

ENTEROME: EOCRC2-22
(EN06)

Statistical Analysis Plan

Date: 30-Jun-2025
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Status: final
Author: [REDACTED]

Study Title: A global multicenter phase 1/2 trial of EO4010, a novel microbial-Derived peptide therapeutic vaccine, in combination with nivolumab and/or bevacizumab, for treatment of patients with previously treated metastatic colorectal carcinoma (the "AUDREY" study)

Investigational Product: EO4010

Clinical Phase: I/II

Enrolment of first patient 08-Jun-2023 FPFV (actual date)

Last Patient Last Visit Feb-2026 (planned date)

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Table of Contents

Signatures	2
Table of Contents	3
1 Document History	5
2 List of Abbreviations.....	5
3 General.....	7
3.1 Analyses Planned and Already Performed.....	7
3.2 SOPs to be Followed	7
4 Overview of the Protocol	8
4.1 Objectives and Endpoints of the Study	8
4.1.1 Objectives	8
4.1.2 Endpoints	9
4.2 Study Design	10
4.3 Sample Size.....	12
4.4 Study Flow Chart	14
5 General Aspects of the Statistical Analysis	19
5.1 Analysis Populations.....	19
5.2 Patient Replacement	19
5.3 Protocol Devations	20
5.4 Changes or Deviations from Planned Analyses	20
6 Definitions for Statistical Analysis.....	23
6.1 Handling of withdrawals (drop-outs), missing values and outliers	23
6.2 For partial dates imputation rules will be given below (if applicable). Reference Day / Day 1.....	23
6.3 Study Day	23
6.4 Baseline	23
6.5 Visit Labels.....	24
6.6 Time interval and duration.....	28
6.7 Body Mass Index (BMI).....	28
7 Statistical Analysis Specification.....	28
7.1 Specifications Related to Whole Analysis	28
7.1.1 Tables	28
7.1.2 Data Listings	28
7.2 Disposition of Patients.....	29
7.3 Demographics and Baseline Characteristics.....	29
7.3.1 Relevant definitions	29
7.3.2 Statistical analysis	30
7.4 Medical History and Concomitant Illnesses.....	31
7.5 Prior, Concomitant, and Post Study Treatment Medication	31
7.6 Procedures and non-drug medical interventions.....	32
7.7 Efficacy Endpoints	33
7.7.1 General aspects of response related endpoints	33
7.7.2 Best overall response, objective response and disease control	34
7.7.3 Time to Response (TTR)	35
7.7.4 Duration of Response (DOR), Duration of disease control (DDC)	35
7.7.5 Progression-free survival (PFS) and overall survival (OS)	36
7.7.6 Carcinoembryonic antigen (CEA)	37
7.8 Safety	37
7.8.1 Study Drug Exposure and Compliance	37

7.8.2	Adverse Events	38
7.8.3	Local administration site conditions at a site of EO4010 local administration	40
7.8.4	Safety Laboratory	41
7.8.5	Vital Signs	43
7.8.6	Other Safety Data	44
7.9	Immunogenicity	44
7.9.1	Definition of tests, parameters and possible results	44
7.9.2	Analysis of immunogenicity test results	46
7.10	Exploratory endpoints.....	48
7.10.1	Immunohistochemistry data	48
7.10.2	Exploratory endpoints not covered by this SAP	49
8	Software and Statistical Programming	50
9	References.....	50
10	Changes to Final Version of the SAP	51
11	List of Tables, Figures and Listings.....	51

1 DOCUMENT HISTORY

Version	Date	Author / editor of new version	Main changes / comments
V01	31-Mar-2025		Initial Version
V02	30-Jun-2025		- Minor and major protocol deviations added - Table headers updated - Efficacy endpoints will be summarized based on RECIST assessments. iRECIST assessments will be provided in patient data listings only. - Time to response and time to 1st last will be summarized descriptively only.

2 LIST OF ABBREVIATIONS

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-containing5
BMI	Body Mass Index
CDC20	Cell Division Cycle 20
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CR	Complete Response
CRC	Colorectal Cancer
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computed Tomography
DC	Disease Control
DCR	Disease Control Rate
DDC	Duration of Disease Control
DFR	Distribution Free Resampling
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DPD	Dihydropyrimidine dehydrogenase
DRM	Data Review Meeting
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

eGFR	estimated Glomerular Filtration Rate
ELISpot	enzyme-linked immunospot
FAS	Full Analysis Set
FIH	First in Human
FOXM1	forkheadboxM1
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
IFN-γ	Interferon-gamma
IHC	immunohistochemistry
INR	International Normalized Ratio
iPR	immune Partial Response
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
iSD	immune Stable Disease
iUPD	immune Unconfirmed Progressive Disease
KIF2C	Kinesin Family member 2C
LASR	Local administration site reactions
LDH	Lactate Dehydrogenase
MDSC	Myeloid-Derived Suppressor Cell
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Mismatch repair
mRNA	message Ribonucleic Acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD1	Programmed cell Death protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-free Survival
PP	Per-Protocol
PR	Partial Response
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QC	Quality Control
rBGC	Relevant Background Control
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
S	Screening
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan

SAS	Statistical Analysis System
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TAA	Tumor Associated Antigen
TAS-102	trifluridine/tipiracil
TCR	T-cell Receptor
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
UBE2C	Ubiquitin conjugating Enzyme E2 C
UCP2	Universal Cancer peptide 2
V	Visit
WBC	White Blood Cells
WHODD	World Health Organization Drug Dictionary

3 GENERAL

This statistical analysis plan reflects study protocol EOCRC2-22 Version 2.0 dated 15-Jan-2024. It follows the principles of the Guidelines International Council for Harmonization (ICH) Topic E3 and ICH Topic E9. It gives all details for all primary, secondary, and almost all exploratory statistical analyses of this study.

3.1 Analyses Planned and Already Performed

This trial aims at assessing the safety and the preliminary efficacy of EO4010 in combination with nivolumab and/or with bevacizumab in patients with non-resectable locally advanced or metastatic colorectal cancer (CRC) previously treated with standard chemotherapy +/- targeted therapy. 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 EO4010, 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.

This statistical analysis plan (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).

The report will be written according to the ICH E3 and other applicable ICH guidelines.

4 OVERVIEW OF THE PROTOCOL

4.1 Objectives and Endpoints of the Study

4.1.1 Objectives

4.1.1.1 Primary Objective

The primary objective of this trial is to evaluate safety and tolerability of EO4010 in combination with nivolumab and/or with bevacizumab in patients with unresectable, previously treated locally advanced or metastatic CRC.

4.1.1.2 Secondary Objectives

To assess the following items at therapy with EO4010 in combination with nivolumab and/or bevacizumab:

- 1. Immunogenicity in relation to T cells of EO2317, EO2318, OMP10, OMP11, OMP12, and Universal Cancer peptide 2 (UCP2) that compose EO4010; T cell cross-reactivity with the human Tumor Associated Antigens (TAAs) forkheadboxM1 (FOXM1), Baculoviral Inhibitor of Apoptosis Repeat-containing5 (BIRC5)/survivin, Ubiquitin conjugating Enzyme E2 C (UBE2C), Cell Division Cycle 20 (CDC2)0, and Kinesin Family member 2C (KIF2C) will also be evaluated,
- 2. objective response rate (ORR), disease control rate (DCR), time to response (TTR), and duration of response (DOR),
- 3. progression-free survival (PFS) and PFS rate at 4 months, and
- 4. overall survival (OS).

4.1.1.3 Exploratory Objectives

[Redacted content]

4.1.2 Endpoints

4.1.2.1 Primary Endpoint

The primary endpoint includes safety and tolerability of EO4010 in combination with nivolumab and /or with bevacizumab 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.

4.1.2.2 Secondary Endpoints

1. Percentage of patients with shown immunogenicity (expansion of specific T cells comparing samples taken at baseline versus on treatment in an individual patient determining if the patient has a positive response to the immunization, or not) in relation to EO2317, EO2318, OMP10, OMP11, OMP12, and UCP2 that compose EO4010 [REDACTED]. Cross reactivities with the human TAAs FOXM1, BIRC5/survivin, UBE2C, CDC20, and KIF2C will also be evaluated by the same methods.
2. ORR, DCR, TTR, and DOR as described by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and Immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) criteria.
3. PFS as described by RECIST 1.1 and iRECIST criteria, defined as the time interval from the date of first study treatment administration to the date of progression (by RECIST 1.1 or iRECIST criteria), or death due to any cause, whichever is earlier. Patients without progression or death are to be censored at the time of the last tumor assessment. The PFS rate at 4 months as assessed from the PFS survival curve.
4. OS defined as the time interval from the date of first study treatment administration to the date of death due to any cause. Patients alive will be censored at the date of the last documented follow-up.

4.1.2.3 Exploratory Endpoints

[REDACTED]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

4.2 Study Design

This is an open-label, multicenter, first-in-human (FIH), phase 1/2 trial to assess safety,

tolerability, immunogenicity, and preliminary efficacy of the microbial-derived therapeutic vaccine EO4010 in combination with nivolumab and/or with bevacizumab for treatment of patients with unresectable, previously treated, metastatic CRC.

The trial is a 3-cohort study intended to recruit a maximum of 42 evaluable patients in total:

- Cohort 1 includes a safety evaluation by a 3-by-3 design of EO4010 monotherapy (2 administrations of EO4010 each followed by a 2-week observation period) planned to be followed in the same individual patients by continued EO4010 in combination with nivolumab (latter at standard doses per registrations in other settings); 3 to 12 evaluable patients will be included depending on the safety profile of the administered treatments.
- Cohort 2 includes an evaluation of EO4010 at the recommended dose found in Cohort 1 in combination with nivolumab in 15 evaluable patients with CRC.
- Cohort 3 will be run once Cohort 2 recruitment is completed.
 - Cohort 3a includes an evaluation of EO4010 in combination with nivolumab and bevacizumab in 10 evaluable patients with CRC.
 - Cohort 3b includes an evaluation of EO4010 in combination with bevacizumab in 5 evaluable patients with CRC.

Generally, patients evaluable for safety will include all patients who have received at least one dose of EO4010. Patients who are not considered evaluable for safety and did not receive any dose of EO4010 will be replaced (reasons for non-evaluability and pre-treatment safety will be reported). In addition, in Cohort 1, if for reasons other than safety a patient does not receive 2 doses of EO4010 and complete the Week 5 visit (V3) assessment, the patient will not be counted towards the 3 -by-3 design and an additional patient should be enrolled (reasons for not being counted towards the 3 -by-3 design will be reported, as well as applicable safety findings).

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

Figure 1: Schematic Trial Design

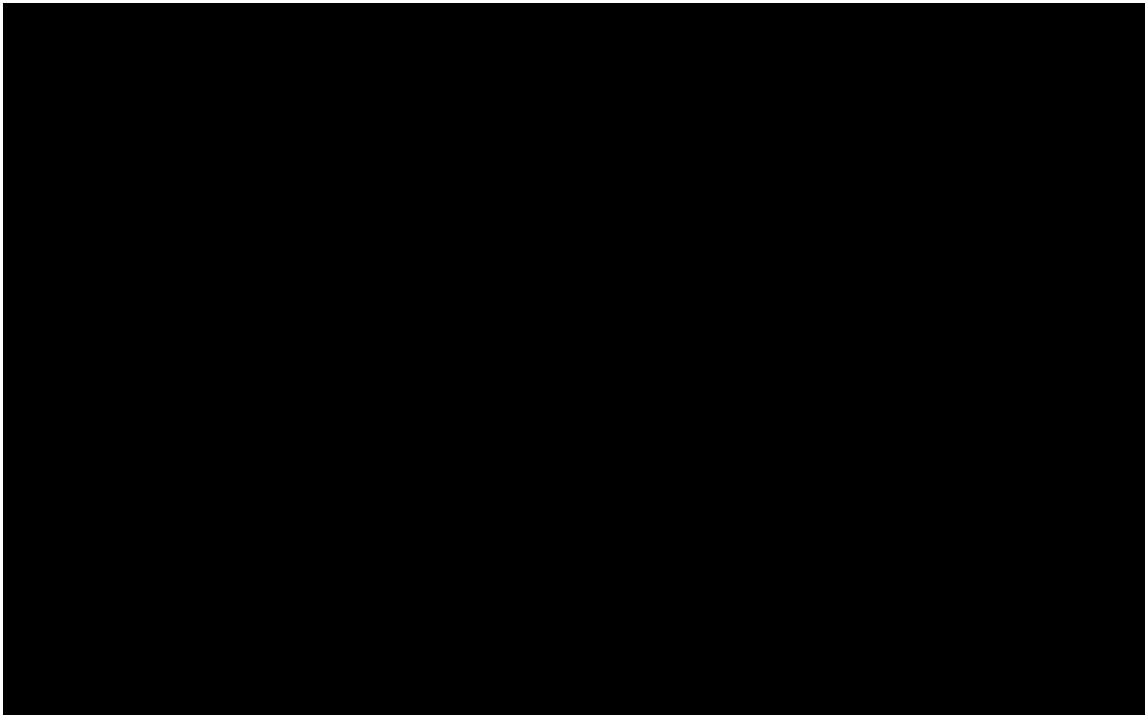
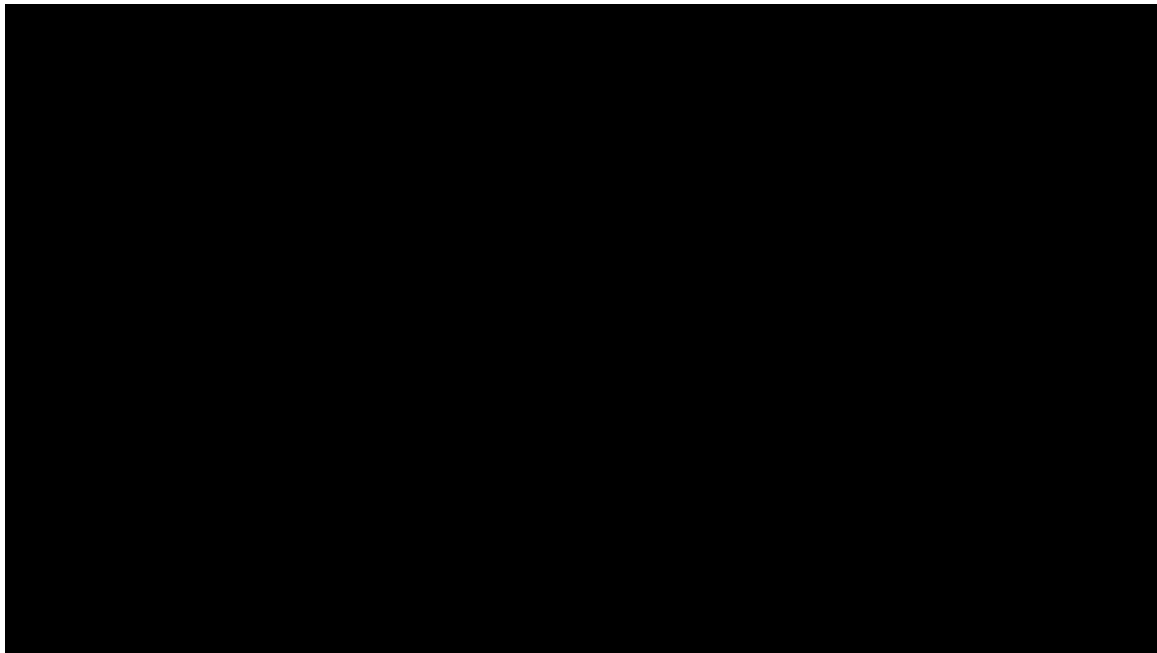


Figure 2: Schematic Cohort Design



4.3 Sample Size

This is an early development, open-label, exploratory, multi-cohort trial to include patients with previously treated metastatic CRC. In this context the sample size of the trial has been determined by practical considerations in collaboration with experts in the field, to facilitate an as fast as possible, and broad in Cohort 2 (in relation to patient baseline characteristics), assessment of safety and tolerability, immunogenicity, and preliminary efficacy. The sequential design of Cohorts 2 and 3, makes it possible to potentially, if needed based on trial data from Cohort 2, to adjust inclusion/exclusion criteria or other study parameters before start of recruitment of Cohort 3. [Redacted]

[REDACTED]

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 2 and 3 (3a and 3b), i.e. 30 evaluable patients in total is considered to be relevant early dataset for safety assessments, and decision making regarding later stage development. From an efficacy perspective, by inference from earlier clinical experience in metastatic CRC, it is judged that if there are at least two interesting outcome parameters to utilize for comparisons with historical groups, including ORR, DOR, DCR, PFS, PFS rate at 4 months, and survival, the sample size would be relevant. The main benchmarking trials will be the phase 3 label enabling trials of trifluridine/tipiracil (TAS-102) and regorafenib. For regorafenib the following outcomes have been reported for the CORRECT phase 3 trial; median survival 6.4 months (95% confidence interval (CI), 5.8 to 7.3), median PFS 2.0 months (95% CI, 1.9 to 2.3), and ORR 1%. For trifluridine/tipiracil (TAS-102) the following outcomes have been reported for the RECURSE phase 3 trial; median survival 7.1 months (95% CI, 6.5 to 7.8), median PFS 2.0 months (95% CI, 1.9 to 2.1), ORR 1.6%, and DCR (Complete Response (CR), Partial Response (PR), and Stable Disease (SD) assessed at least 6 weeks after randomization) 44%. For TAS-102+ bevacizumab the following outcomes have been reported for the SUNLIGHT phase 3 trial; median survival 10.8 months (95% CI, to 9.4 to 11.8), median PFS 5.6 months (95% CI, 4.5 to 5.9), ORR 6.1%. For fruquintinib the following outcomes have been reported for the FRESCO-2 phase 3 trial; median survival 7.4 months, median PFS 3.7 months; ORR 2%.

If there would be at least two interesting outcomes in the current study within a group of 15 patients (which might be ORR, DOR, DCR, PFS, PFS rate at 4 months, or survival) as judged by considering the above trial outcomes (i.e. at least at pair with these trials), 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.

Statistical Analysis Plan

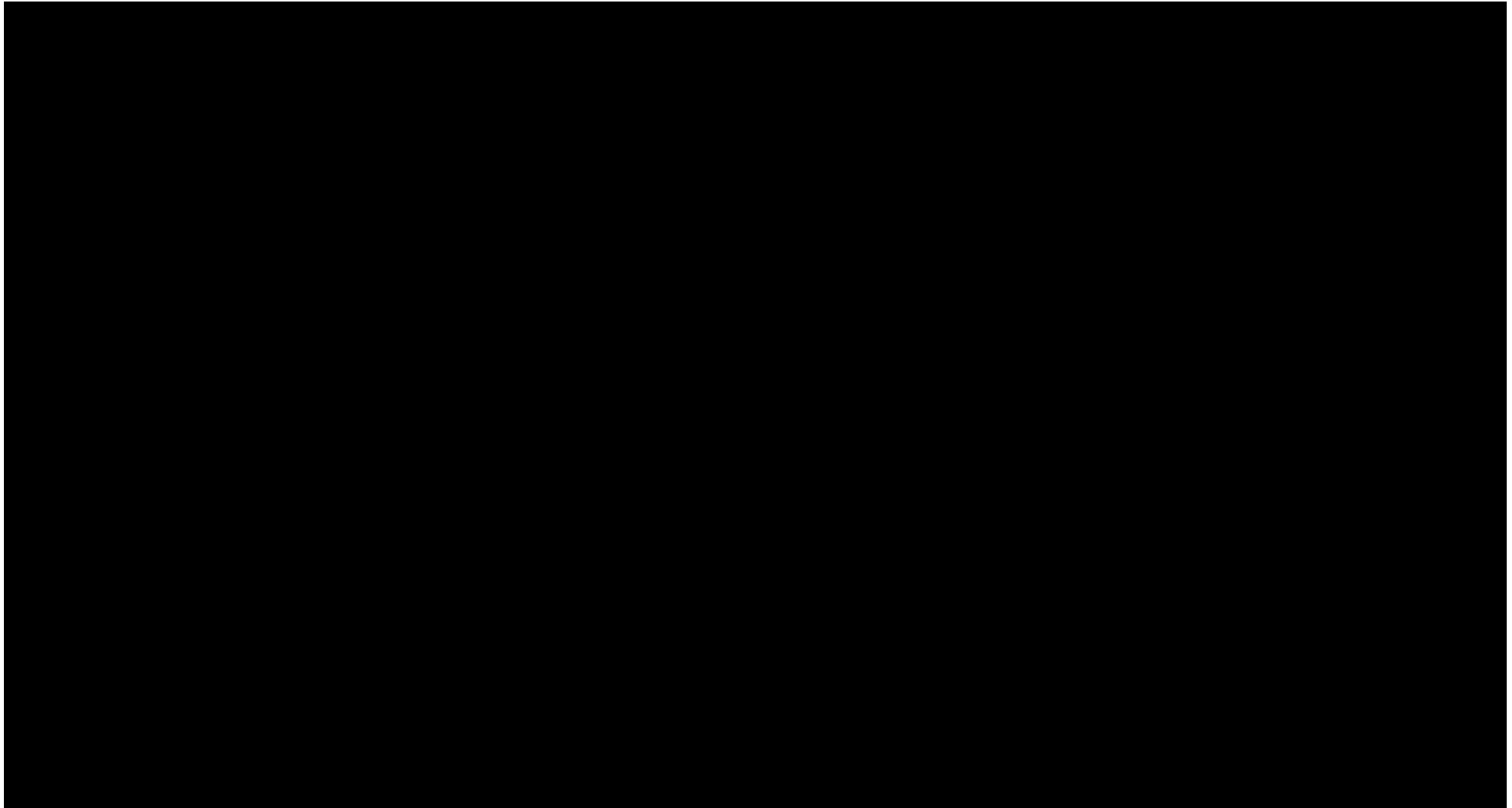
Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 14 of 51

4.4 Study Flow Chart



Statistical Analysis Plan

Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 15 of 51

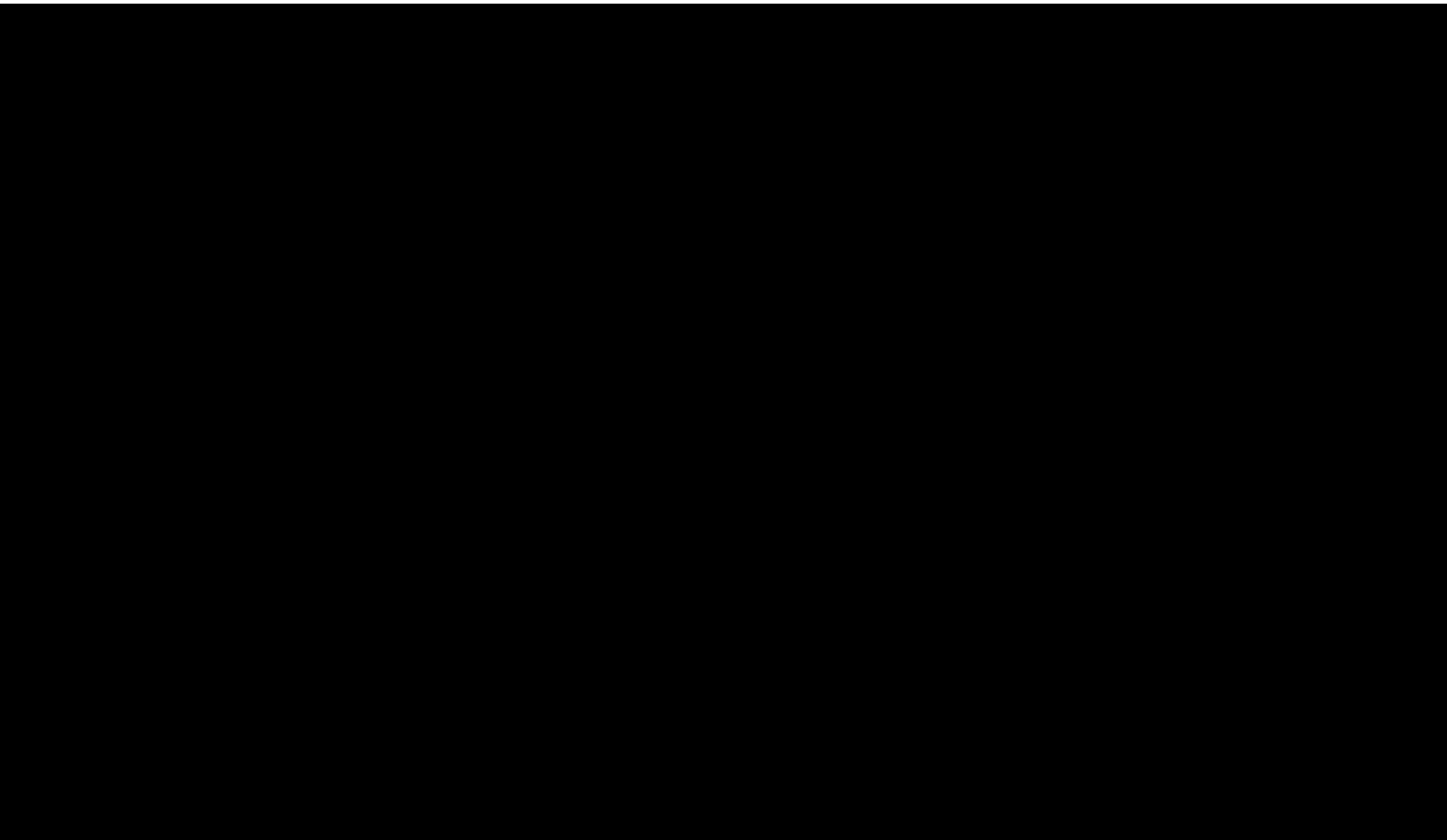
Statistical Analysis Plan

Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 16 of 51



Statistical Analysis Plan

Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 17 of 51

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Statistical Analysis Plan

Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 18 of 51

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5 GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

5.1 Analysis Populations

The following analysis populations will be included:

- 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 EO4010 and for whom no important protocol deviations occurred (for a protocol deviation, to qualify for excluding a patient from the FAS population, there should be an assessment and recommendation to exclude the patient at the Data Review Meeting (DRM) at the end of the study, and this assessment and recommendation should be approved by the Chief Medical Officer of Enterome).
- The Safety Population (SAF) will consist of patients who received at least one dose of EO4010.

- The population evaluable for the 3-by-3 design in Cohort 1 will consist of patients who receive EO4010 and complete

Patients who are not evaluable for the 3-by-3 design in Cohort 1 will be replaced for the 3-by-3 design assessment; however, if such a patient has received at least one dose of EO4010 he/she should be evaluated in the Safety Population.

5.2 Patient Replacement

There is generally no replacement of patients who has started study treatment. However, the primary analysis for each cohort builds on an assessment of 15 patients (10 patients in 3a and 5 patients in 3b arms) in the Full Analysis Set (FAS; patients who received at least one dose of EO4010 and for whom no important protocol deviations occurred). Thus, if there would be relevant important protocol deviation(s) in a patient impacting for instance the possibility to assess the primary endpoint the patient might be replaced based on a decision by the Sponsor.

[REDACTED] Patients who are not evaluable for the 3 -by-3 design in Cohort 1 are replaced for the 3-by-3 design assessment; however, if such a patient has received at least one dose of EO4010 he/she is evaluated in the Safety Population.

5.3 Protocol Deviations

Protocol deviations and other reasons for exclusion from any analysis set will be reported according to the Protocol Deviation Plan. During the DRM, all deviations will be classified into minor and major as well as important (leading to exclusion from FAS) and non-important (not leading to exclusion from any analysis set) deviations. 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 hard lock.

All major protocol deviations regardless of their source will be listed in Appendix 16.2.2 in the CSR for each patient together with the categorization into important or not important.

5.4 Changes or Deviations from Planned Analyses

Summary of protocol content including reference to section	Summary of SAP content including reference to section	Description and rationale for change
<u>Section 3.1.3 Explorative objectives:</u> [REDACTED]	<u>Section 4.1.1.3 Explorative Objectives:</u> [REDACTED]	[REDACTED]

Summary of protocol content including reference to section	Summary of SAP content including reference to section	Description and rationale for change
<u>Section 3.2.3 Exploratory endpoints:</u> [Redacted]	<u>Section 4.1.2.3 Explorative Endpoints:</u> [Redacted]	[Redacted]

Summary of protocol content including reference to section	Summary of SAP content including reference to section	Description and rationale for change
<u>Section 9.1 Analysis population:</u> The population evaluable for the 3-by-3 design in Cohort 1 will consist of patients who receive [REDACTED] and complete [REDACTED] and patients who receive at least one dose of EO4010 [REDACTED] [REDACTED] Patients who are not evaluable for the 3-by-3 design in Cohort 1 will be replaced for the 3-by-3 design assessment; however, if such a patient has received at least one dose of EO4010 he/she should be evaluated in the Safety Population.	<u>Section 5.1 Analysis Populations:</u> The population evaluable for the 3-by-3 design in Cohort 1 will consist of patients who receive [REDACTED] and [REDACTED] and patients who receive at least one dose of EO4010 [REDACTED] [REDACTED] however, if such a patient has received at least one dose of EO4010 he/she should be evaluated in the Safety Population. Note, the Cohort 1, safety-lead in, included only 3 patients, of whom all are evaluable, and thus the specification of a population “evaluable for the 3-by-3 design in Cohort 1” is not meaningful, and analyses will only include all patients in Cohort 1 as described below.	Details regarding the actual situation for the study added.
<u>Section 9.1 Analysis population:</u> The Per-Protocol (PP) population will consist of patients who received at least 4 doses of EO4010, for whom no important protocol deviations occurred, and who have at least one evaluable post-screening tumor assessment.	<u>Section 5.1 Analysis Populations:</u> No analyses per PP population planned in the SAP. Definition of PP population removed from the Analysis population section.	Efficacy analyses per PP population is regarded no longer necessary.

Summary of protocol content including reference to section	Summary of SAP content including reference to section	Description and rationale for change
<u>Section 9.2 Statistical methods:</u> TTR, DOR, PFS, and OS will be analyzed using the method of Kaplan-Meier and Cox proportional hazards model.	<u>Section Time to Response (TTR), Duration of Response (DOR), Duration of disease control (DDC)</u> DDC can only be determined for patients with BOR equal to (i)CR, (i)PR, and (i)SD as defined above. According to RECIST, the DDC ... TTR will be summarized using basic summary statistics, by cohort and overall.	Duration of disease control was added. TTR will be summarized by basic summary statistics instead of Kaplan-Meier and Cox proportional hazard model.
<u>Section 9.2 Statistical methods:</u> Objective response rate by the RECIST 1.1/iRECIST criteria will be estimated with two-sided exact 95% confidence intervals.	<u>Section 7.7 Efficacy Endpoints</u> During the DRM no valid differences between RECIST/iRECIST in terms of best overall response or progression were confirmed, therefore summary tables and figures will be provided based on RECIST assessments only. iRECIST assessments will be provided in the patient data listings only.	Due to limited differences between RECIST and iRECIST response assessments, results will be provided for RECIST assessments only. iRECIST assessments will be listed only.

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 For partial dates imputation rules will be given below (if applicable). Reference Day / Day 1

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

6.3 Study Day

Study day for a particular event can be calculated as

$$\text{date of respective event} - \text{date of first treatment with study drug} + 1$$

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.

Change from Baseline = Value at a given visit / visit window – Value at the baseline visit

6.5 Visit Labels

In protocol version 2.0 dated 15-Jan-2024 two additional visits were included, one visit during Week 21 – Day 141 and one during Week 29 – Day 197. Therefore, e.g. Visit 11 will be assessed during Week 23 - Day 155 for patients following protocol version 1.0 and during Week 21 – Day 141 for patients following protocol version 2.0.

To be able to analyze visits taken during the same period in the study together the following approach will be followed. In the SDTM data the original visits will be found as given in the eCRF. For ADaM data visits will be defined based on study weeks and days only. Table 1 presents the mapping between both definition of visits.

Summary tables, figures and listings provided by visit will present visit based on variable AVISIT, which is presenting Week xx – Day yy during treatment phase. If there is not enough space to provide variable AVISIT, the shortened format AVISIT1 can be used instead.

Table 1 Mapping of Visit Number and Label in SDTM and ADaM Data

[Redacted Table Content]

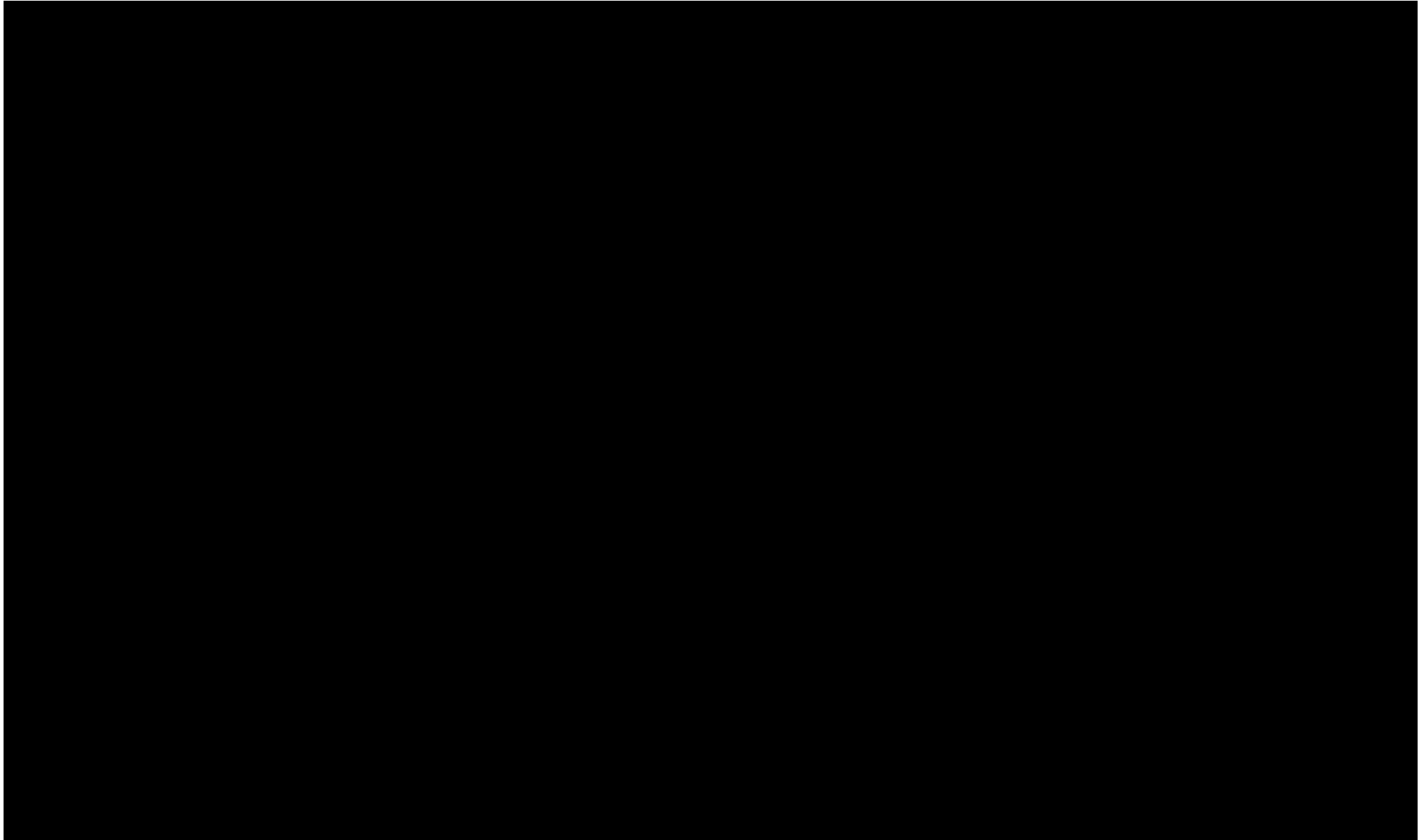
Statistical Analysis Plan

Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 26 of 51



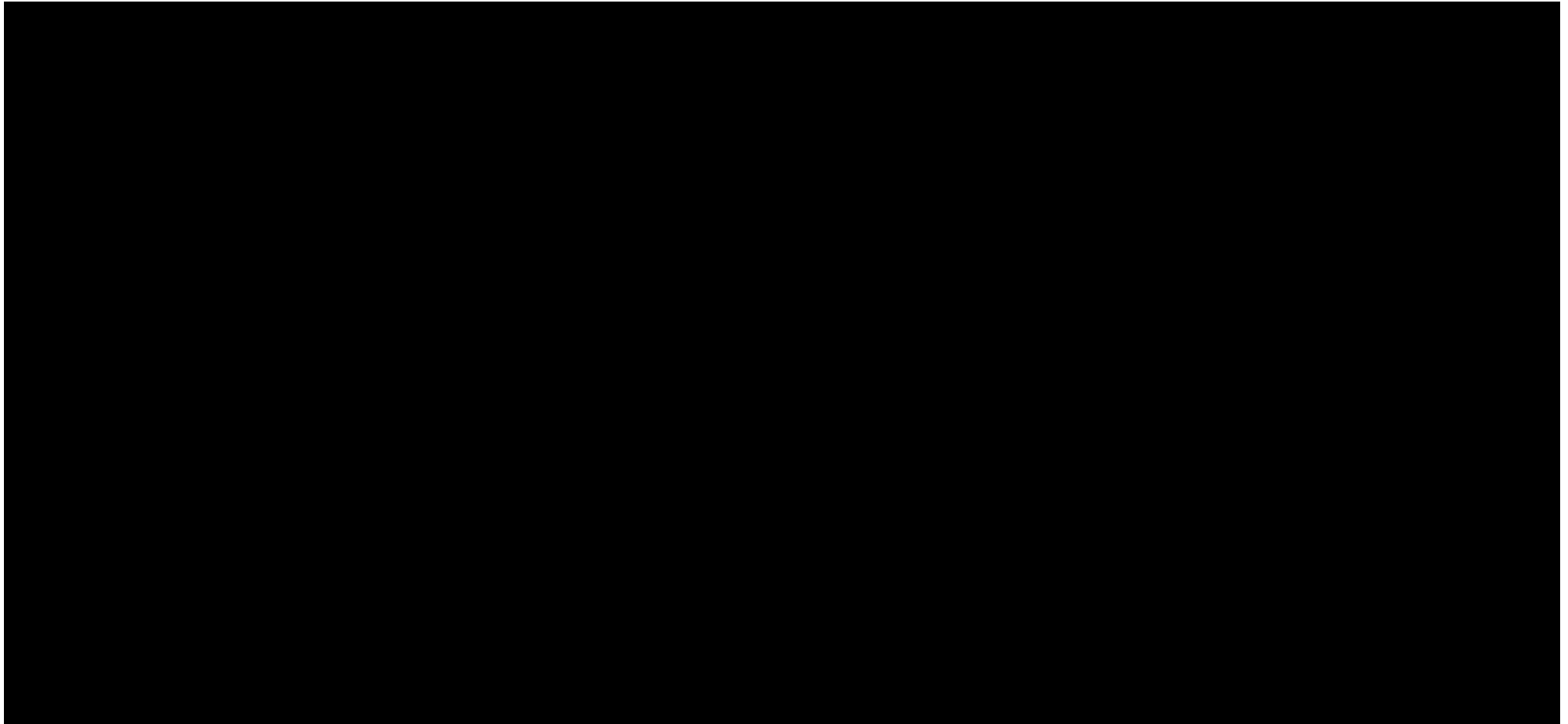
Statistical Analysis Plan

Version/Status/Date: v02/final/30-Jun-2025

ENTEROME: EOCRC2-22

(EN06)

Page 27 of 51



6.6 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

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

6.7 Body Mass Index (BMI)

Body Mass Index (BMI) is calculated as

$$\frac{weight\ in\ kg}{(height\ in\ m)^2}$$

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 (for details see Section 6.5), where appropriate. For continuous data, the basic statistics, i.e., the sample size, 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 (for details see Section 6.5) 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, Q1, and Q3 will be reported with one more decimal, SD with two more decimal. Percentage values will be rounded to one decimal place.

Tables will generally be presented with the following table header:

Cohort 1A (N = XX)	Cohort 2 (N = XX)	Cohort 1A + 2 (N=XX)	Cohort 3A (N = XX)	Overall (N = XX)
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See Appendix to the SAP for a full table of contents of all summary tables and graphs planned for the CSR Section 14 along with mock-up tables that show the exact structure and content of example summary tables and graphs.

7.1.2 Data Listings

Electronic case report form (eCRF) and external laboratory data will be listed as

documented, and include all data captured without exceptions. All relevant generated and transformed variables will be listed next to the original data items as well. In all listings, cohort and center will be included. The listings will be sorted by cohort and patient identifier.

7.2 Disposition of Patients

The study duration in days is defined as

$$\frac{\text{date of last patient last visit including post treatment followup} - \text{date of first patient first visit}}{1} + 1.$$

Study duration will be presented for APP.

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 were treated with a least one study drug will be summarized for APP.

Patients who got allocated to cohort, who received EO4010, who received nivolumab, who received bevacizumab, completed, terminated early from the study, completed (i.e. reached individual maximum defined study treatment period) or terminated early from treatment (EO4010, nivolumab and bevacizumab separately) will be summarized as absolute and relative frequencies by cohort and overall for the APP.

Analysis population (FAS, SAF) as well as the reasons for exclusion from each population will be summarized as absolute and relative frequency by cohort and overall.

The reason for study termination and the reason for treatment termination (EO4010, nivolumab and bevacizumab separately) will be summarized as absolute and relative frequency by cohort and overall for the SAF.

The categorical summary of patients participating at each scheduled study visit (for details see Section 6.5) will be summarized by cohort for the SAF.

All disposition data will be listed based on APP.

7.3 Demographics and Baseline Characteristics

7.3.1 Relevant definitions

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

$$\text{date of first treatment with study drug} - \text{date of respective event} + 1.$$

Incomplete dates will be estimated using the first possible date. If year is missing, the date will be set to missing.

Time in months will be calculated as time in days / 30.5 (rounded to one decimal) and time in years will be calculated as time in days / 365.25 (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.

7.3.2 Statistical analysis

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

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; if more than one was ticked, provide new categories, e.g. White and Asian)
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline
- Height [cm], weight [kg], BMI [kg/m²] (calculated)
- Tumor diagnosis
 - Time since primary diagnosis [years]
 - Primary tumor location (Proximal tumor, Distal tumor, Rectum)
 - Stage (Stage 0, Stage I, Stage IIA, Stage IIB, Stage IIC, Stage IIIA, Stage IIIB, Stage IIIC, Stage IVA, Stage IVB, Stage IVC)
 - Time since diagnosis of metastatic disease [years]
 - Number of organs with metastases
 - Time since most recent progression [days]
 - Overall current number of organs involved
 - Number of prior systemic lines of treatment for metastatic CRC (1, 2, 3, 4, 5)
 - 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)
- Histology and mutation status
 - Histology (Adenocarcinoma, Adenosquamous carcinoma, Mucinous carcinoma, Carcinoma, not otherwise specified, Undifferentiated carcinoma, Other)
 - Dihydropyrimidine dehydrogenase (DPD) testing performed (No, Yes, Not known)
 - DPD test outcome (No deficiency, Partial deficiency, Complete deficiency, Not known, Other)
 - Mismatch repair (MMR) status (Proficient, Deficient, Not known, Other)
 - Microsatellite (Stable, Instable high, Instable low, Not known, Other)
 - Tumor mutational burden (Low, High, Not known, Other)
 - BRAF status (Wildtype, Mutation, Not known, Other)
 - KRAS status (Wildtype, Mutation, Not known, Other)
 - NRAS status (Wildtype, Mutation, Not known, Other)

- HRAS status (Wildtype, Mutation, Not known, Other)
- ERBB2 status (Negative, Positive, Not known, Other)
- Other mutation (No, Yes)

Tumor diagnosis and histology and mutation status data will be summarized separately. 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 7.8.3, 7.8.4 and 7.8.6). 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.

All demographic and baseline data including results of human immunodeficiency virus (HIV), hepatitis B and hepatitis C, and Follicle Stimulating Hormone (FSH) testing will be listed for SAF.

7.4 Medical History and Concomitant Illnesses

Medical history and concomitant illnesses will be coded for SAF using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary using the specified version and update strategy as defined in the coding specification for this study.

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.

Categorical summary tables of patients with medical history and with concomitant illnesses by MedDRA system organ class (SOC) and MedDRA preferred term (PT) will be provided by cohort and overall for SAF. In these tables, SOC and PTs within SOC will be ordered with decreasing frequency in overall. PTs within SOC with same frequency will be ordered alphabetically.

All medical history and concomitant illness data will be listed for SAF.

7.5 Prior, Concomitant, and Post Study Treatment Medication

All medications documented in the eCRF will be coded using the World Health Organization Drug Dictionary (WHODD), using the specified version and update strategy as specified in the coding specification for this study.

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 absolute and relative frequency of patients with medication will be summarized separately for prior, concomitant, and post-treatment medication by cohort and overall for SAF. 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).

In addition, a summary table presenting absolute and relative frequency of patients with medications belonging to ATC Classification (1st level) “Antineoplastic and immuno-modulating agents” will be summarized separately for prior and post study treatment medication by cohort and overall for SAF. In this table, the medications will be presented by split PT according to WHODD, where split PT means that the existing PT will be split in separate PTs if separated by “;”. For example, a medication coded to *Calcium folinate;flououracil; irinotecan hydrochloride* would be split into three medications *Calcium folinate*, *flououracil*, and *irinotecan hydrochloride*.

Prior and concomitant medication will be listed together with a flag indicating whether it is classified as prior, concomitant or post study treatment medication and type of medication (anti-CRC drug therapy, investigational study medication and other therapies) for SAF.

7.6 Procedures and non-drug medical interventions

Procedures and non-drug medical interventions will be coded using the MedDRA dictionary using the specified version and update strategy as defined in the coding specification for this study.

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 absolute and relative frequency of patients with procedures and non-drug medical interventions by MedDRA SOC and MedDRA PT will be provided by cohort and overall for SAF separately for surgeries related to primary diagnosis, surgeries not related to primary diagnosis, radiotherapies and other procedures and non-drug medical interventions. In these tables, SOC and PTs within SOC will be ordered with decreasing frequency in overall. PTs within SOC with same frequency will be ordered alphabetically.

Prior, concomitant and post study treatment procedures and non-drug medical interventions data will be listed for SAF separately for surgeries related to primary diagnosis, surgeries not related to primary diagnosis, radiotherapies and other procedures and non-drug medical interventions.

7.7 Efficacy Endpoints

The FAS Population will be the basis for the analysis of efficacy data.

7.7.1 General aspects of response related endpoints

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, all response related endpoints will be reviewed and discussed during the DRM. In case of additional available information that lead to response assessments that should not be evaluated or assessed differently, further actions will be described in the DRM minutes. This might lead to additional analyses presenting response related endpoints based on a sponsor's assessment.

During the DRM no valid differences between RECIST/iRECIST in terms of best overall response or progression were confirmed, therefore summary tables and figures will be provided based on RECIST assessments only. iRECIST assessments will be provided in the patient data listings only.

7.7.2 Best overall response, objective response and disease control

7.7.2.1. Definitions

Objective response (OR) is when the best overall response is partial response (PR) / complete response (CR) according to RECIST during the whole study period. No confirmation of PR/CR is required.

The objective response rate (ORR) [%] is defined as the relative number of patients achieving OR according to RECIST in the respective cohort.

Disease Control (DC) is when the best overall response is stable disease (SD) / partial response (PR) / complete response (CR) according to RECIST during the whole study period.

The DCR [%] is defined as the relative number of patients achieving DC according to RECIST in the respective cohort.

7.7.2.2. Objective Response Rate (ORR)

The ORR according to RECIST will be summarized with two-sided 95% exact Clopper-Pearson CIs for binomial proportions by cohort. Additionally, categorical summary with absolute and relative frequency will be presented.

Reference SAS Code:

```
proc freq data=<Input dataset>;  
by Cohort;  
tables Outcome/exact binomial;  
run;
```

7.7.2.3. Disease Control Rate (DCR)

The DCR according to RECIST will be summarized with two-sided 95% exact Clopper-Pearson CIs for binomial proportions by cohort. Additionally, categorical summary with absolute and relative frequency will be presented.

Reference SAS Code: Refer to Section 7.7.2.2

7.7.2.4. Best Overall Response

The best overall response according to RECIST will be summarized with absolute and relative frequencies by cohort using the following categories and hierarchy:

According to RECIST,

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)
- Not evaluable (NE)

7.7.2.5. Per Patient Summaries

The maximal shrinkage in tumor burden derived as the maximum percentage decrease in sum of longest diameter from the corresponding baseline value for each patient by cohort will be displayed in a waterfall plot. The bars will be colored according to best overall response according to RECIST. Two different colors will be used for PD with new lesion and PD without new lesion.

All response assessments (RECIST/iRECIST) will be listed.

7.7.3 Time to Response (TTR)

7.7.3.1. Definitions

TTR will be determined for patients with OR as defined above only.

TTR using RECIST criteria is defined as the period from the first dose of study drug until PR or CR, whichever comes first.

7.7.3.2. Summary

TTR will be summarized using basic summary statistics, by cohort and overall.

7.7.4 Duration of Response (DOR), Duration of disease control (DDC)

7.7.4.1. Definitions

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 7.7.5 for details). Patients alive with no progression will be censored following the same censoring rules as for PFS (see Section 7.7.5).

DDC can only be determined for patients with BOR equal to (i)CR, (i)PR, and (i)SD as defined above.

According to RECIST, the DDC is measured from the time at which the measurement criteria according to RECIST are first met for CR or PR or SD (whichever is first recorded) until the first date that PD is objectively documented according to RECIST (see Section 7.7.5 for details). Patients alive with no progression will be censored following the same censoring rules as for PFS (see Section 7.7.5).

7.7.4.2. Event Summary

Time-to-event statistics including number of subjects with event, censored as well as median time, 25th and 75th quartiles along with 95% CI will be reported in a summary table for values corresponding to RECIST.

Reference SAS Program:

```
proc lifetest data = <input> plots=survival;  
time <duration>*<ensor> (1);  
strata <cohort>;  
run;
```

7.7.4.3. Cox Proportional Model

If the number of events is sufficient, Cox regression will be performed to compare hazard between the cohorts and to estimate hazard ratio. Hazard Ratio along with 95% CI will be reported in the same table.

Reference SAS Program:

```
proc phreg data=<data>;  
class cohort;  
model <duration>*<ensor> (1) = cohort;  
run;
```

7.7.4.4. Kaplan-Meier Curve

Time to event will also be analyzed by cohort (once for Cohort 1A, Cohort 2, Cohort 3A and once for Cohort 1A+2 and Cohort 3A) using Kaplan-Meier curves. X-axis will be the duration (months) and Y-axis will be the survival probability.

7.7.5 Progression-free survival (PFS) and overall survival (OS)

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

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

- Progression criteria according to RECIST met
- death from any cause within 112 days (16 weeks) after last post-baseline CT assessment or within 112 days (16 weeks) after first study treatment administration, if no post-baseline CT assessment is available.

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.

Start of non-trial systemic anti-CRC treatments prior to progression will either lead to censoring of the patient for relapse related endpoints at the time of start of the therapy or assessment of the patient as having relapsed disease if relevant criteria would be fulfilled. Decisions how a start of non-trial systemic anti-CRC treatment will be considered for PFS will be taken during the DRM and documented in the DRM minutes.

Patients without an event as defined above will be censored based on the rules in Table 2.

Table 2 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 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

[REDACTED]

[REDACTED]

[REDACTED]

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 (incl. survival follow-up visits not performed in person) will be censored at the last visit date.

Summaries for both PFS and OS will be presented as in Section 7.7.4.2, 7.7.4.3 and 7.7.4.4.

3-months, 4-months, 6-months, 9-months, 12-months PFS estimate and corresponding 95% pointwise CI will also be presented along with the PFS summary.

3-months, 6-months, 9-months, 12-months, 15-months, 18-months, 21-months, and 24-months survival estimate and corresponding 95% pointwise CI will also be presented along with the survival summary.

All results of the CT scans will be listed.

7.7.6 Carcinoembryonic antigen (CEA)

CEA results will be listed by visit providing results, units, normal range, assessment of clinically relevance (incl. details) and absolute changes from baseline. If assessment was not done as planned the respective reason will be listed.

7.8 Safety

As described in Section 5.1, the SAF will be the basis for the analysis of safety data.

7.8.1 Study Drug Exposure and Compliance

The duration of study drug exposure will be calculated separately for EO4010, nivolumab and bevacizumab 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 and overall.

The number and percentages of patients with 0, 1, 2, ... administered doses of EO4010 or

nivolumab or bevacizumab, with administered doses of nivolumab/bevacizumab without interruption, and with full amount of nivolumab/bevacizumab administered will be provided. Basic statistics for the total number of EO4010 administrations, the total number of nivolumab/bevacizumab administrations, the total number of nivolumab/bevacizumab administrations without interruption and the total number of nivolumab/bevacizumab administrations during which the full amount was administered per patient will be provided by cohort.

Listings on study treatment administration for EO4010, nivolumab and bevacizumab will be presented for SAF.

7.8.2 Adverse Events

AEs will be coded using the MedDRA dictionary in the version and using the update strategy as specified in the coding specification for this study.

The investigator could assess the relationship of an AE to all three study drugs either individually (i.e. for EO4010, nivolumab and bevacizumab separately) or combined. In context of the intended study treatment, as composed of administered in combination s, 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).

Hence, an AE related to study treatment is defined as any AE with a suspected relationship to any of the three treatments individually or combined or with no information with respect to relatedness (i.e. NA cases).

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 at the post-treatment visit for safety assessment.

Therefore, the following AEs will be considered as **not** treatment emergent and will be excluded from summary tables:

- AEs starting after last treatment date + 30 days
- AEs occurring in patients not treated with any study drug
- AEs starting prior to first study drug administration for which no deterioration in CTCAE grade was documented during the active phase (e.g. patient for that the CTCAE grade improved only)

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

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.

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 the absolute and relative frequency of patients and the number of AEs in the following categories will be created for the SAF, by cohort and overall:

- Any AE
- Any TEAE
- Any local administration site conditions at a site of EO4010 local administration
- Any disease progression-related TEAE
- TEAE leading to death
- Any TEAE related to any study treatment
- Any TEAE related to any study treatment with worst grade ≥ 3 (NCI CTCAE v5.0)
- Any TEAE leading to withdrawal of any study drug
- Any TEAE leading to withdrawal of EO4010
- Any TEAE leading to withdrawal of nivolumab
- Any TEAE leading to withdrawal of bevacizumab
- Any TEAE leading to interruption of EO4010
- Any TEAE leading to interruption of nivolumab
- Any TEAE leading to interruption of bevacizumab
- Any serious TEAE
- Any serious TEAE related to any study treatment
- 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 serious TEAE with worst grade ≥ 3 (NCI CTCAE v5.0)
- Any serious TEAE related to any study treatment with worst grade ≥ 3 (NCI CTCAE v5.0)

TEAEs, TEAEs related to any study treatment, serious TEAEs, non-serious TEAEs, serious TEAEs related to any study treatment, TEAEs leading to withdrawal of EO4010, TEAEs leading to withdrawal of nivolumab, TEAEs leading to withdrawal of bevacizumab, and TEAEs leading to interruption of EO4010, TEAEs leading to interruption of nivolumab, and TEAEs leading to interruption of bevacizumab, TEAEs related to any study treatment with worst grade ≥ 3 (NCI CTCAE v5.0), serious TEAEs with worst grade ≥ 3 (NCI CTCAE v5.0), serious TEAEs related to any study treatment with worst grade ≥ 3 (NCI CTCAE v5.0) will be summarized by the absolute and relative frequency of patients, stratified by cohort and overall. In these tables, adverse events 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 absolute and relative frequency 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.

A by patient overview will be provided presenting patient id, cohort, MedDRA PT, seriousness, worst CTCAE grade, outcome, and causality of EO4010, nivolumab, and bevacizumab for all AEs with a worst CTCAE grade ≥ 3 .

All AEs, all serious AEs, all AEs leading to death, all AEs related to disease progression, all TEAEs leading to withdrawal of any study treatment (EO4010, nivolumab, bevacizumab), all TEAEs leading to interruption of any study treatment (EO4010, nivolumab, bevacizumab) will be listed in separate by-patient listings for SAF.

7.8.3 Local administration site conditions at a site of EO4010 local administration

Local administration site reactions (LASR) at a site of EO4010 local administration will be summarized by the absolute frequency of events, and absolute and relative frequency of patients, stratified by cohort and overall. In these tables, adverse events will be presented by MedDRA PT, CTC grade/intensity, outcome, and time to onset. All local administration site conditions at a site of EO4010 local administration will be listed in separate by-patient listings for SAF.

Further, number of events as well as number and percentage of patients with local administration site reactions will be summarized by visit (for details see Section 6.5),

cohort, location (left arm, left leg, right arm, right leg), and type (pain, erythema, induration, ulceration).

Further the time to 1st LASR event for all LASR events will be summarized using basic summary statistics, by cohort and overall.

The duration of all LASR events will be assessed by a Kaplan-Meier-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”. If the end of LASR date is given partial only, the rules for incomplete end dates defined above will be used. Duration of all LASR events will be described by Kaplan-Meier plots by cohort. 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.

7.8.4 Safety Laboratory

The following safety laboratory parameters were collected in the eCRF:

- **Hematology:** Hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count, and differential (percentage and total neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts)
- **Serum chemistry:** albumin, protein, sodium, potassium, chloride, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, creatinine, serum urea, C-reactive protein (CRP), lactate dehydrogenase (LDH)
- **Coagulation:** prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT).
- **Hormones:** serum cortisol, TSH, and free T4FSH
- **Urinalysis:** protein, glucose, ketones, bilirubin, blood, leucocytes
- **Serology:** HIV-status, hepatitis B (HBsAg, anti-HBcAg, anti-HBsAg), and hepatitis C (hepatitis C antibody), and Hepatitis C Virus Ribonucleic Acid (RNA)

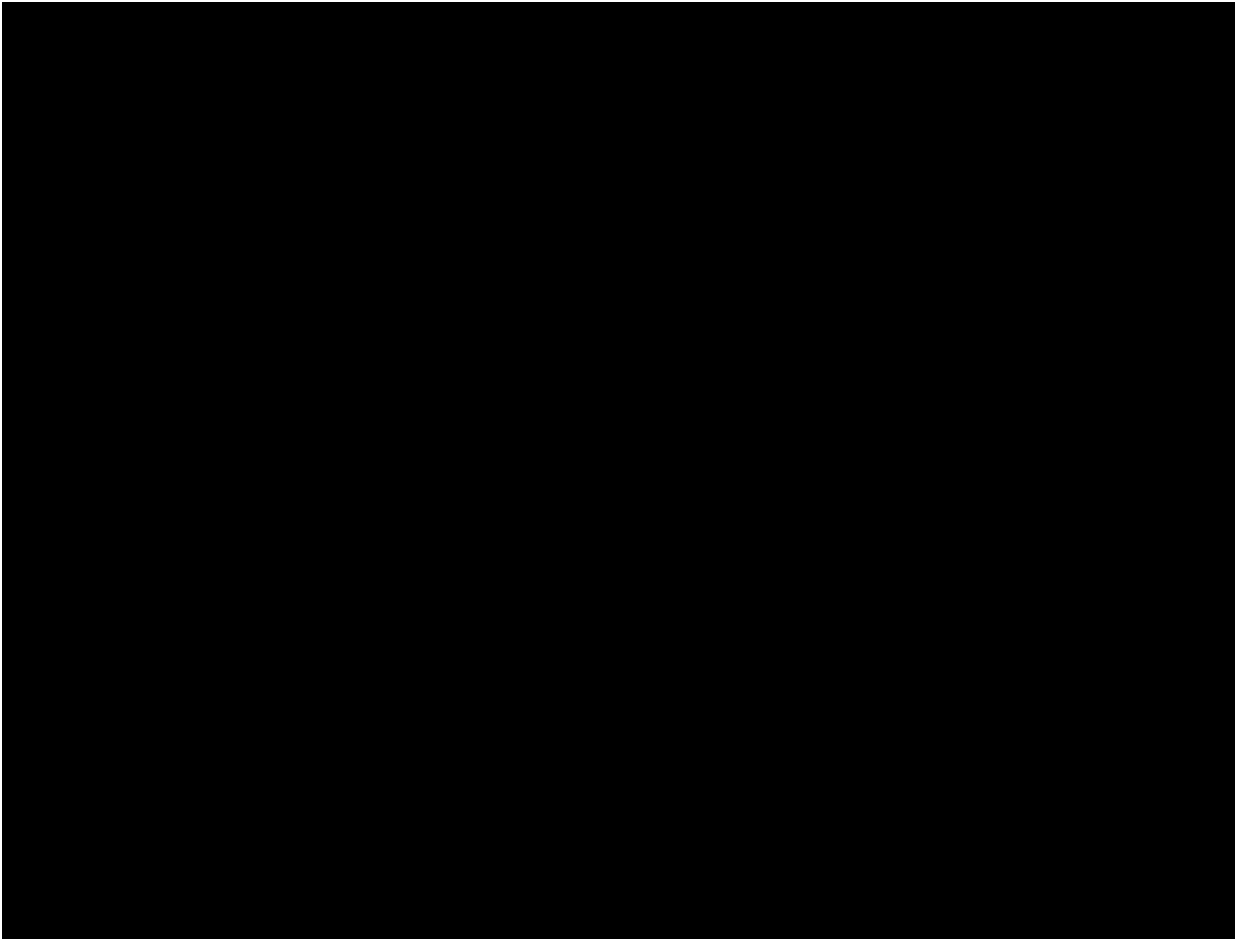
Additional parameters could be documented. These additional parameters were reviewed and if belonging to any parameter will be analyzed with the above parameters (e.g. hormones provided for visits for that no hormone assessment was planned).

Serology and urinalysis results as well as results from FSH test and additional parameters documented will be listed only.

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.

Table 3 Definition of time windows for analysis of hematology, differential blood count, serum chemistry and coagulation parameters



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

Table 4 Definition of time windows for analysis of serum cortisol and thyroid function parameters

The content of Table 4 is entirely redacted, shown as a large black rectangle. The table is intended to define time windows for serum cortisol and thyroid function parameters.

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

Table 5 Direction of “worst” laboratory parameters

[REDACTED]

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) by study week/period and cohort.

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.

All lab 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 considered. The worst CTCAE 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 separately. Further, the maximum improvement/worsening in CTCAE grade (i.e. minimum/maximum grade post-baseline minus CTCAE grade at baseline for improvement/worsening) 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 one 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 CTCAE grades from baseline to worst grade post baseline will be presented per parameter and cohort.

7.8.5 Vital Signs

Height collected in in will be converted to cm using the following formula:

$$in * 2.54 = cm$$

Weight collected in lbs. will be converted to kg using the following formula:

$$\frac{lbs}{2.2} = kg$$

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

$$(^{\circ}F - 32) * 5/9 = ^{\circ}C.$$

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 study week/period, as defined in Table 3.

7.8.6 Other Safety Data

Physical examination results will be listed only.

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 (for details see Section 6.5). 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.

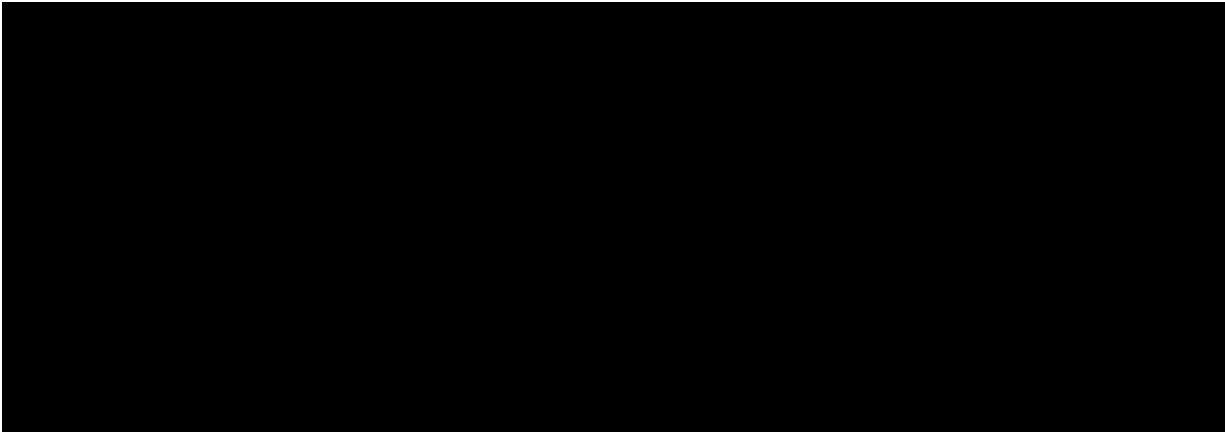
The number and percentage of patients with normal, abnormal but not clinically significant, and abnormal and clinically significant ECG will be presented by visit (for details see Section 6.5) as shift from the ECG evaluation at baseline for each cohort. The denominator will be the number of patients 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.

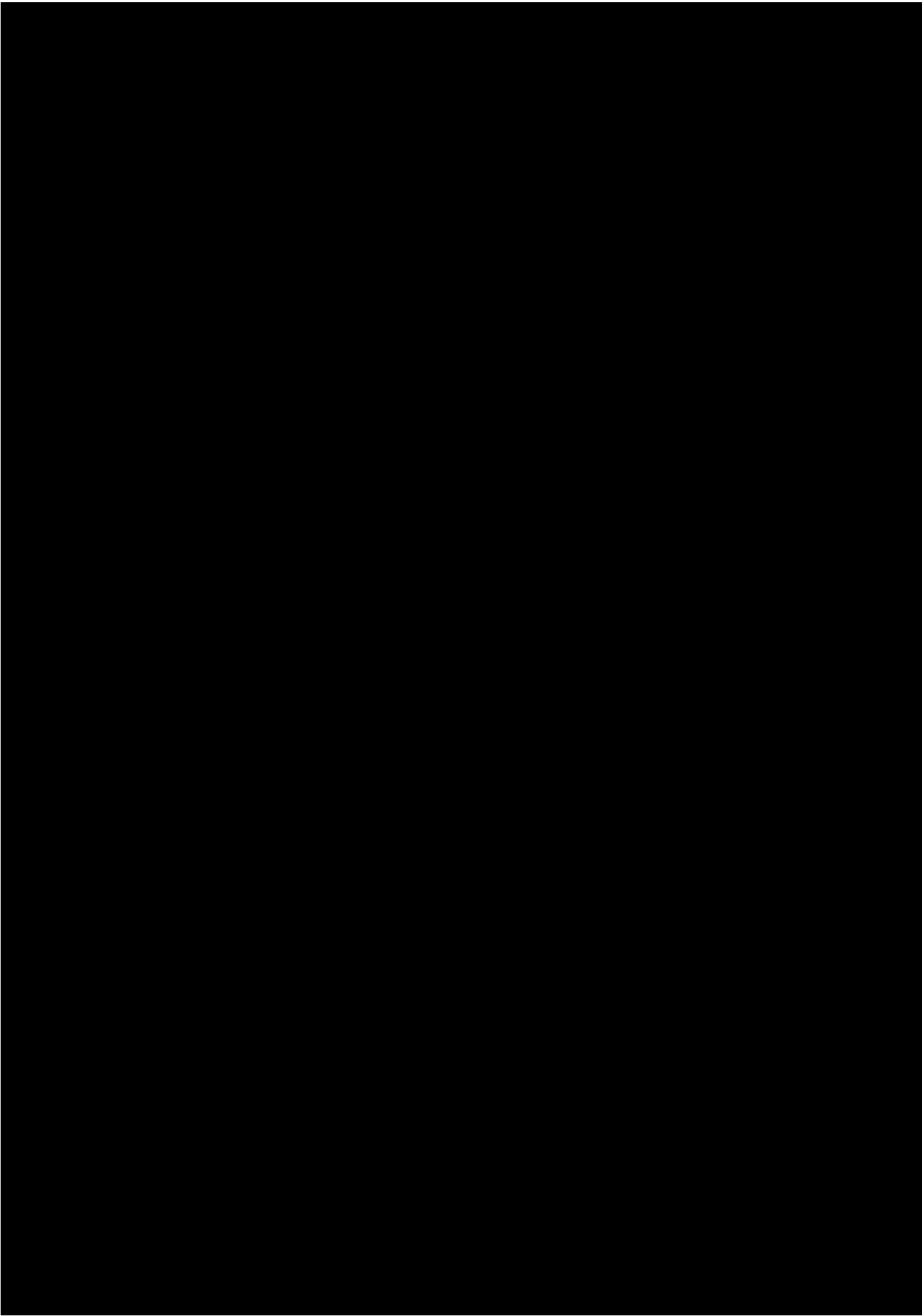
7.9 Immunogenicity

The FAS will be the basis for the analysis of immunogenicity data. Summary tables will be presented by cohort.

7.9.1 Definition of tests, parameters and possible results

Those positivity criteria will be provided by the central laboratory for each of the 6 peptides separately (EO2317, EO2318, OMP10, OMP11, OMP12 and UCP2) if possible, otherwise for all peptides together (pool, e.g. for intracellular cytokines staining). The boosting criteria will be derived by statistical programming.





[REDACTED]

Cross reactivities with the human TAAs FOXM1, BIRC5 (survivin), UBE2C, CDC20, and KIF2C will also be tested: In order to define the cross-reactivities, multimer staining test will be also performed by the central laboratory for the 5 TAAs (UBE2C, CDC20, BIRC5 (survivin), KIF2C and FOXM1).

[REDACTED]

7.9.2 Analysis of immunogenicity test results

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

- The immunogenicity of the 6 compounds (EO2317, EO2318, OMP10, OMP11, OMP12 and UCP2) separately or as a pool (without UCP2; 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.
- The immunogenicity of each of the 6 compounds (EO2317, EO2318, OMP10, OMP11, OMP12 and UCP2) separately or as a pool (without UCP2; according to availability from central laboratory) [REDACTED]
 - Frequency of positive patients. [REDACTED]

- [REDACTED]
- 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) will be provided for each of the 6 compounds [REDACTED]

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

- Cross reactivities of the 6 compounds (EO2317, EO2318, OMP10, OMP11, OMP12 and UCP2) with the five human TAAs (UBE2C, CDC20, BIRC5 (survivin), KIF2C and FOXM1):
 - Prior to cross-reactivity, positivity of human TAAs as a pool will be analyzed [REDACTED]

[Redacted]

[Redacted]

7.10 Exploratory endpoints

[Redacted]

[Redacted]

7.10.2 Exploratory endpoints not covered by this SAP

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

8 SOFTWARE AND STATISTICAL PROGRAMMING

The statistical analysis will be performed using the SAS® statistical software package in Version 9.4 or higher. Statistical Analysis System (SAS) programming will be performed according to [REDACTED] standards as defined in BM-08-SOP “Statistical Analysis and Programming” and related work instructions. Special attention will be paid to planning and performance of quality control measures as documented in the Quality Control (QC) plan for the analysis of this study (see also BM-08-WIN03 “How to Plan and Document QC for Statistical Analysis”).

9 REFERENCES

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

SAS 9.4 <https://support.sas.com/documentation/94/index.html>. Copyright © SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved .

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10 CHANGES TO FINAL VERSION OF THE SAP

Not Applicable.

11 LIST OF TABLES, FIGURES AND LISTINGS

See separate document: Appendix to the SAP.