followed by a rapid taper as tolerated and as clinically indicated.

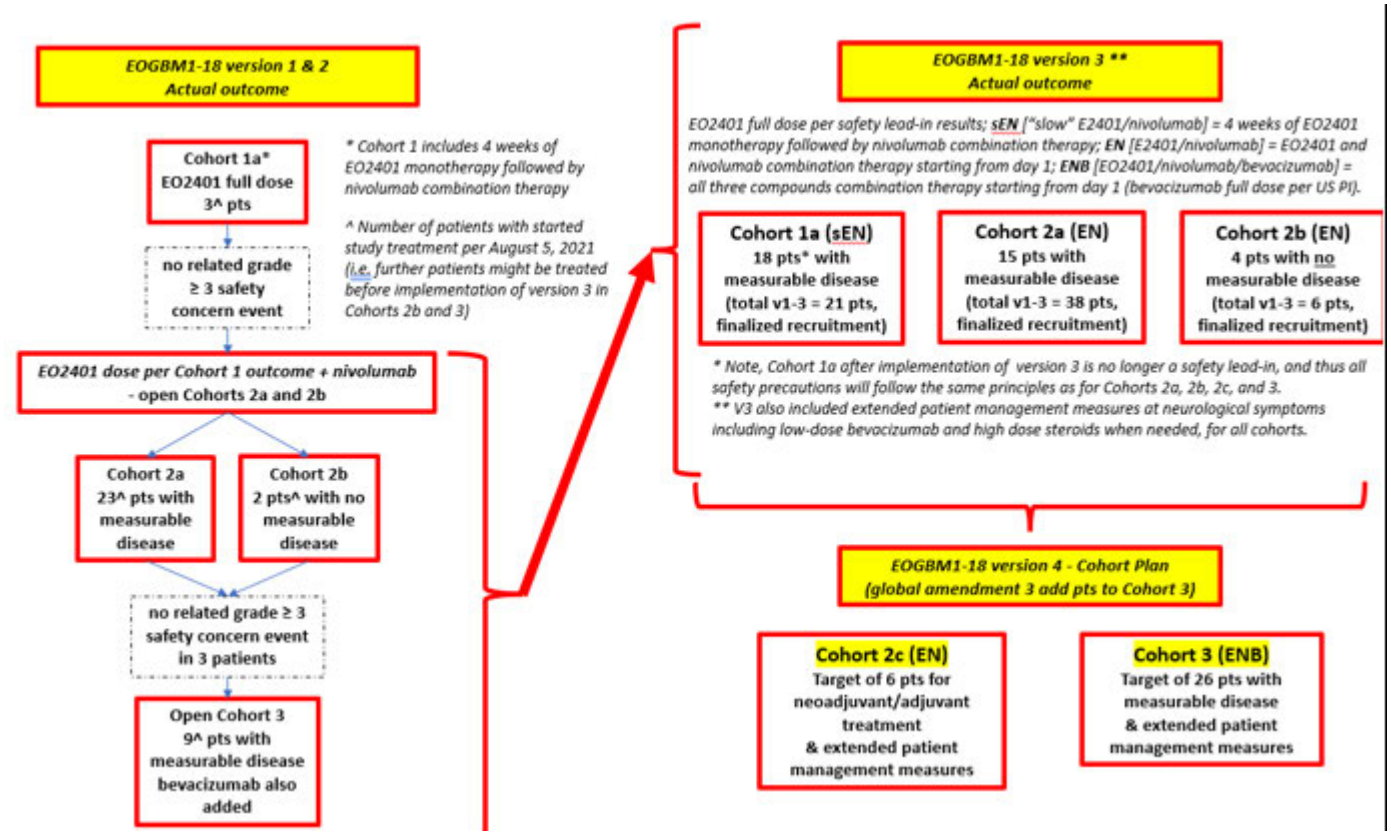
i. A dexamethasone high dose refers to a higher dose to start and followed by a rapid taper off dexamethasone such as 8-10 mg once or twice a day for 2 days, followed by 4 mg once or twice a day for 2 days, followed by 2 mg once or twice a day for 2 days followed by 2 mg once a day for 2 days and then discontinue. However, adjustment to this regimen is at the prerogative of the treating physician based on her/his judgement of what is medically best suited for the patient. The high dose regimen could be repeated as medically necessary. During a dexamethasone high dose regimen, study therapy should be interrupted.

The above-described extended patient management measures are essential and prompt analyses of the sub-cohorts as described above, mainly the differentiation between C2a/1 and C2a/2 is crucial, and the possibility to consider for efficacy analyses also a combined group of patients treated with EO2401/nivolumab plus bevacizumab overall (bevacizumab either delivered as per-need symptomatic treatment or prophylactically from day 1), i.e. C2a/2 + C3. The split in sub-cohorts is also the foundation for the contrasting of C1a/2 vs C2a/2, two cohorts with only difference being the start of nivolumab, delayed 4 weeks vs from day 1, otherwise the same and recruited at the same time with central Sponsor assignment of treatment cohort (i.e. for the site/patient blinded selection of treatment schedule, but otherwise open for all involved).

Details of the IDMC process and procedures, and cohort management plan are outlined in a separate IDMC Charter.


EOGBM1-18 version 1 & 2
Actual outcome
Cohort 1a*
EO2401 full dose
3^ pts
* Cohort 1 includes 4 weeks of EO2401 monotherapy followed by nivolumab combination therapy
^ Number of patients with started study treatment per August 5, 2021 (i.e. further patients might be treated before implementation of version 3 in Cohorts 2b and 3)
no related grade ≥ 3 safety concern event
EO2401 dose per Cohort 1 outcome + nivolumab
- open Cohorts 2a and 2b
Cohort 2a
23^ pts with measurable disease
Cohort 2b
2 pts^ with no measurable disease
no related grade ≥ 3 safety concern event in 3 patients
Open Cohort 3
9^ pts with measurable disease
bevacizumab also added
EOGBM1-18 version 3 - Cohort Plan
(underlined = global amendment 2)
EO2401 full dose per safety lead-in results; sEN ["slow" E2401/nivolumab] = 4 weeks of EO2401 monotherapy followed by nivolumab combination therapy; EN [E2401/nivolumab] = EO2401 and nivolumab combination therapy starting from day 1; ENB [EO2401/nivolumab/bevacizumab] = all three compounds combination therapy starting from day 1 (bevacizumab full dose per US PI)
Cohort 1a (sEN)
Add 12 pts* with measurable disease & extended patient management measures
Cohort 2a (EN)
Add 10 pts with measurable disease & extended patient management measures
Cohort 2b (EN)
Continue to recruit to 15 pts with no measurable disease (adjuvant treatment) & extended patient management measures
Cohort 2c (EN)
Add 6 pts for neoadjuvant/ adjuvant treatment & extended patient management measures
Cohort 3 (ENB)
Continue to recruit to 10 pts with measurable disease & extended patient management measures
* Note, Cohort 1a after implementation of version 3 is no longer a safety lead-in, and thus all safety precautions will follow the same principles as for Cohorts 2a, 2b, 2c, and 3


EOGBM1-18 version 1 & 2
Actual outcome
Cohort 1a*
EO2401 full dose
3^ pts
no related grade
≥ 3 safety
concern event
EO2401 dose per Cohort 1 outcome + nivolumab
- open Cohorts 2a and 2b
Cohort 2a
23^ pts with
measurable
disease
Cohort 2b
2 pts^ with no
measurable
disease
no related grade ≥ 3
safety concern event
in 3 patients
Open Cohort 3
9^ pts with
measurable disease
bevacizumab also
added
* Cohort 1 includes 4 weeks of EO2401 monotherapy followed by nivolumab combination therapy
^ Number of patients with started study treatment per August 5, 2021 (i.e. further patients might be treated before implementation of version 3 in Cohorts 2b and 3)
EOGBM1-18 version 3 **
Actual outcome
EO2401 full dose per safety lead-in results; sEN ["slow" E2401/nivolumab] = 4 weeks of EO2401 monotherapy followed by nivolumab combination therapy; EN [E2401/nivolumab] = EO2401 and nivolumab combination therapy starting from day 1; ENB [EO2401/nivolumab/bevacizumab] = all three compounds combination therapy starting from day 1 (bevacizumab full dose per US PI).
Cohort 1a (sEN)
18 pts* with
measurable disease
(total v1-3 = 21 pts,
finalized recruitment)
Cohort 2a (EN)
15 pts with
measurable disease
(total v1-3 = 38 pts,
finalized recruitment)
Cohort 2b (EN)
4 pts with no
measurable disease
(total v1-3 = 6 pts,
finalized recruitment)
* Note, Cohort 1a after implementation of version 3 is no longer a safety lead-in, and thus all safety precautions will follow the same principles as for Cohorts 2a, 2b, 2c, and 3.
** V3 also included extended patient management measures at neurological symptoms including low-dose bevacizumab and high dose steroids when needed, for all cohorts.
EOGBM1-18 version 4 - Cohort Plan
(global amendment 3 add pts to Cohort 3)
Cohort 2c (EN)
Target of 6 pts for
neoadjuvant/adjuvant
treatment
& extended patient
management measures
Cohort 3 (ENB)
Target of 26 pts with
measurable disease
& extended patient
management measures


EOGBM1-18 version 1 & 2
Actual outcome
Cohort 1a*
EO2401 full dose
3^ pts
no related grade
≥ 3 safety
concern event
EO2401 dose per Cohort 1 outcome + nivolumab
- open Cohorts 2a and 2b
Cohort 2a
23^ pts with
measurable
disease
Cohort 2b
2 pts^ with no
measurable
disease
no related grade ≥ 3
safety concern event
in 3 patients
Open Cohort 3
9^ pts with
measurable disease
bevacizumab also
added
* Cohort 1 includes 4 weeks of EO2401 monotherapy followed by nivolumab combination therapy
^ Number of patients with started study treatment per August 5, 2021 (i.e. further patients might be treated before implementation of version 3 in Cohorts 2b and 3)
EOGBM1-18 version 3 **
Actual outcome
EO2401 full dose per safety lead-in results; sEN ["slow" E2401/nivolumab] = 4 weeks of EO2401 monotherapy followed by nivolumab combination therapy; EN [E2401/nivolumab] = EO2401 and nivolumab combination therapy starting from day 1; ENB [EO2401/nivolumab/bevacizumab] = all three compounds combination therapy starting from day 1 (bevacizumab full dose per US PI).
Cohort 1a (sEN)
18 pts* with
measurable disease
(total v1-3 = 21 pts,
finalized recruitment)
Cohort 2a (EN)
15 pts with
measurable disease
(total v1-3 = 38 pts,
finalized recruitment)
Cohort 2b (EN)
4 pts with no
measurable disease
(total v1-3 = 6 pts,
finalized recruitment)
* Note, Cohort 1a after implementation of version 3 is no longer a safety lead-in, and thus all safety precautions will follow the same principles as for Cohorts 2a, 2b, 2c, and 3.
** V3 also included extended patient management measures at neurological symptoms including low-dose bevacizumab and high dose steroids when needed, for all cohorts.
EOGBM1-18 version 4 - Cohort Plan
(global amendment 3 add pts to Cohort 3)
Cohort 2c (EN)
Target of 6 pts for
neoadjuvant/adjuvant
treatment
& extended patient
management measures
Cohort 3 (ENB)
Target of 26 pts with
measurable disease
& extended patient
management measures

## Cohort 1 (see

**Figure 2)**

Cohort 1 in the safety lead-in part of the trial will be evaluated in a 3-by-3 design to assess, first safety and tolerability of EO2401 alone during a 4 weeks period (2 administrations of EO2401, each followed by a 2-week observation period), planned to be followed in each patient by further administrations of EO2401 in combination with nivolumab for assessment of safety, tolerability, immunogenicity, and preliminary efficacy of the combination. The safety lead-in part of the trial included 3 evaluable patients (sub-cohort C1a/1) starting treatment in Cohort 1a, after which the safety lead-in was closed after a recommendation from the IDMC, and Cohorts 2a and 2b opened.

In global amendment 2 (EOGBM1-18 protocol version 3), plus via re-distribution of patients from Cohort 2b, 18 evaluable patients (sub-cohort C1a/2) were added to Cohort 1a for further evaluation of the treatment schedule with a 4-weeks delayed start of nivolumab, i.e. with the same schedule as for Cohort 1 described in this section, but with extended patient management measures (see protocol Section 6.3). Recruitment to Cohort 1 was finalized before global amendment 3.

[redacted]

Priming injections of EO2401 will be started as soon as possible after confirmation of disease progression; study baseline/screening MRI should be done no longer than 14 days before the start of treatment (MRI confirming progression of GB might be done earlier). The initial dosing regimen will be 4 priming injections administered SC at 2-weekly intervals for the first 6 weeks, followed by monthly boosting injections of EO2401 starting at 4 weeks after the fourth priming injection (i.e., at Week 10). In sub-cohorts 1a and 1b, the full dose of EO2401 [redacted] will be administered, and if implemented the sub-cohorts 1c and 1d will include half the dose of EO2401 [redacted] Thus, Cohort 1a after global amendment 2 (EOGBM1-18 version 3) should also include full dose of EO2401 [redacted]

Nivolumab will be administered as an IV infusion at a dose of 3 mg/kg every 2 weeks from the third priming injection of EO2401 (i.e., from start of Week 4). The nivolumab infusion is to start [redacted] after the EO2401 administration.

## Cohorts 2a and 2b (see Figure 3A)

Cohorts 2a and 2b are planned to be initiated following a decision by the Sponsor after a recommendation from the IDMC based on the review of the safety and tolerability data from Cohort 1 (see above). The Cohorts 2a and 2b will include administration of EO2401 in combination with nivolumab from the start of treatment in the individual patients for assessment of safety, tolerability, immunogenicity, and preliminary efficacy of the combination. Cohorts 2a and 2b were planned to include a total of approximately 48 evaluable patients, but were with amendments and re-distribution of patients finally including 44 patients divided as follows:

- Cohort 2a before global amendment 2, 23 evaluable patients (sub-cohort 2a/1)
- Cohort 2a after global amendment 2, addition of 15 evaluable patients (sub-cohort C2a/2)
- Cohort 2b (C2b, no sub-cohorts), planned 15 patients (both before and after global amendment 2), but number of patients lowered to 6 by re-distribution of patients to Cohorts 1a and 2a
- Recruitment to Cohorts 2a and 2b finalized before global amendment 3

Patients in Cohort 2a with at least one measurable lesion and patients in Cohort 2b with no measurable enhancing disease (i.e. Cohort 2b study treatment was planned as adjuvant treatment, i.e. after surgery for first recurrent GB).

Priming injections of EO2401 will be started as soon as possible after confirmation of disease progression; study baseline/screening MRI should be done no longer than 14 days before the start of treatment (MRI confirming progression of GB might be done earlier). The schedule of administration includes SC injections of EO2401 at 2-weekly intervals (4 times total) during the priming phase and then 4-weekly in the boosting phase starting from Week 10 (i.e., 4 weeks after the fourth administration of EO2401). The dose of EO2401 will depend on the outcome of Cohort 1, i.e., it can be either full dose [redacted] or half dose [redacted] Thus, Cohorts 2a and 2b should include full dose of EO2401 [redacted]

Nivolumab will be administered as an IV infusion at a dose of 3 mg/kg every 2 weeks in combination with EO2401 starting from the first priming injection. The nivolumab infusion is to start [redacted] after the EO2401 administration.

For all patients in Cohorts 2a and 2b, the general safety rules as described in the protocol applies, [redacted]

At the global amendment 2 extended patient management measures are included for both Cohorts 2a and 2b (see protocol Section 6.3).

After availability of safety and tolerability data for a 4-weeks period (2 administrations of EO2401 in combination with nivolumab, each followed by a 2-week observation period), in at least 3 patients of Cohorts 2 (the patients can be treated in either of the Cohorts 2a or 2b, respectively), the IDMC should convene and assess the totality of the safety data to recommend on the opening, or not, of Cohort 3.

**Cohort 2c (see Figure 3B)**

Cohort 2c is a cohort introduced by global amendment 2 (EOGBM1-18 version 3), to include 6 evaluable patients to assess safety and feasibility of a neoadjuvant/adjuvant treatment strategy including EO2401/nivolumab (both

compounds started at the same time).

The treatment strategy includes the following important elements:

- The population includes patients assessed as candidates, and scheduled, for gross total resection of first recurrent GB, which can be safely postponed for 4-6 weeks according to local standards and treating physician's expertise.
- All screening measures per protocol Section 7.1 and Section 7.2 should be followed; however, to shorten the time until planned surgery, the target for screening period #2 is 14 days (+/- 7 days). Note, due to patient specific circumstances the time window can be extended if deemed adequate by the treating physician after consultation with the Sponsor Medical Monitor.
- Neoadjuvant EO2401 (full dose SC, [redacted] plus nivolumab (IV infusion at a dose of 3 mg/kg) administered twice with 2 weeks interval. The nivolumab infusion is to start [redacted] after the EO2401 administration.
    - All safety precautions and rules (e.g. treatment stopping rules) apply as for Cohorts 2a/2b.
    - Table 1 Schedule of Assessments Cohort 2c should be followed, and assessments and procedures as outlined in protocol Section 7.3 for V1 and V2 are also guiding.
    - Note, there will be a study-specific MRI at the day of the second dose of EO2401/nivolumab (V2) to ensure that the tumor is still suited for the intended surgery; key reason for the MRI is to make the assessment if surgery still is possible to postpone, or immediate surgery is advised.
    - If there would be no possibility to perform surgery as planned after V2, the patient can still be evaluated for continued study treatment (from V3 and onwards) according to the same rules as for patients in Cohorts 2a/2b; e.g. if the MRI at V2 would show progression which does not allow surgery, but the patient does still not have significant symptoms (or symptoms can be controlled by symptom management, e.g. according to protocol Section 6.3), study treatment may continue per the judgement of the treating physician until either confirmation of progression according to iRANO criteria, or establishment of PsPD. In the latter case, especially in situations of tumor shrinkage (no time limit), a delayed surgery can be performed, if in the best interest of the patient per the judgement of the treating physician and the patient concur (in such cases an individualized planning of study treatments should be done together with the Medical Monitor).
        - [redacted]
- Planned surgery of recurrent disease:

- Surgery, including associated treatments and measures, is a standard-of-care procedure outside of the clinical trial EOGBM1-18; it is indicated here to explain the treatment gap between the study procedures V2 and V3. Also note, surgery of recurrent glioblastoma is a highly individualized procedure and therefore exact timing cannot be stipulated; time window between V2 and V3 is assumed to be approximately 4-6 weeks.
- The surgery as such including normal pre-, peri-, and post-operative care will be considered standard-of-care, and will only be documented in summary fashion in the CRF (e.g. date/time of surgery, type of procedure, outcome of procedure, length of primary hospitalization, reasons and lengths for possible further hospitalizations, and procedure related MRIs) and not considered AE/SAEs as long as the procedures are pre-planned or part of normal care/outcome of surgery for recurrent glioblastoma per judgement of the treating physician.
- AEs, and when applicable per normal reporting rules SAEs, for events during the surgery period (time between V2 and V3, alternatively until the patient is declared to not be fit for further study therapy) will be reported for all events with a possible relationship to study drug treatment (irrespective of grade), for all surgery complications (irrespective of grade) which are not expected (per assessment by the treating physician), surgery complications ≥ Grade 3, and any events ≥ Grade 3.
- In case a patient who has started study therapy cannot continue study therapy, e.g. study therapy in the adjuvant setting cannot be initiated after surgery, i.e. in case of study treatment discontinuation, a follow-up visit should be completed if at all possible (end-of-treatment visit including safety assessments per Table 1) approximately 30 days after completion of last dose of study treatment.
- A key item is collection of tissue (for patients in Cohort 2c this is a mandatory consent item) from performed surgery for assessment of all applicable objectives and endpoints as outlined in protocol Section 2.1 and Section 2.2.

- Adjuvant EO2401 (full dose SC, [redacted]) plus nivolumab (IV infusion at a dose of 3 mg/kg) administered twice with 2 weeks interval, then switch to EO2401 on a 4-weekly schedule in the boosting phase, and continued nivolumab 2-weekly. The nivolumab infusion is to start [redacted] after the EO2401 administration.
  - All safety precautions and rules (e.g. treatment stopping rules) apply as for Cohorts 2a/2b.
  - Table 1 Schedule of Assessments Cohort 2c should be followed, and assessments and procedures as outlined in protocol Section 7.3 for V3 and V4 are also guiding, as are visits, assessments, and procedures for the treatment-boosting period outlined in protocol Section 7.4.

- For all patients in Cohort 2c the general safety rules as described in the protocol applies, [redacted]
- At the global amendment 2 extended patient management measures are included also for Cohort 2c (see protocol Section 6.3).

## Cohort 3 (see Figure 4)

[redacted]

Cohort 3 is planned to be initiated following a decision by the Sponsor after a recommendation from the IDMC based on the review of the safety and tolerability data from Cohorts 2a and 2b (see above). Cohort 3 will include administration of EO2401 in combination with nivolumab and bevacizumab from the start of treatment in the individual patients for assessment of safety, tolerability, immunogenicity, and preliminary efficacy of the combination. A total of 10 evaluable patients were planned for inclusion in Cohort 3 before global amendment 3 which increased the target recruitment to 26 patients.

Priming injections of EO2401 will be started as soon as possible after confirmation of disease progression; study baseline/screening MRI should be done no longer than 14 days before the start of treatment (MRI confirming progression of GB might be done earlier). The schedule of administration includes SC injections of EO2401 at 2-weekly intervals (4 times total) during the priming phase and then 4-weekly in the boosting phase starting from Week 10 (i.e., 4 weeks after the fourth administration of EO2401). The dose of EO2401 will depend on the outcome of Cohort 1, i.e., it can be either full dose [redacted] or half dose [redacted] Thus, Cohort 3 should include full dose of EO2401 [redacted]

Nivolumab will be administered as an IV infusion at a dose of 3 mg/kg every 2 weeks in combination with EO2401 starting from the first priming injection. The nivolumab infusion is to start [redacted] after the EO2401 administration.

Bevacizumab in Cohort 3 dose and schedule will be used according to the US label for patients with recurrent GB. Bevacizumab will be administered as an IV infusion at a dose of 10 mg/kg every 2 weeks, in combination with EO2401/nivolumab. Bevacizumab will be administered [redacted] after the start of nivolumab administration per local practice at the study sites and in accordance with local labels for bevacizumab (e.g. regarding methods of administration, dilutions, etc.).

For all patients in Cohort 3, the general safety rules as described in the protocol applies, [redacted]

At the global amendment 2, extended patient management measures are included generally for all Cohorts, i.e. also for Cohort 3, but the need for use of low-dose bevacizumab to treat tumor edema is assumed to be very limited (see protocol Section 6.3).

Study procedure and their timings are summarized in the Schedule of Assessments for Cohorts 1, 2 and 3 (Table 1 ie Table 1A and AB). [redacted]

Note, global amendment 2 (leading to EOGBM1-18 version 3) includes allowance for extended patient management measures of tumor site edema for all cohorts, and one component of these measures is low-dose bevacizumab; i.e. bevacizumab might also be used as symptomatic therapy in Cohorts 1a, 2a, 2b, and 2c, according to the rules outlined in protocol Section 6.3.

**Table 1A: Schedule of Assessments Cohorts 1, 2a, 2b, and 3**

[redacted]

[redacted]

[redacted]

[redacted]

## Table 1B: Schedule of Assessments Cohort 2c

[redacted]

[redacted]

[redacted]

[redacted]

## 2.3 Sample Size and Power

As this is the First-In-Human (FIH) trial of EO2401, there is no formal statistical analysis planned. Individual patient data and summary tables of data will be presented. The design builds on a 3-by-3 approach for Cohort 1 (as study safety lead-in, before global amendment 2) and then a goal of having a sufficient, but not unnecessarily high, number of evaluable patients for safety data, immunogenicity, and early efficacy assessments in each of the cohorts (for safety and feasibility only assessments less patients are accepted); the actual and planned patient numbers per cohort are:

- Cohort 1a (sEN* treatment of patients with measurable disease): 3 patients in the safety lead-in part (sub-cohort C1a/1), plus 18 added patients (sub-cohort C1a/2) by the global amendment 2 plus re-distribution of patients from Cohort 2b, also including extended patient management measures = total of 21 patients (C1a; i.e. the total cohort without split in sub-cohorts) (recruitment finalized before global amendment 3)

- Cohort 2a (EN* treatment of patients with measurable disease): 23 patients (sub-cohort C2a/1) before adding 10 further patients by the global amendment 2 plus re-distribution of patients from Cohort 2b leading to a total of 15 patients (sub-cohort C2a/2), also including extended patient management measures = total of 38 patients (C2a; i.e. the total cohort without split in sub-cohorts) (recruitment finalized before global amendment 3)

- Cohort 2b (EN* adjuvant treatment, no measurable disease): lowered from 15 patients to 6 patients (C2b, no sub-cohorts) by re-distribution to Cohorts 1a and 2a (recruitment finalized before global amendment 3), by the global amendment 2 also including extended patient management measures

- Cohort 2c (EN* neoadjuvant treatment - surgery - adjuvant treatment); cohort added by the global amendment 2 to evaluate safety and feasibility of the approach in 6 patients, also including extended patient management measures; actual study treatment starting 9 patients (C2c, no sub-cohorts)

- Cohort 3 (ENB* treatment of patients with measurable disease): by global amendment 3 target recruitment increased from 10 to 26 patients (C3, no sub-cohorts), by the global amendment 2 also including extended patient management measures

- *Total of 100 patients;*

**sEN = "slow" EO2401/nivolumab (delayed N for 4 weeks); EN = EO2401/nivolumab (combination treatment from start); ENB = EO2401/nivolumab/bevacizumab (bevacizumab full dose according to US label, from global amendment 3 recruiting at all sites and in all regions, not only recruiting in the US as initially during study conduct)*

The differences in sample size between cohorts 2a, 2b and 3 were for protocol versions 1-3 based on practical considerations in light of patient availability and the territories for possible recruitment, i.e. Cohort 3 was then only recruited in the USA (one site planned), while Cohorts 2a/2b was recruited globally (10 sites planned); however, the Cohort 2b population (adjuvant treatment after surgery for recurrent disease) constitutes only roughly 10-20% of the population of patients with recurrent GB in Europe. The sample size increase of Cohort 3 in global amendment 3 has been done to increase the precision in assessing safety and tolerability, and also other early outcome measures related to immunogenicity and efficacy. The limited size of Cohort 2c is explained by the fact that this treatment concept was added late in the trial conduct phase, and only an early safety and feasibility assessment is expected (but necessary for future study planning).

Gradual findings during study conduct made it clear that bevacizumab, either as per-need symptomatic treatment or prophylactic from day 1, was necessary to counteract neurological symptoms due to edema (assumed due to fast infiltration of EO2401 expanded T cells into tumor tissue). It also has become clear that an as fast expansion of T cells as possible is necessary for efficacy, and to this end the early start of a blocking agent of normal negative feedback loops at T cell activation is important (i.e., early start of nivolumab). Thus, split analyses of especially C2a/1 and C2a/2 are essential for understanding study outcomes, while the above understanding also opens the possibility for pooling of C2a/2 and C3 to achieve a population of 41 patients, and thereby a higher precision in the efficacy estimates. The latter being of importance for the future design of clinical studies.

Given the exploratory nature of this Phase Ib/IIa study, the sample size is not based on power calculation. The number of patients to be included will provide sufficient safety, tolerability and immunogenicity data, as well as preliminary efficacy data without exposing too many patients.

# 3. Efficacy and Safety Variables

## 3.1 Primary Endpoint(s)

The primary endpoint includes the incidences of AEs, treatment-emergent AEs (TEAEs), SAEs, deaths, and laboratory abnormalities using the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE) v5.0.

Safety endpoints will be assessed by review of summaries of AEs/TEAEs/SAEs, unless otherwise stated. Adverse events will be categorized by system organ class (SOC) and preferred term (PT) using the current Medical Dictionary for Regulatory Activities (MedDRA) version and will be graded according to NCI-CTCAE v5.0.

## 3.2 Secondary Endpoints

The secondary endpoints are:

1. Overall survival (OS), defined as the time interval from the date of first study treatment administration to the date of death due to any cause at any time. Patients alive at time of analysis will be censored at the last date patient alive. Last date patient being alive will be computed as maximum (Date of last visit

(only for on treatment patients), Date of last known to be alive (from "Survival status" CRF page), Date of last contact with patient (from "End of Study" CRF page)). OS will be computed in months: (date of event/censor – first EO2401 administration + 1) / (365.25/12). Missing or incomplete death date will be imputed as specified in section 6.2.

2. The tumor progression and response by using the iRANO criteria ([1], [2]) will be evaluated by the following endpoints:
    - Progression-free survival (PFS) using the iRANO criteria and defined as the time interval from the date of first study treatment administration to the date of first occurrence of progression or death from any cause, whichever occurs first
    - Objective response rate (complete response (CR) + partial response (PR), sustained, and non-sustained which equals confirmed and non-confirmed, respectively)
    - Duration of objective response (only applicable for confirmed responses, and counted from the time of FIRST appearance of either PR or CR, i.e., a PR can proceed a CR, and the duration is then counted from the start of the PR)
    - Time to objective response (only applicable for confirmed responses)
    - Disease control rate (CR + PR + stable disease (SD) without any demand on length of SD or CR or PR, i.e., includes both confirmed and non-confirmed objective responses)
    - Duration of disease control (this duration is for ALL CLASSES of response to be included counted from day 1 of study treatment)
    - Best iRANO response; % change vs baseline
    - Time to best iRANO response (as counted from study day 1)

Progression is defined by an immune Unconfirmed Progressive Disease (iUPD) immediately followed by an immune Confirmed Progressive Disease (iCPD), regardless if iRANO assessment is scheduled or unscheduled. Answer to "iRANO Overall Response Assessment" on CRF page "iRANO assessment" will be used to look for such progressions. Date of progression will be the date of the MRI assessment showing the iUPD, provided the iUPD is not due to a pseudoprogression (i.e., followed by a iSD, iPR, or iCR; if followed by a iUPD there is still no determination if it is a pseudoprogression, or not). Thus, iUPD signifies a PFS event only if followed by iCPD or not followed by other iRANO assessments and there are clinical grounds to accept the iUPD as the PFS event. Assessments until end of study (until last follow-up visit) or start of a new anticancer treatment will be taken into account assessing PFS events.

Considering the multiple ways PD might be assessed in relation to the use of iRANO, e.g. based on a single MRI assessment of PD (iUPD by iRANO) in context of worsening symptoms, and potentially increased use of steroids, a medical review of all patients will take place before final assessment of the date of progression, and the medical review outcome will take precedence for determining the actual date of progression. Therefore, a medical review from the Sponsor including all study patients will be reported in an external file (***Sponsor-Excel***) including the following parameters:

| Cohort | Pat | Patient has received sLDB; yes = 1 | Cohort 2b starting date for "surgery incl.analysis" | Progression / censor | Date_prog | Date_censor | Rationale | Best iRANO response; % change vs baseline | Date of best iRANO response | iRANO Date of First Objective Response | iRANO Best Target | iRANO Best Target Date | iRANO Best overall | iRANO Best overall Date | Enterome comments | Last date to be used for NANO assessments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | |

- **Cohort:** Obvious, cohort number – for easy understanding/finding of patients in the Excel – can be used for assessments as well
- **Pat:** Obvious, patient number
- **Patient has received sLDB;** yes = 1: If there is a 1 in the column the patient has received low dose bevacizumab as symptomatic treatment during study treatment per protocol (the search for patients was done per medical review of all comedications on the eCRF per 2024-03-14) and should be included in the special patient group "received sLDB" to be analyzed for safety; note, the cells with a "1" (n=20) have also been marked in orange to be easy to find
- **Cohort 2b starting date for "surgery incl. analysis":** The dates for patients in Cohort 2b in this column are the dates to be used for "start of time dependent items" (e.g., duration of treatment, duration of disease control, time to progression, survival; please note patients in Cohort 2b since having non-measurable disease they cannot have an objective response of PR or CR, so duration of objective response is not applicable) in the special analyses where C2b should be contrasted to C2c (Cohort 2c does not need any special dates since the cohort includes surgery after start of study treatment with EO240; while patients in Cohort 2b should have had surgery before start of EO2401, i.e., for the patients with surgery, 4 of the 6, one must use the date of surgery per the Excel to contrast C2b vs C2c). Please note, the dates in this column for C2b are ONLY for the special analyses contrasting efficacy vs C2c, for all other analyses (including efficacy for normal outputs) the first study day treatment of EO2401 should be used for the time dependent items!

- **Progression/ censor:** Patient has progression, or should be censored for progression dependent analyses (e.g., PFS, duration of objective response, duration of disease control)
- **Date_prog:** Medically reviewed and decided date of progression
- **Date_censor:** Medically reviewed and decided date of censoring
- **Rationale:** Explanation for the medical review (it is not assumed any analyses should be done on this column, but necessary to explain medical decision)
- **Best iRANO response; % change vs baseline:** Best percentage of change (i.e., it can be a positive number for patients with tumor growth or negative number for patients with tumor shrinkage; a specific explanation of how calculated and rules applied will be included in the SAP) at on study MRI vs baseline MRI per iRANO; C2b = NA since non-measurable disease at baseline, C2c = NA since overall response assessment includes surgery (so not comparable to any other cohort), other NA = no information available (e.g., lack of on study MRI) or information not interpretable in context of the clinical situation
- **Date of best iRANO response:** The date for above percentage
- **iRANO Date of First Objective Response:** This is for calculation of duration of objective response since there might be a different start date of OR if there is a conversion of a PR to a CR, i.e., this column is needed
- **iRANO Best Target:** The best target response per iRANO criteria (per SAP we are going to use OVERALL RESPONSE but we still need in the documentation the best target response); note, the cells with a "unconfirmed PR" (n=4) have also been marked in orange to be easy to find (all other ORs are confirmed)
- **iRANO Best Target Date:** The date for the best target response per iRANO criteria (per SAP we are going to use OVERALL RESPONSE but we still need in the documentation the best target response)
- **iRANO Best overall:** The best overall response per iRANO criteria; note, the cells with a "unconfirmed PR" (n=4) have also been marked in orange to be easy to find (all other ORs are confirmed)
- **iRANO Best overall Date:** The date for the best overall response per iRANO criteria
- **Enterome comments:** Enterome medical comments in relation to the assessment, needed for documentation but nothing for assessment by [redacted]
- **Last date to be used for NANO assessments:** The last date (including this date) to be used for any NANO assessment in each individual patient based on medical review of dates of progression, start of new-anti

cancer treatments (systemic and non-systemic), withdrawn consents, and end of study treatments due to completed 24 months study treatment

[redacted]

New anticancer treatments will be detected, and defined, among medications collected in CRF form "Prior and Concomitant Medications" by sponsor medical review (medical review will exclude any concomitant low-dose bevacizumab outside of cohort 3 if allowed by protocol), that started after first study drug administration.

Patients without progression or death at time of analysis will be censored at the date of their last investigation/MRI NOT showing progression by iRANO (meaning investigation/MRI at any time during study, i.e. on treatment and during follow-up after treatment, whichever investigation comes later). Date of last post-baseline MRI assessment (regardless scheduled or unscheduled) will be considered as date of censor, provided that no new anticancer treatment was started prior to this date. If any new anticancer treatment is started, censor will be the date of last post-baseline MRI assessment before start of new anticancer treatment, otherwise assessed by the medical review. In absence of such date, censor will be at the date of first study treatment administration. Definition of date of PFS or censoring refers to Food and Drug Administration guidelines for PFS ([3]) (definition including documented PFS only) and are specified in Table 2 below. The medical review from sponsor might also lead to consider censor dates earlier than censoring dates as defined below, and therefore the external file should also be used for defining PFS censors.

PFS will be computed in months: (date of event/censor – first EO2401 administration + 1) / (365.25/12).

**Table 2: Censoring rules for PFS**

| Situation | Date of Event or Censoring | Outcome |
|---|---|---|
| No MRI assessment at baseline | Date of first study treatment administration | Censored |
| Progression documented based on iRANO (meaning | Date of earliest MRI assessment showing progression based on iRANO [meaning that the event date is the | Event |

| | | |
|---|---|---|
| iUPD followed by iCPD as defined above) during treatment and follow-up period or progression assessed by sponsor medical review | date of the iUPD MRI assessment in the sequence of iUPD followed directly by iCPD (without any intervening assessments with other outcome)] or date of progression assessed by sponsor medical review, whichever comes first | |
| No progression nor death during study or censor assessed by sponsor medical review | Date of last post-baseline MRI (meaning investigation/MRI at any time during study, i.e. on treatment and during follow-up after treatment, whichever investigation comes later) or date of censor assessed by sponsor medical review, whichever comes first.<br>Note, the censoring date selected by medical review in cases like this might be beyond the first study treatment date provided that from a medical perspective it seems reasonable that no progression has occurred. | Censored |
| Death without any MRI assessment under treatment, and within 112 days (16 weeks) after first study treatment administration. | Date of death | Event |
| Death within 112 days (16 weeks) after last MRI assessment without documented progression | Date of death | Event |
| Death more than 112 days (16 weeks) after last post-baseline MRI assessment | Date of last post-baseline MRI (meaning MRI at any time during study, i.e. on treatment and during follow-up after treatment, whichever investigation comes later) | Censored |
| Progression after ≥2 consecutive missing MRI assessments or after 112 days (16 weeks) after previous MRI assessment | Date of last post-baseline MRI (meaning MRI at any time during study, i.e. on treatment and during follow-up after treatment, whichever investigation comes later) before missing assessments | Censored |

- Objective Response Rate (ORR), defined as the proportion of patients with complete response (CR) and partial response (PR) according to the iRANO criteria.

  As per iRANO criteria, CR and PR should be sustained at least 4 weeks (see protocol Appendix 1), meaning that a patient will be accounted in the numerator of ORR if he/she shows sustained CR or PR. This patient will be considered as sustained responder. The sustained (confirmed responders by CR and PR), including the date of the response, are outlined in the Sponsor-Excel.

  The rate of CR, PR and ORR will be displayed (sustained responses). Of note, iPR followed by iCR will be considered as sustained PR and therefore as a responder.

  Another analysis will be performed with unconfirmed responses, i.e. CR or PR that occurred without being confirmed (without sustainment criteria). The rate of unconfirmed CR and unconfirmed PR will be displayed.

  The non-sustained (non-confirmed responders by CR and PR), including the date of the non-confirmed response, are outlined in the Sponsor-Excel.

  Then, the rate of "Total" responders will be presented, as the sum of both sustained and unconfirmed responders: Rate of CR, rate of PR, rate of responders.

  Best overall response according to the iRANO criteria will also be presented, defined as the best assessment collected as "iRANO Overall Response Assessment": iCR confirmed, iCR non-confirmed, iPR confirmed, iPR non-confirmed, iSD, iUPD, iCPD, NE. Patients will have best response as NE in case they do not have any available iRANO assessment.

- Time to sustained objective response, defined as the time interval from treatment start to first occurrence of CR or PR (whichever is first recorded) will be calculated. The time for first occurrence of CR and PR is outlined in the Sponsor-Excel per responding patient. If no objective response is observed censoring will be done at the date of first documentation of disease progression (based on iRANO and using MRI date as date of progression) or death from any cause, whichever occurs first.
- Disease Control Rate (DCR), defined as the proportion of patients with CR, PR, and Stable Disease according to the iRANO criteria (per Sponsor-Excel). A patient will be accounted in the numerator of DCR if he presented with CR, PR or Stable disease at least once.
- Duration of Response (DoR), defined as the time interval from the date of first occurrence of CR or PR (whichever is first recorded) to the date of first documentation of disease progression (based on iRANO and using MRI date as date of progression) or death from any cause, whichever occurs first (data per Sponsor-Excel).

  Duration of Response will be calculated in the subpopulation of responder patients as defined above, i.e. patients with sustained responses.

  Patients without documented progression at time of analysis will be censored at the date of their last iRANO assessment (regardless scheduled or unscheduled).

DoR will be computed in months: (date of event/censor – first response + 1) / (365.25/12).

- Duration of Disease Control, defined as the time interval from study day 1 in patients with CR, PR (confirmed or non-confirmed) or SD to the date of first documentation of disease progression (based on iRANO and using MRI date as date of progression) or death from any cause, whichever occurs first (data per Sponsor-Excel).

  Patients without documented progression at time of analysis will be censored at the date of their last iRANO assessment (regardless scheduled or unscheduled).

- Best iRANO response; % change vs baseline

  Data has been generated by medical review of all patients all MRI assessments based on the following criteria:

  - Target size ($mm^2$) is the key assessment from the iRANO assessment by the investigator; percentage change = (investigation considered – baseline)/investigation considered,
  - With the following special rules:
    - If new lesion(s) the target size ($mm^2$) of the lesion(s) is added to the target size of the investigation considered
    - If the new lesion(s) is not measured and the iRANO assessment is iUPD or iCPD specify the investigation considered to be at least +25% vs baseline, and thus if target lesion(s) have a higher percentage increase that increase will be selected, and the new lesion(s) disregarded
    - If a measure is termed "too small to measure" (tstm), i.e. per protocol <10*10mm, the size will be assumed to be $99mm^2$ if there is no real measures in numbers (MRI size can be judged also below 10mm) indicating a smaller size, in which case the actual numbers will be used
    - If a measure of tstm and the assessment of PR is given by the investigator the assumed response will be -50%, per iRANO.

Thus, based on above the Sponsor-Excel is outlining for each patient in the study "Best iRANO response; % change vs baseline" which should be used for waterfall plots per later definition in the SAP.

- Time to best iRANO response (as counted from study day 1) should also be assessed based on the Sponsor-Excel

3. For Cohort 2b, there will for all standard analyses be used the same principles as for all other cohorts when calculating OS, PFS, duration of disease control (in this cohort it is not applicable with objective CR and PR responses since no measurable baseline target), i.e. start of counting from study day 1. However, in a SPECIAL analysis contrasting C2b to C2c, i.e. adjuvant EN vs

neoadjuvant/adjuvant EN, meaning that surgery must be taken into account in both groups, the endpoints OS, PFS and Duration of Disease Control will be calculated based on the start of surgery in case the patients received it (the starting dates for all 6 patients are outlined in the Sponsor-Excel).

4. The immunogenicity of EO2316, EO2317, EO2318, and UCP2 that compose EO2401 [redacted]

   A central laboratory will assess the T cell immune responses [redacted] for each peptide, from which positivity and boosting criteria are defined thereafter.

   Data will be collected by the central laboratory [redacted]

   Those positivity criteria will be provided by the central laboratory for each of the 4 peptides separately (EO2316, EO2317, EO2318, and UCP2) if possible, otherwise for all peptides together (EO2316, EO2317, EO2318).

   [redacted]

   Positivity and boosting criteria are defined as follows:

[redacted]

[redacted]

[redacted]

## 3.3 Exploratory endpoints

The exploratory endpoints will be:

1. Neurologic function assessed by the NANO scale. The NANO is a simple neurologic assessment by a means of a questionnaire conducted and reported by a trained health care professional who evaluates the patient in 9 domains: gait, strength, upper extremity ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behaviour. Each domain contains a score from 0 to 3 or 0 to 2, depending on the domain, with higher scores indicating worse neurologic function. The cumulative score goes from 0 to 23.
2. Correlation between immunogenicity of EO2316, EO2317, EO2318, and UCP2 that compose EO2401 and the outcome parameters PFS, ORR, DoR, DCR, and OS. [redacted]
3. [redacted]

4. [redacted]

# 5. Analysis populations

## 5.1 All Patient Population

The All Patient Population will consist of any patient who signed informed consent including Screen failures.

As protocol V2.0 is planning a 2-stage consent and screening procedure, any reference to signature of the ICF are referring to the signature of this second part of the ICF.

In this population, patients are analyzed according to their assigned treatment (assigned cohort). Assigned cohort is defined as the cohort indicated in CRF if the patient was treated, otherwise as screening failure.

## 5.2 Safety Population

Safety Population will consist of any patients who received at least 1 dose of study drug (EO2401 alone or EO2401 in combination with nivolumab or nivolumab/bevacizumab). Patients who are not considered evaluable for this population will be replaced.

For summaries of safety assessments during study, patients from Safety population are analyzed according to their actual treatment received.

## 5.3 Full Analysis Set (FAS)

Full Analysis Set will consist of any patients who received at least 1 dose of study drug (EO2401 alone or EO2401 in combination with nivolumab, or nivolumab/bevacizumab) for whom no important protocol deviations occurred.

Patients who are not considered evaluable for this population will not be replaced.

FAS patients are analyzed according to their assigned treatment (assigned cohort).

[redacted]

[redacted]

# 6. Data Handling

## 6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of treatment.

Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date).

The day prior to Day 1 is Day -1.

All data will be organized and analyzed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point.

The following visit windows will be used for the by-visit analyses of any assessment, regardless the population for analysis.

| Analysis Visit | Target Day of Visit[a] | Acceptable visit window |
|---|---|---|
| **0** Pre-Screening | Any day before -28 | Up to Day of second ICF |
| **1** Screening | Day –14 | Day -28 (or second ICF) to Day -1 [b] |
| **2** Week 0 | Day 1 | Day 1 |
| **3** Week 2 | Day 14 | Days 2 to 21 |
| **4** Week 4 | Day 28 | Days 22 to 35 |
| **5** Week 6 | Day 42 | Days 36 to 49 |
| **6** Week 8 | Day 56 | Days 50 to 63 |
| **…** Week N | Day X, X=N*7 | Days (X-6) to (X+7) |
| **99** End of Treatment | Last scheduled visit Day X + 14 days | Days (X+8) to (X+21) |

[a] Relative to the date of first dose of treatment.
[b] For patients who were not treated, the visit window for "Screening" includes all visits not previously considered as "Pre-Screening".

All visits posterior to the date of the analysis visit assigned as End of Treatment will be considered as follow-up analysis visits.

If more than one record (regardless scheduled or unscheduled visit or assessment) occurs within the same visit window where only one assessment is expected, then the following rule should be applied:

- for baseline/pre-treatment assessments the last non-missing result prior to study drug administration should be used;
- for post-baseline assessments:
    - For Laboratory data and vital signs (LB and VS domains): Based on the assumption that worst value/grade is the later one, the later assessment within time window will be selected for by-visit analysis. Specifically, for CTCAE gradable laboratory parameters (in LB), in case an earlier assessment within same time window has a higher abnormality grade, this assessment will be selected for by-visit analysis (rather than the later assessment).

- For other domains: If assessment is the same date as the visit, analysis will use the last available one. Else, the assessment closest to the target day of the visit window will be used in the analysis. If there is a tie, the later assessment will be used in the analysis.

This is applicable for all analysis populations.

No time windows will be applied for follow-up visits.

Repeat and unscheduled readings

Repeat assessments occur when the original result requires confirmation. Repeat assessments are included in the listings. For the analysis (summaries showing results per visit), repeat assessment and unscheduled assessments will be handled according to visit windows defined above, similarly to scheduled assessments.

Prior to first dosing, all assessments taken in addition to the original assessment are defined as predose repeats.

## 6.2 Handling of Dropouts, Missing Data, and Outliers

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification) or "> x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Note that 0 should not be used as an imputed value in case the endpoint requires a log transformation. Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events (AE) or concomitant medications (CM). The imputed dates are not advised to be used to calculate durations where the results would be less accurate.

- For missing diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.
- Partial or missing AE or CM start dates will be imputed as follows:
  a) Missing day - Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date
  b) Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date. If this rule leads to an imputed start date posterior to the end date (after imputation of end date if needed), then impute 1st January for start date rather than first dose date.
  c) Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
- Partial or missing AE or CM end dates will be imputed as follows:
  a) Missing day - impute the last day of the month. If the patient died in the same month, then set the imputed date as the death date

b) Missing day and month – impute 31st December. If the patient died in the same year, then set the imputed date as the death date

c) Completely Missing – No imputation.

If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

a) For Missing day only – using the 1st of the month

b) For Missing day and Month – using the 1st of January

No rules for outlier detection are planned.

# 7. Statistical Methods

## 7.1 General Principles

All data collected in this study will be documented with the help of patient data listings and summary tables and figures. Data listings will be provided for the All Patient Population, otherwise stated in listing shell, and will list all available assessments, regardless scheduled or unscheduled. A listing will also be provided for Comments collected in the CRF. Summary statistics and statistical analysis, where required, will be performed for patients included in the relevant analysis populations (Safety/FAS). Unless stated otherwise, descriptive summary statistics will include frequency counts and percentages for categorical variables and number of observations, mean, standard deviation, median, minimum, and maximum and the first and third quartiles for continuous variables.

Kaplan-Meier plots will be displayed using separate plots:

- A combined figure with 7 curves for Cohort 1, Cohort 2a/1, Cohort 2a/2, Cohort 2b, Cohort 2c, Cohort 3, Cohort 2a/2 + 3 (for efficacy)
- A single curve for each of these cohorts (for efficacy)
- A single curve for Cohort 1, Cohort 2a, Cohort 2b, Cohort 2c, Cohort 3 (for safety)

Unless otherwise stated, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

All data processing, summarization and analyses will be performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The SAS codes are listed in Appendix.

The following principles will be applied to all TFLs unless otherwise stated:

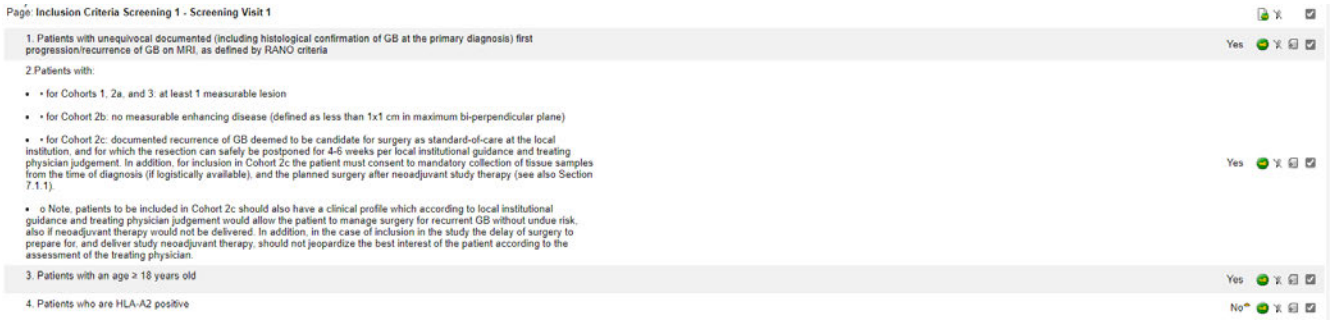
| Principle | Value |
|---|---|
| Treatment group labels and order presented | Cohort 1<br>Cohort 1/1<br>Cohort 1/2<br>Cohort 2a<br>Cohort 2a/1<br>Cohort 2a/2<br>Cohort 2b<br>Cohort 2c<br>Cohort 3<br>Cohort 2a/2 + 3<br>Overall |
| Tables | Data in summary tables presented by treatment group as defined above, assessment and visit (where applicable).<br>Efficacy, exposure and certain baseline tables will use all the cohorts mentioned above. The remaining baseline and safety tables will use Cohorts C1, C2a, C2b, C2c, C3 and Overall. |
| Listings | All data collected presented by cohort (1/1, 1/2, 2a/1, 2a/2, 2b, 2c, 3), patient id, visit, date/time of |

| Principle | Value |
|---|---|
| | assessment (with study day), unless otherwise specified. |
| Descriptive summary statistics for continuous variables | Number of patients/observations (N), mean, standard deviation (SD), first and third quartiles (Q1;Q3), median, minimum, and maximum. 95% confidence intervals as appropriate. |
| Descriptive summary statistics for categorical variables | Frequency counts and percentages [n (%)] |
| Denominator for percentages | Number of patients in the analysis population, unless stated otherwise in table shell(s) |
| Include "Missing" as category | Demographics and Other Baseline Characteristics only, when the number missing is greater than zero for at least one treatment group. |
| Display for 0 percentages | 0% |
| Display to one more decimal place than collected value | Mean, Median, Q1, Q3 |
| Display to two more decimal place than collected value | SD, Confidence interval |
| Limit of precision for displays | 5 decimal places |
| Date Format | DDMMMYYYY |

## 7.2 Patient Disposition and Data Sets Analyzed

All patients signing the first ICF will be documented in the CSR by a listing including patient number, and outcome of inclusion criteria #1, #2, #3, and #4 assessments. There should also be in the disposition part of the CSR the possibility to outline:

- Total number of enrolled patients in the study (not by cohort, just number of patients signing the first ICF)
- For patients signing the first ICF, number of patients having YES on all 4 inclusion criteria (i.e. in principle possible to continue to screening 2 and ICF #2)
- For patients signing the first ICF, number of patients having NO for at least 1 of the 4 inclusion criteria (i.e. screen failures at stage 1)
- Specification of which inclusion criteria was not YES
    - #1
    - #2
    - #3
    - #4



| Page: Inclusion Criteria Screening 1 - Screening Visit 1 | |
|---|---|
| 1. Patients with unequivocal documented (including histological confirmation of GB at the primary diagnosis) first progression/recurrence of GB on MRI, as defined by RANO criteria | Yes |
| 2.Patients with: | |
| • for Cohorts 1, 2a, and 3: at least 1 measurable lesion | |
| • for Cohort 2b: no measurable enhancing disease (defined as less than 1x1 cm in maximum bi-perpendicular plane) | |
| • for Cohort 2c: documented recurrence of GB deemed to be candidate for surgery as standard-of-care at the local institution, and for which the resection can safely be postponed for 4-6 weeks per local institutional guidance and treating physician judgement. In addition, for inclusion in Cohort 2c the patient must consent to mandatory collection of tissue samples from the time of diagnosis (if logistically available), and the planned surgery after neoadjuvant study therapy (see also Section 7.1.1). | Yes |
| • o Note, patients to be included in Cohort 2c should also have a clinical profile which according to local institutional guidance and treating physician judgement would allow the patient to manage surgery for recurrent GB without undue risk, also if neoadjuvant therapy would not be delivered. In addition, in the case of inclusion in the study the delay of surgery to prepare for, and deliver study neoadjuvant therapy, should not jeopardize the best interest of the patient according to the assessment of the treating physician. | |
| 3. Patients with an age ≥ 18 years old | Yes |
| 4. Patients who are HLA-A2 positive | No* |

Patient disposition will be listed and summarized by cohort and overall for the All Patient Population. The table will include the number and percentage of:

- Screened patients (by signing ICF #1 and ICF #2)
- Treated patients
- Included patients in each study population (Safety, FAS)
- Patients who discontinued the study (Screening Failure/End of Treatment), including a breakdown of the primary reasons for end of treatment

In addition, the number of patients screened and included in each analysis population will be displayed by center.

Patients excluded from the efficacy analysis (i.e. excluded from FAS) will be listed with the reason for exclusion from FAS.

All visit dates will be listed.

Listings will be also provided for Signed informed consent Form, Patient eligibility, Inclusion and Exclusion criteria not met.

## 7.3 Protocol Deviations

All important protocol deviations will be listed for the All Patients populations. All protocol deviations will be summarized by cohort and overall, for the Safety Population.

All important protocol deviations leading to exclusion from the FAS population (see Section 5.3) will be listed and summarized by cohort and overall, for the Safety Population.

## 7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by cohort and overall for Safety population. Standard descriptive statistics will be presented for the continuous variables, and total counts and percentages of patients will be presented for the categorical variables.

Following variables will be presented:

- Age (years) as captured in the eCRF
- Sex (F/M)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Weight (kg)
- Height (cm)
- ECOG
- Karnofsky performance status
- Karnofsky performance status (Categorized)
- Cancer history:
    - Current tumor location (Post gross total resection, Local brain tumor, Local brain tumor + metastatic disease, Other)
    - Histopathologic diagnosis (yes/no)
    - Time since initial diagnosis of Glioblastoma in months, computed as (date of second ICF - date of initial diagnosis of Glioblastoma + 1) / (365.25/12)
    - Diagnosis of lower grade Glioma before diagnosis of Glioblastoma (yes/no)
    - If yes, Histopathologic diagnosis (GLIOMA GRADE I, GLIOMA GRADE Io, GLIOMA GRADE IoI, OTHER) and Time since Diagnosis of lower grade Glioma, computed in months as (date of second ICF - date of diagnosis of lower grade Glioma + 1) / (365.25/12)
    - Status of MGMT promotor methylation (Methylated, Unmethylated, Undetermined, Unknown)
    - Status of IDH1 (Mutated, Unmutated, Undetermined, Unknown)
    - Status of IDH2 (Mutated, Unmutated, Undetermined, Unknown)
- Neurological function assessed by NANO questionnaire at Baseline

Since not both ECOG and Karnofsky performance status were measured the following categorized Karnofsky performance status will be calculated based on available ECOG values according to the following table (see [4]):

| | |
|---|---|
| KPS 100-90 | ECOG 0 |
| KPS 80-70 | ECOG 1 |
| KPS 60-50 | ECOG 2 |
| KPS 40-30 | ECOG 3 |
| KPS 20-10 | ECOG 4 |
| KPS 0 | ECOG 5 |

No formal tests of statistical significance will be performed on the demographic and baseline data (if no inferential tests planned).

Demographics and baseline characteristics will be presented in listings by cohort.

Collected data on fertility status and childbearing potential will be listed.

Other baseline measurements (vital signs, ECG and laboratory tests) will be summarized overall and per cohort, and listed with the post-baseline measurements as described in section 7.7.

### 7.4.1 Prior therapies for Glioblastoma

Prior therapies due to Glioblastoma or Lower Grade Glioma include systemic therapies, radiotherapies, and surgeries, analyzed separately.
Number and percentage of patients with at least one prior radiotherapy will be provided, along with number and percentage of patients per site of radiotherapy and type of radiotherapy, for each cohort and overall.

Number and percentage of patients with at least one prior surgery will be provided, for each cohort and overall. Location of surgery will also be summarized. Among patients with prior brain surgery, specification and type of brain surgery will be provided similarly.

Prior systemic therapies will be coded using the WHODrug Dictionary Version March 2019 Enhanced Dictionary Version B3, as applicable (or a later version if updated during the study).

The number and percentage of patients with prior systemic therapy will be summarized by system organ class (SOC) and preferred term (PT), or Anatomical Therapeutic Chemical (ATC) level 2 and 4 Classification codes, as applicable, for each cohort and overall.

All prior therapies will be then listed separately (systemic therapies, radiotherapies, surgeries, other therapies) sorted by therapy start date.

Concomitant Surgeries reported in Cohort 2c will be listed separately.

| Page: Surgery - Cohort 2c | |
|---|---|
| Date of Surgery | 01 SEP 2022 |
| Type of procedure | Gross Total Resection |
| If Type is Other, Specify | |
| Outcome | Complete resection (100%) |
| Other Outcome | |
| Date of hospitalisation admission | 31 AUG 2022 |
| Date of Hospitalisation Discharge | 03 SEP 2022 |
| Did patient return for further hospitalisation visits related to surgery? | No |
| Any other comments | |

### 7.4.2 Medical History

Medical and surgical history includes relevant history other than GB. Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 (or a later version if updated during the study). All medical and surgery history will be listed, and the number and percentage of

patients with any history will be summarized for the Safety population by system organ class (SOC) and preferred term (PT) for each cohort and overall.

### 7.4.3 Previous and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded [redacted] using the WHODrug Dictionary Version March 2019 Enhanced Dictionary Version B3 (or a later version if updated during the study) and Anatomical Therapeutic Chemical (ATC) Classification codes.

Previous medications and concomitant medications are defined as follows:

- Previous medications are those with a stop date prior to the first dose date of study treatment.
- Concomitant medications are those with a start date on or after the first dose date of treatment, or those with a start date before the first dose date of treatment and a stop date on or after the first dose date of treatment or ongoing end of study.

If a medication cannot be classified as "previous" or "concomitant" after applying imputation rules for missing/incomplete dates (see Section 6.2), it will be classified as concomitant.

Previous medications and concomitant medications will be listed together using therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4) and generic term, and sorted by medication start date.

Concomitant medications will be summarized separately, for Safety population. The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2) and chemical subgroup (ATC-Level 4).

### 7.4.4 Concomitant Procedures or Non-Drug Therapies

Procedures or non-drug therapies received concomitantly with treatment will be coded [redacted] using the MedDRA Version 22.0 (or a later version if updated during the study), and will be listed.

Post-study procedures and non-drug therapies (i.e. starting on or after the date of last study treatment) will be listed by efficacy cohort and patient, including all parameters from the concomitant procedures/non-drug therapies page. From this listing there will be a medical review to assess post-study anti-cancer procedures/non-drug treatments which will then be summarized in the CSR.

# 7.5 Measurements of Treatment Adherence

For each patient, adherence will be computed for overall study period, for each treatment: EO2401, nivolumab, bevacizumab.

Percentage adherence is calculated as:

100 * number of administrations performed/number of administrations scheduled, where number of administrations scheduled is based on following theoretical schedule:

- For EO2401, bi-weekly administrations from Week 0 to Week 6 included, then monthly administrations until permanent discontinuation of study drug.
- For nivolumab in Cohort 1, bi-weekly administrations from Week 4 until permanent discontinuation
- For nivolumab in Cohorts 2a, 2b, 2c and Cohort 3, bi-weekly administrations from Week 0 until permanent discontinuation
- For bevacizumab in Cohort 3 only, bi-weekly administrations from Week 0 until permanent discontinuation

Percentage adherence will be summarized descriptively by cohort and overall for the Safety population.

The number and percentage of compliant patients will be presented, where compliant is defined as percentage adherence between 70.0% and 120.0%, inclusive. The following percentage adherence categories will be presented:

- <70.0%
- Compliant
- >120.0%

Bevacizumab Adherence will only be computed for patients of Cohort 3.

# 7.6 Efficacy

The efficacy assessments in this study are considered secondary and exploratory and will be performed on the FAS Population, per cohort and overall.

## 7.6.1 Primary Efficacy Analysis

The OS will be summarized descriptively overall and per cohort using the Kaplan-Meier method. The median survival time will be presented with its associated 95% confidence interval (CI) calculated according to Brookmeyer and Crowley. Survival rates will be provided at 6, 12, 18 and 24 months with 95% CI using the log-log transformation according to Kalbfleisch and Prentice. The results will also be presented graphically in Kaplan-Meier plot.
Follow-up for survival using the reversed Kaplan-Meier method will be presented for overall and efficacy cohorts, including medians and 95% CI in an additional table.

## 7.6.2 Secondary Efficacy Analysis

- The PFS will be summarized descriptively overall and per cohort using the Kaplan-Meier method. The median survival time will be presented with its associated 95% CI. Survival rates will be provided at 6, 12, 18 and 24 months. The results will also be presented graphically in Kaplan-Meier plot.
- ORR and DCR will be summarized overall and per cohort, with 95% exact Clopper-Pearson CI for binomial proportions. In the listing, a single CR or PR followed by an iUPD will be flagged to allow identify PsR (pseudo response).
- Response duration will be calculated on responder patients (CR and PR) only and will be displayed as time to event parameter using the Kaplan-Meier analysis per cohort and overall.
- Time to objective response will be summarized descriptively overall and per cohort using the Kaplan-Meier method. The median survival time will be presented with its associated 95% CI. The results will also be presented graphically in Kaplan-Meier plot.
- Duration of Disease control will be summarized descriptively overall and per cohort using the Kaplan-Meier method. The median survival time will be presented with its associated 95% CI. The results will also be presented graphically in Kaplan-Meier plot.
- In a special analysis, overall Survival, PFS, DCR and Duration of Disease Control based on the start of surgery in Cohort 2b will be compared to Cohort 2c in a similar way as described above, but without Kaplan-Meier plots.

A listing of iRANO assessments (including MRI dates), target lesions and new lesions will be provided.

Listings of OS, PFS, DCR and Duration of Disease Control based on the start of surgery will be listed for Cohort 2b.

A waterfall plot for tumor shrinkage will be displayed for Cohorts 1, 2a/1, 2a/2, 3 and Cohort 2a/2 + 3, respectively.

For T cell immunogenicity, following analyses of immune response will be provided [redacted] at Screening and at different timepoints detailed in the Schedule of Assessments:

- The immunogenicity of the 4 compounds (EO2316, EO2317, EO2318, and UCP2) separately or as a pool [redacted] pooling EO2316/EO2317/EO2318 together, according to availability from central laboratory) for each of the 5 tests* by visit:
  - Frequency of positive patients. For ICS, CD4+, CD8+ and CD4- will be analyzed if available, separately. [redacted]
  - Frequency of patients with boosting response [redacted]
  - For the two above analyses, we will use two types of denominators: the first will be the number of patients with available test result at the given visit, the second will be the number of patients in the cohorts.
  - * [redacted]
- The immunogenicity of each of the 4 compounds (EO2316, EO2317, EO2318, and UCP2) separately or as a pool [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

For analysis, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

A listing of T cell immunogenicity results will be provided, with presence of positive/boosting response from each test and each compound, by patient and by visit.

A[redacted]

- Cross reactivities of the 3 compounds (EO2316, EO2317, EO2318) with the three human TAAs (IL-13Rα2 and BIRC5 (survivin) and FOXM1):
  - [redacted]

[redacted]

### 7.6.3 Sensitivity Analysis

[redacted]

### 7.6.4 Subgroup Analysis

Not applicable.

### 7.6.5 Exploratory Analysis

The NANO score will be summarized descriptively overall and per cohort on the FAS. Mean change from baseline will be added to the standard descriptive statistics. Assessments performed at follow-up visits will be included in the analysis, provided they occurred before or on the day of medically reviewed and accepted progressive disease assessment or before or on the day of start of any new anticancer treatment per medical review. Patients who withdraw consent can be followed until, and including, the day of withdrawn consent, and patients who stop study treatment at 24 months per protocol can be followed until, and including, the day of end of study treatment assessment. The last date (including this date) to be used for a NANO assessment in each individual patient based on medical review will be included in the Sponsor-Excel column Q titled "Last date to be used for NANO assessment".

## 7.7 Safety

All safety analyses will be based on the Safety Population, per cohort and overall. No formal statistical analysis of the safety data will be performed.

### 7.7.1 Extent of Exposure

Duration of exposure will be defined in months as:

(last administration date – first administration date + 1) / (365.25/12).

It will be computed separately to EO2401, nivolumab, bevacizumab.

If date of first dose date is missing, then the date of first dose dispensed will be used. If last dose date is missing then date of last known administration will be used.

Duration of exposure to each of the three treatments will be listed and summarized using descriptive statistics for each cohort for the Safety population.

The number and percentage of patients with duration of exposure in the following categories will be summarized for EO2401 for the Safety population:

- >0-<=3 months
- >3-<=6 months
- >6-<=12 months
- >12 months

Also, number of EO2401 administrations will be described.

Data listings for EO2401, nivolumab and bevacizumab administration will be provided.

Moreover, a similar listing of exposure displaying the duration of treatment exposure based on the start of surgery in Cohort 2b (if applicable) will be presented. Furthermore, descriptive statistics of duration of treatment will be compared to the usual duration of treatment in Cohort 2c.

### 7.7.2 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary Version 22.0 (or a later version if updated during the study) and classified as either baseline signs and symptoms or treatment – emergent AEs (TEAEs) as follows:

- Baseline signs and symptoms are events that start prior to the date of first dose of treatment.
- TEAEs are events with start date and time on or after the date and time of first dose of treatment and up to 30 days after date of last dose of treatment, or events with start date and time prior to the date and time of first dose of treatment whose severity worsens on or after the date and time of first dose of treatment.

An overview table will summarize the number and percentage of patients with at least one of the following TEAEs, by cohort and overall for all safety cohorts (i.e. C1, C2a, C2b, C2c, C3, overall), and all the parameters in this list will also be outlined more thoroughly in summary tables and listings for these cohorts:

- AE;
- AE by severity (NCI-CTCAE grade, version 5.0);
- treatment-related AE;
- treatment-related AE by severity (NCI-CTCAE grade, version 5.0);
- treatment-related AE with Grade >=3 (NCI-CTCAE grade, version 5.0);
- AE leading to discontinuation of EO2401;
- AE leading to discontinuation of nivolumab;
- AE leading to discontinuation of bevacizumab;
- AE leading to interruption of EO2401;
- AE leading to interruption of nivolumab;
- AE leading to interruption of bevacizumab;
- SAE;
- SAE leading to death;

This overview table will be repeated for the following cohorts/populations:

Cohort 1 patients, with following 3 periods displayed in columns:

- Cohort 1 Monotherapy, defined as all AEs occurring between first administration of EO2401 and first administration of nivolumab (planned at Week 4)
- Cohort 1 Combination, defined as all AEs occurring from first administration of nivolumab (planned at Week 4). Percentages will be based on the number of patients in Cohort 1 with at least one administration of nivolumab.
- Cohort 1 Overall

Patients with symptomatic bevacizumab (EN+received sLDB; Sponsor-Excel defined patients) and

Cohort 2a/1 patients.

Patients with symptomatic bevacizumab are those who received bevacizumab (Avastin) as concomitant medication during study treatment per protocol Version 3. The final determination of these patients can be found in the Sponsor-Excel.

A listing of these patients will be provided.

Also, the incidence of TEAEs, related TEAEs, SAEs, AEs leading to discontinuation of EO2401, AEs leading to discontinuation of Nivolumab and AEs leading to discontinuation of Bevacizumab (applying only to Cohort 3), and for patients with local administration site reactions (LASR) will be presented by the current MedDRA version, SOC and PT. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total.

LASR are identified by the corresponding tick box in the eCRF. A separate listing for these including specifications and comments will be presented.

This analysis of incidence of TEAEs and a separate table presenting number and percentage of patients with at least one Treatment-Related TEAE with Grade >=3, by MedDRA System Organ Class and Preferred Term will be presented on the five cohorts/populations displayed above.

The TEAE summary tables will include counts of patients. Therefore, if a patient experiences more than 1 episode of a particular AE, the patient will be counted only once for that event. If a patient has more than 1 TEAE that is coded to the same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than 1 TEAE within an SOC, the patient will be counted only once in that SOC.

In addition, the incidence of TEAEs by severity will be summarized by SOC and PT. For summary by severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. This analysis will be repeated for LASR.

A similar analysis by severity will be based on all LASR events. In this case all LASR events will be counted with their respective severities.

In the above summaries, patients with more than one AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one AE within a particular PT are counted only once for that PT. For summaries by severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. AEs with missing intensity/severity will be included (as Grade 4) in the overall count of patients with AEs, but will not be included in the counts of patients with AEs within a SOC or PT.

All AE tables will be based on TEAEs.

All AE data will be listed by cohort with a flag for identifying the TEAEs. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of SAEs, AEs leading to discontinuation of EO2401, AEs leading to discontinuation of nivolumab, AEs leading to discontinuation of bevacizumab, AEs leading to interruption of EO2401, AEs leading to interruption of nivolumab, AEs leading to interruption of bevacizumab and AEs resulting in death will be produced.

Also, the listing of all AEs will be repeated on the monotherapy period of Cohort 1, defined as all AEs occurring between first administration of EO2401 and first administration of nivolumab (planned at Week 4).

No statistical comparisons of AEs between cohorts will be performed.

For all patients with LASRs the time to onset of the first LASR will be summarized descriptively overall and per cohort using the Kaplan-Meier method. The median survival time will be presented with its associated 95% confidence interval (CI). The results will also be presented graphically in Kaplan-Meier plot.

A similar analysis will be done for the time to onset of each LASR event as well as for the duration of all LASR events. In cases there is no end date for a LASR event, the duration of LASR events will be censored by taking the last physical examination date with skin result equal to Abnormal as the censoring date.

### 7.7.3 Laboratory Evaluations

Data for the following parameters recorded in the eCRF will be listed for the All Patient population and summarized by cohort and visit for the Safety population.

[redacted]

[redacted]

All laboratory data will be reported in International System of Units (SI) units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

Laboratory data (hematology, Biochemistry/Electrolytes/Renal function, Hormones, Coagulation, Urinalysis) will be summarized overall and per cohort, and by visit for the Safety population, adding mean change from baseline to the standard descriptive statistics of continuous parameters. For each laboratory analyte, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

If applicable, shift tables (low, normal, high) presenting movement in and out of reference range from baseline to each scheduled post-baseline visit will be provided for each cohort and overall.

Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries, but will be listed (e.g. serology).

In addition, for all clinical laboratory tests when possible to convert, a conversion to NCI-CTCAE grades will be done and summaries based on NCI-CTCAE grades will be presented, by actual values per visit, grading per visit, and by shift tables from baseline to worst value during the trial for individual patients. Also, for same parameters, number and percentage of patients will be provided by worst NCI-CTCAE grade during the study.

The listing of following laboratory panels will be provided on the monotherapy period of Cohort 1, for all visits until the first administration of nivolumab [redacted] Hematology, Biochemistry/Electrolytes /Renal function, Hormones, Coagulation, Urinalysis.

### 7.7.4 Vital Signs

The following vital signs will be listed for the All Patient population and summarized overall and per cohort, and by visit for the Safety population.

- Weight (kg)
- Body temperature (°C). Temperatures collected in °F will be converted to °C using following formula: (°F – 32) x (5/9) = °C.
- Systolic and diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (breaths/min)

For weight, change from baseline will be summarized for each post-baseline visit.

For each vital sign, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

### 7.7.5 Electrocardiograms

The ECG clinical interpretation will be summarized overall and per cohort, and by visit for the Safety population, with following categories: "normal", "abnormal, not clinically significant" and "abnormal, clinically significant".

Corresponding listing will be provided.

### 7.7.6 Physical Examination

Physical examination results (normal/abnormal) and details of abnormalities will be listed for each patient and visits.

### 7.7.7 Other Safety Variables

- The Karnofsky Performance Status groups (see Section 7.4), including a transformation of ECOG status to the KPS groups, will be summarized overall and per cohort, and by visit for the Safety population, presenting the number and percentage of patients in each category. Listing of all ECOG, Karnofsky Performance Status assessments, and KPS groups data will be provided.

## 7.8 Exploratory assessments

- Correlation between immunogenicity of EO2316, EO2317, EO2318, and UCP2 that compose EO2401 and the outcome parameters PFS, ORR, DoR, DCR, and OS will be analyzed according to a separate analysis plan.
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

## 7.9 Interim Analysis

[redacted]

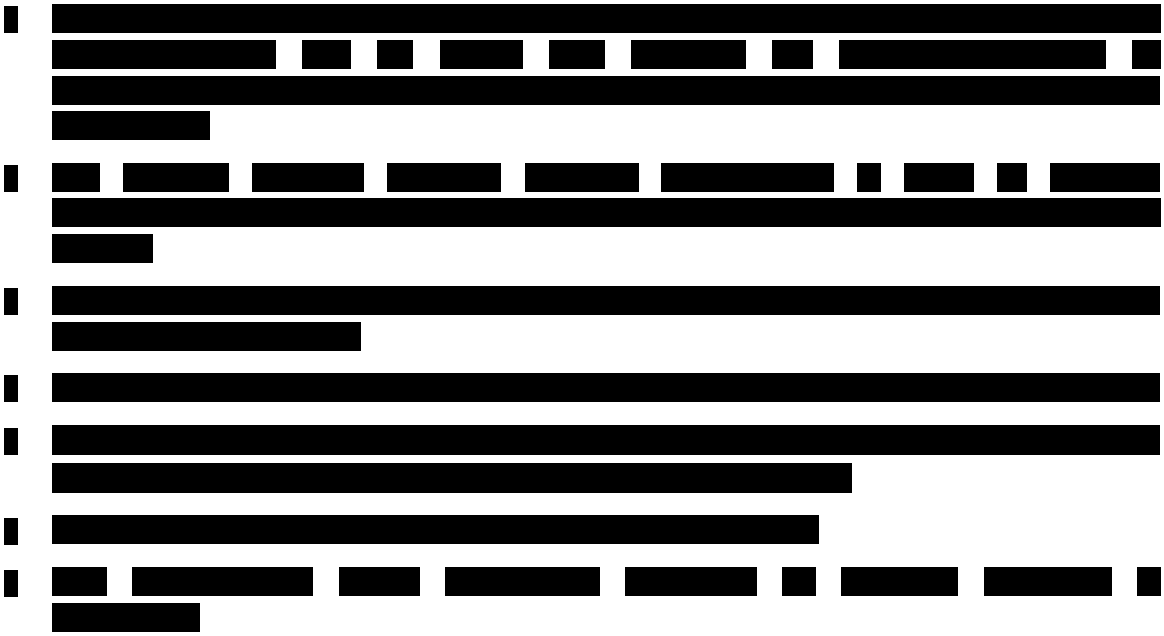
## 7.10 Overall Survival Interim Analysis and Final Analysis

An update of OS analysis and listings of efficacy and safety parameters for patients who are still alive in the study after the interim analysis will be performed on a regular basis (every 3 to 6 months, as appropriate).

The final analysis will be done when the last patient completes the study treatment, all assessments for disease response, and monthly Follow-up Visits. However, as stated in study protocol, timing of the final analysis will be possibly amended in relation to the outcome of interim analysis 1 and 2.

Each patient will participate in the study for a maximum of 24 months from the time of informed consent through final study contact. It is planned for all patients to be followed for survival for 24 months after last patient enrollment, if possible, via hospital records or other registers.

# 8. Changes in Planned Analysis



# 9. Data Issues

Not applicable.

# 10. References

[1] Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology (iRANO): A Report of the RANO Working Group. *Lancet Oncol*. 2015;16(15):e534-e542.

[2] Elligson B, Wen P, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. *Neurotherapeutics*. 2017;14:307-320.

[3] US Food and Drug Administration, Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, December 2018.

[4] Performance Scales: Karnofsky & ECOG Scores Practice tools (esmo.org)

# 11. Appendices

The list and shells of Tables, Figures and Listings will be provided in a separate document.

## 11.1 Appendix 1: Document History

| Document Version, Status, Date | Summary/Reason for Changes |
|---|---|
| Version 1, Final, 21 June 2021 | Not applicable; the first version |
| Version 2, Final, 03 April 2024 | Alignment on Protocol Version 3.0 dated 17Aug2021:<br>- Adjustment of sample size in existing cohorts,<br>- Addition of Cohort 2c<br>- Addition of Disease Control Rate<br>- Addition of OS survival rates<br>- Keep DTH analysis?<br>Alignment on Protocol Version 4.0 dated 27Apr2022:<br>- Adjustment of sample size in cohorts<br>- Cohort 3 is not only in US<br>Consideration of sponsor's medical review for ORR/DCR<br>Removal of listing for drug accountability<br>IHC: Computation of score replaced by available measurements and addition of ranking values.<br>Clarifications in immunogenicity analyses<br>[redacted]<br>Other minor adjustments |

# 11.2 Appendix 2: Sample SAS® code for analyses

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 …varn;
    BY byvar; (optional)
    OUTPUT OUT=outname;
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that need 95% CIs within group for binomial proportions:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var1;
    EXACT BINOMIAL;
RUN;
```

- **Tables that need number of events/censored and probabilities of failure/survival at cut off times:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=LT INTERVALS=12, 24;
    TIME duration*censor (0 or 1);
    ID patient;
    STRATA treatment;
RUN;
```

- **Tables that need life table with estimates of survival with CIs:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM;
     TIME duration*censor (0 or 1);
    ID patient;
    STRATA treatment;
RUN;
```

- **Kaplan-Meier curves for treatment:**

```
PROC LIFETEST data=dataset plots=survival(strata=individual);
    TIME time*event(0);
    STRATA treatment;
RUN;
```