# ENTEROME: EOADR1-19 (EN01)

## Statistical Analysis Plan

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|---|---|
| **Date:** | **06-Nov-2024** |
| **Version:** | **v01** |
| **Status:** | **final** |
| **Author:** | [redacted] |

| | |
|---|---|
| Study Title: | A phaSe 1/2 trial of EO2401, a novel microbial-derived Peptide therapeutic vaccine, in combination with PD-1 check point blockadE, for treatment of patients with locally advaNced or metastatic adrenocortical Carcinoma, or malignant phEochromocytoma/paRaganglioma (the *Spencer* study) |
| Investigational Product: | EO2401 |
| Clinical Phase: | I/II |
| Enrolment of first patient | 23-Jul-2020 |
| Sponsor: | ENTEROME<br>94/96 avenue Ledru-Rollin<br>75011 Paris<br>France |
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## Contents

# 1 DOCUMENT HISTORY

| Version | Date | Author / editor of new version | Main changes / comments |
|---|---|---|---|
| v01 | 06-Nov-2024 | [redacted] | First version |

# 2 LIST OF ABBREVIATIONS

| Abbreviation | Text |
|---|---|
| ACC | Adrenocortical carcinoma |
| AE | Adverse event |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| APP | All patient population |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| BIRC5 | Baculoviral inhibitor of apoptosis repeat-containing 5 |
| BMI | Body mass index |
| BUN | Blood urea nitrogen |
| CI | Confidence interval |
| CR | Complete response |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| CT | Computed tomography |
| DCR | Disease control rate |
| DNA | Deoxyribonucleic acid |
| DOR | Duration of response |
| DP | Drug product |
| DRM | Data review meeting |
| [redacted] | [redacted] |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| eGRF | Estimated glomerular filtration rate |
| ELISpot | Enzyme-linked immunospot |
| ENSAT | European Network for the Study of Adrenal Tumors |
| FAS | Full analysis set |
| FOXM1 | Forkhead box M1 |
| FSH | Follicle-stimulating hormone |
| HIV | Human immunodeficiency virus |
| HLA | Human leukocyte antigen |
| ICH | International Council for Harmonization |
| iCPD | Immune confirmed progressive disease |
| iCR | Immune complete response |
| IDMC | Independent data monitoring committee |
| IEC | Independent ethics committee |
| IFN-γ | Interferon-gamma |
| IHC | Immunohistochemistry |
| IL-13Rα2 | Interleukin-13 receptor alpha-2 |
| IL-6 | Interleukin-6 |
| INR | International normalized ratio |
| iPR | Immune partial response |
| IRB | Institutional review board |
| iRECIST | Immune-related response evaluation criteria in solid tumors |

| Abbreviation | Text |
|---|---|
| iSD | Immune stable disease |
| iUPD | Immune unconfirmed progressive disease |
| KM | Kaplan-Meier |
| LASR | Local administration site conditions at a site of EO2401 local administration |
| LDH | Lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEN | Multiple endocrine neoplasia |
| mENSAT | Modified European Network for the Study of Adrenal Tumors |
| MPP | Malignant pheochromocytoma/paraganglioma |
| NCI-CTCAE | National Cancer Institute-common terminology criteria for adverse events |
| Nmiss | Number of missing values |
| NE | Not evaluable |
| OS | Overall survival |
| ORR | Objective response rate |
| PBMC | Peripheral blood mononuclear cells |
| PFS | Progression-free survival |
| PD | Progressive disease |
| PD-1 | Programmed death-1 |
| PD-L1 | Programmed death-ligand 1 |
| PP | Pheochromocytoma/paraganglioma |
| PR | Partial response |
| PT | Preferred term |
| RECIST | Response evaluation criteria in solid tumors |
| Q1 | First quartile |
| Q3 | Third quartile |
| SAE | Serious adverse event |
| SAF | Safety population |
| SAP | Statistical analysis plan |
| SD | Stable disease |
| SOC | System organ class |
| SDHB | Succinate dehydrogenase B |
| SOP | Standard operating procedure |
| TAA | Tumor associated antigen |
| TCR | T cell receptor |
| TERT | Telomerase reverse transcriptase |
| TEAE | Treatment emergent adverse event |
| UCP2 | Universal cancer peptide 2 |
| TSH | Thyroid stimulating hormone |
| VHL | Von Hippel–Lindau |
| WHO | World health organization |
| WHO DD | World health organization drug dictionary |

# 3 GENERAL

This statistical analysis plan (SAP) reflects study protocol EOADR1-19 Version 5.0 dated 24-Jan-2024. It follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9. It gives all details for all primary, secondary, and selected exploratory statistical analyses of this study [redacted]

## 3.1 Analyses planned and already performed

The nature of the study, i.e. an early exploratory development trial aiming at generating as much knowledge as possible before potential decisions related to further development of EO2401, makes it important to assess especially safety, but also efficacy and possible biomarkers, on an ongoing basis during trial conduct. Exploratory preliminary data from the trial might be utilized in relation to e.g. scientific discussions and presentations to facilitate input regarding possible improvements of development parameters.

In particular, the independent data monitoring committee (IDMC) will examine the safety of study participants throughout the duration of the study. The IDMC will examine the safety data of Cohort 1, including possible transitions between sub-cohorts (1a, 1b, 1c, and 1d) and provide advice and guidance regarding the recruitment start of Cohorts 2A, 2B, 3A, and 3B. The safety of patients in Cohorts 2A, 2B, 3A and 3B are also subject to assessments of the IDMC. In addition, in relation to the randomized extension of Cohort 2A, the IDMC will oversee and validate the interim first stage analysis of the Simon's two-stage design as performed by the Sponsor (or designee); see Section 9.4.2 of the protocol.

This SAP covers the analyses of the study which will constitute the content of the primary Clinical Study Report (CSR) and the needed addenda.

## 3.2 SOPs to be followed

The analysis will be carried out according to [redacted] standard operating procedure (SOP).

# 4 OVERVIEW OF THE PROTOCOL

## 4.1 Objectives of the study

### 4.1.1 Primary objective

- The primary objective of the phase 1 part of this trial is to evaluate safety and tolerability of EO2401 in combination with nivolumab in patients with unresectable, previously treated, and previously untreated, locally advanced or metastatic adrenocortical carcinoma (ACC), and progressive malignant pheochromocytoma/paraganglioma (MPP).
- The primary objective of the phase 2 part of this trial is to determine the effect of EO2401/nivolumab on the progression-free survival (PFS) rate at 6 months, per investigator/local site assessments, for patients treated in the randomized extension of Cohort 2A (patients treated with EO2401 monotherapy and nivolumab monotherapy, respectively, will constitute internal concurrent controls in the randomized extension). Cohort 2A comprises patients with ACC who had prior systemic therapy for established locally advanced or metastatic disease.

### 4.1.2 Secondary objectives

The key secondary objectives of the trial are:

immunogenicity in relation to T cells of EO2316, EO2317, EO2318, and Universal cancer peptide (UCP2) that compose EO2401; T cell cross-reactivity with the human tumor associated antigens (TAAs) interleukin-13 receptor alpha-2 (IL13Rα2), forkhead box M1 (FOXM1), and baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5)/survivin will also be evaluated.

The other secondary objectives of the trial are:

- Objective Response Rate (ORR), time to response, and duration of response (DOR).
- PFS and Overall Survival (OS).
- [redacted]

### 4.1.3 Exploratory objectives

The exploratory objectives include the exploration of:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

## 4.2 Study design

The trial is a 5-cohort study intended to recruit a maximum of approximately 120 evaluable patients in total per the below outline. The actual recruitment per cohort for the study has been:

- Cohort 2A (ACC previously treated), non-randomized = 26 patients treated with EO2401/nivolumab (including 2 patients from Cohort 1)
- Cohort 2B (ACC previously systemically not treated for metastatic disease), non-randomized = 7 patients treated with EO2401/nivolumab
- Cohort 3A (MPP previously treated), non-randomized = 13 patients treated with EO2401/nivolumab
- Cohort 3B (MPP previously systemically not treated for metastatic disease), non-randomized = 5 patients treated with EO2401/nivolumab
- Cohort 2A-I (ACC previously treated), randomized = 13 patients treated with EO2401/nivolumab
- Cohort 2A-II (ACC previously treated), randomized = 2 patients treated with EO2401 monotherapy
- Cohort 2A-III (ACC previously treated), randomized = 4 patients treated with nivolumab monotherapy

Intended maximum recruitment:

- Cohort 1 (previously treated patients) includes an evaluation by a safety lead-in 3-by-3 design of EO2401 in combination with nivolumab at standard dose; patients with ACC and MPP will be included. Three to 12 evaluable patients will be included depending on the safety profile of the administered treatments. At an IDMC meeting [redacted], there was a consensus decision, after 3 evaluable patients had been treated without any reported safety concern event to recommend finalizing the recruitment to Cohort 1 of trial EOADR1-19 and open Cohorts 2A/3A (see Section 1.3.3 of the Protocol). [redacted]

[redacted]

- Cohorts 2A (previously treated patients) and 2B (previously untreated patients) include an evaluation of EO2401 at the recommended dose found in Cohort 1 in combination with nivolumab in 30 evaluable patients (15 each for Cohorts 2A and 2B) with ACC (note, evaluable patients with ACC from Cohort 1 can be assessed in Cohort 2A as well, leading to the potential need of recruitment of less than 15 patients specifically for Cohort 2A). After a re-distribution of patients between Cohorts 2A and 2B (see Section 1.3.3 of the Protocol) the final recruitment number in the non-randomized part of Cohort 2A was 26 treated patients, and in Cohort 2B, 7 treated patients, i.e. in total 33 patients. After analysis of the initial non-randomized part of Cohort 2, the global protocol amendment 2 (leading to protocol EOADR1-19 version 3.0) is implementing the randomized phase 2 portion of the trial for patients with ACC, by extension of Cohort 2A with an additional 65 patients (see Section 1.3.3 and Section 4.1 of the protocol).
- Cohorts 3A (previously treated patients) and 3B (previously untreated patients) includes an evaluation of EO2401 at the recommended dose found in Cohort 1 in combination with nivolumab in 30 evaluable patients (15 each for Cohorts 3A and 3B) with progressive MPP (note, evaluable patients with MPP from Cohort 1 can be assessed in Cohort 3A as well leading to the potential need of recruitment of less than 15 patients specifically for Cohort 3A). The global protocol amendment 2 (leading to protocol EOADR1-19 version 3.0) is implementing an adjustment of planned patient number in Cohort 3, from current 30 patients (with a target of 15 patients each for Cohorts 3A and 3B; see above) to approximately 20 patients without a specific split between Cohorts 3A and 3B (see Section 1.3.3 of the protocol for the rationale of the adjustment). The global protocol amendment 3 (leading to protocol EOADR1-19 version 4.0) is stopping the recruitment of new patients in Cohort 3 considering the very low recruitment rate (see Section 1.3.3 of the protocol for the rationale of the adjustment).

The schematic trial and cohort designs are presented in Figure 1 and Figure 2.

[redacted]

## 4.3 Sample size

Cohorts 1, non-randomized 2A, 2B, 3A, and 3B

This is an early development, open-label, exploratory, multi-cohort trial to include patients with very rare malignant adrenal tumors; i.e. ACC and MPP. In this context, the sample size of the trial has been determined by practical considerations in collaboration with experts in the field, aiming at the possibility to recruit different patient populations to facilitate an as fast as possible, and broad (in relation to patient baseline characteristics), assessment of safety and tolerability, immunogenicity, and preliminary efficacy; [redacted] Based on these factors, the trial was designed to include an initial safety lead-in, 3-by-3 design, cohort including 3 to 12 patients, followed by 4 cohorts, including distinct patient populations, to be recruited in parallel each enrolling 15 patients evaluable for safety.

Patients in Cohort 1 who are evaluable [redacted] will, besides being part of Cohort 1, also be assessed as part of the planned Cohorts 2A or 3A. Thus, the number of evaluable patients to be recruited to Cohorts 2A and 3A might be decreased based on the number of evaluable patients already recruited in Cohort 1.

The 3-by-3 approach for Cohort 1 includes predefined stopping rules if concerning safety events would be encountered; in short 0 (zero) concerning safety event in 3 patients, or 1 concerning safety event in 6 patients, are considered acceptable.

The number of evaluable patients aimed at in Cohorts 2A, 2B, 3A, and 3B, i.e. 60 evaluable patients in total can in the context of adrenal malignancies be seen as a large dataset for safety assessments.

From an efficacy perspective, by inference from earlier clinical experience in the rare adrenal malignancies, it is judged that if there would be at least two interesting outcomes (which might be objective tumor responses, and/or assessable relevant biomarker responses, and/or prolonged Disease Control Rate (DCR) of ≥ 6 months for patients with ACC, and ≥ 12 months for patients with MPP) within one of the cohorts, i.e. within a group of 15 patients it would be an interesting outcome, and it could be considered to explore the treatment in further patients in a new trial (or via an amendment of the current trial).

Based on the above it is assumed that the current trial will include enough patients to provide adequate safety and tolerability information, immunogenicity data, as well as preliminary efficacy data without demanding a too high (and long) patient recruitment and without exposing too many patients.

Randomized extension of Cohort 2A

As outlined above, an interesting outcome within one of the cohorts, i.e. within a group of 15 patients, could be the trigger to explore the treatment in further patients via an amendment of the current trial.

[redacted]

[redacted]

The above efficacy parameters taken together constitute an interesting outcome both regarding ORR/DCR and the time dependent endpoints PFS and early survival, even if the outcome is dependent on de-selecting patients without any appreciable benefit from study treatment. [redacted] Thus, it seems appropriate to explore EO2401/nivolumab treatment further and considering the need to first (before embarking on a larger trial) prospectively confirm the population selection parameters it seems appropriate to make the exploration in an extension of the ongoing trial via an amendment.

Thus, the current trial EOADR1-19 is amended in such a way that further patients are enrolled into an extension of Cohort 2A with adjusted inclusion/exclusion criteria to allow for further investigation of this orphan indication. The patients enrolled after the extension of the Cohort 2A shall be handled independently from patients who were enrolled in the non-randomized part of Cohort 2A from a statistical point of view.

The primary objective is to determine the effect of EO2401 in combination with nivolumab on the PFS rate at 6 months, per investigator/local site assessments, in patients with unresectable ACC who had prior systemic therapy for established locally advanced or metastatic disease. A secondary objective is to determine the effect of EO2401 monotherapy and nivolumab monotherapy on the PFS rate at 6 months, per a secondary independent scan review regarding progression in the same population.

Patients shall thus be randomized into three different treatment groups: EO2401+nivolumab (Cohort 2A-I) vs. EO2401 monotherapy (Cohort 2A-II) vs. nivolumab monotherapy (Cohort 2A-III) in a 4:1:1 ratio. No direct statistical comparison between the three treatment groups is planned. The EO2401/nivolumab treatment group shall have a Simon’s two-stage design on its own. The EO2401 monotherapy and the nivolumab monotherapy treatments groups shall ensure the assay sensitivity of the randomized extension of Cohort 2A. For the assessment of assay sensitivity, both monotherapy groups may be pooled, and analyzed separately (latter might be more appropriately for instance in case the EO2401 monotherapy outcome is closer to EO2401/nivolumab than to nivolumab monotherapy).

[redacted]

The trial has an IDMC implemented with the primary role to examine the safety and tolerability of study participates throughout the duration of the study. In addition, the IDMC will oversee and validate the interim first stage analysis of the Simon's two-stage design as performed by the Sponsor (or designee).

The selected, among alternative assessed designs (Table 6), design is a two-stage Simon

design (optimal design), with alpha = 5% and power = 80%. The statistical hypothesis to be tested:

- [redacted]

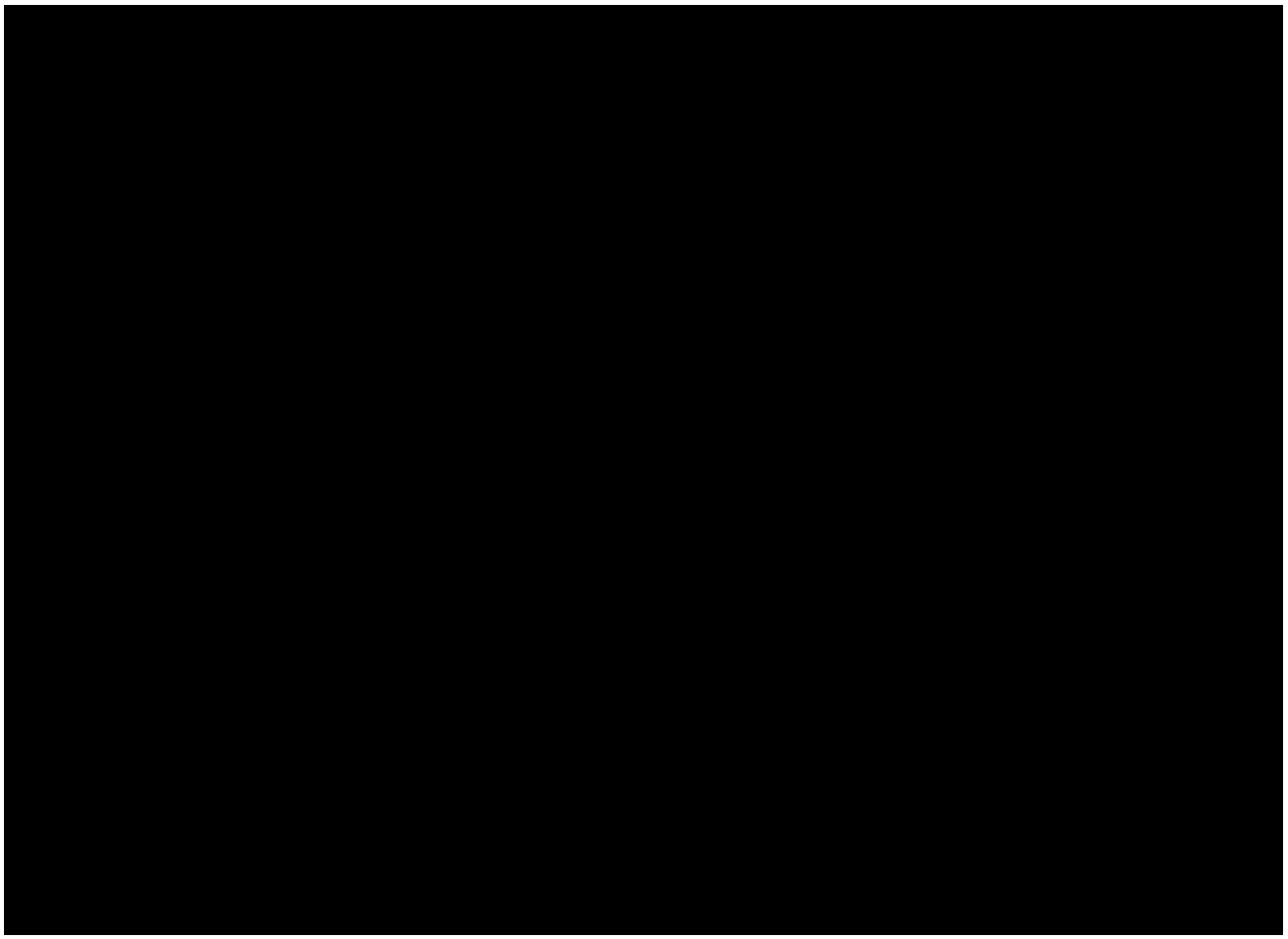
with $r$ being the PFS rate at 6 months in the EO2401/nivolumab group, calculated as the number of patients alive without progression at 6 months after start of treatment with EO2401/nivolumab, divided by the number of patients randomized to EO2401/nivolumab treatment in the relevant analysis set. Randomization will be done 4:1:1 (Cohort 2A-I ; Cohort 2A-II ; Cohort 2A-III), aiming at a total sample size of 65 patients.

[redacted]

- [redacted]
- [redacted]

[redacted]

There are going to be two randomized internal concurrent controls, EO2401 monotherapy (Cohort 2A-II) and nivolumab monotherapy (Cohort 2A-III): the two-sided 90% CIs (Clopper-Pearson) of the PFS rate at 6 months will be calculated for the internal controls separately and pooled together. [redacted]



[redacted]

As soon as 13 patients are randomized and start treatment with EO2401/nivolumab, there will be a temporary halt of the recruitment of new patients until the result of this first stage analysis is known. [redacted]

## 4.4 Endpoints

### 4.4.1 Primary endpoint

- Primary endpoint of the phase 1 part includes safety and tolerability of EO2401 in combination with nivolumab by a descriptive medical assessment of the combined profile of incidences of adverse events (AEs), treatment emergent AEs (TEAEs), serious

AEs (SAEs), deaths, reasons for treatment discontinuation/delays, and laboratory abnormalities using the National Cancer Institute-common terminology criteria for AEs (NCI-CTCAE) v5.0 grading system.

- Primary endpoint of the phase 2 part is the rate of patients without progression (according to immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) criteria [Seymour et al]) or death due to any cause at 6 months after the first dose of randomized treatment. Six months after the first dose of randomized treatment will be determined for each patient and is dependent on the exact time point of evaluation of the CT investigation scheduled at week 25 (day 169). The primary endpoint is to be determined per investigator/local site assessments of progression. The denominator will be all patients who started the randomized treatment in Cohort 2A and will be determined for each randomized treatment group separately. Patients will be followed up for progression or death during the first 6 months after start of randomized treatment regardless of whether they stop treatment and continue on other regimens. Patients who are completely lost to follow-up will be counted as if they had a PFS event during the first 6 months.

The evaluation of the primary endpoint is described in Section 7.8.2.

### 4.4.2 Secondary endpoints

The key secondary endpoints of the trial are:

- Percentage of patients with shown immunogenicity [redacted] in relation to EO2316, EO2317, EO2318, and UCP2 that compose EO2401 [redacted]
- Cross reactivities with the human TAAs IL13Rα2, FOXM1, and BIRC5 (survivin)

[redacted]

The other secondary endpoints of the trial are:

- ORR, time to response, and DOR as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer et al] and iRECIST criteria.
- PFS as defined by RECIST 1.1 and iRECIST criteria
- OS.
- Safety and tolerability of EO2401 in combination with nivolumab will be assessed in the same way as the primary endpoint for phase 1.

The definitions of the secondary endpoints can be found in Sections 7.8 (response related endpoints) and Section 7.9 (immunogenicity endpoints) together with the specification of statistical analyses.

### 4.4.3 Exploratory endpoints

[redacted]

[redacted]

[redacted]

## 4.5 Study flow chart

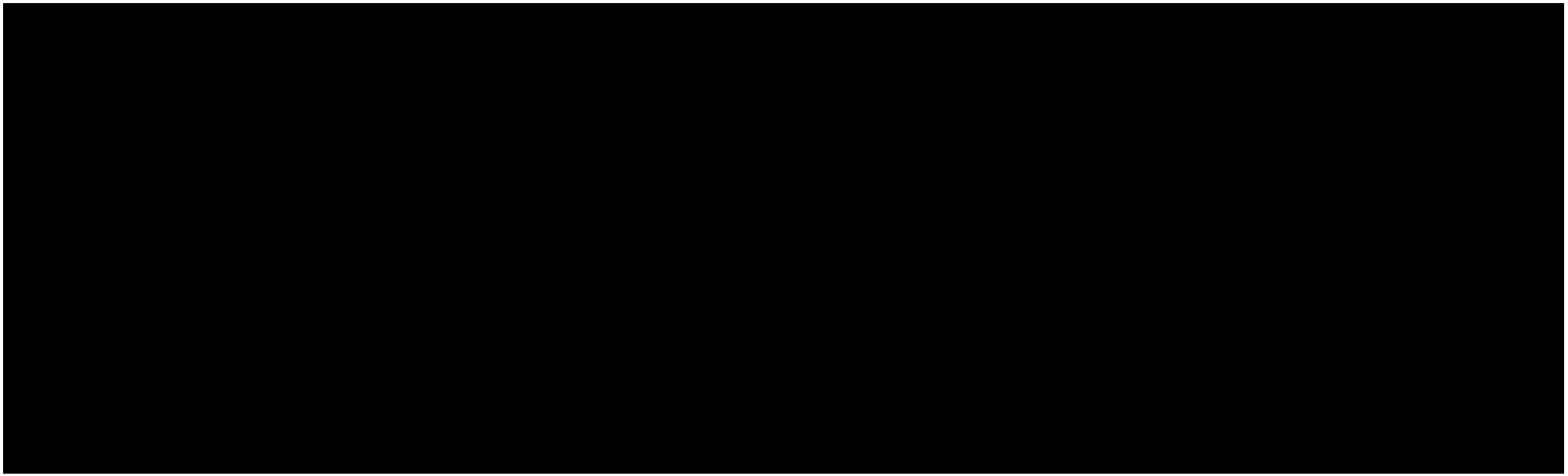
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



# 5 GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

## 5.1 Analysis sets

The following analysis sets are defined:

- The All Patient Population (APP) will consist of any patient who signed informed consent including screen failures.
- The Full Analysis Set (FAS) will consist of patients who received at least one dose of EO2401. [redacted]
- The Safety Population (SAF) will consist of patients who received at least one dose of EO2401. [redacted]
- The population evaluable for the 3-by-3 design in Cohort 1 will consist of patients who receive [redacted] EO2401 [redacted]

Summary tables will be based on the populations given in Table 2:

**Table 2 Summaries by analysis set**

| Summary | APP[1] | SAF | FAS | 3-by-3 |
|---|---|---|---|---|
| Patient disposition | see Section 7.3 | | | |
| Protocol deviations | | x[2] | | |
| Demographics and relevant baseline characteristics | | x[2] | | |
| Medical history | | x[2] | | |
| Prior and concomitant medications | | x[2] | | |
| Procedures and non-medical drug interventions | | x[2] | | |
| Efficacy endpoints | | | x | |
| Immunogenicity endpoints | | | x | |
| Exploratory endpoints | | | x | |
| Safety | | x | | see Section 7.11.2 |

[1] Data of patients included in the All Patient Population (APP), but not qualifying for the Full Analysis Set (FAS) or Safety Population (SAF) (i.e. screen failures) will only be displayed in listings.
[2] For cohort 1, only SAF will be presented; for cohorts 2 and 3 one summary table will be provided only, if SAF and FAS are identical, which is expected.

## 5.2 Protocol deviations

Protocol deviations and other reasons for exclusion from any analysis set will be reported and collected as described in the Protocol Deviation Management Plan. During the data review meeting (DRM) all protocol deviations will be reviewed regarding classification. All decisions and the reasons for these decisions will be documented in the DRM meeting

minutes, which will be finalized and signed prior to database lock for the primary Clinical Study Report.

A protocol deviation is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the independent ethics committee (IEC)/institutional review board (IRB). Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

A major protocol deviation is defined as any change, divergence, or departure from the study design or procedures of the research protocol that affects the patient's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data constitutes a major protocol deviation, if it not classified as a minor deviation per below.

A minor protol deviation is defined as changes or alterations in the conduct of the trial which do not have a major impact on the patient's rights, safety or well-being, or the completeness, accuracy, and reliability of the study data are considered minor protocol deviations.

Any deviation that does not meet the criteria of Major Deviation or Serious Breach.

All decisions regarding the type of deviations (minor or major) will be made prior to commencing the final analysis on the final locked database. A listing of all patients with protocol deviations will be maintained by the Sponsor and a listing of all major protocol deviations will be presented in the final study report.

Investigational sites will report protocol deviations to their IEC/IRB per institutional reporting requirements.

## 5.3 Changes or deviations from planned analyses

[redacted]

[redacted]

[redacted]

# 6 DEFINITIONS FOR STATISTICAL ANALYSIS

## 6.1 Handling of withdrawals (drop-outs), missing values and outliers

If not specified otherwise, missing values will not be displayed and no imputations will be performed. Patients who dropped out from the study will be analyzed with all data provided.

## 6.2 Study drug

EO2401 and nivolumab constitute study drug in this trial. If any patient receives only one of the two medications, the patient will still be counted as having received at least one dose of study drug.

## 6.3 Reference day / Day 1

The day of first treatment with study drug will be Day 1. The day prior to Day 1 will be Day -1.

## 6.4 Baseline

A baseline assessment is the last assessment prior to the first dose of study drug. A baseline assessment may take place on Day 1, prior to the first dose.

## 6.5 Time interval and duration

Time intervals will generally be calculated as

$$end\ date - start\ date + 1.$$

If the time of the day is provided for both time points, the time interval will be calculated as

$$end\ date/time - start\ date/time.$$

## 6.6 Subgroup analysis

For Cohort 2A, randomized, inclusion/exclusion criteria were adjusted to exclude, to the largest possible extent, further treatment of patients who seem to not have any appreciable benefit from treatment with EO2401/nivolumab.

For patients belonging to Cohort 2A, non-randomized the subgroups of patients fulfilling and not fulfilling these extended criteria will be considered for efficacy endpoints.

[redacted]

# 7 STATISTICAL ANALYSIS SPECIFICATION

## 7.1 Specifications related to whole analysis

### 7.1.1 Tables

Unless otherwise specified, summary tables will be stratified by cohort (see below), and visit, where appropriate. For continuous data, the basic statistics, i.e., the sample size, the number of missing values (Nmiss), the (arithmetic) mean, and standard deviation, minimum, first quartile (Q1), median, third quartile (Q3) and maximum will be shown and calculated on non-missing data. Categorical data will be displayed in frequency tables showing sample size and absolute and relative frequency. If not stated otherwise, percentages will be based on all observed values in the corresponding cohort and visit if appropriate. The time course of continuous data will be presented using the basic statistics for each visit and the absolute differences from baseline.

For the display in summary tables, minimum and maximum values will be reported with the same number of decimals as the raw data unless otherwise stated. Mean, median, standard deviation, Q1, and Q3 will be reported with one more decimal. Percentage values will be rounded to one decimal place.

Patients enrolled who are evaluable at the Week 5 visit (V3) safety assessment in Cohort 1 will be presented and evaluated within Cohorts 2A and 3A, non-randomized, according to their primary tumor type (i.e. such patients with ACC will also be assessed in Cohort 2A

and patients with MPP will also be assessed in Cohort 3A). Data from patients in Cohort 1, who can be evaluated within Cohorts 2A or 3A will thus be included in tables for Cohort 1 and in tables for Cohorts 2 and 3. Comparisons between cohorts should therefore be performed carefully taking into account that the same patient might be presented twice.

The wording 'by cohort' in this document refers to

- baseline and safety summary tables for Cohort 1.
- tables for Cohorts 2 and 3, non-randomized, with columns for Cohorts 2A, 2B, 3A, 3B, and totals for 2A and 2B together, and for 3A and 3B together and a total column for Cohorts 2 and 3 combined.
- tables for Cohort 2, randomized, with columns for Cohorts 2A-I, 2A-II, 2A-III, and a column presenting all cohorts that were treated with EO2401 as monotherapy or in combination with Nivolumab (i.e. all cohorts, randomized and non-randomized, except Cohort 2A-III). The column all cohorts treated with EO2401 will **not** be presented for all summaries of efficacy endpoints, immunogenicity endpoints, and exploratory endpoints.

The following table header shall be used for baseline and safety summary tables for Cohort 1:

| Cohort 1 |
|---|

As only patients in Cohort 1a were treated, the table header will only have one column.

Tables for Cohort 2 and 3, non-randomized, will generally be presented with the following table header:

| Cohort 2A | Cohort 2B | Cohort 2 | Cohort 3A | Cohort 3B | Cohort 3 | Cohorts 2 + 3 |
|---|---|---|---|---|---|---|

Tables for Cohort 2A, randomized, will generally be presented with the following table header:

| Cohort 2A-I | Cohort 2A-II | Cohort 2A-III | Cohorts receiving EO2401 |
|---|---|---|---|

See Appendix I to the SAP for a full table of contents of all summary tables and graphs planned for the CSR Section 14; and Appendix II to the SAP for mock-up tables that show the exact structure and content of example summary tables and graphs.

## 7.2 Data listings

Electronic case report form (eCRF) and external laboratory data will be listed as documented. All relevant generated and transformed variables will be listed next to the original data items. In all listings, cohort, and center for each patient will be included. The listings will be sorted by cohort and patient identifier. Patients from Cohort 1 who can be evaluated within Cohort 2A or 3A will be marked as such in all listings.

See Appendix I to the SAP for a full table of contents of all patient data listings planned for the CSR Appendix 16.2.

## 7.3 Disposition of patients

The overall duration of investigation in days is defined as

$$date\ of\ last\ patient\ last\ visit - date\ of\ first\ patient\ first\ visit + 1.$$

The summary tables will provide the relevant dates and the calculated durations in weeks and months (1 month = 30.5 days), for the APP and the SAF/FAS, respectively.

The number of patients screened, identified as screen failures at Screening 1 together with the reason for screen failure, entering Screening 2, identified as screen failures at Screening 2 together with the reason for screen failure, allocated to cohort, and belonging to the SAF/FAS will be summarized overall. The number of patients allocated to a cohort, and the number of patients who received EO2401 and/or nivolumab, and are belonging to SAF/FAS will be summarized by cohort for the APP. The reasons for screening failure will only be listed.

The number of patients screened and patients treated with any study drug (i.e. EO2401 and/or nivolumab) will be tabulated based on the APP by site and cohort (except for Cohort 1).

For Cohort 1, the number and percentage of patients in the 3-by-3 Evaluable Population and in the SAF, and reasons for exclusion from the 3-by-3 Evaluable Population will be summarized by cohort based on the SAF.

Number and percentage of patients of Cohort 2A, non-randomized, fulfilling and not fulfilling extended in/exclusion criteria [redacted] will be summarized.

The primary reason for EO2401 treatment termination, for nivolumab treatment termination and for study termination will be summarized by cohort (except for Cohort 1) for the SAF/FAS in terms of numbers of patients and percentages.

The number and percentage of patients participating at each scheduled study visit will be summarized by cohort (except for Cohort 1) for the SAF/FAS.

## 7.4 Demographics and baseline characteristics

### 7.4.1 Relevant definitions

The times since the primary diagnosis, since the diagnosis of metastatic disease and since the most recent progression are defined in the following way

$$(date\ of\ first\ treatment\ with\ study\ drug - date\ of\ respective\ event + 1).$$

Time since the primary diagnosis and time since the diagnosis of metastatic disease will be presented in years (1 year = 365.25 days) and the time since the most recent progression will be given in months (1 month = 30.5 days) (rounded to one decimal):.

For primary diagnosis, diagnosis of metastatic disease and most recent progression, incomplete dates will be estimated using the first possible date. If year is missing, the date will be set to missing.

Time since (second) last mitotane plasma assessment before most recent progression is defined as:

$$(date\ of\ most\ recent\ progression -$$
$$date\ of\ (second)\ last\ mitotane\ plasma\ level\ assessment\ before\ most\ recent\ progression +$$

1).

Time since last mitotane plasma assessment before most recent progression and time since second last mitotane plasma assessment before most recent progression before most recent progression will be given in months (1 month = 30.5 days) (rounded to one decimal).

Listings will present the incomplete dates as documented and a flag will be added, whenever estimation for the above mentioned variables is performed.

### 7.4.2 Statistical analysis

Demographic data and other baseline characteristics will be summarized by cohort.

The following data will be summarized:

- Age (years)
- Gender (female, male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Asian, Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- ECOG performance status at baseline
- Height [cm], weight [kg], body mass index (BMI) [kg/m²] (calculated)
- Tumor diagnosis
    - Time since primary diagnosis [years]
    - Primary diagnosis (ACC, Pheochromocytoma/paraganglioma [PP])
    - Histological confirmation at primary diagnosis (yes, no)
    - Initial location of primary tumor (cervical, thoracic, abdominal, pelvic, other)
    - Resectable (not resectable, fully resectable, partially resectable, other)
    - Previously treated (yes, no)
    - Metastatic disease (yes, no)
    - Time since diagnosis of metastatic disease [years]
    - Stage of metastatic disease (Chromaffin tissue in non-chromaffin organs present (MPP), ENSAT/AJCC stage III (ACC), ENSAT/AJCC stage IV (ACC), Other): percentage based on patients with metastatic disease
    - Number of organs with metastases
    - Progression prior to the study (yes, no)
    - Time since most recent progression [months]
    - Presence of different HLA-A types (HLA-A* 02:01, HLA-A* 02:02, HLA-A* 02:03, HLA-A* 02:04, HLA-A* 02:05, HLA-A* 02:06, HLA-A* 02:07, Other)
- Baseline pheochromovytoma/paraganlioma information): percentage based on patients with PP
    - RECIST defined progression within a maximum period of 18 months (yes,

no)
    - Presence of SDHB germline mutations (yes, no, not done)
    - Presence of MMAL fusion mutations (yes, no, not done)
    - Any other germline mutations (yes, no, not done)
    - Any other somatic mutations (yes, no, not done)
    - Secretor (no, yes, unknown, other)
    - Predominant catecholamine and rank order of secretion
        - Epinephrine (adrenaline) / based on metanephrine (dominant, second most, third most, no secretion, other)
        - Norepinephrine (noradrenaline) / based on normetanephrine (dominant, second most, third most, no secretion, other)
        - Dopamine / based on 3-Methoxytyramine (dominant, second most, third most, no secretion, other)
    - TNM-classification at primary diagnosis
        - T classification (T1, T2, T3, Other)
        - N classification (N0, N1, Other)
        - M classification (M0, M1, Other)
        - WHO stage (Stage I, Stage II, Stage III, Stage IV, Other)
- Baseline ACC information: percentage based on patients with ACC
    - Secretion
        - Evidence for a glucocorticoid-secreting ACC (no, yes, other)
        - Evidence of relevant endogenous cortisol excess (no, yes, difficult to judge)
        - Receiving glucocorticoid replacement therapy (no, yes)
    - TNM-classification at primary diagnosis
        - T classification (T1, T2, T3, Other)
        - N classification (N0, N1, Other)
        - M classification (M0, M1, Other)
    - Modified European Network for the Study of Adrenal Tumors (ENSAT) (mENSAT)
        - Number of tumor involved organs (0, 1, 2, 3, 4, 5, >5)
        - mENSAT at the time of diagnosis (III, IVa, IVb, IVc, Other)
        - mENSAT at baseline (III, IVa, IVb, IVc, Other)
    - GRAS
        - Histopathology criteria by Weiss
            - High nuclear grade (Fuhrman criteria) (0, 1)
            - > 5 mitoses per 50 high power field (0,1)
            - Atypical mitotic figures (0,1)
            - <25% of tumor cells are clear cells (0,1)

- Diffuse architecture (>33% of tumor) (0,1)
- Necrosis (0,1)
- Venous invasion (smooth muscle in wall) (0,1)
- Sinusoidal invasion (no smooth muscle in wall) (0,1)
- Capsular invasion (0,1)

- Weiss score in categories (≤ 6, > 6)
- Weiss score (numeric)
- Ki67 index in categories (< 20, ≥ 20),
- Ki67 index (numeric)
- R status (R0: complete resection, R1: microscopic residual disease, R2: macroscopic residual disease, Rx: resection unknown, Other)
- Age (< 50 years, ≥ 50 years)
- Symptoms (yes, no, other)

- Mitotane treatment assessed as Screening (for Cohort 2, non-randomized, i.e. presenting Cohort 2A, 2B, and Cohort 2A, non-randomized, as columns, and Cohort 2A, randomized, without column Cohorts receiving EO2401, i.e. presenting Cohort 2A-I, 2A-II, 2A-III as columns):
  - Patient received mitotane therapy before study entry (yes, no)
  - Patient continues mitotane therapy during study (yes, no): percentages based on patients receiving mitotane therapy before study entry
  - Mitotane therapeutic plasma level before most recent progression (above 14 mg/L, below 14 mg/L, maximum tolerated dose, other): percentages based on patients continuing mitotane therapy during study
  - Time since last mitotane plasma assessment before most recent progression [months]
  - Second last mitotane therapeutic plasma level before most recent progression (above 14 mg/L, below 14 mg/L, maximum tolerated dose, other): percentages based on patients continuing mitotane therapy during study
  - Time since second last mitotane plasma assessment before most recent progression [months]

Further, the following demographic data and other baseline characteristics will be summarized by subgroup (see Section 6.6):

- Age (years)
- Gender (female, male)
- ECOG performance status at baseline
- Time since primary diagnosis [years]
- Secretion: Evidence for a glucocorticoid-secreting ACC (no, yes, unknown)
- mENSAT at baseline ((III, IVa, IVb, IVc, Other)
- mENSAT: number of tumor involved organs (0, 1, 2, 3, 4, 5, >5)

- Ki67 index in categories (< 20, ≥ 20),
- Ki67 index (numeric)
- R status (R0: complete resection, R1: microscopic residual disease, R2: macroscopic residual disease, Rx: resection unknown, Other)
- prior treatment with mitotane (see details in Section 6.6)
- maximum individual lesion size at baseline.

Other baseline measurements, such as vital signs, electrocardiogram (ECG), and laboratory tests from Screening (S1 and S2) and Day 1 visit (V1) will be summarized together with the post-baseline measurements (see Sections 7.11.3 and 7.11.4 for details). If relevant, the calculated baseline values per parameter (see 6.4) will be summarized in addition to the visits prior to the first dose of study drug. Results of human immunodeficiency virus (HIV), hepatitis B and hepatitis C, and follicle-stimulating hormone (FSH) testing will only be listed.

## 7.5 Medical history and concomitant illnesses

Medical history and concomitant illnesses will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 27.0.

A concomitant illness is defined as any diagnosis for which either no stop date was documented or the stop date is later than the Day 1. Incomplete stop dates will be estimated using the last possible date in order to define whether a diagnosis is concomitant.

Summary tables presenting the numbers and percentages of patients with medical history and with concomitant illnesses by MedDRA system organ class (SOC) and MedDRA PT will be provided by cohort. In these tables, SOCs and PTs within SOCs will be ordered with decreasing frequency in the Cohort 2+3 or Cohorts receiving EO2401, respectively.

## 7.6 Prior and concomitant medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD), WHO DDE-B3 March 2020.

Prior medication is defined as medication that started and stopped prior to Day 1. Concomitant medication is defined as medication with at least one dose taken between Day 1 (including) and last treatment date (including). Post-study treatment medication is defined as medication that started after last treatment date. Incomplete start and stop dates will be estimated using, the following rules in order to define whether a treatment was taken concomitantly.

- Partial or missing 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 (after imputation of end date if needed) 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 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.

Summary tables presenting the numbers and percentages of patients with medication will be summarized separately for prior, concomitant, and post treatment medication by cohort. In these tables, the medications will be decoded on PT according to WHODD and grouped by the first level (Anatomical Main Group) terms of the Anatomical Therapeutic Chemical (ATC) Classification (e.g. Blood and blood forming organs).

All prior, concomitant, and post treatment medication will be listed.

Further, a summary table presenting number and percentage of patients with

- Mitotane therapy prior to start of study treatment
- Mitotane therapy continued during study treatment for the whole treatment period
- Mitotane therapy continued during study treatment, but stopped during treatment period
- Mitotane therapy (re)started during study treatment period

by cohort will be provided. Mitotane therapy is defined as any medication with PT (i.e. variable CMDECOD) equal to MITOTANE.

For Cohort 2, randomized (without Cohorts receiving EO2401 column), absolute values and changes from baseline of Mitotane plasma levels will be summarized by visit. A patient data listing providing all details of Mitotane therapy and a patient data level of Mitotane plasma levels during study will be provided.

## 7.7 Procedures and non-drug medical interventions

Procedures and non-drug medical interventions will be coded using the MedDRA dictionary version 27.0.

Prior procedure/non-drug medical intervention is defined as procedure that started and stopped prior to Day 1. Concomitant procedure/non-drug medical intervention is defined as procedure/non-drug medical intervention taking place between Day 1 (including) and last treatment date (including). Post-study treatment procedure/non-drug medical intervention is defined as procedure/non-drug medical intervention that started after last treatment date. Incomplete start and stop dates will be estimated using, the following rules

in order to define whether a procedure/non-drug medical intervention took place concomitantly.

- Partial or missing 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 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.

Summary tables presenting the number and percentage of patients with procedures and non-drug medical interventions by MedDRA SOC and MedDRA PT will be provided by cohort for the SAF separately for surgeries, radiotherapies, and other procedures and non-drug medical interventions. In these tables, SOCs and PTs within SOCs will be ordered with decreasing frequency in the Cohort 2 and 3 or Cohorts receiving EO2401 column. Prior, concomitant, and post treatment procedures non-drug medical interventions will be listed separately for surgeries, radiotherapies, and for all other procedures and non-drug medical interventions.

## 7.8 Efficacy endpoints

As described in Section 5.1, the FAS will be the basis for the analysis of efficacy data. Only summary tables for Cohorts 2 and 3, non-randomized, and Cohort 2, randomized, (without Cohorts receiving EO2401 column) and none for Cohort 1 are planned (cf. Section 7.1). Further, all summary tables, all Kaplan-Meier (KM) plots, and waterfall plots will be provided by patients fulfilling and not fullfiling extended in/exclusion criteria [redacted] for Cohorts 2A, non-randomized.

### 7.8.1 General aspects of response related endpoints

The response assessments during the treatment period follow the scheduled CTs post

baseline, planned for the visits at study weeks 9, 17, 25 (+/- 4 days), and from Week 25 onwards every 8 weeks (+/- 4 days). Unscheduled CT assessments as well as planned CT scans performed on the day of study drug administration [redacted] are also possible. For patients who are discontinuing all study treatment without having had confirmation of progressive disease (PD) according to iRECIST criteria [Seymour et al], CT assessments are scheduled every 8 weeks (+/- 4 days) after the latest performed CT assessment during the time period they received study treatment.

If not otherwise stated, all response assessments collected by investigator (local assessments) during the study will be considered, regardless of whether they come from scheduled or unscheduled assessments and if they were assessed during or after study treatment.

In principle, any further anti-cancer treatment during the study, i.e. prior to the individual study treatment termination, is prohibited. If nevertheless a patient is treated with further anti-cancer treatment during the study, the inclusion of CT assessments after introduction of further anti-cancer treatment in the derivation of response related and time to event endpoints will be agreed on and documented during the DRM. Also, the non-trial systemic anti-cancer treatments defined in Section 7.8.5 and 7.8.6 will be confirmed during the DRM.

### 7.8.2 Primary endpoint of the phase 2 part: progression-free survival (PFS) rate at 6 months based on investigator / local assessment

[redacted]

[redacted] All available data from the monotherapy groups will be reviewed at the same time point.

[redacted]

As the first stage of Simon's two-stage design was not concluant, only number and percentage of patients regarded as progression-free survivor at 6 months according to iRECIST and not regarded as progression-free survivor with subcategories patient died, patient alive, but progressive disease (immune unconfirmed progressive disease [iUPD] or immune confirmed progressive disease [ICPD]), and patient lost to follow-up will be provided in a summary table for Cohort 2A-I, randomized. Further, two-sided 95% exact Clopper-Pearson CIs for binomial proportions will be provided for the progression-free survivor rate at 6 months by cohort.

No further CIs will be provided and no overall analysis for Cohort 2A-II and 2A-III will be performed.

### 7.8.3 Best overall response, objective response, and disease control rate (DCR)

OR is defined as the best overall response during the whole study period equal to PR or complete response (CR) according to RECIST [Eisenhauer et al] or as best overall response during the whole study period equal to immune partial response (iPR) or immune complete response (iCR) according to iRECIST. No confirmation of PR/CR and iPR/ iCR is required.

The ORR [%] is defined as the relative number of patients achieving OR according to iRECIST/RECIST in the respective cohort. The DCR [%] is defined as the relative number of patients achieving at least one assessment of iCR, iPR, or iSD according to iRECIST in the respective cohort or as the relative number of patients achieving at least one assessment of CR, PR, or SD according to RECIST.

The ORR/DCR according to iRECIST/RECIST will be summarized with two-sided 95% exact Clopper-Pearson CIs for binomial proportions by cohort.

The best overall response according to RECIST will be summarized by cohort, using the following categories and hierarchy: OR (RECIST) with subcategories CR and PR, SD, PD, not evaluable.

The best overall response according to iRECIST will be summarized by cohort using the following categories and hierarchy: OR (iRECIST) with subcategories iCR, iPR, iSD, iUPD, iCPD, not evaluable.

The disease control according to RECIST will be summarized by cohort, using the following categories and hierarchy: disease control (RECIST) with subcategories CR, PR, and SD, and PD, not evaluable.

The disease control according to iRECIST will be summarized by cohort using the following categories and hierarchy: disease control (iRECIST) with subcategories iCR, iPR, and iSD, and iUPD, iCPD, not evaluable.

The maximal shrinkage in tumor burden (i.e. maximal percentage decrease in sum of longest diameter compared to baseline = relative change from baseline) will be displayed

in a waterfall plot. The bars will be colored according to best overall response according to RECIST/iRECIST Two different colors will be used for PD with new lesion and PD without new lesion. iUPD and iCPD will have the same color. Waterfall plots will be provided for Cohort 2A, Cohort 2B, Cohort 2, non-randomized, for Cohort 3A, Cohort 3B, Cohort 3, and Cohort 2A-I, Cohort 2A-II, and Cohort 2A-III, randomized, and for patients fulfilling and not fullfiling extended in/exclusion criteria (see Section 6.6) of Cohorts 2A, non-randomized.

All response assessments will be listed.

### 7.8.4 Time-to-OR

Time-to-OR using RECIST criteria is defined as the period from the first dose of study drug until PR or CR, whichever comes first. Patients without PR or CR (RECIST) will be right-censored at the time of progression (the same time point as the event time point for PFS according to RECIST, see Section 7.8.6). If no progression occurred, patients will be right-censored following the same censoring rules as for PFS (see Section 7.8.6).

Time-to-OR using iRECIST is defined as the period from the first dose of study drug until iPR or iCR, whichever comes first. Patients without iPR or iCR (iRECIST) will be right-censored at the time of progression (the same time point as the event time point for PFS according to iRECIST, see Section 7.8.6). If no progression occurred, patients will be right-censored following the same censoring rules as for PFS (see Section 7.8.6).

### 7.8.5 Duration of response (DOR) & Duration of disease control (DDC)

DOR can only be determined for patients with OR as defined above.

According to RECIST, the DOR is measured from the time at which the measurement criteria according to RECIST are first met for CR or PR (whichever is first recorded) until the first date that PD is objectively documented according to RECIST (see Section 7.8.6 for details).

- According to iRECIST, the DOR is measured from the time at which the measurement criteria according to iRECIST are first met for iCR or iPR (whichever is first recorded) until the first date progression criteria according to iRECIST are met (see Section 7.8.6 for details).

Patients alive with no progression will be censored following the same censoring rules as for PFS (see Section 7.8.6).DDC can only be determined in patients with disease control as defined above. DDC according to RECIST/iRECIST is measured from the start of study treatment until the first date that PD is objectively documented according to RECIST/iRECIST (see Section 7.8.6 for details); alternatively censoring is applied according to the rules for PFS.

### 7.8.6 Progression-free survival (PFS) and overall survival (OS)

According to RECIST, PFS is defined as the period from the first dose of study drug until PD or death from any cause (whatever occurs first).

PFS is defined as the period from the first dose of study drug until the first time one of following events occurs

- Progression criteria according to iRECIST/RECIST met

- Start of non-trial systemic anti-cancer treatment (which is regarded as progression according to the protocol).
- death from any cause [redacted] after last post-baseline CT assessment [redacted] after first dose of study drug, if no post-baseline CT assessment is available.

Non-trial systemic anti-cancer treatment is defined as concomitant or post-study treatment/medication that is classified as chemotherapy in the eCRF. Mitotane therapy is not considered as non-trial system anti-cancer treatment.

According to RECIST the progression criteria is met at the first date of post-baseline CT assessment with PD documented as response, if not more than one scheduled CT assessment is missing or not evaluable before this CT assessment and the previous CT assessment was performed within [redacted] to this CT assessment.

According to iRECIST the progression criteria is met at the date of CT assessment with response documented as iUPD for that the next CT assessment documents iCPD as response (without any intervening assessments with other outcome), i.e. PD is confirmed, and if not more than one scheduled CT assessment is missing or not evaluable before the CT assessment with iUPD documented and the previous CT assessment was performed within [redacted] to CT assessment with IUPD documented. If progression is not confirmed and there is no subsequent CT assessment with iSD, iPR or iCR as response then the iUPD date will still be used as date of progression met in the following scenarios:

- no further response assessments are done or
- the next timepoint responses are all iUPD, and iCPD never occurs.

Non-trial systemic anti-cancer treatment is defined as concomitant or post-study treatment medication that is classified as chemotherapy in the eCRF. Mitotane therapy is not considered as non-trial system anti-cancer treatment.

Patients without an event as defined above will be censored based on the rules in Table 3.

**Table 3 Censoring rules for PFS**

| Situation | Date of Event or Censoring |
|---|---|
| No CT assessment at baseline | Date of first study treatment administration |
| No progression nor death nor non-trial systemic anti-cancer treatment documented | Date of last post-baseline CT assessment |
| Death more than [redacted] after last post-baseline CT assessment | Date of last post-baseline CT assessment |
| Death more than [redacted] after first study treatment and without post-baseline CT assessment | Date of first study treatment administration |
| Progression criteria met after ≥2 consecutive schedule missing CT assessments | Date of last post-baseline CT assessment before missing CT assessment |
| Progression criteria met [redacted] after previous CT assessment | Date of previous CT assessment |

OS is defined as the period from the first dose of study drug until death due to any cause. Patients alive at their last visit will be censored at the last visit date.

### 7.8.7 Analyses of DOR, time-to-OR, PFS and OS endpoints

DOR, DDC, time-to-OR, PFS and OS will be described by KM plots along the number of patients at risk. Separate plots will be created including the curves of following cohorts:

- Cohorts 2A, 2B, 3A, and 3B, non-randomized
- Cohorts 2A, 2B, and 2, non-randomized
- Cohorts 3A, 3B, and 3, non-randomized
- Cohort 2A-I, Cohort 2A-II, and Cohort 2A-III, randomized
- For patients fulfilling and not fullfiling extended in/exclusion criteria of Cohorts 2A, non-randomized

The number of patients with an event of interest and being censored and the median, as well as 1st and 3rd quartiles of the estimated times of interest will be presented with their associated two-sided 95% CIs according to Klein and Moeschberger using a log-log-transformation. If reasonable, non-parametric competing risks techniques will be applied for time-to-OR as a sensitivity analysis, if a non-negligible number of deaths is recorded without earlier objective responses. For PFS and OS, 6-months, 12-months, 18-months, and 24-months PFS/survival estimates and corresponding 95% pointwise confidence limits will be provided in addition.

If the number of events is sufficient, DOR, time-to-OR, PFS and OS will be analyzed using Cox proportional hazards model. For Cohort 2 and 3, non-randomized, the following covariates will be included in the Cox-proportional hazards model

- Primary diagnosis (ACC vs. MPP)
- Previously treated (yes vs. no).

For cohort 2, randomized, the variable cohort (Cohort 2A-I, Cohort 2A-II, vs Cohort 2A-III) will be included in the Cox-proportional hazards model as covariate. No Cox-proportional hazard models will be provided for by patients fulfilling and not fullfiling extended in/exclusion criteria of Cohorts 2A, non-randomized.

All results of the CT scans will be listed.

## 7.9 Immunogenicity

As described in Section 5.1, the FAS Population will be the basis for the analysis of immunogenicity data. Only summary tables for Cohorts 2 and 3, non-randomized, with columns for Cohorts 2A, 2B, 3A, 3B, and totals for 2A and 2B together, and for 3A and 3B together and a total column for Cohorts 2 and 3 combined, and Cohort 2, randomized with columns for Cohorts 2A-I, 2A-II, 2A-III, and a column presenting all cohorts that were treated with EO2401 as monotherapy or in combination with Nivolumab (i.e. all cohorts, randomized and non-randomized) , and none for Cohort 1 are planned.

### 7.9.1 Definition of tests, parameters and possible results

[redacted]

Positivity and boosting criteria are defined as follows:

[redacted]

[redacted]

### 7.9.2 Analysis of immunogenicity test results

For T cell immunogenicity, the 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 (according to availability from central laboratory) [redacted]
  - Frequency of positive patients. [redacted]
  - Frequency of patients with boosting response (only for post-Screening assessments). [redacted]
  - For the two above analyses, two types of denominators will be used: the first will be the number of patients with available test results 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] by visit:
  - Frequency of positive patients. [redacted]

[redacted]

- Denominators will be the number of patients with at least one available test among the 4 at the given visit, and the second will be the number of patients in the cohorts.
- Frequency of patients with boosting response (only for post-Baseline assessments). [redacted]
- A shift table showing immune response at Baseline versus immune response at each visit (negative as defined thereafter/positive as defined above/missing), for each of the 4 compounds (EO2316, EO2317, EO2318, and UCP2). A[redacted] Percentages will be based on tested patients (per cohort/overall) rather than per number of patients in the cohorts/overall.

[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.

[redacted]

- Cross reactivities of the 3 compounds (EO2316, EO2317, EO2318) with the three human TAAs (IL-13Rα2 and BIRC5 (survivin) and FOXM1):
  - Prior to cross-reactivity, positivity of human TAAs as pool will be analyzed [redacted]
    - [redacted]
  - [redacted]
  - [redacted]

[redacted] As before, we will use two types of denominators: the first will be the number of patients with at least one available test result among the 3 tests at the given visit, the second will be the number of patients in the cohorts.

- [redacted]
- [redacted]
- [redacted]

[redacted]

## 7.10 Exploratory endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

### 7.10.3 Exploratory endpoints not covered by this SAP

[redacted]

## 7.11 Safety

As described in Section 5.1, the SAF will be the basis for the analysis of safety data. Some additional summary tables will be given for the 3-by-3 Evaluable Population. If this is the case, these will be stated below. Cohorts evaluated for safety analyses are described in Section 7.1.1. For safety laboratory no tables for Cohort 1 will be provided.

### 7.11.1 Study drug exposure and compliance

The duration of study drug exposure will be calculated separately for EO2401 and nivolumab and is defined in months as

$$(last\ treatment\ date - first\ treatment\ date + 1)/30.5$$

(rounded to one decimal). The duration of study drug exposure will be summarized using basic summary statistics, by cohort. Additionally, the duration of exposure will be summarized by cohort using the following categories:

- ≤ 3 months
- > 3 and ≤ 6 months
- > 6 and ≤ 12 months
- >12 months.

The number and percentages of patients with 0, 1, 2, … administered doses of EO2401 or nivolumab, with administered doses of nivolumab without interruption, and with full amount of nivolumab administered will be provided. Basic statistics for the total number of EO2401 administrations, the total number of nivolumab administrations, the total number of nivolumab administrations without interruption and the total number of nivolumab administrations during which the full amount was administered per patient will be provided by cohort

### 7.11.2 Adverse events (AEs)

AEs will be coded using the MedDRA dictionary version 27.0.

The investigator could assess the relationship of an AE to both study drugs either individually (i.e. for EO2401 and nivolumab separately) or combined (i.e. for both EO2401 and nivolumab together). In context of the intended study treatment, as composed of administered in combination with nivolumab, it is most of the times in principle not possible to make causality assessments for each component by itself (due to the nature of the combination treatment and the mode of action of the components). Only in rare cases (e.g., an AE that appears in the 3-hour time interval between the first injection of EO2401 and the first infusion of nivolumab or in cases where nivolumab administrations have been terminated but treatment continues with EO2401) an individual assessment seems reasonable.

Hence, an AE related to study treatment is defined as any AE with a suspected relationship to EO2401/nivolumab combined, with a suspected relationship to EO2401 alone or a suspected relationship to nivolumab alone or with no information with respect to relatedness (i.e. NA cases).

According to the protocol an AE is considered to be treatment emergent if it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or it is present at the start of the active phase of the study or as

part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends [redacted] after the last study drug administration. Therefore, the following AEs will be considered as not treatment emergent and will be excluded from summary tables:

- AEs starting more than [redacted] after last study drug administration
- AEs occurring in patients not treated with EO2401 and/or nivolumab
- AEs starting prior to first study drug administration for that no deterioration in CTCAE grade was documented during the active phase (e.g. patient for that the CTCAE grade improved only)

The following rules will be applied to identify if an AE is regarded as TEAE in case of missing or incomplete start and/or end dates.

- Partial or missing AE 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 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.

All AE classified as **not** TEAE via programming will be reviewed and confirmed during the DRM meeting.

In case of worsening of an AE, the worst grade (NCI CTCAE v5.0) will be used for the analysis and will be counted as one AE.

An overview table presenting number and percentage of patients and the number of AEs in the following categories will be created for the SAF, by cohort:

- Any AE
- Any TEAE

- Any local administration site conditions at a site of EO2401 local administration (LASR)
- Any TEAE with worst grade 1 (NCI CTCAE v5.0)
- Any TEAE with worst grade 2 (NCI CTCAE v5.0)
- Any TEAE with worst grade 3 (NCI CTCAE v5.0)
- Any TEAE with worst grade 4 (NCI CTCAE v5.0)
- Any TEAE with worst grade ≥ 3 (NCI CTCAE v5.0)
- Any TEAE leading to death
- Any disease progression-related TEAE
- Any TEAE related to study treatment
- Any TEAE related to study treatment with worst grade ≥ 3 (NCI CTCAE v5.0)
- Any TEAE leading to definitive discontinuation of any study drug
- Any TEAE leading to definitive discontinuation of EO2401
- Any TEAE leading to definitive discontinuation of nivolumab
- Any TEAE leading to interruption of EO2401
- Any TEAE leading to interruption of nivolumab
- Any serious TEAE
- Any serious TEAE related to study treatment

TEAEs, TEAEs related to study treatment, serious TEAEs, serious TEAEs related to study treatment, non-serious TEAEs, LASRs, TEAEs leading to definitive discontinuation of EO2401, and TEAEs leading to interruption of EO2401 will be summarized by the number of events, and the number and percentage of patients, stratified by cohort. In these tables, AEs will be presented by MedDRA PT and grouped by MedDRA SOC. These tables will be sorted by the overall frequency of MedDRA PTs within each MedDRA SOC. An additional table will present TEAEs by MedDRA PT only, and will be sorted by overall frequency of MedDRA PTs.

Furthermore, TEAEs, serious TEAEs, and TEAEs with a worst CTCAE grade of at least 3 will be summarized by the number and percentage of patients per MedDRA SOC and MedDRA PT, stratified by cohort and by worst CTCAE grade. Multiple occurrences of the same AE in the same patient will be counted once using the worst CTCAE grade. In case of missing CTCAE grade the category "missing" will be added. Missing will be counted as the least severe category.

TEAEs [redacted] will be summarized by MedDRA PT and grouped by MedDRA SOC for Cohort 1, using the 3-by-3 Evaluable Population.

In addition, time to 1st LASR event will be assessed by a KM-analysis, with censoring if no LASR was reported. If no LASR event was documented, the censoring date will be the date of the latest physical examination with a normal finding for "skin" and "extremeties". If no LASR event was documented, and physical examination for extremeties was abnormal for baseline and all post-baseline visits, but no change compared to baseline was documented for the post-baseline visits, the censoring date will be the date of the latest physical examination. If no LASR event was documented, and no post baseline

physical examination assessment is available, the censoring date will be the date of first study treatment. If no LASR event was documented, physical examination for “skin” and “extremeties” was normal at baseline, but abnormal post-baseline, the censoring date will be the date of first study treatment. The duration of all LASR events will be assessed by a KM-analysis, with censoring if there is no end date reported. The censoring date will be the date of the latest physical examination with an abnormal finding for “skin” or “extremities”. If the end of LASR date is given partial only, the rules for incomplete end dates defined above will be used. Time to 1st LASR, and duration of all LASR events will be described by KM plots. Separate plots will be created including the curves of following cohorts:

- Cohorts 2A, 2B, 3A, and 3B, non-randomized
- Cohorts 2A, 2B, and 2, non-randomized
- Cohorts 3A, 3B, and 3, non-randomized
- Cohort 2A-I, Cohort 2A-II, and Cohort 2A-III, randomized.

The median, as well as 1st and 3rd quartiles of the estimated times of interest will be presented with their associated two-sided 95% CIs according to Klein and Moeschberger using a log-log-transformation.

All AEs, all serious AEs, all LASR, all AEs leading to death, all AEs related to disease progression, all TEAEs leading to definitive termination of EO2401 or of nivolumab, all TEAEs leading to interruption of EO2401, and all TEAEs leading to interruption of nivolumab will be listed in separate by-patient listings. One AE listing will include all details of changes in CTCAE grades for those AE, where changes in CTCAE grade were documented.

TEAEs with a suspected relationship to EO2401 alone and TEAEs with a suspected relationship to nivolumab alone will be presented in separate by-patient listings.

### 7.11.3 Safety laboratory

The following safety laboratory parameters and hormones were collected in the eCRF:

- **Hematology**: [redacted]
- **Serum chemistry**: [redacted]
- **Coagulation:** [redacted]
- **Hormones**: [redacted]
- **Urinalysis**: [redacted]
- **Virus serology**: [redacted]

On the serum chemistry additional parameters could be documented. These additional parameters were reviewed and if belonging to any parameter above (e.g. hormones collected on additional visits) will be analysed with the above parameters. [redacted]

Laboratory parameters are to be taken at several scheduled visits during the course of the study. In addition, it is expected that laboratory parameters will be assessed at unscheduled visits also. As those unscheduled values might be of special interest, analysis will be based on the worst value within a pre-defined time window. The following time windows will be used for hematology, differential blood count, serum chemistry, and coagulation parameters. If the same worst value is available in a time window, more than once, the earliest one will be used for analysis.

[redacted]

The following time windows will be used for data from serum cortisol assessments, and data from thyroid function assessments:

[redacted]

The following categorization will be used for the safety laboratory parameters:

[redacted]

The derivation of eGFR is based on the CKD-EPI formula given in Section 12.5 of the protocol. Note, “American Indian or Alaska Native” and “Native Hawaiian or other Pacific Islander” will be considered as other race for eGRF calculation.

Summary tables will be provided presenting the worst absolute value (excluding baseline) and the respective absolute change from baseline in International System of Units (SI) during the treatment period (i.e., until the safety visit) as well as by study week (as defined above) overall for Cohorts 2 and 3, non-randomized, and by Cohort 2, randomized. If the direction of ‘worst’ is not unique (e.g. for WBC) then the lowest and the highest values per patient and time period will be summarized in separate tables.

The identified worst values will be classified according CTCAE v5.0 grades if possible (see Appendix III). This classification is done based on the laboratory raw values only and no additional information like “life-threatening” or “death” can be taken into account. The worst CTCAE v5.0 grades during the whole study period (including assessments prior to treatment) will be displayed in a summary table in terms of absolute numbers and percentages of patients by cohort. The denominator will be the number of patients in the respective cohort. If the direction of ‘worst’ is not unique (e.g. for white blood cell count) then the worst CTCAE grade based on the worst lowest and the worst highest values per patient and time period will be summarized in separate tables. Further, the maximum improvement/worsening in CTCAE v5.0 grade (i.e. minimum/maximum grade post-baseline minus CTCAE grade at baseline for improvement/worsening) will be will be displayed in a summary table in terms of absolute numbers and percentages of patients by cohort. This means if there is at least on post-baseline value documented with a worse grade than at baseline, a worsening is considered for the table and the maximum change from baseline is given. If post-baseline values do not change or are improving only, the maximum improvement is presented in the summary table, i.e. the minimum change from baseline. Furthermore, shift tables for NCI-CTCAE grades from baseline to worst grade during the whole study will be presented per parameter and cohort.

Serum pregnancy tests, data from urinalysis assessments, serology, and data on secretion status will be included in by patient listings only. Listings will present clinically significant values only by patient, parameter and visit.

### 7.11.4 Weight and vital signs

Body temperature collected in °F will be converted to °C using the following formula:

$$(°F - 32) * 5/9 \; = \; °C.$$

For weight, temperature, systolic blood pressure, diastolic blood pressure, and heart rate, the basic statistics as described above will be displayed for absolute values and absolute changes from baseline using the highest and lowest (except for temperature) value for each patient within the analysis periods, as defined in Table 4.

### 7.11.5 Other safety data

Physical examination results will only be listed. The ECOG performance status will be summarized in shift tables showing the frequencies of transitions from the baseline grade to the grades assessed at each visit. The denominator will be the number of patients with the respective baseline ECOG grade. Patients without an ECOG assessment will be counted as ‘missing’ if the visit was performed but the ECOG assessment was not done.

The number and percentage of patients with normal, abnormal but not clinically significant, and abnormal, clinically significant ECG will be presented by scheduled visit as shift from the ECG evaluation at baseline for Cohort 2+3 together, Cohort 2A-I, 2A-II and 2A-II, randomized, and Cohorts receiving EO2401. The denominator will be the number of patients with the respective baseline ECG assessment. Patients without an ECG assessment will be counted as ‘missing’, if the visit was performed but the ECG assessment was not done.

# 8 SOFTWARE AND STATISTICAL PROGRAMMING

The statistical analysis will be performed using the SAS® statistical software package (Statistical Analysis System, Version 9.4) under Microsoft Windows Operating System.

SAS programming will be performed according to [redacted] standards [redacted] Special attention will be paid to planning and performance of quality control measures as documented in the QC plan for the analysis of this study [redacted]

# 9 REFERENCES

Carneiro BA, Konda B, Costa RB, et al. Nivolumab in Metastatic Adrenocortical Carcinoma: Results of a Phase 2 Trial. J Clin Endocrinol Metab. 2019; 104(12): 6193–6200.

Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Published: November 27, 2017. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health National Cancer Institute, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 29 August 2019.

Eisenhauer EA, Therasse P, J. Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European J Cancer 2009, 45, 228-247.

Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 2012; 366: 2189–2197.

ICH Topic E3: Structure and Content of Clinical Study Reports, adopted by CPMP, December 1995, issued as CPMP/ICH/137/95

ICH Topic E9: Statistical Principles for Clinical Trials 5 February 1998, adopted by CPMP, March 1998, issued as CPMP/ICH/363/96

Klein, J. P. and Moeschberger, M. L. (1997). Survival Analysis: Techniques for Censored and Truncated Data. New York: Springer-Verlag.

Le Tourneau C, Hoimes C, Zarwan C, et al. Avelumab in patients with previously treated metastatic adrenocortical carcinoma: phase 1b results from the JAVELIN solid tumor trial. JITC, 2018, 6:111

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017, 18(3), e143–e152. doi:10.1016/S1470-2045(17)30074-8.

SAS Institute Inc. 2017. Base SAS® 9.4 Procedures Guide, Seventh Edition. Cary, NC: SAS Institute Inc.
https://documentation.sas.com/?cdcId=pgmsascdc&cdcVersion=9.4_3.4&docsetId=pgmsashome&docsetTarget=home.htm&locale=en

Moodie Z, Price L, Gouttefangeas C, Mander A, Janetzki S, Lower M, et al. Response definition criteria for ELISPOT assays revisited. Cancer immunology, immunotherapy: CII. 2010;59(10):1489–501.

# 10 CHANGES TO FINAL VERSION OF SAP

Not applicable.

# 11 LIST OF TABLES, FIGURES AND LISTINGS

See separate document: appendices I and II to the SAP.