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Clinical Trial Protocol EOADR1-19

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
EudraCT number:	2019-003396-19
IND number	19229
Protocol version number:	5.0
Date:	24 January 2024

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For reporting of immediately reportable related Grade ≥3 adverse events, and any medical questions regarding study conduct.

[redacted]

Signature for Protocol Approval and Release

I, the undersigned, have read this protocol and the appendices and agree that they contain all the necessary information required for the conduct of the study.

[redacted] 26-Jan-2024

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Chief Medical Officer

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Sponsor information:

The Spencer Bell Legacy Project is keeping alive the artistic legacy of Spencer Bell, poet, musician and artist, by promoting artists and musicians of all kinds and supporting adrenal cancer research and those affected by the disease. Spencer Bell passed away at the age of 20 in December 2006 from adrenocortical carcinoma.

GLOBAL COORDINATING INVESTIGATOR AGREEMENT

I, the undersigned, have read this protocol and the appendices and agree that they contain all the necessary information required for the conduct of the study, and I agree to conduct the

[redacted]

Date

SITE PRINCIPAL INVESTIGATOR AGREEMENT

I, the undersigned, have read this protocol and the appendices and agree to conduct the study as described herein.

Site Principal Investigator Signature: _____

Date: _____

Printed Name: _____

Site location: _____

TABLE OF CONTENTS

LIST OF FIGURES

[redacted]

LIST OF TABLES

[redacted]

ABBREVIATIONS

$^{123}I/^{131}I$-MIBG	$^{123}I/^{131}I$-metaiodobenzylguanidine
ACC	Adrenocortical carcinoma
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
B2M	β-2-microglobulin
BIRC5	Baculoviral inhibitor of apoptosis repeat-containing 5
BP	Blood pressure
bpm	Beats per minute
BSA	Body surface area
CD	Cluster of differentiation
CDD	Cyclophosphamide, dacarbazine, doxorubicin
CFR	Code of Federal Regulations
CI	Confidence interval
ConA	Concanavalin A
COVID	Coronavirus disease
CPI	Check point inhibitor
CR	Complete response
CRA	Clinical research associate

CRO	Contract research organization
CRP	C-reactive protein
CSA	Clinical study agreement
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CVD	Cyclophosphamide, vincristine, dacarbazine
CVDD	Cyclophosphamide, vincristine, dacarbazine, doxorubicin
DB	Database
DCR	Disease Control Rate
[redacted]	
DNA	Deoxyribonucleic acid
DOR	Duration of response
DP	Drug product
DSUR	Development safety update report
[redacted]	
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDP-M	Etoposide, doxorubicin, cisplatin, mitotane
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
ENSAT	European Network for the Study of Adrenal Tumors
ESMO	European Society for Medical Oncology
EudraCT	European clinical trials database
FAS	Full analysis set

FDA	Food and Drug Administration
FIH	First-in-human
FOXM1	Forkhead box M1
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GMP	Good manufacturing practice
Hb	Hemoglobin
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification number
IDMC	Independent data monitoring committee
IHC	Immunohistochemistry
IEC	Independent ethics committee
IFA	Incomplete Freund's adjuvant
IFN-γ	Interferon-gamma
IHC	Immunohistochemistry
IL-13Rα2	Interleukin-13 receptor alpha-2
IL-6	Interleukin-6

IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional review board
IV	Intravenous(ly)
JAK	Janus kinase
KPS	Karnofsky Performance Status
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MedDRA	Medical dictionary for regulatory activities
MEN	Multiple endocrine neoplasia
MHC	Major histocompatibility complex
MMR-D	Mismatch repair-deficient
MPP	Malignant pheochromocytoma/paraganglioma
MSI-H	Microsatellite instability-high
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-common terminology criteria for adverse events
NCCN	National Comprehensive Cancer Network
NE	Non-evaluable
NIH	National Institute of Health
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PI3K	Phosphatidyl inositol 3-kinase
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1

PFS	Progression-free survival
PI	Product information
P-M	Cisplatin, mitotane
PP	Per-protocol
PR	Partial response
PT	Preferred term
RBC	Red blood cells
RNA	Ribonucleic acid
PV	Pharmacovigilance
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SD	Stable disease
SDHB	Succinate dehydrogenase B
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
Sz-M	Streptozotocin, mitotane
TAA	Tumor-associated antigen
TCR	T cell receptor
TEAE	Treatment emergent adverse event
TERT	Telomerase reverse transcriptase
TSH	Thyroid-stimulating hormone
TTP	Time to progression

UCP2	Universal cancer peptide 2
ULN	Upper limit of normal
V	Visit
VHL	Von Hippel–Lindau
W	Week
WBC	White blood cells

SYNOPSIS

Full trial 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)

Rationale

Treatment options for patients with unresectable malignant adrenal disease are few and new treatment options have not been developped recently. Novel therapeutic approaches are needed to enhance the treatment outcomes for patients with adrenal malignancies. An innovative option which is available to test in the clinic, and proposed with the current trial, is the microbiome-derived peptide therapeutic cancer vaccine approach in combination with nivolumab, an anti-PD-1 blockade.

Objectives

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 pheochromocytoma/paraganglioma (MPP).
The primary objective of the phase 2 part of this trial is to determine the effect of EO2401 in combination with nivolumab on the progression-free survival rate (PFS) at 6 months, for patients treated in the randomized extension of Cohort 2A (patients with ACC who had prior systemic therapy).
The secondary objectives of the trial include assessment of immunogenicity of each peptide composing EO2401 in relation to T cells and cross-reactivity with the human Tumor Associated Antigens, objective response rate (ORR), time to response, and duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety and tolerability of EO2401 in combination with nivolumab in the randomized extension of Cohort 2A.

Primary trial endpoints

The primary endpoint of the phase 1 part is the number, type and severity of adverse events.
The primary endpoint of the phase 2 part is the percentage of patients from the randomized extension of Cohort 2A who achieve a response during 6 months of treatment with EO2401 in combination with nivolumab.

Secondary trial endpoints

The secondary trial endpoints include the percentage of patients with shown immunogenicity from baseline to up to 24 months, the percentage of patients by trial cohort who achieve a response for up to 24 months, time from onset of response to progression or death due to any reason, the time interval from first study treatment administration to progression, or death due to any cause, and the time interval from first study treatment administration to death due to any cause. It also includes the number, type and severity of adverse events for the randomized extension of the Cohort 2A.

Trial design

The trial is a global multi-center, 5 cohorts, phase 1/2 trial, intended to investigate EO2401 in combination with nivolumab in the treatment of patients with ACC or MPP. The maximum treatment duration for each participant is 24 months followed by a long-term survival follow up until patient's death or sponsor decision.
The number of patients recruited is as follows:

- Cohort 1 (patients with ACC or MPP, previously treated): 3 patients have been included in view of the safety profile of the study drugs.

- Cohorts 2A (patients with ACC, previously treated) and 2B (patients with ACC, previously untreated): 33 patients in total.
- Cohorts 3A (patients with MPP, previously treated) and 3B (patients with MPP, previously untreated): 17 patients in total.
- Randomized extension of the cohort 2A (patients with ACC, previously treated): 19 patients.

In total, 70 patients have been administered in the study.
The study treatment is EO2401 in combination with nivolumab for the cohorts 1, 2A, 2B, 3A and 3B; in the randomized extension of the Cohort 2A, patients are randomized between this combination, EO2401 monotherapy and nivolumab monotherapy using a ratio of 4:1:1.

Trial population

The main inclusion criteria are patients HLA-A2 positive with histologically proven ACC or MPP and with at least one measurable lesion; the main exclusion criteria are patients previously treated by immunotherapy or treated with high doses of corticosteroids or with significant abnormal clinical findings or laboratory values for hematology, liver and renal function. Please refer to the protocol for the full list of selection criteria.

Interventions

There are 5 cohorts in this trial and the planned interventions are described in the figure below:

[redacted]

Please refer to the protocol for the details of each study drug administration and each visit.
Specific regular safety monitoring of blood values, physical examination, and ECG are implemented as well as monitoring of all adverse events. The disease is followed by CT scan. Stool, blood samples and tumor biopsies (if consent is given for this) are also collected for research purposes.

Ethical considerations related to the clinical trial including the expected benefit to the individual patient or group of patients represented by the trial participants as well as the nature and extent of burden and risks

This trial aims to assess the safety and the preliminary efficacy of EO2401 in combination with nivolumab in patients with ACC or MPP. EO2401 is designed to stimulate an immune response against tumor proteins and stimulate immune-mediated killing of tumor cells and may potentially lead to an anti-tumor response. EO2401 has demonstrated good tolerability in animal models and a good safety profile in 170 patients treated so far (70 patients in this trial and 100 in a clinical trial performed in patients with recurrent glioblastomas).
The main anticipated adverse events caused by EO2401 are local administration site reactions (redness, local pain, swelling, inflammation, ulceration), mainly mild or moderate. The safety profile of EO2401 in combination with nivolumab is consistent with the one of nivolumab monotherapy, except the local administration sites reactions. These potential side effects will be closely monitored via regular blood tests and study visits. The selected peptides included in EO2401 have shown to induce strong immune responses in non-clinical models and considering the safety profile of the

combination and the preliminary clinical data observed so far, the benefit/risk ratio for the proposed therapeutic-vaccination approach is considered to be positive.

1 BACKGROUND

1.1 Background adrenal malignancies

Two different primary malignancies can arise from the adrenal gland: adrenocortical carcinoma (ACC) from the adrenal cortex, which are in most cases steroid hormone-producing, and malignant pheochromocytoma from the adrenal medulla. Pheochromocytomas are catecholamine-producing (epinephrine and norepinephrine) neuroendocrine tumors arising from chromaffin cells which can be located, except in the adrenal medulla, also in extra-adrenal paraganglia, the latter referred to as paraganglioma, and the two entities combined are in the following, and in view of this trial protocol, referred to as malignant (defined as metastatic disease, i.e. presence of chromaffin tissue in non-chromaffin organs) pheochromocytoma/paraganglioma (MPP) [1, 2, 3, 4].

From a diagnostic perspective, a comprehensive hormonal analysis is recommended pre-surgery by the European Network for the Study of Adrenal Tumors (ENSAT; www.ensat.org) in all cases of an adrenal mass to support establishing the origin of the tumor (cortex versus medulla versus other). Furthermore, the preoperative hormone pattern may serve as a fingerprint of the tumor during follow-up. A hormonal work-up might include assessment of excess of glucocorticoids, sexual steroids and steroid precursors, mineralocorticoids, and catecholamines. In patients with a clearly established diagnosis of ACC, one can omit the workup on catecholamine excess, and conversely for established MPP, one can omit the steroid analyses [1].

Surgery is of utmost importance, and the only curative treatment modality, in the treatment of both ACC and pheochromocytoma both at the primary diagnosis, and when possible also at recurrence (especially if recurrence appears a longer time after the primary surgery). Most patients with ACC have disease possible to resect at presentation, however, more than half of the patients who have undergone complete removal of the tumor are destined to have a relapse, often with metastases [5]. Similarly, radical resection is not a guarantee of cure for pheochromocytomas either. In one series of 171 patients followed up after surgical resection of a chromaffin cell tumor, 29 patients (17%) had recurrent or new tumors, which were malignant in 15 (9%) cases [9].

Treatments for adrenal malignancies not amenable to surgery are further outlined in Section 1.1.3 and Section 1.1.4.

1.1.1 Characteristics of adrenocortical carcinoma

ACC has an estimated incidence of ~0.7–2 new cases per million people per year [2]. It follows a bimodal age distribution, with peaks in childhood and in the fourth to fifth decades of life. ACC is more frequent in women than in men (ratio 1.5:1). Most ACCs are sporadic; however, sometimes these malignancies form part of hereditary syndromes such as the Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, multiple endocrine neoplasia (MEN) 1, congenital adrenal hyperplasia, familial polyposis coli, and β-catenin mutations [5].

About 50–60% of patients with ACC have clinical hormone excess. Hypercortisolism (Cushing syndrome; including weight gain, weakness, hypertension, psychiatric disturbances, hirsutism, centripetal obesity, purple striae) or mixed Cushing and virilizing syndromes are observed in the majority of patients. Pure androgen excess is less frequent while estrogen or mineralocorticoid excess are very rare [2].

The median overall survival (OS) of all patients with ACC is about 3–4 years. Prognosis for patients with locally advanced inoperable and metastatic ACC is poorer, the 5-year overall survival being <15%. Generally, five-year survival is 60–80% for tumors confined to the

adrenal space, 35–50% for locally advanced disease, and much lower in case of metastatic disease with reported percentages ranging from 0% to 28% [1, 2]. The prognosis is, however, heterogeneous; for instance, extremely long survival has been reported in patients with oligometastatic disease possible to resect.

The median survival of patients with advanced ACC not amenable to radical surgical resection treated with polychemotherapy as first line therapy in the FIRMACT trial (the first randomized trial in ACC) was 14.8 months [14].

1.1.2 Characteristics of malignant pheochromocytoma/paraganglioma

The incidence of pheochromocytoma/paraganglioma is ~2–8 per million adults per year [6]. Up to 40% of pheochromocytomas are associated with a variety of inherited conditions, including MEN 2, Von Hippel–Lindau (VHL) disease, neurofibromatosis type 1, and heredity paraganglioma syndromes. The peak incidence of occurrence of pheochromocytomas is between the third and fifth decades of life, but generally occur at a younger age and are more likely to be bilateral in patients with familial disease [4]. Approximately 10% - 15% of pheochromocytomas and paragangliomas are malignant (defined as metastatic disease due to lack of other specific markers; metastatic defined as presence of chromaffin tissue in non-chromaffin organs) [3]. However, generally paragangliomas are more likely to be malignant than pheochromocytomas in the adrenal medulla (about 40% versus 10%). It has been speculated that patients with a pheochromocytoma with mutations in the succinate dehydrogenase B (SDHB) gene and/or extra-adrenal locations, might be more prone to develop malignant tumors (30%–50%) [1].

Pheochromocytomas release catecholamines (epinephrine and dopamine) and their metabolites metanephrine and methoxytyramine, resulting in hypertension, arrythmia, and/or hyperglycemia. About 40% of paragangliomas secrete catecholamines. However, head and neck paragangliomas only secrete catecholamines about 5% of the time and often it is dopamine.

Malignant MPP is characterized by prognostic heterogeneity. A retrospective multicenter study of malignant MPP including 169 patients from 18 European centers diagnosed between 1998 and 2010 indicated some main characteristics of the disease: primary pheochromocytoma was found in 53% of patients, tumor or hormone-related symptoms in approx. 57%, positive plasma or urine hormones in 81%, and identification of a SDHB mutation in 42 % of patients. Metastatic sites included bone (64%), lymph nodes (40%), lung (29%) and liver (26%); mean time between initial and malignancy diagnosis was 43 months (0-614 months). Median follow-up was 68 months and median survival 6.7 years. Using univariate analysis, better survival was associated with head and neck paraganglioma, age <40 years, metanephrines <5-fold the upper limits of the normal range, and low proliferative index. In multivariate analysis, hypersecretion (Hazard Ratio 3.02 [1.65-5.55]; p = 0.0004) was identified as an independent significant prognostic factor of worse overall survival. In this trial it was not confirmed that SDHB mutations have any major prognostic impact in malignant MPP [7].

Another analysis of twenty retrospective non-comparative studies reported on 1338 patients with metastatic pheochromocytoma (685, 53%) and paraganglioma (611, 47%), diagnosed at a mean age of 43.9 ± 5.2 years. Mean follow-up was 6.3 ± 3.2 years. Of 532 patients with reported data, 40% had synchronous metastases. Five-year (7 studies, n = 738) and 10-year (2 studies, n = 55) mortality rates for patients with metastatic MPP were 37% (95% CI, 24–51%) and 29% (95% CI, 17–42%), respectively [8].

1.1.3 Treatment of adrenocortical carcinoma

Surgery is of utmost importance, and the only curative treatment modality, in the treatment of ACC both at the primary diagnosis, and when possible also at recurrence (especially if recurrence appears a longer time after the primary surgery). However, even if most patients with ACC have disease possible to resect at presentation the majority will relapse, often with metastatic disease [5].

The aggressive behavior and the high recurrence rate of ACC provide the rationale for the use of adjuvant therapy. Adjuvant radiotherapy to the tumor bed is considered in patients with incomplete/R1 resection or Rx resection [10]. Mitotane has been the reference drug for the management of ACC for decades. In a case control study involving 177 patients, the outcome of 47 patients followed in Italian reference centers that systematically adopted adjuvant mitotane for all patients with radically operated ACC was significantly higher (in terms of both disease free survival and overall survival) than the outcome of 55 Italian patients and 75 German patients followed in institutions not administering adjuvant mitotane therapy [11]. On the basis of these findings, a panel of international experts unanimously stated that patients with potential residual disease (R1 or Rx resection) and/or Ki67 more than 10% should be offered adjuvant mitotane, whereas adjuvant therapy was not considered mandatory in patients fulfilling all of the following criteria: stage I or II disease, histologically proven R0 resection; and Ki67 expressed in ≤10% of neoplastic cells [12]. There are no data regarding the optimal duration of adjuvant mitotane; a recommendation is that adjuvant mitotane should be administered for at least 2 years since the greatest frequency of disease recurrence is expected within this timeframe [1]. However, while mitotane is well tolerated by a fraction of patients, a majority find mitotane a difficult therapy that markedly impacts the quality of their lives. Thus, the treatment duration is assessed individually.

Mitotane has also been used since a long time, and is also registered, in patients with locally advanced inoperable and metastatic ACC. Response rates vary between 13% and 35%; including many results derived from retrospective series in the 1960s [5, 13]. Patients with hormonal excess often experience clinical benefit by this strategy and continuation of mitotane treatment can be indicated in these patients even after radiological progression when alternative strategies to inhibit the hormonal excess are lacking [1]. Owing to the latency of mitotane to attain the therapeutic range, mitotane monotherapy is indicated in the management of patients with a low tumor burden and/or more indolent disease, when possible in combination with locoregional therapies (for instance radiofrequency ablation). In case of rapidly progressing extensive metastatic disease and/or radiological progression under mitotane, cytotoxic chemotherapy is indicated. Response rates for chemotherapy vary between 7% and 54% (building on an assessment of 11 prospective single-arm trial with a total of 239 patients), again with variability in the response criteria. The association of mitotane to chemotherapy seems to be more active than chemotherapy alone, although no randomized trials have formally demonstrated this superiority [5].

In the first international randomized trial in advanced or metastatic adrenocortical carcinoma treatment (FIRM-ACT trial), the two most active treatment regimens namely etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) and streptozotocin and mitotane (Sz-M) were compared in 304 chemotherapy-naïve patients. Patients with disease progression received the alternate regimen. The results of this trial indicate that EDP-M is the superior regimen [14]. Although no statistically substantial increase in OS was documented in patients receiving EDP-M as the first-line therapy, significantly better response rates (23.2% versus 9.2%) and progression-free survival (PFS), median 5.0 versus 2.1 months, were achieved with EDP-M in comparison with Sz-M. The rate of serious adverse events (SAEs) was comparable. Of note, the results of the second-line regimens replicated the rates observed

with the first-line therapy. Since EDP-M was superior to Sz-M in terms of progression-free survival either as first-line or second-line therapy, the crossover design may have attenuated its advantage on overall survival. On this basis, EDP-M is usually recommended as the first-line therapy for ACC requiring cytotoxic therapy. In patients unfit for the EDP-M regimen P-M may constitute a reasonable alternative [15].

1.1.4 Treatment of malignant pheochromocytoma/paraganglioma

The therapeutic strategy of metastatic MPP aims to control excessive catecholamine secretion and tumor burden, but no curative treatment is achievable. Treatment choices include a wait and see policy, locoregional therapies, systemic chemotherapy, and radiopharmaceutical agents [6].

In the absence of any randomized studies and demonstrated impact on survival, the patients' quality of life should always be considered. Indeed, due to the indolent course of subgroups of patients, a wait and see policy coupled with a watchful follow-up can be considered as an option in asymptomatic patients with a low tumor burden.

An antineoplastic treatment is often recommended in case of rapid progression and/or symptom onset. In the absence of tumor progression, surgery of the primary tumor or metastases can reduce hormone secretion and may prevent complications related to a critical anatomical location and improve the efficacy of subsequent therapies [6]. Metastatic disease palliation may also benefit from local therapy with embolization and or radiofrequency ablation.

Radionuclide therapy is an effective treatment and ^{131}I-MIBG is the most frequently used. Approximately 50% of patients are eligible for ^{131}I-MIBG therapy based on the uptake on diagnostic scans. Several studies have been published on the efficacy of ^{131}I-MIBG treatment [6]; objective responses were observed in 22–47% of patients, mainly in patients with soft tissue metastases. ^{131}I-MIBG therapy might be considered as a first-line approach in patients with a good uptake of ^{123}I-MIBG and unresectable, progressive MPP or patients with symptoms (not amenable to locoregional control), or patients with a high tumor burden with a low number of bone metastases.

Cyclophosphamide- and dacarbazine-based regimens combined with vincristine (CVD) or doxorubicin (CVDD or CDD) are the best studied chemotherapy regimens [6]. In one of the larger published studies (n = 52 patients), 40% of patients treated with CVD, CDD, or CVDD experienced clinical benefits, including a reduction in tumor size in 25% of cases [16]. Systemic chemotherapy is debated as a first-line therapy in patients with a low uptake of ^{123}I-MIBG and unresectable, rapidly progressive MPP, or patients with high tumor burden or with a high number of bone metastases.

Most recently, at ESMO 2021, the first international randomized study in malignant progressive pheochromocytoma and paragangliomas (FIRSTMAPPP) was presented [68]. Patients with progressive MPP were randomized 1:1 for sunitinib therapy or placebo. The primary endpoint was progression-free survival (PFS) at 12 months. On the basis of a two-step Simon model (alpha 10%, power 90%), the investigators aimed for 74 patients, assuming a PFS improvement at 12 months from 20 to 40%. Eleven or more patients out of 37 with no progression at 12 months were expected to conclude that sunitinib is effective. The placebo group served as an internal control to validate the hypothesis of the Simon design with a 12-month PFS equal to 20%.

A total of 78 patients were enrolled (39 randomized in each arm) including adrenal/paraganglioma primaries, each 50%, and 60% patients with prior therapy. The primary endpoint was met: PFS at 12 months was 35.9% with sunitinib versus 18.9% with

placebo. Median PFS was 8.9 months (95% CI: 5.5-12.7) versus 3.6 months (95% CI: 3.1-6.1). The investigators conclusion was that sunitinib becomes the first-line option in patients with progressive MPP.

1.2 Novel therapies and immunotherapy in adrenal malignancies

Different types of newer targeted therapies have already been tested in both ACC and MPP, for instance sunitinib and pazopanib [2, 17], but generally it has not led to any spectacular breakthroughs.

Immunotherapy, currently changing the treatment landscape in many tumor indications have also been tested, or trials are under way, in ACC and MPP. Initial preliminary data in a limited number of patients showed an acceptable safety profile of anti-PD-1 inhibition in patients with metastatic ACC [18; nivolumab, NCT02720484], and hints of objective tumor regression [19; pembrolizumab case report]. Pembrolizumab is currently tested in phase 2 trials for patients with advanced ACC (NCT02673333) and for patients with metastatic MPP (NCT02721732). In addition, there are also ongoing trials in ACC including both nivolumab and ipilimumab (NCT03333616 and NCT02834013).

Data from the pembrolizumab phase 2 trial (NCT02673333) in ACC was presented at the 2019 ASCO meeting [35]. Thirty-nine patients with a median age of 62 years (range, 19-87) were treated. At time of analysis, the median follow-up among survivors was 17.8 months (range, 5.4-34.7). The objective response rate (ORR) was 23.1% (95% CI, 11.1-39.3); 0 CR, 9 PR. Seven patients (17.9%) had SD as best response. Among the 9 PRs, median time to PR was 4.1 months (range, 1.7-10.5) and median duration of response (DOR) was not reached (95% CI, 4.1-not reached). Three patients achieving PR have completed 2 years of treatment with ongoing response noted. Median PFS was 2.1 months (95% CI, 2.0-10.7), and median OS was 24.9 months (95% CI, 4.2-not reached); 2-year OS rate was 50% (95% CI, 36-69%). There was no association between tumor PD-L1 status ($p > 0.95$), MSI-H/MMR-D status ($p = 0.61$), or somatic alterations and objective response to pembrolizumab (data presented in poster at the conference). Thirteen percent (n=5) of patients had grade 3/4 treatment-related adverse events according to the presented poster. The conclusions from the investigators was that pembrolizumab demonstrated antitumor activity and was well tolerated in advanced ACC.

A large already published trial (n = 50) in patients with metastatic ACC included treatment with avelumab (anti-PD-L1 inhibition) and allowed continuation of mitotane in patients with metastatic ACC and prior platinum-based therapy [20]. Twenty-six percent of patients had received one prior line of systemic therapy, 36% two prior lines, and 38% 3 or more lines of prior therapy. The ORR was 6.0% (95% CI, 1.3% to 16.5%; partial response in 3 patients). Twenty-one patients (42.0%) had SD as best response (disease control rate, 48.0%). Median PFS was 2.6 months (95% CI, 1.4 to 4.0), median OS was 10.6 months (95% CI, 7.4 to 15.0), and the 1-year OS rate was 43.4% (95% CI, 27.9% to 57.9%).

The objective efficacy noted in the trial with avelumab might be seen as low and different possible mechanisms linked to potential mechanisms of ACC immune-resistance has been discussed, including WNT/β-catenin pathway activation and TP53 mutations influencing CD8+ T cell action, low PD-L1 expression, and steroid excess (hormone-secreting disease) and/or steroid replacement therapy [21].

The avelumab trial possibly indicated a link between objective response and PD-L1 expression; in evaluable patients with PD-L1+ (n = 12) or PD-L1− (n = 30) tumors (≥5% tumor cell cutoff), the objective response rate was 16.7% vs 3.3% (P = 0.192) [20]. This was however not the case when pembrolizumab was used (see above regarding the

pembrolizumab phase 2 trial; NCT02673333); still assessment of PD-L1 expression in future immunotherapy trials in adrenal tumors seems an adequate step.

Monitoring of steroid access seems also to be a factor for consideration in relation to immunotherapy trials in ACC, and the combination with mitotane might also be helpful (as implemented in the avelumab trial; 50% of patients continued mitotane but mitotane levels during the study were not recorded [20]). Mitotane, used for decades in ACC, is an adrenal cytotoxic agent with an unknown mechanism of action, but assumed to modify the peripheral metabolism of steroids and directly suppresses the adrenal cortex. A reduction in 17-hydroxycorticosteroids in the absence of decreased corticosteroid concentrations and increased formation of 6-β-hydroxycortisol have been reported [22]. There are recommendations for monitoring of blood concentration of mitotane and a general aim to reach a mitotane blood level of 14 to 20 mg/L [2, 22].

1.3 EO2401 an adrenal malignancy targeted therapeutic vaccine

1.3.1 EO2401 background and non-clinical development

Extensive pre-clinical studies have been conducted to characterize the multi-peptide therapeutic cancer vaccine EO2401. Summarized information about the compound is presented below; for more details see the current Investigator's Brochure (IB) of EO2401.

Three 9- or 10-amino acid microbiome-derived peptides (EO2316, EO2317, and EO2318; CD8+ cytotoxic T cell epitopes) that mimic specific TAAs which are overexpressed in adrenal malignancies have been identified. These peptides were shown to induce a strong immune response in non-clinical models and represent the specificity included in EO2401.

The microbiome-derived peptides were selected based on their prevalence in the general population in order to be present in an as large proportion of the population as possible. It is assumed that the general human population has generated a memory repertoire of tolerized T cells recognizing the selected microbiome-derived peptides. Thus, the strategy is to identify and then use these peptides to re-activate their associated memory T cells. Because the peptides are almost identical to known TAAs, they are assumed to activate memory T cells that will cross-react with the TAAs, and thereby inducing a strong attack against the tumor cells themselves.

Before identifying the EO2316, EO2317, and EO2318 peptides, proof-of-concept studies were achieved with EO2315, a 9 amino acid microbiome-derived peptide with homology to a human IL13Rα2 peptide. EO2315 elicited a strong binding affinity to the human leukocyte antigen (HLA)-A2. This peptide drove a strong immunogenicity in non-clinical models (HLA-A2 transgenic mice) and T cells generated against EO2315 demonstrated cross reactivity against the human peptide counterpart. The ability of EO2315 to promote cytotoxic T cell expansion in combination with anti-programmed cell death-1 (anti-PD-1) was demonstrated in vivo using adoptive transfer of lymphocytes from immunized HLA-A2 transgenic mice into tumor-engrafted nude mice. Additionally, the immunogenicity of the UCP2 CD4+ helper peptide was demonstrated in the HLA-A2 transgenic mouse model when administered together with EO2315 and shown to improve the immunogenicity driven by EO2315.

After proof-of-concept of EO2315, EO2316, a 10-amino acid bacterial peptide sharing 8-amino acid with EO2315, was identified. While EO2316 shares the same immunogenic properties in mice as EO2315, EO2316 has been selected as a preferred candidate for EO2401 in comparison with EO2315 because of higher prevalence of EO2316 within the human gut microbiota.

EO2401 Drug Product (DP)

EO2401 DP [redacted] is [redacted] mixture solution of one synthetic [redacted] microbiome-derived peptide (EO2316), and two synthetic [redacted] microbiome-derived peptides (EO2317 and EO2318), and the synthetic [redacted] UCP2 (CD4+ helper) peptide. EO2316, EO2317, and EO2318 were found in the human microbiota and display high homology with TAAs expressed by adrenal malignancies (IL13Rα2, BIRC5/survivin, and FOXM1, respectively). The total of three microbiome-derived peptides which mimic three different TAAs were selected to overcome possible tumor heterogeneity and possibly reduce tumor escape. All three peptides demonstrated high MHC binding affinity, and induction of strong immune responses as well as cross reactivity against the human corresponding peptides in non-clinical models. The peptide mixture EO2401 DP will be emulsified [redacted] before subcutaneous administration.

EO2316

EO2316 is a [redacted] bacterial peptide which shows high homology to a cognate epitope on human IL13Rα2 that is known as a decoy receptor for IL-13 [46]. IL13Rα2 is an inhibitory subunit of the type II receptor. Normal function of IL-13 is to activate STAT6, which exerts transcriptional control over genes promoting apoptosis through increased caspase-3 activity. Sequestration of IL-13 by IL13Rα2 is considered being an apoptosis escape mechanism of tumor cells [47]. In addition, IL13Rα2 acts as a receptor for the chitinase-like protein Chi3l1 and mediates signaling leading to activation of mitogen-activated protein kinase/ERK, AKT, and Wnt/β-catenin pathways, all involved in the process of tumorigenesis [48]. The link between IL13Rα2 and tumorigenesis is supported by many in vitro and in vivo studies showing that increased expression of IL13Rα2 promotes tumor progression in several tumor models [49]. IL13Rα2 has also been shown to promote tumor invasion and migration, as well as to protect tumor cells from induction of apoptosis [47]. Importantly, IL13Rα2 appears to be expressed on cancer stem cells. It may be considered as a driver oncogene [50].

It has been shown that IL13Rα2 is overexpressed (mRNA) in primary malignant adrenocortical cancers compared with benign adrenocortical tumors and normal adrenal tissue [23, 52]. Immunohistochemistry also confirmed higher protein expression in malignant and benign tumors than normal adrenocortical tissues. Treatment of IL13Rα2 expressing ACC cell lines (NCI-H295R and SW13) with an IL-13-targeting immunotoxin induced tumor size reduction, tumor necrosis, and a survival impact versus control. Also, direct IL13Rα2 knock-down decreased cellular proliferation and invasion [23].

Likewise, it has been shown that IL13Rα2 is overexpressed in malignant MPP and has an impact on prognosis of MPP [51].

IL13Rα2 is not, or very low expressed, in normal tissues (except in testis, which is an immune protected organ) [53]. Thus, IL13Rα2 could be considered as a specific tumor-associated protein and a good target candidate for immunotherapy using a therapeutic vaccine approach in adrenal tumors.

EO2317

EO2317 is a[redacted] microbiome-derived peptide with homology to BIRC5/survivin. Survivin is a member of the inhibitor of apoptosis gene family, which encodes negative regulatory proteins that function as endogenous inhibitors of caspases and preventing apoptotic cell death [54]. Survivin also has a role as a mitosis regulator, physically associated with the mitotic apparatus thereby ensuring the proper completion of various stages of cell division probably via the regulation of microtubule dynamics and stability [55]. These molecular functions are supported by a number of in vitro and in vivo pre-clinical studies that demonstrated that modulation of survivin expression reduced tumor growth, increased apoptosis, and sensitized tumor cells to chemotherapeutic drugs [56]. Overexpression of survivin in cancer may overcome an apoptotic checkpoint and favor aberrant progression of transformed cells through mitosis [57].

Survivin mRNA in ACC has been shown to be significantly overexpressed when compared with adrenocortical adenoma or normal adrenal glands [24]. IHC confirmed survivin protein expression in 97 % of ACCs. In 83 % of samples, staining was moderate or high and clinical outcome in this subgroup showed a trend towards poorer prognosis (Figure 1). In addition, survivin knockdown in SW13 cells significantly increased the rate of apoptosis [24].

[redacted]

In a study utilizing IHC assessment all MPP specimens stained 2+ or 3+, and there was no significant difference between the staining intensity of benign and malignant samples [25]. All normal adrenal medulla specimens stained positively with anti-survivin but to a lesser degree than the chromaffin cell tumors [25]. Thus, survivin represents a neuroendocrine marker for chromaffin cell tumors, and survivin does not appear to reliably distinguish benign from malignant MPP (i.e. does not identify patients at risk of recurrent disease). In addition, in a study of samples from Chinese patients with adrenal tumors (39 cortex adenoma, 22 cortex adenocarcinoma, 35 pheochromocytoma, 20 malignant pheochromocytoma) the expression intensity of survivin was significantly lower in adrenal cortex adenoma than in adrenal cortex adenocarcinoma ($P<0.05$), and was significantly lower in pheochromocytoma than in malignant pheochromocytoma ($P<0.05$) [26].

While survivin is strongly expressed in embryonic tissues where it plays a role in development, expression of survivin in normal adult tissue is scarce [30]. Overall, the pattern of overexpression of survivin in adrenal tumors, associated with its critical role in tumorigenesis, makes survivin an interesting target for a therapeutic vaccine approach.

EO2318

EO2318 is a [redacted] peptide identified from human gut microbiome that targets FOXM1. It follows the same principles as for EO2316 and EO2317 so that it is highly homologous with the FOXM1 antigen overexpressed on tumor tissue. FOXM1 is a member of the Fox transcription factors involved in G1-S and G2-M progression [31]. FOXM1 exhibits a proliferation-specific expression pattern and its expression is regulated by proliferation and antiproliferation signals as well as by proto-oncoproteins and tumor suppressors. While its expression is turned off in terminally differentiated cells, it is upregulated in a multitude of human solid tumors.

In a meta-analysis including 23 studies it was found that elevated FOXM1-protein expression was significantly associated with worse 3-year OS (OR = 3.30, 95% CI = 2.56 to 4.25, $P < 0.00001$), 5-year OS (OR =3.35, 95% CI = 2.64 to 4.26, $P < 0.00001$), and 10-year OS (OR = 5.24, 95% CI = 2.61 to 10.52, $P < 0.00001$) of human solid tumors [27]. Similar results were observed for disease-free survival. High expression level of FOXM1 was also associated with advanced tumor stage [27]. Thus, elevated FOXM1 expression is associated with poor survival in most solid tumors.

A recent analysis has identified FOXM1 as being associated with the progression and prognosis of ACC and might lead to poor outcomes by regulating the cell cycle [28]. The below figures illustrate stage and grade plots of FOXM1 in ACC (Figure 2 A-B), and overall and disease-free survival (Figure 3 A-B) analyses of the association between the expression levels of FOXM1 and survival time in ACC [28].

FOXM1 expression is higher in MPP than in the normal corresponding tissue [29]. As also indicated above the expression of FOXM1 in ACC is higher than in the normal corresponding tissue (and increases by grade and stage of ACC; Figure 2 A-B) and a Kaplan–Meier analyses of overall survival according to FOXM1 expression levels in ACC further corroborates the detrimental effect of high expression (Figure 4) [29].

[redacted]

[redacted]

FOXM1 with its high expression in adrenal tumors and limited expression in the normal counterpart together with the general strong correlation with survival outcomes in a multitude of solid tumors, including ACC, is an interesting target for a therapeutic vaccine approach.

UCP2

In order to generate an efficient immune response, the helper peptide UCP2 will be included in EO2401. This Th1 helper peptide will be able to sustain efficient dendritic cell activation and specific cytotoxic T cell activation. UCP2 was initially described by Godet et al [32].

It is a telomerase derived $CD4^+$ epitope that binds to most commonly found human MHC class II alleles. The role of telomerase in tumor progression is well documented. Cancer cells overcome senescence via telomere length maintenance mechanisms involving telomerase activation. Telomerase reverse transcriptase (TERT) overexpression achieved via multiple genetic and epigenetic mechanisms has been observed in 80% to 90% of malignant tumors. Ability of UCP2 to elicit specific $CD4^+$ T cell responses have been demonstrated in in vivo models. Furthermore, spontaneous T cell responses against UCP2 were observed in various types of cancers [33].

[redacted]

[redacted]

Check point blockade in the context of EO2401

Check point inhibitors as anti-PD-1 and anti-PD-L1, approved for the treatment of different types of malignancies, release the breaks on the immune system; however, only a small subset of patients treated with these type of compounds as single-agents will achieve a clinical complete response (see for instance Section 1.2 regarding the use of anti-PD-L1 in ACC). Nevertheless, deep and durable responses in some tumor types makes these therapies an important step forward in the treatment of malignancies.

Check point inhibitors allow patient's existing T cell population to attack the tumor and, in order for this therapy to be effective, the patients must have corresponding T cells able to recognize antigens presented by the tumor. It is likely that patients who do not respond to this type therapy do not have adequate numbers of T cells to overcome tumor growth. Therapeutic vaccination stimulates the immune system leading to the activation of the required T cell population for a more effective impact of check point inhibition, and the check point inhibition allows the T cell population to infiltrate the tumor and act without the negative impact of e.g. PD-1/PD-L1 interactions.

Nivolumab is an anti-PD-1 fully human monoclonal antibody (immunoglobulin G4) promoting antitumor immunity allowing the immune system to attack the tumor, blocking the interaction between PD-1 and its ligands (PD-L1 and PD-L2), and stop a negative regulator of T cell activation and response, thus allowing the immune system to attack the tumor.

Nivolumab is approved for use for the treatment of multiple tumor types including melanoma, non-small cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell cancer of the head and neck, urothelial carcinoma, mismatch repair deficient or microsatellite instability-high colorectal cancer, esophageal squamous cell carcinoma, esophageal/gastro-esophageal junction cancer, gastric/gastro-esophageal junction/esophageal adenocarcinoma, hepatocellular carcinoma [42, 43]. However, it is not currently approved for any of the adrenal malignancies (regarding early clinical trial experiences of anti-PD-1 blockade, including with nivolumab, see Section 1.2).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3.2 EO2401 early clinical development

The initial clinical development of EO2401 is planned to include two phase 1/2 trials, one in glioblastoma (EOGBM1-18; EudraCT 2018-002279-16) and the current trial in adrenal tumors (EOADR1-19).

The early clinical development of EO2401 aims at showing that therapeutic cancer vaccination with EO2401 in combination with anti-PD-1 blockade is safe and tolerable, and can achieve expansion of T cells not only recognizing the microbiome derived peptides used for immunization but also recognizing the targeted nominal TAAs expressed by human tumor cells in patients with malignancies (i.e. immunological proof of concept). In addition, preliminary efficacy aspects of EO2401 are going to be studied, as will multiple translational exploratory endpoints.

The development strategy encompassing trials EOGBM1-18 and EOADR1-19, assumed to run mainly in parallel, is selected to achieve the same objectives in different biologically

very diverse types of malignancies (i.e. glioblastoma, adrenocortical carcinoma, and malignant pheochromocytoma/paraganglioma; being not only differentiated by standard histology but also in relation to a multitude of other biological aspects as for example growth and metastases patterns) to enable early learning to advice regarding later development paths and possibilities.

The first-in-human (FIH) trial is assumed to be EOGBM1-18 with a targeted start end of 2019. The trial is a multicenter (assumed countries involved are Germany, France, Spain, and USA), phase 1/2 trial, in patients with unequivocal evidence of progressive or first recurrent glioblastoma. The study design builds on an initial cohort for assessment of mainly safety and tolerability of monotherapy EO2401 and EO2401 in combination with nivolumab (a cohort with a 3-by-3 design), and expansion cohorts for assessment of further safety and tolerability, immunogenicity, and preliminary efficacy during treatment with EO2401 in combination with nivolumab (without any EO2401 monotherapy component), and EO2401 in combination with both nivolumab and bevacizumab concomitantly (the latter treatment option will only be available for sites in the USA due to local health authority authorization of bevacizumab for recurrent glioblastoma).

Considering the proposed parallel conduct of trials EOGBM1-18 and EOADR1-19 it is of importance highlighting that both trials will be overseen by independent data monitoring committees (IDMCs) which, even if the populations in the two trials are very different, will be cross-sharing information. Of note, is also that the tasks, decision rules, etc. for the two IDMCs are aligned and similar, to the extent possible taking the individual trial designs into account.

Details of the IDMC processes and procedures, and cohort management plans for the current trial and trial EOGBM1-18 are outlined in separate IDMC Charters which will be/have been submitted to applicable health authorities and review boards.

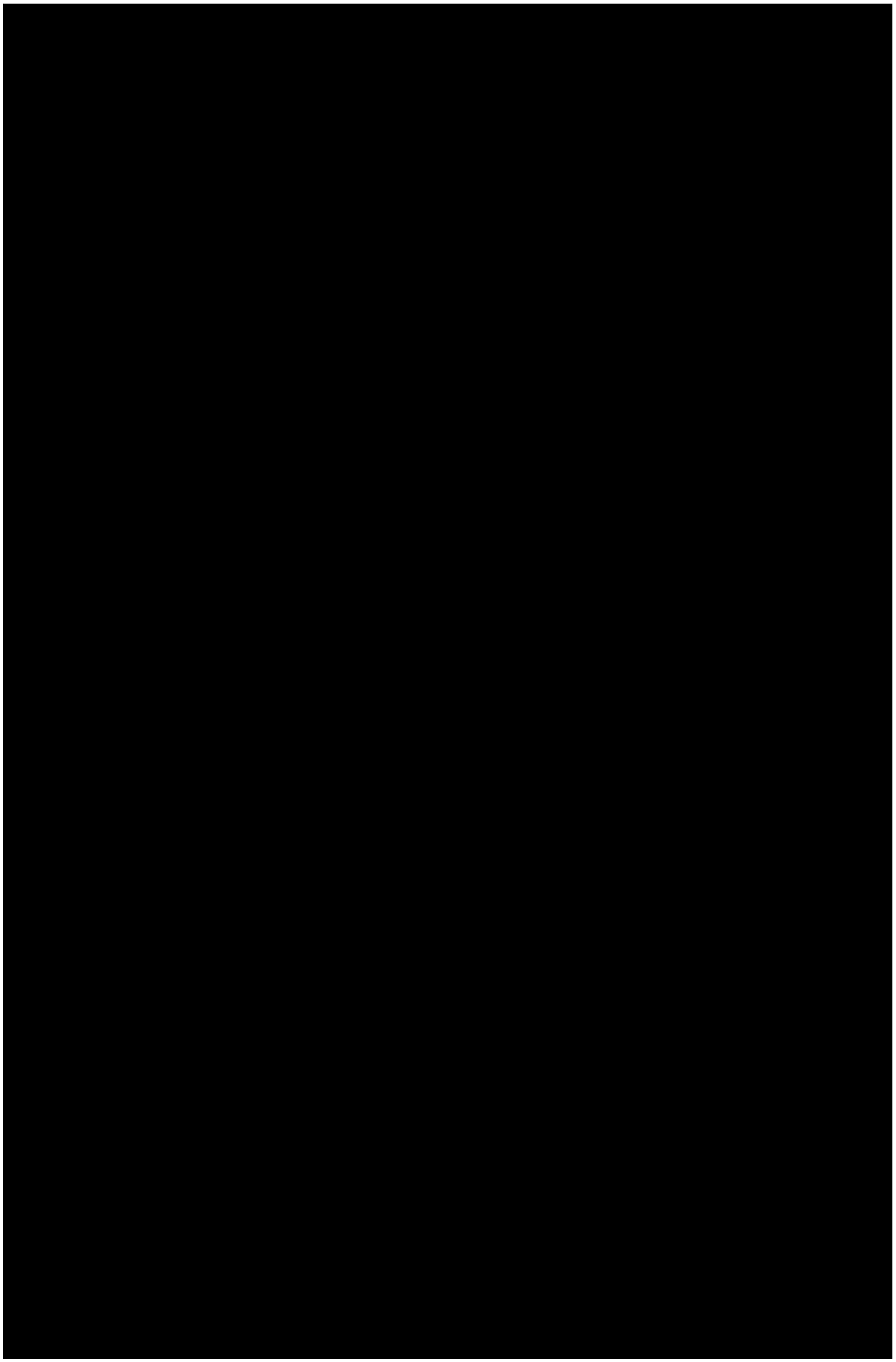
For further details regarding the EOGBM1-18 trial please see the current IB of EO2401.

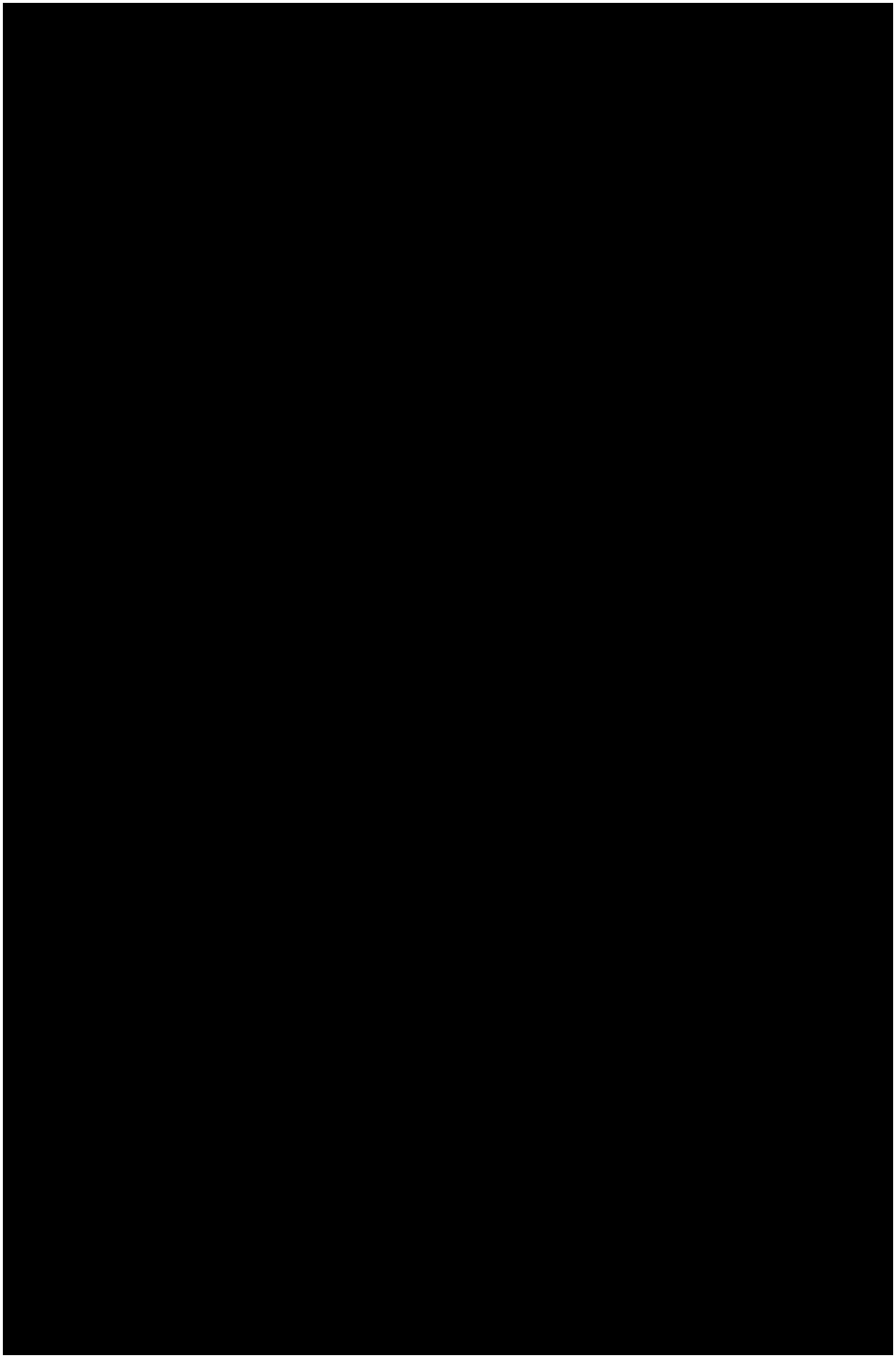
1.3.3 EO2401 clinical information & Rationale and high-level outline for global amendment #2 (leading to protocol EOADR1-19 version 3)

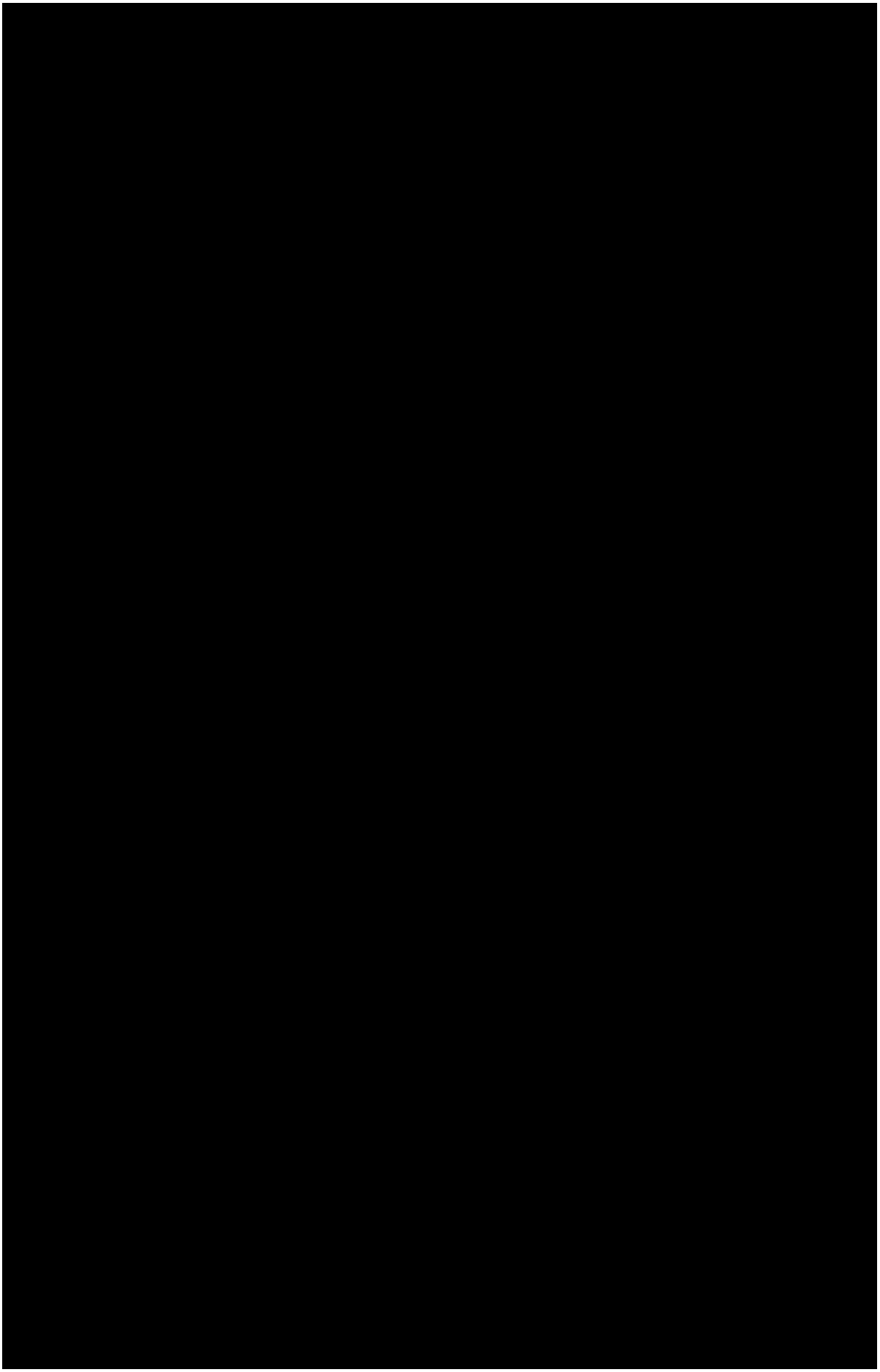
To date, no final human trial data is available on safety and efficacy of EO2401, as the early clinical development trials are still running.

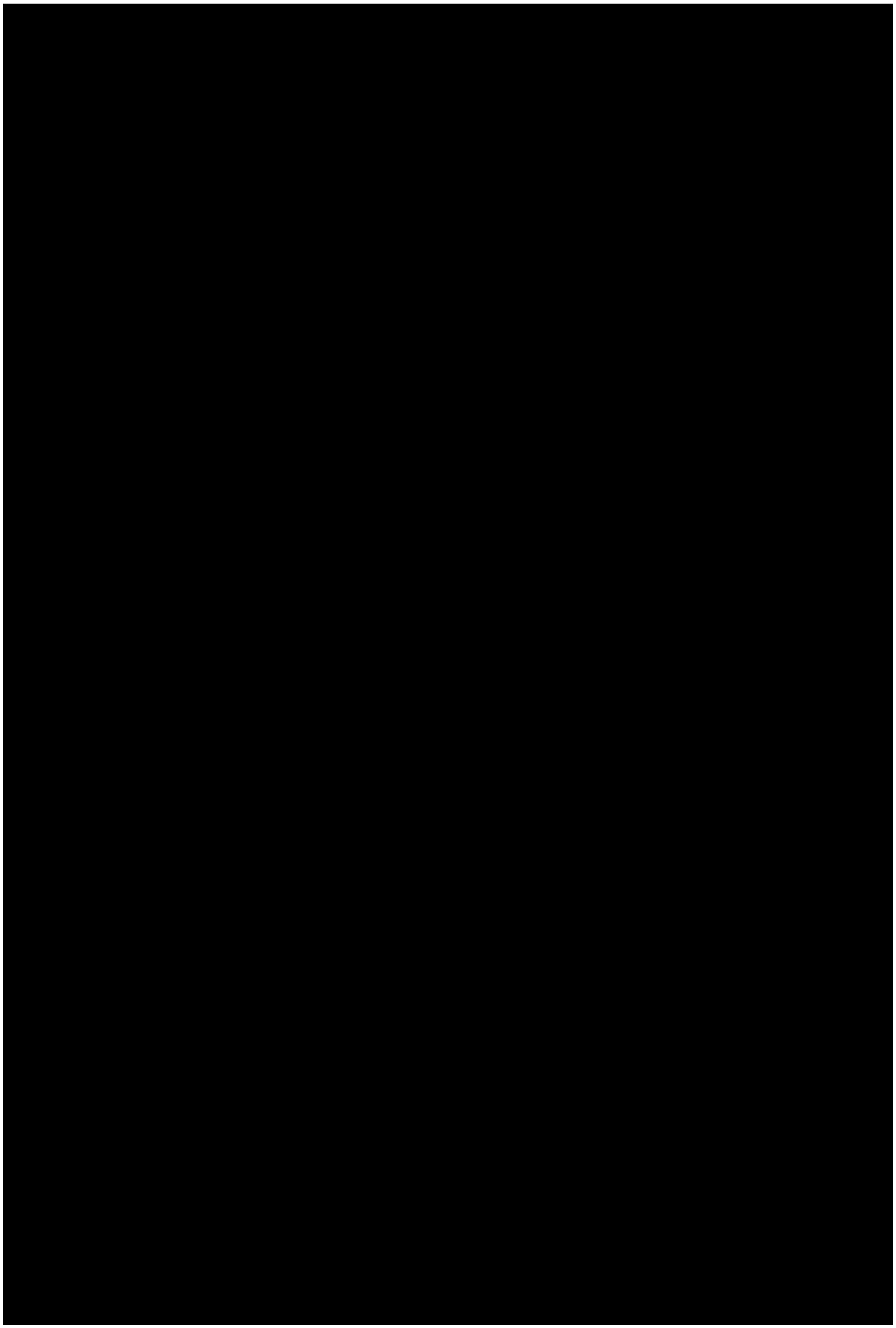
As described in Section 1.3.2, EO2401 is evaluated in two phase 1/2 trials running in parallel, trial EOGBM1-18 in patients with recurrent glioblastoma (EudraCT#: 2018-002279-16; IND#: 19,229), and trial EOADR1-19 in patients with adrenal tumors (adrenocortical carcinoma [ACC], and malignant pheochromocytoma/paraganglioma [MPP]) (EudraCT#: 019-003396-19; IND#: 19,229); and both trials are conducted under the supervision of IDMCs.

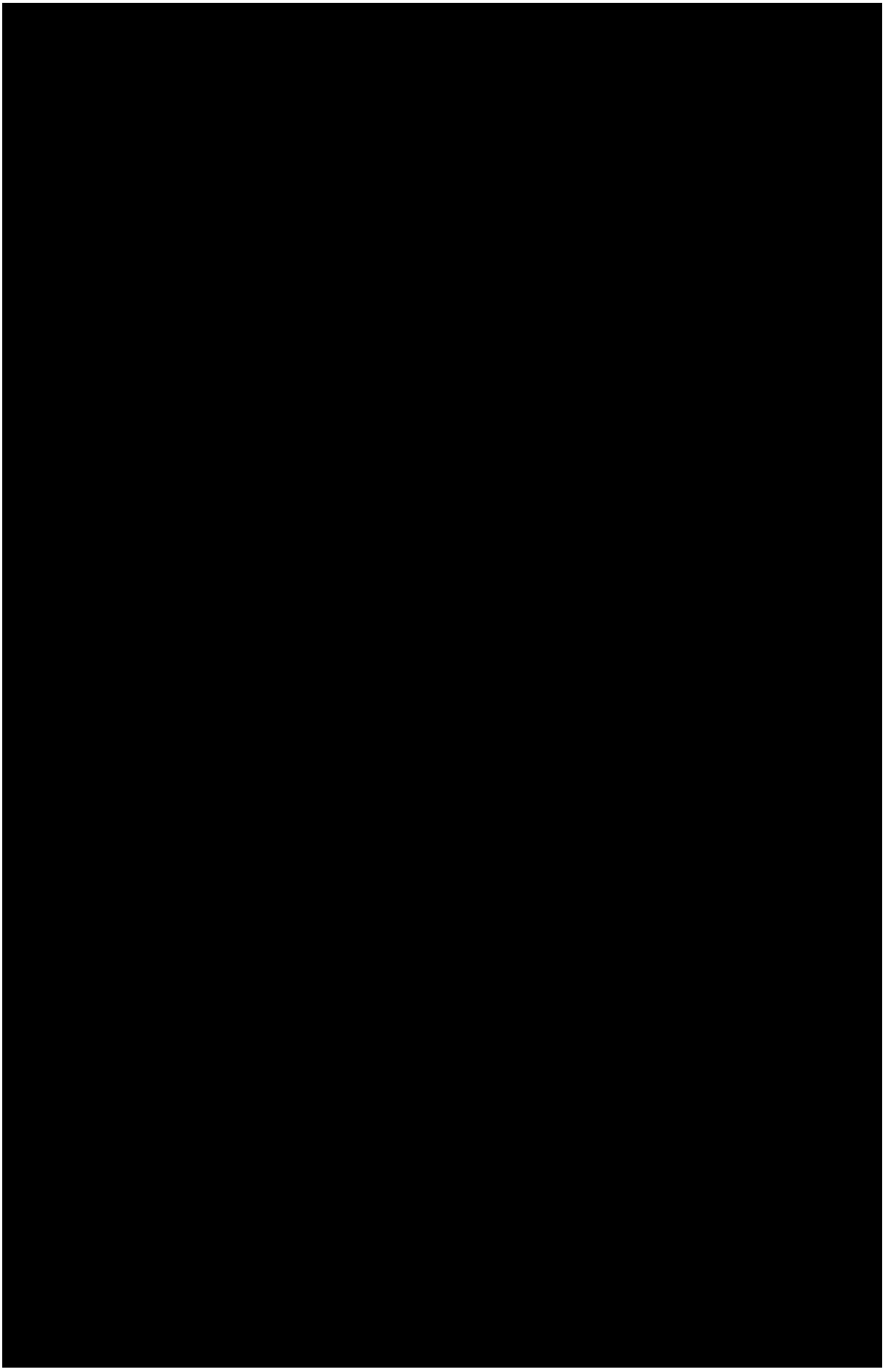
[redacted]

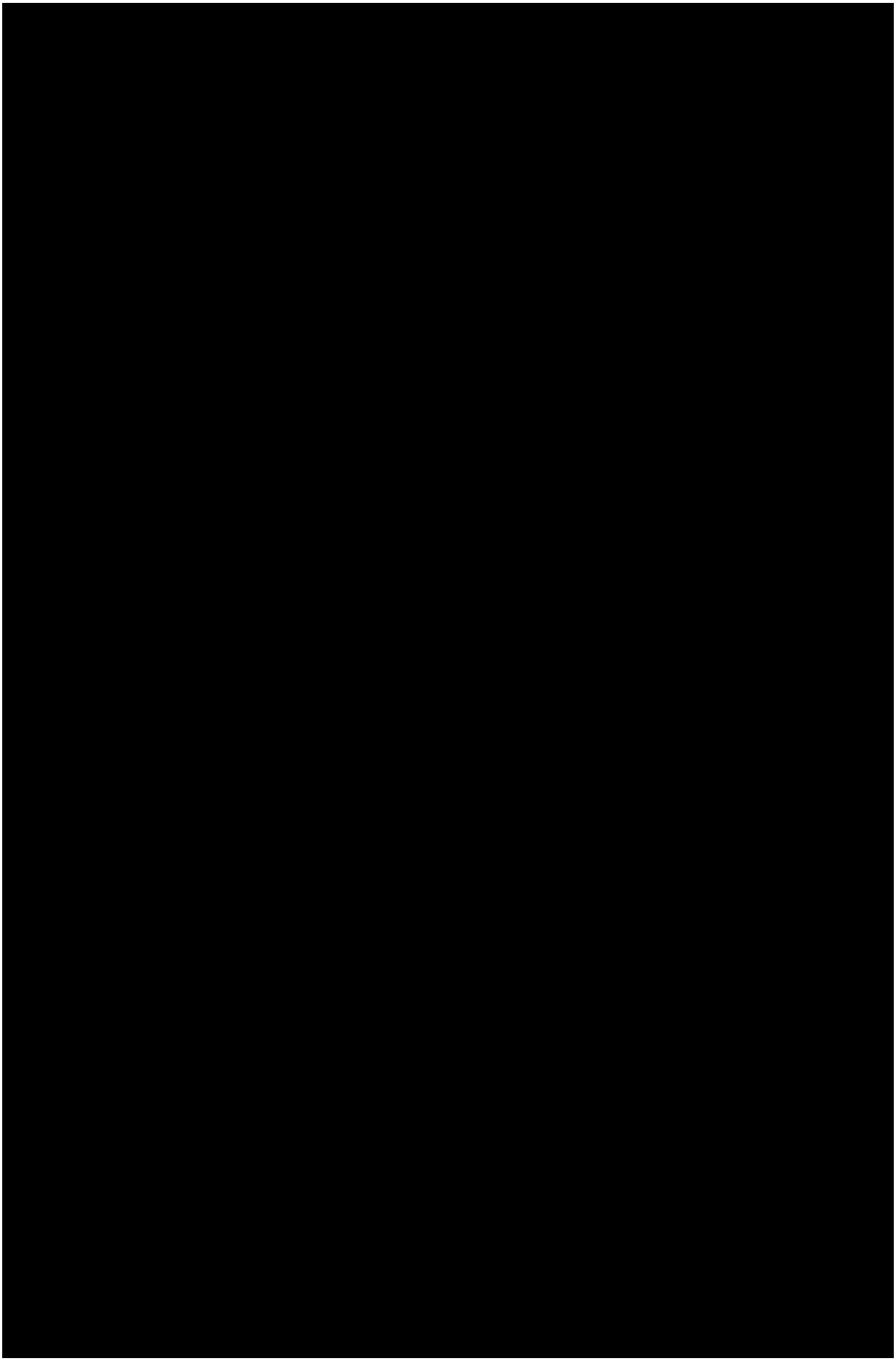


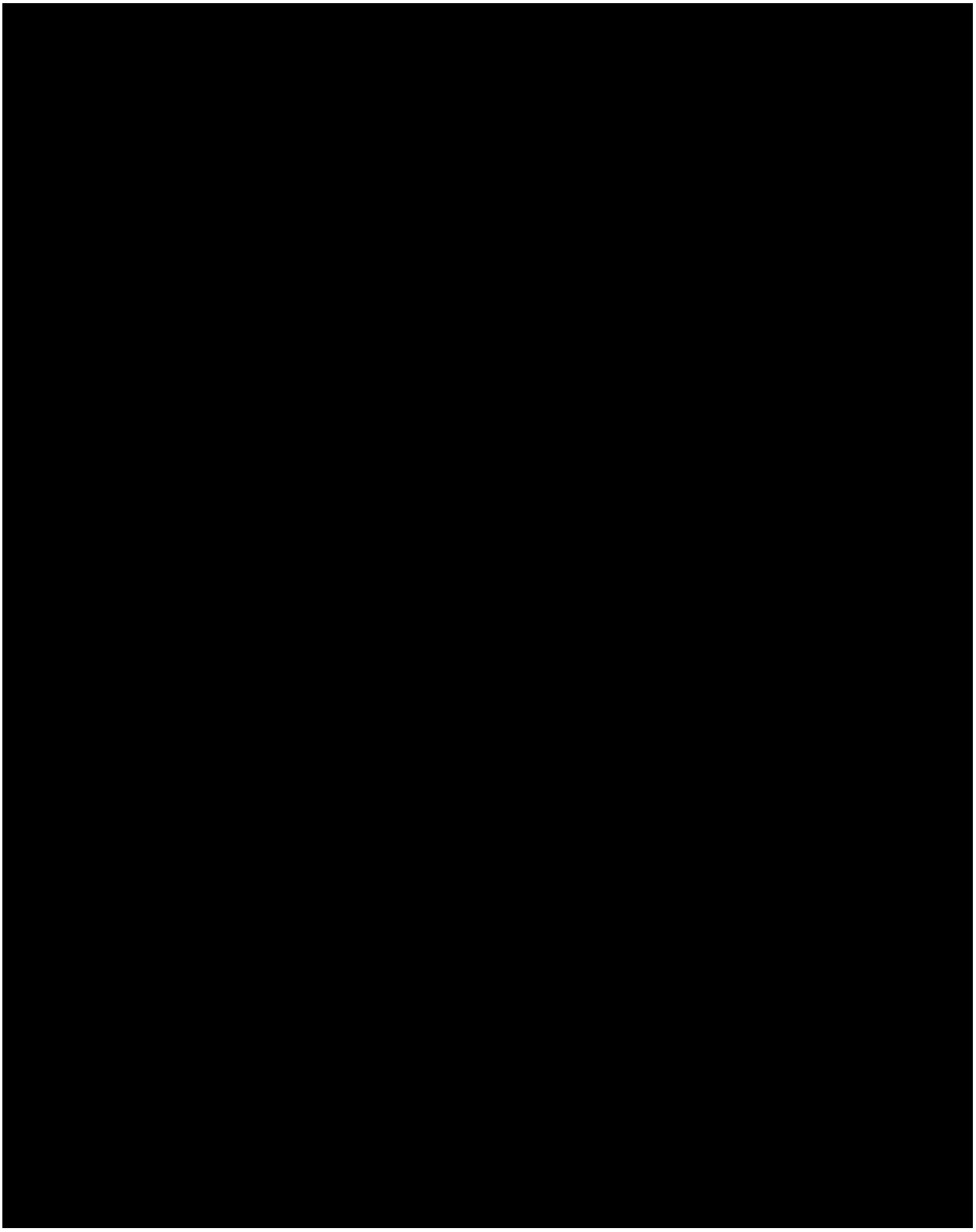












1.3.4 Protocol amendment 2 leading to Protocol version 3.0 overview

The amendment is included in detail in the following protocol sections, and summarized at a high level in the following:

- Adjustment of inclusion/exclusion criteria for Cohort 2A to exclude, to the largest possible extent, further treatment of patients who seems to not have any appreciable benefit from treatment with EO2401/nivolumab. The adjusted criteria in short format are:
    - prior treatment with mitotane (yes)
    - ECOG performance status (≤1)
    - time from primary diagnosis of ACC (> 9 months)
    - maximum individual lesion size (≤125 mm)
    - number of organs involved by ACC (≤ 3)
    - lymphopenia (≤ grade 1)
- Randomized extension of Cohort 2A [redacted]
    - Combination treatment with EO2401 plus nivolumab (Cohort 2A-I) = 43 patients.
    - Treatment with EO2401 monotherapy (Cohort 2A-II; same schedule for EO2401 as in combination treatment) = 11 patients.
    - Treatment with nivolumab monotherapy (Cohort 2A-III; same schedule for nivolumab as in combination treatment) = 11 patients.

[redacted]

- Inclusion of immune testing in all running cohorts including EO2401 also at visit V2; rationale is to investigate how early an expansion of T cells occur to further

advise on possible schedule optimizations [redacted]

- Inclusion of testing of lactate dehydrogenase (LDH) as part of blood chemistry testing in all running cohorts, and also retrospective collection of the parameter at least at baseline for prognostic scoring in all patients.
- Exclusion of stool sampling for patients in the randomized extension of Cohort 2A, except for those patients who specifically consent to paired tumor biopsies; for such patients stool sampling for microbiome analyses will still be taken at baseline. [redacted]
- Adjustment of planned patient number in Cohort 3, from current 30 patients (with a target of 15 patients each for Cohorts 3A and 3B) to approximately 20 patients [redacted]

[redacted]

In addition to above, two further types of changes are included in global amendment 2 (leading to EOADR1-19 version 3):

- Recommendations regarding vaccination against SARS-CoV-2/COVID-19 as applied in trial EOADR1-19 via investigator communications (current text is from a letter to the investigators 2021-NOV-24), are included in Section 6.9.2.
- Updates of management principles for immune-related adverse events as outlined in Section 6.4.1, based on the most recently available labelling documents for Opdivo [42] and standard protocol guidance from Bristol-Myers Squibb (marketing authorization holder for nivolumab).

1.3.5 Benefit/risk assessment and description of and justification for the route of administration, dosage, dosage regimen, and treatment period

The two primary malignancies which can arise from the adrenal gland (or chromaffin cells located in extra-adrenal paraganglia), i.e. ACC and MPP, are tumors with quite different characteristics from many biological perspectives. However, from a general treatment perspective they show similarities:

- Surgery is of utmost importance, and the only curative treatment modality, provided radical surgery can be performed.
- Treatment options for patients with unresectable disease are few and new treatment options have not been added recently.
- The currently available first line therapies in both entities are only achieving tumor regression in approximately one in four patients at the cost of a relatively high toxicity burden, especially from the utilized polychemotherapy (EDP-mitotane first line objective response rate 23% in ACC; CVD therapy tumor size reduction in 25% of patients with MPP; in addition 50% of patients with MPP might be eligible for ^{131}I-MIBG therapy based on uptake, if they have limited tumor burden and not rapidly progressive disease, objective responses with ^{131}I-MIBG therapy were observed in 22–47% of patients), leading to the notion that even first line treatments might be challenged by new treatment concepts.

- Even though the median survival in patients with MPP (approx. 6-7 years) is longer than for patients with ACC (around 12-15 months when at a stage of need of first line chemotherapy treatment per the FIRMACT trial), half of the patients with MPP have progressive disease within one year and require active management [58]. Thus, it seems fair to conclude that for both entities there are unmet medical needs with respect to new efficacious systemic therapies.

To date, no final human data is available on safety and efficacy of EO2401 since the early clinical development trials as outlined in Section 1.3.2 are still running. However, preliminary data is available from the current trial EOADR1-19 and a trial including patients with recurrent glioblastoma (EOGBM1-18), showing a safety profile consistent with expectations, i.e. the added event type by EO2401 to the background treatments (nivolumab and nivolumab/bevacizumab, depending on trial and cohort) are the expected events of local administration site skin reactions (e.g. erythema, induration, and pain); see further Section 1.3.3.

The current trial as proposed is including a combination treatment of EO2401 and nivolumab (anti-PD-1 blocking agent), a concept with a very comprehensive biological rationale and pre-clinically indicated strong efficacy benefit as compared with the utilization of EO2401 as monotherapy (Section 1.3.1 and the current version of the EO2401 IB).

For details regarding the non-clinical safety evaluations of EO2401 see the current IB of EO2401; in summary:

- Neither off-target (non-specific), nor other adverse effects that may occur following binding of the peptides included in EO2401 to HLA molecules have been observed in HLA-A2 transgenic mice.
- It has been demonstrated in wild type mice that activation of T-cells by vaccination with mouse microbial-derived peptides does not cause toxic immune reactions against microbial gut contents; the obtained results suggest a good tolerability and no obvious sign of toxicity.
- Assessment of the safety of the concomitant administration of microbial-derived peptides with anti-PD-1 showed that the combination of mouse bacterial peptides with anti-PD-1 revealed no sign of toxicity; confirming that induction of a systemic immune response against a bacterial antigen does not affect gut homeostasis.

Anti-PD-1 blockade has been applied in patients with ACC and MPP and shown to have a similar safety profile as in other patient groups treated with this type of compounds, and in addition the potential to also have efficacy in individual patients (see Section 1.2).

From a risk perspective, based on the above and already achieved clinical experiences utilizing efficacious immunization approaches together with anti-PD-1 blockade [59], the assessment of the Sponsor, before the start of trials EOGBM1-18 and EOADR1-19 was, and based on preliminary data as outlined in Section 1.3.3, continues to be that the safety profile of the combination of EO2401 and nivolumab will be similar to the well described safety profile of nivolumab, to which no addition of serious additional non-specific off-target safety issues are expected. However, provided EO2401 induces an efficacious expansion of T cells specific for the targeted TAAs with ability to kill tumor cells expressing one, or multiple, of these TAAs, it cannot be ruled out that such antigen specific T cells might also recognize these antigens if expressed, and presented by MHC, at a high enough level on non-cancerous cells. Thus, if killing of tumor cells by T cells expanded by EO2401 immunization could occur, normal cells might also be killed by such T cells leading to symptoms like for the immune-related adverse reactions which might be seen during treatment with anti-PD-1 (or

similar compounds) alone (e.g. see the European SmPC or the US PI for nivolumab [42, 43]). It can be assumed that the immune-related adverse reactions seen during treatment with e.g. nivolumab are driven by self-reactive T cells, even if in the case of nivolumab the specific targets for these T cells are not known due to the non-specific mode of action of nivolumab in relation to antigen-specificity. Thus, the mechanism for possible normal tissue toxicity by EO2401 immunization is assumed to be the same as for nivolumab induced immune-related toxicity and by that safety measures have been instituted which directly follows the measures already well established for nivolumab and similar compounds (see Section 6.4). Considering the disease under investigation, i.e. adrenal tumors, and the expression of the targeted antigens in adrenal tissue (higher in tumor than in normal tissue; see Section 1.3), a safety measure to monitor for adrenal function (serum cortisol) has been instituted in addition to the standard safety parameters usually used in trials of immunotherapy compounds.

In addition to above, as for all immunization approaches some degree of mild to moderate local injection events of short duration might be expected for EO2401; the expected addition of local injection events to the safety profile of nivolumab utilizing the combination EO2401/nivolumab has been confirmed (see Section 1.3.3). Also, as for all administrations of immunogens, it cannot be excluded that immediate type allergic reactions might occur at injections of EO2401; special precautions are outlined for this type of potential reactions

In this trial subcutaneous (SC) administration of EO2401 is applied based on the general notion that this is a well-accepted, and clinically easy and reproducible way for vaccine administration. The peptide dose utilized in non-clinical testing of EO2401 and its components was

The dosage regimen for EO2401 including a priming schedule was chosen to induce an efficient immune response (every 2 weeks, 4 times), and to avoid exhaustion by a 4-week

break thereafter. The priming period is followed by a boosting period with injections every 4 weeks to maintain an adequate immune response. The prime-boost approach was based on general immunization concepts, especially from the field of therapeutic cancer vaccines.

Considering the nature of this early development trial, the maximum length of the treatment period was chosen in an exploratory way; it is assumed that especially the immune monitoring findings from the initial trials (both EOGBM1-18 and EOADR1-19) might guide future adjustments of the treatment duration with regard to immunizations (possibly also the schedule of the boosting period). Stopping treatment early at confirmed progression (immune therapy response criteria will be used) or individual patient safety concerns is considered standard oncology practice.

Nivolumab route of administration, dosage, dosage regimen, and treatment periods are aligned with current labeling for other indications, since there is no label specifically for adrenal tumors [42, 43]. Of note, the interval between nivolumab administrations is adjusted according to the administrations of EO2401, i.e. with every 2 weeks administrations 4 times followed by every 4 weeks during the boosting period of EO2401. The nivolumab schedule of administration was selected based on the wish to minimize the number of necessary patient visits.

The expected safety profile of EO2401 in combination with nivolumab as outlined above is considered supportive of the initiation of an early clinical development program. Thus, given the potential for a therapeutic benefit of nivolumab alone in individual patients with adrenal malignancies (Section 1.2), tumor model data showing synergy of microbiome-derived peptide immunization and anti-PD-1 in combination (Section 1.3.1), and the foreseen safety profile of the combination of EO2401 and nivolumab as outlined above, the assessment of the Sponsor is that the benefit/risk ratio is positive for the start of the proposed phase 1/2 trial EOADR1-19.

The findings from the early part of trial EOADR1-19 described in Section 1.3.3, including a satisfactory safety profile (i.e. expected profile and absence of emerging safety concerns), fast and strong induction of cytotoxic T cells targeted against tumor cells, and interesting clinical activity in a subpopulation of patients with ACC which could be retrospectively defined by clinical parameters, serves as the rationale for a second global protocol amendment to extend Cohort 2A (patients with previously treated ACC) for further assessment of safety and confirmation (or not) of the ability to adjust inclusion/exclusion criteria to avoid treating patients with ACC without appreciable benefit of EO2401/nivolumab. It is the Sponsors opinion that the findings presented in Section 1.3.3 from trials evaluating EO2401 in combination with nivolumab supports a positive benefit-risk for extension of trial EOADR1-19 for treatment of further patients according to the second global amendment (leading to EOADR1-19 version 3).

1.3.6 Rationale for global amendment #3 (leading to protocol EOADR1-19 version 4)

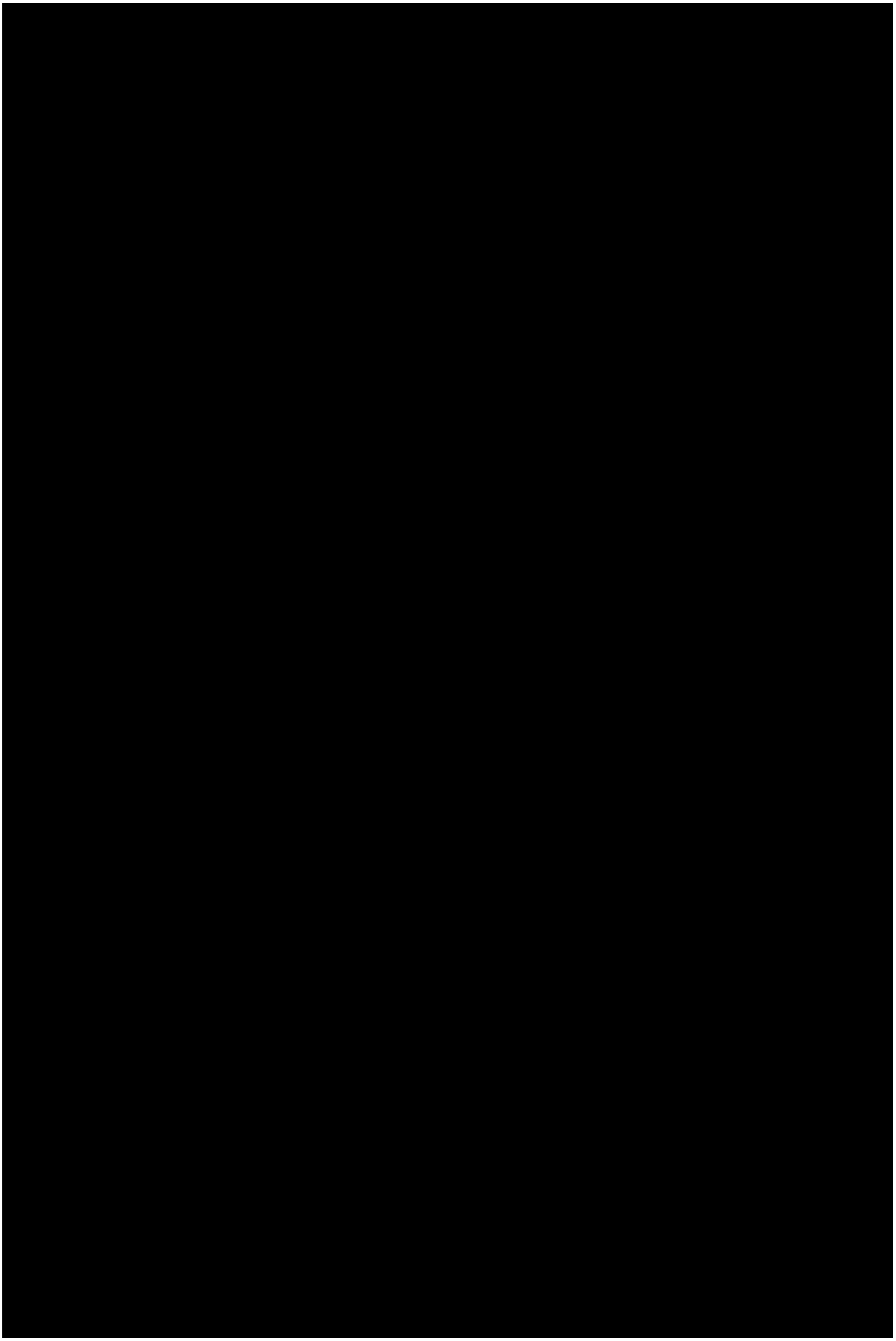
The rationale of the global amendment #3 (leading to protocol EOADR1-19 version 4) is as follows:

[redacted]

[redacted]

1.3.7 Rationale for global amendment #4 (leading to protocol EOADR1-19 version 5)

[redacted]



[redacted]

1.4 History of amendments

EOADR1-19 protocol version (date)	Key points of protocol version (only substantial changes listed)
Version 1.0 (12-SEP-2019)	For initial authority submissions

[redacted]

2 RATIONALE

2.1 Rationale for the study

Treatment options for patients with unresectable ACC and MPP are few and new treatment options have not been added recently for ACC; currently available first line therapy options including polychemotherapy in both entities are only achieving tumor regression in approximately one in four patients at the cost of a relatively high toxicity burden (Sections 1.1.3 and 1.1.4). However, for MPP a randomized clinical trial supporting the use of sunitinib as an alternative to chemotherapy was presented recently (ESMO 2021; see Section 1.1.4 [68]).

In any case, based on the facts that the median survival in patients with ACC is 12-15 months (first line polychemotherapy; FIRMACT trial), and that half of the patients with MPP have progressive disease within one year and require active management [58], it is considered that therefore both entities are unmet medical needs with respect to new efficacious systemic therapies.

Currently immunotherapy, including compounds of the anti-PD-1/PD-L1 group, is changing treatment paradigms in many tumor indications. Anti-PD-1/PD-L1 blockade has also been tested in ACC and MPP, and early data indicate acceptable tolerability. However, the efficacy in a large (for these indications) finalized trial [see Section 1.2] has not been overwhelming and different possible reasons for this have been discussed [21]. One relevant reason for immune resistance leading to low activity of PD-1/PD-L1 blockade in adrenal malignancies might be lack of enough T cells specific for antigens expressed by the tumor cells. A peptide-based therapeutic vaccination approach could counteract such a problem aiming at delivering immunogenic peptides corresponding to specific TAAs to patients. The goal would be to target the patient's antigen presenting cells to induce efficient presentation of cancer epitopes to T cells that in turn leads to an efficient sustained immune response against cancer cells expressing the same antigens at the tumor site.

In the past, despite promising pre-clinical results in animal models, the therapeutic cancer vaccination approach has not demonstrated unequivocal efficacy in patients. The lack of efficacy may be related to numerous factors including the status of the patient's immune system, the efficacy and specificity of antigen delivery, the lack of ability of T cells to infiltrate the tumor microenvironment, and the tumor's ability to escape immune-mediated inhibition. A definite key item for lack of efficacy is the possible in-ability of used "tumor antigens" to generate a strong immune response. The ability for antigens to induce strong responses depends on a number of factors, including the affinity for the MHC I or MHC II complexes, the capacity of the antigen to be recognized by the immune system as self or non-self, and pre-existence of T cell clones that are able to be efficiently reactivated by a vaccine boost and that leads to a durable immune response.

To counteract earlier problems with the antigens used for therapeutic cancer vaccinations, the concept behind the current trial includes an innovative microbiome-based approach for the development of therapeutic peptide cancer vaccines. Numerous peptides mimicking specific TAAs that are overexpressed in adrenal tumors have been identified in the human microbiome; such peptides can from an immunological perspective be considered as non-self. Specific peptides, further selected based on multiple parameters including high-affinity binding to MHC class I, have been shown to induce strong immune responses in non-clinical models, not only recognizing the microbiome-derived peptide used for immunization but also the nominal human TAA expressed by tumor cells (i.e. cross-reactivity have been shown; see the current version of the EO2401 IB).

Although tumor cell overexpressed TAAs are presented via the MHC class I receptors in the form of short peptide sequences (a prerequisite for the possibility to target the TAAs with T cells for tumor cell killing), these peptides are weak inducers of the immune system as they are self-epitopes for which (auto) reacting T cells (especially the most reacting ones) are naturally depleted through thymic deletion. However, the gut immune system, where around 70% of all T cells reside, is tolerant to the equivalent, non-self, microbiome-derived epitopes [44]; such epitopes are included in the microbiome-derived peptides developed to mimic adrenal TAAs as part of the compound EO2401. Furthermore, it has been demonstrated that the general human population has generated a memory repertoire of the mentioned tolerized T cells recognizing the peptides from the microbiome [45]. These T cells are surprisingly abundant, can be circulating, and display memory phenotypes, all properties that make them ideal to be targeted in a therapeutic vaccination protocol. The tolerance of the T cells can be overcome by repeated antigen challenges together with an adjuvant, which is the immunization principle proposed for the current trial (for supportive data of the use of adjuvant and a helper peptide at immunizations see the current version of the EO2401 IB).

Thus, the strategy behind the current trial is to identify and then use microbiome-derived peptides to reactivate their associated memory T cells, where the peptides are almost identical to portions of known TAAs (the microbiome-derived peptides are mimicking the known TAAs). The mimicking peptides will activate memory T cells that will cross-react with the nominal TAAs, thereby enabling an attack against the tumor cells.

Building on the already known mechanisms of action of anti-PD-1/PD-L1 blockade there is a strong support for the combination of EO2401 and such blockade, which in addition is supported by pre-clinical data obtained in a tumoral model (see Section 1.3.1 and the current version of the EO2401 IB). Thus, the combination of EO2401 and nivolumab is intended to increase the EO2401-specific T cell response infiltration in the tumor and the killing effects directed against the tumor cells. An initial response might also lead to antigen spreading through the killing of the tumor cells by EO2401 expanded T cells and the induction of responses to other antigens than the ones of EO2401.

In conclusion, novel therapeutic approaches are needed to enhance the treatment outcomes for patients with adrenal malignancies. An innovative option which is available to test in the clinic, and proposed with the current trial, is the above described microbiome-derived peptide therapeutic cancer vaccine approach in combination with anit-PD-1 blockade.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study objectives

3.1.1 Primary objectives

- ***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 ACC, and progressive 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 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 = patients with ACC who had prior systemic therapy for established locally advanced or metastatic disease*

3.1.2 Secondary objectives

The key secondary objectives of the trial:

- immunogenicity in relation to T cells of EO2316, EO2317, EO2318, and UCP2 that compose EO2401; T cell cross-reactivity with the human TAAs IL13Rα2, FOXM1, and BIRC5/survivin will also be evaluated *(Note, blood sampling for purification of PBMC will only be done at baseline for patients treated with nivolumab monotherapy in the randomized extension of Cohort 2A, and thus immunogenicity in relation to EO2401 will not be done in these patients except when applicable as internal controls)*,

The other secondary objectives of the trial are:

- objective response rate (ORR), time to response, and duration of response (DOR), and
- progression-free survival (PFS) and overall survival (OS).
- In addition, in the randomized extension of Cohort 2A safety and tolerability of EO2401/nivolumab assessed versus internal concurrent controls (groups of patients treated with EO2401 monotherapy and nivolumab monotherapy, respectively).

3.1.3 Exploratory objectives

The exploratory objectives include the exploration of:

[redacted]

[redacted]

3.2 Study endpoints

3.2.1 Primary endpoint

- ***The 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 NCI-CTCAE v5.0 grading system [60].
- ***The primary endpoint of the phase 2 part*** is the rate of patients without progression (according to iRECIST criteria [37]) 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.

** Cohort 2A = patients with ACC who had prior systemic therapy for established locally advanced or metastatic disease*

3.2.2 Secondary endpoints

The key secondary objectives of the trial are:

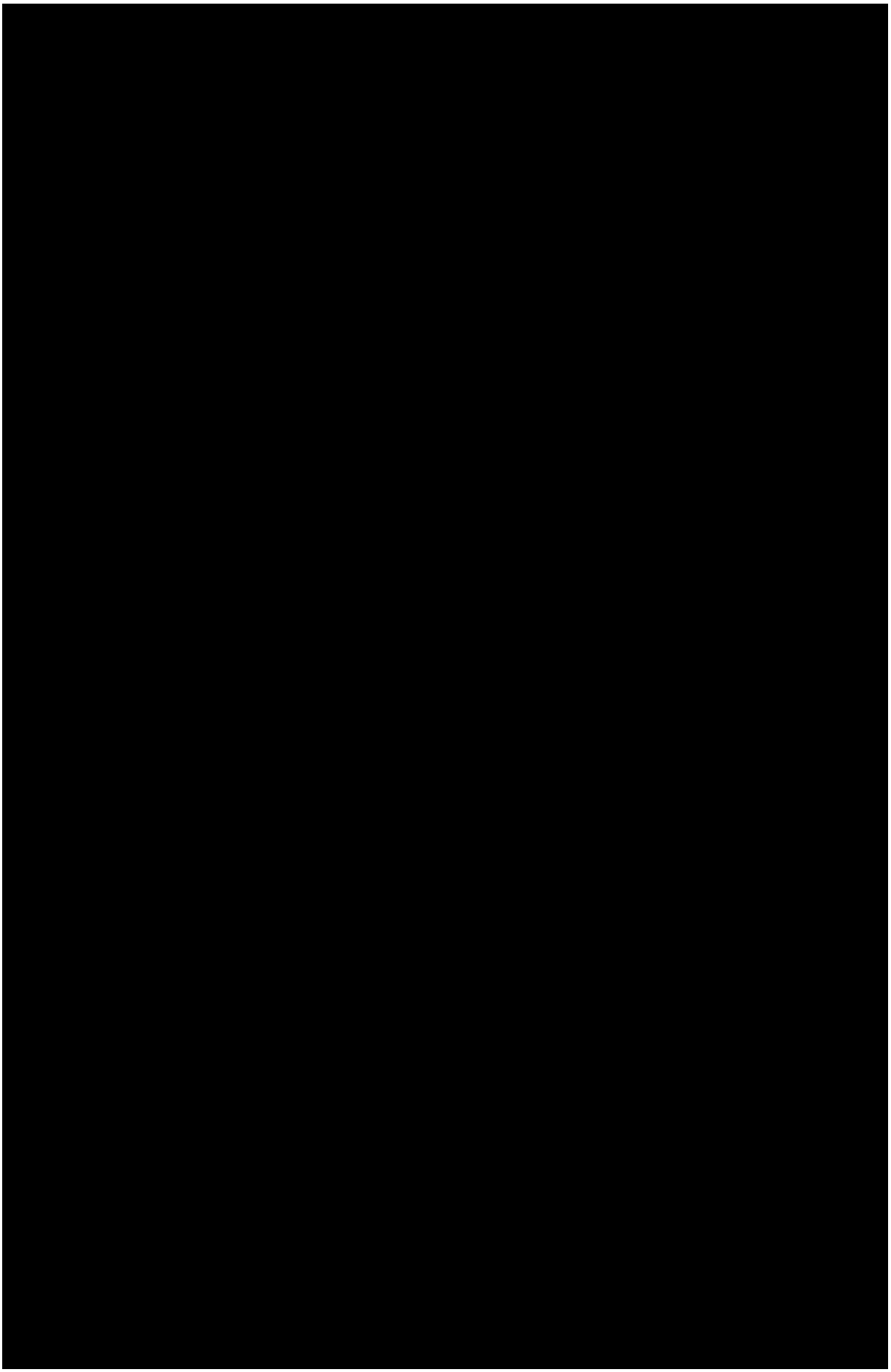
- Percentage of patients with shown immunogenicity [redacted] to EO2316, EO2317, EO2318, and UCP2 that compose EO2401 [redacted] Cross reactivities with the human TAAs IL13Rα2, FOXM1, and BIRC5/survivin will also be evaluated [redacted]

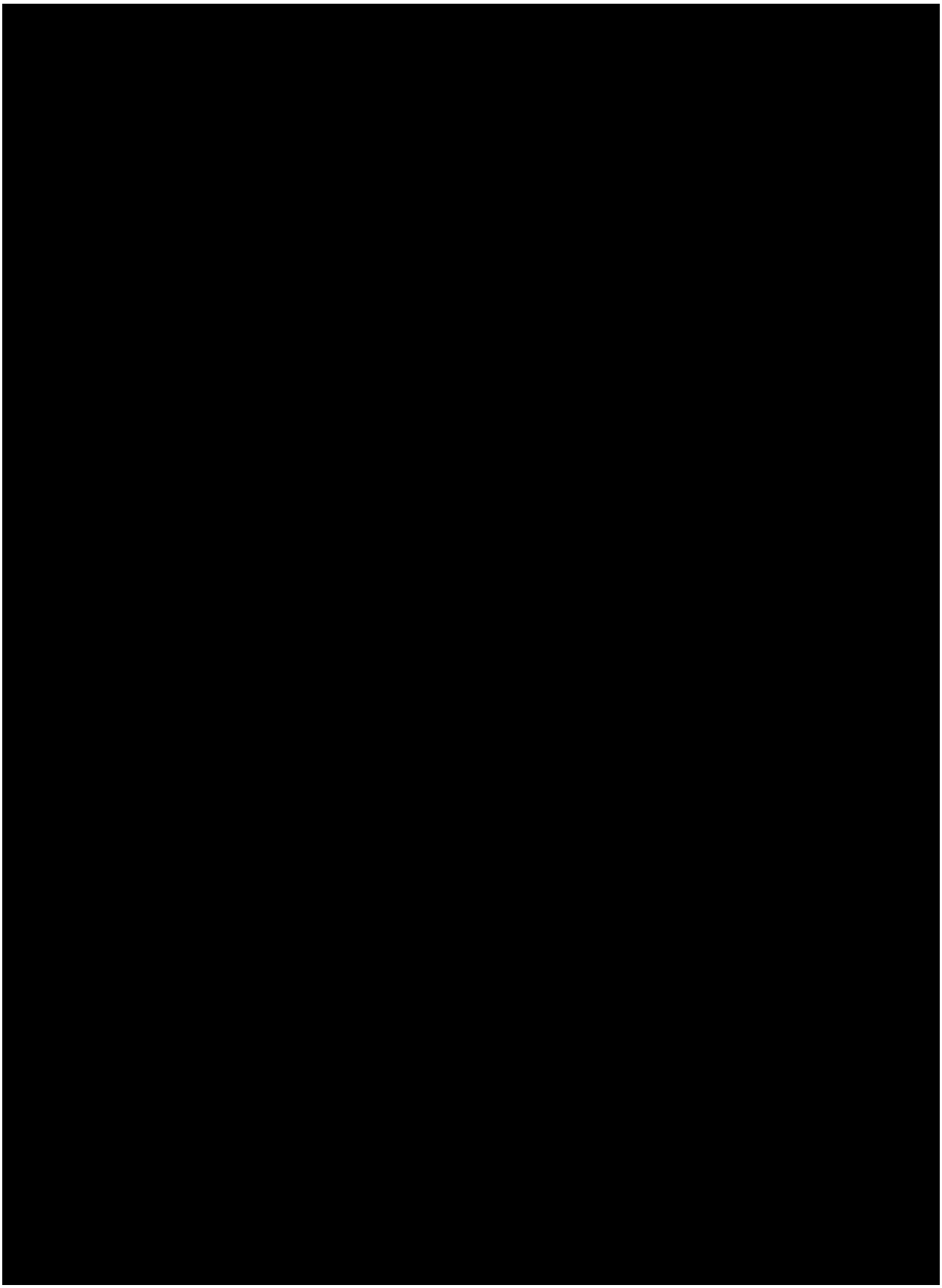
The other secondary endpoints of the trial are:

- ORR, time to response, and DOR as described by RECIST 1.1 [36] and iRECIST criteria [37]; see Section 12.1 for an outline of response criteria.
- 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.
- 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.
- In addition, in the randomized extension of Cohort 2A safety and tolerability of EO2401/nivolumab will be assessed versus internal concurrent controls (groups of patients treated with EO2401 monotherapy and nivolumab monotherapy, respectively), by incidences of adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs); AEs will be analyzed irrespective of relationship, and as related events.

3.2.3 Exploratory endpoints

[redacted]





4 STUDY DESIGN

4.1 Main study design

This is an open-label, multicenter, phase 1/2 trial to assess safety, tolerability, immunogenicity, and preliminary efficacy of EO2401 in combination with nivolumab for treatment of patients with unresectable, previously treated, and previously untreated, locally advanced or metastatic ACC, or progressive MPP.

An extension of Cohort 2A has been made via global amendment 2 (leading to protocol EOADR1-19 version 3.0) including patients with ACC who had prior systemic therapy for established locally advanced or metastatic disease as in the initial part of the study (Cohort 2A non-randomized portion), [redacted]

The primary objective of the open-label, randomized, extension of Cohort 2A is to confirm that the retrospectively (in the initial part of the trial) defined inclusion/exclusion criteria can exclude patients with a profile not benefiting from study treatment by determining the effect of EO2401/nivolumab on the progression-free survival rate at 6 months (per investigator/local site assessments. Patients in the extension of Cohort 2A will be randomized 4:1:1 to EO2401/nivolumab, EO2401 monotherapy, and nivolumab monotherapy; patients treated with EO2401 monotherapy and nivolumab monotherapy, respectively, will constitute internal concurrent controls to ensure assay sensitivity in the randomized extension.

4.2 Overall study design and plan

The trial is a 5-cohort study intended to recruit a maximum of approximately 120 evaluable patients in total:

- 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.

[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).

[redacted]

[redacted]

- Cohorts 3A (previously treated patients) and 3B (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 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).

[redacted]

Generally, patients evaluable for safety will include all patients who have received at least one dose of EO2401. Patients who are not considered evaluable for safety and did not receive any dose of EO2401 will be replaced (reasons for non-evaluability and pre-treatment safety will be reported; note the replacement strategy is also applied for the randomized extension of Cohort 2A). In addition, in Cohort 1, if for reasons other than safety a patient does not receive 2 doses of EO2401 and complete the [redacted] 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).

There will be a 2-stage consent procedure for the trial, including a first consent for HLA-typing (or the use of already available information in the patients file; such information even if based on testing before the screening period is acceptable) since a large proportion of the patients will not match the HLA-A2 prerequisite to receive the HLA-A2 specific EO2401 immunization compound. The reason for the initial minimized consent (related to the procedure of HLA-testing, and before testing also establishing based on available information that the patient has ACC or MPP, and an age ≥ 18 years) is to spare the necessity of all other testing for possible enrollment in the trial for patients who are not known to be HLA-A2 positive. The second stage of the consent procedure will be related to all other aspects of the trial including procedures.

Eligible patients who meet the inclusion criteria and do not meet any of the exclusion criteria and have provided informed consent per above will be enrolled in the study.

The procedures for cohort management and enrollment are outlined in a study specific Charter and also described in Section 6.8.

Patients' data will be collected until the clinical data cut-off (see section 4.3.1); the time will be dependent on when the patient is enrolled in the trial; survival follow-up will be collected until patient's death or sponsor's decision to stop the study(see Section 4.3); the time of study participation might be shorter in individual patients due to individual patient factors

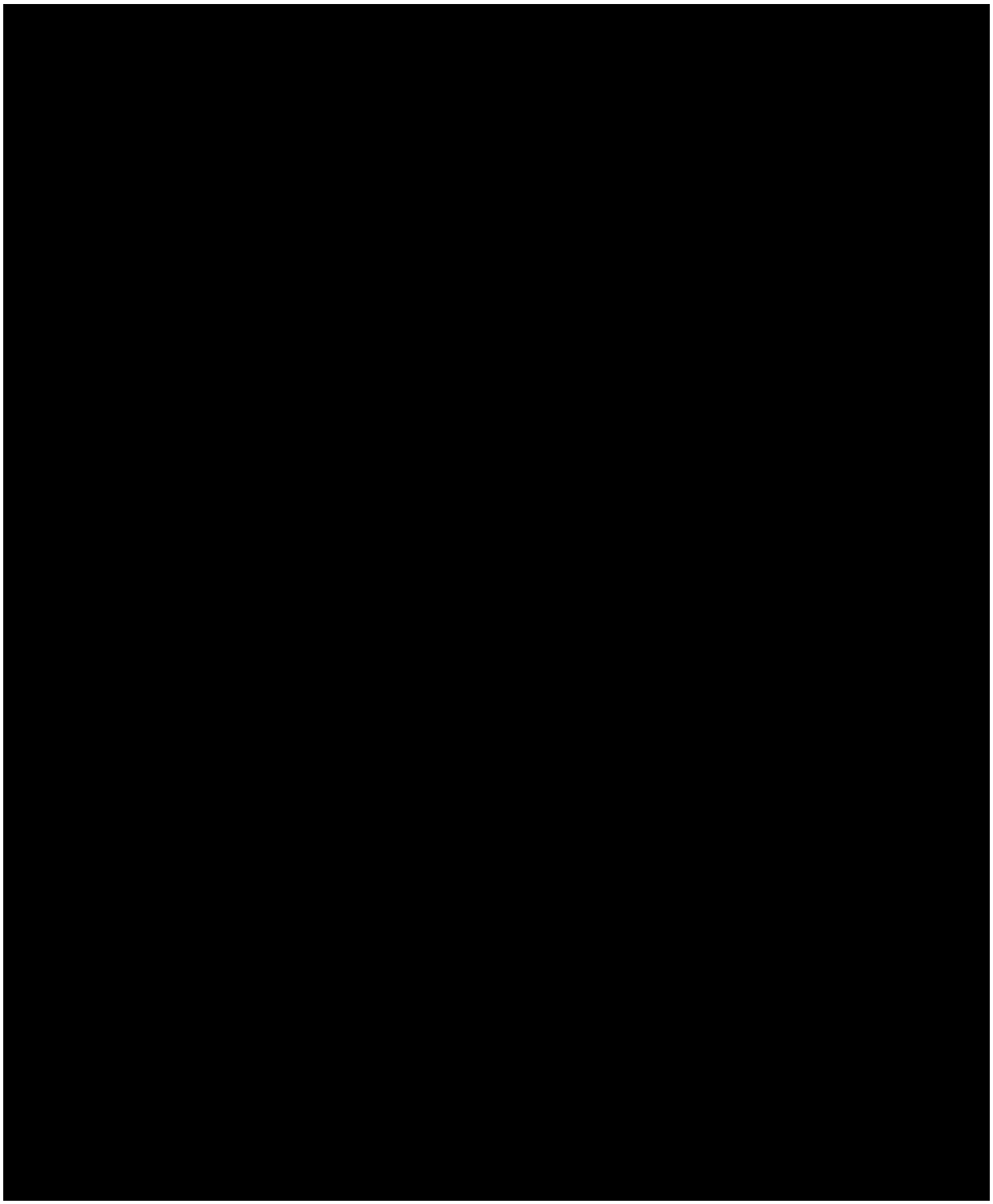
or general trial conduct decisions (e.g. planned trial termination when reaching a pre-specified follow-up time).

Study treatments will be administered until confirmed tumor progression (iRECIST criteria for confirmed tumor progression are to be used; see Section 12.1), intolerable toxicity, death, patient or Investigator decision, or planned or early termination of the study (see also Section 5.3). At the time of stopping study treatment, appropriate other treatment will be advised by the Investigator on an individual patient basis. The patient should continue study follow-up measures for as long as the individual patient consent for follow-up is not withdrawn, the site is open, and the study not terminated per plan, or early.

Of special note, unlike RECIST 1.1, the iRECIST criteria requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD. Thus, in the current trial, provided that the individual patient is tolerating the administered treatment adequately, it is allowed continuing trial treatment beyond progression as assessed by the RECIST 1.1. criteria for evaluation of progression according to the iRECIST criteria. Provided good tolerability of the trial treatment and lack of new important symptoms indicating clinical tumor progression the confirmatory scans might be obtained at the current trials planned 8 weekly tumor assessment timepoints.

In the context of confirmation of PD per iRECIST, and the timeline of confirmatory scans to be performed at least 4 weeks, but no longer than 8 weeks after iUPD, it should be specifically noted that in case of any signs of rapidly progressing disease establishment of PD and a following therapy switch should be made also earlier than 4-8 weeks after iUPD when necessary.

For all cohorts, and all patients during the whole trial treatment, the following safety rules will apply:



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

The schematic trial and cohort designs are presented in Figure 6 and Figure 7.

[redacted]

4.2.1 Cohort 1

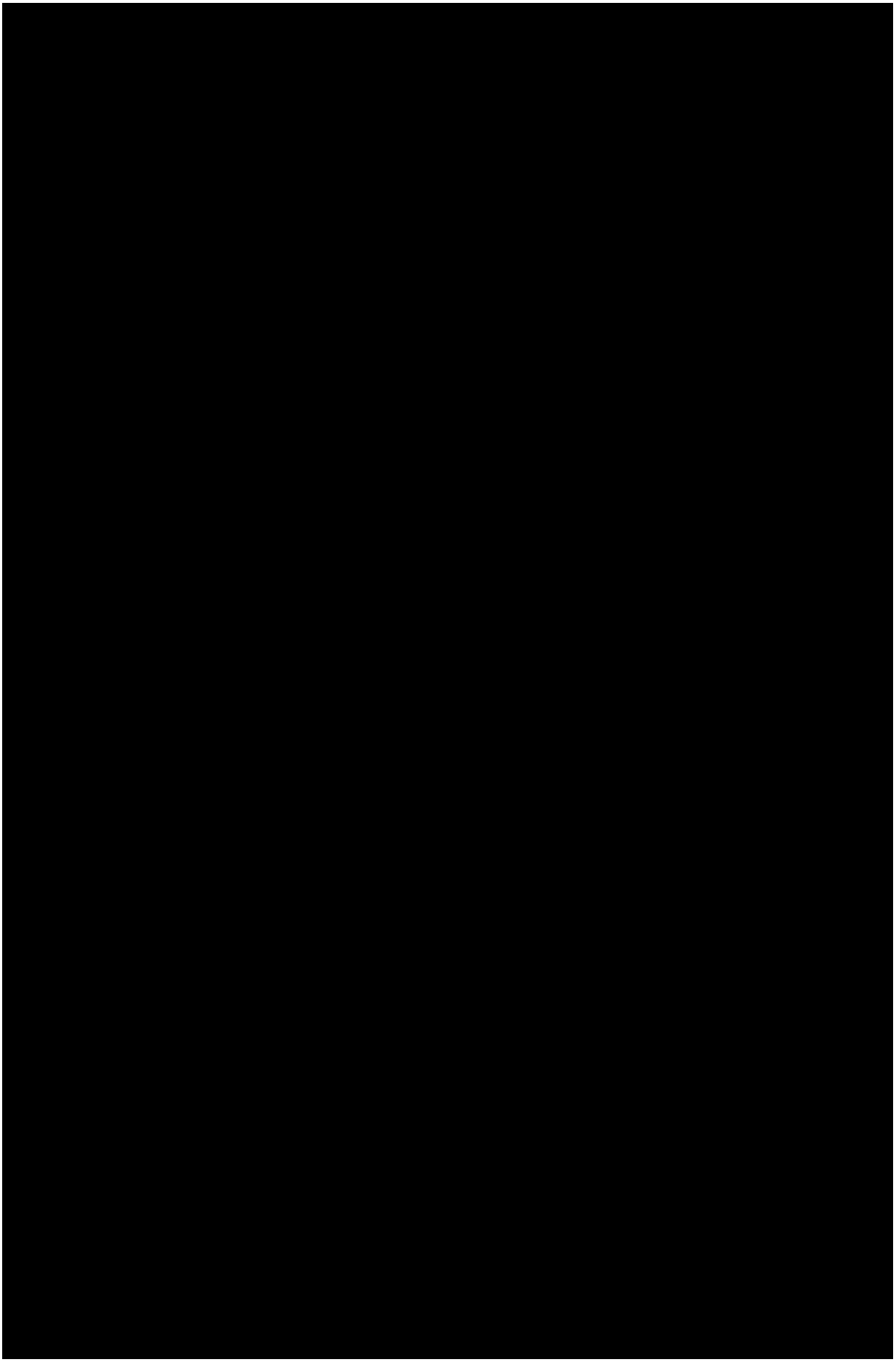
Cohort 1 will utilize a safety lead-in 3-by-3 design to assess safety and tolerability of EO2401 in combination with nivolumab in an initial safety evaluation period during 4 weeks (2 administrations of EO2401 in combination with nivolumab, each administration followed by a 2 week observation period; safety assessment [redacted] before administration of the third administration of EO2401 in combination with nivolumab), planned to be followed in each patient by further administrations of EO2401 in combination with nivolumab for further assessments of safety, tolerability, immunogenicity, and preliminary efficacy of the combination. [redacted]

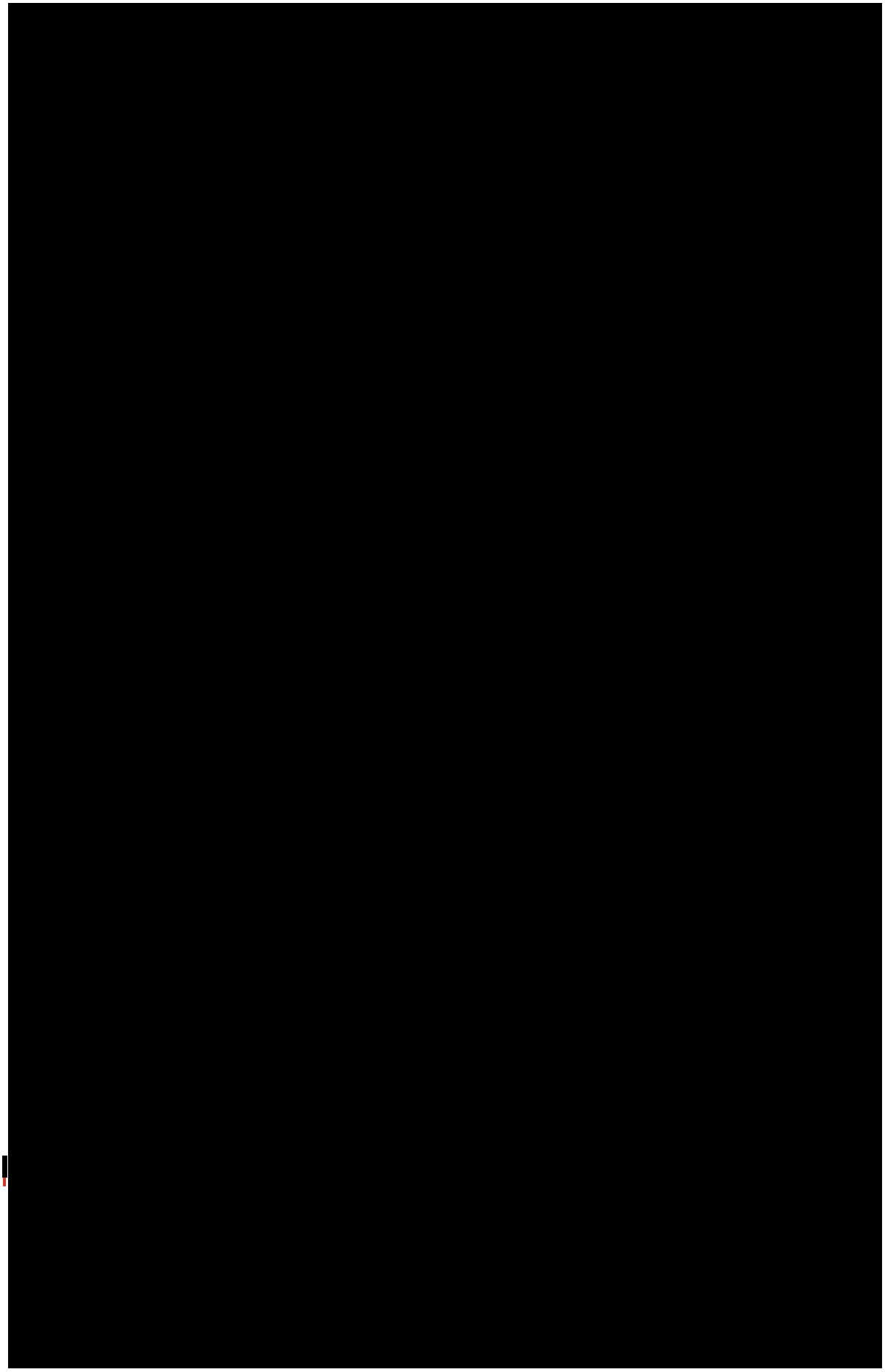
Priming injections of EO2401 will be started at the latest within [redacted] of the baseline tumor assessment. The initial dosing regimen will be 4 priming injections administered SC at 2-weekly intervals, followed by 4-weekly boosting injections of EO2401 starting at 4 weeks after the fourth priming injection (i.e. at Week 11). In sub-cohorts 1a and 1b, the full dose of EO2401 (i.e. 1 mL of emulsified EO2401 DP in adjuvant) will be administered, and if implemented, the sub-cohorts 1c and 1d will include half the dose of EO2401 (i.e. 0.5 mL of the emulsion will be injected).

Nivolumab will be administered as an intravenous (IV) infusion in combination with EO2401, starting from the first priming injection of EO2401 (see Figure 7; W1). The nivolumab infusion is to start 3 hours after the EO2401 administration. The dose of nivolumab should be 240 mg every 2 weeks for the first 3 administrations (see Figure 7; W1, W3, and W5), and from the fourth administration (see Figure 7; W7 and onwards) a nivolumab dose of 480 mg every 4 weeks is to be applied.

In Cohort 1, the patients' recruitment will be conducted in accordance with the following rules:

[redacted]





[redacted]

[redacted]

[redacted]

4.2.2 Cohorts 2A (non-randomized part), 2B, 3A, and 3B

Cohorts 2A (non-randomized part), 2B, 3A, and 3B are independent cohorts to recruit patients with ACC (Cohorts 2A and 2B) and MPP (Cohorts 3A and 3B), respectively. The cohorts are planned to be initiated following a decision by the Sponsor after a recommendation from the IDMC based on the review of the safety and tolerability data from Cohort 1 (see above).

Cohorts 2A (non-randomized part), 2B, 3A, and 3B will include administration of EO2401 in combination with nivolumab from the start of treatment in the individual patients for assessment of safety, tolerability, immunogenicity, and preliminary efficacy of the combination. A total of approximately 30 evaluable patients are planned for inclusion in Cohort 2 (irrespective of 2A or 2B, respectively) and a total of approximately 20 evaluable patients are planned for inclusion in Cohort 3 (irrespective of 3A or 3B, respectively).

[redacted]

[redacted]

The schedule of EO2401 and nivolumab administrations are the same in Cohorts 2A (non-randomized part), 2B, 3A, and 3B as in Cohort 1 (see Section 4.2.1). The dose of EO2401 will depend on the outcome of Cohort 1, i.e. it can be either full dose (1 mL of emulsified EO2401 DP in adjuvant), or half dose (0.5 mL of emulsified EO2401). The dose of nivolumab will be as outlined for Cohort 1 (see Section 4.2.1).

For all patients in Cohorts 2A (non-randomized part), 2B, 3A, and 3B, the general safety rules as described in Section 4.2 applies, [redacted]

4.2.3 Randomized extension of Cohort 2A

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 (patients who had prior systemic therapy for established locally advanced or metastatic disease) with an additional 65 patients (see Section 1.3.3 and Section 4.1).

In the randomized extension of Cohort 2A, patients will be randomized in a ratio of 4:1:1 to EO2401/nivolumab, EO2401 monotherapy, and nivolumab monotherapy, respectively. Patients treated with EO2401 monotherapy will constitute an internal concurrent experimental control. Patients treated with nivolumab monotherapy constitutes an internal concurrent control to the combination therapy to ensure assay sensitivity in the randomized extension, since there is information available from other trials.

The randomized extension of Cohort 2A will include administration of study drugs per the following:

- Cohort 2A-I (43 patients) = treatment with EO2401 in combination with nivolumab

[redacted]

- Cohort 2A-II (11 patients) = treatment with EO2401 monotherapy

[redacted]

- Cohort 2A-III (11 patients) = treatment with nivolumab monotherapy

[redacted]

For all patients in the randomized extension of Cohorts 2A, the general safety rules as described in Section 4.2 apply[redacted]

4.3 End of study

4.3.1 Planned study completion and study duration

.

The primary analysis of the study will be performed when the last patient included in the study will reach 6 months of study treatment; additional data will be generated:

[redacted]after the last patient under treatment has stopped the study treatment.

- Generally, all patients will be followed until death, or until a stable long-term survival outcome has been determined for the respective sub-cohorts of the study; the needed length of survival follow-up for each of the four sub-cohorts of the study differ, and the exact needed duration of survival follow-up time will be data driven. Decision regarding termination of survival follow-up for a specified sub-cohort will be taken by the Sponsor in consultation with the global coordinating investigator.

For administrative purposes, e.g. data cleaning including query resolution, document collection, etc., it is assumed that study sites will remain open approximately 2-3 months after the clinical cut-off.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed, except for the sites without any patients included which could be administratively closed by a close-out letter.

4.3.2 Early site closure and early study termination

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

Reasons for early study termination may include, but are not limited to:

- safety findings unknown to date (i.e. not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration), or significantly changed frequency, severity, or duration of known/anticipated/previously reported safety events,
- medical or ethical reasons affecting the continued performance of the study,
- difficulties in the recruitment of patients,
- regulatory authority request, and
- cancellation of development of EO2401.

The Investigator may initiate study site closure at any time, provided there is reasonable cause, and adequate notice is given to the Sponsor in advance of the intended site closure.

Reasons for the early closure of a study site by the Sponsor may include, but are not limited to:

- failure of the Investigator to comply with the protocol, the requirements of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines, and
- inadequate recruitment of participants by the Investigator.

4.4 Discussion of study design

This open label, multicenter, phase 1/2 trial, is part of an early development strategy including two similarly designed trials to primarily evaluate safety and tolerability of EO2401 in combination with anti-PD-1 blockade in diverse populations with malignancies (see Section 1.3.2). Secondary objectives include assessments of immunogenicity, and preliminary efficacy. In addition, multiple exploratory objectives to further support the understanding of microbiome based therapeutic cancer vaccination are also included in the trial.

Adrenal malignancies are very rare disease entities with an unmet medical need making any clinical trial design potentially challenging (see Section 1.1 and Section 2.1). However, patients with these diseases are usually treated at highly specialized centers, usually responsible by governmental decisions or clinical practice for larger regions. Thus, one prerequisite for efficient recruitment is present (specialized center participation in a multicenter setting) and by the study design in the proposed trial, a second prerequisite, might be achieved; broad possibilities for recruitment (i.e. both types of adrenal malignancies, ACC and MPP, and accepting both previously untreated and previously treated patients). It is judged that accelerated learning of the impact of the trial treatment can be achieved by the proposed 5-cohort design, including one common initial cohort for safety and tolerability assessment, followed by disease entity and population specific cohorts for further assessments.

It is judged that the early development nature of the trial makes an open label design appropriate. Also, considering that the aim of the development of EO2401 is to define a treatment schedule including EO2401 and anti-PD-1 blockade it is judged that for the current trial in adrenal malignancies it is adequate to immediately target the combination, i.e. to not include any EO2401 monotherapy part in Cohort 1. In the companion early development

trial, EOGBM1-18 in patients with glioblastoma, there is a period of EO2401 monotherapy before initiation of anti-PD-1 blockade in the safety-lead-in cohort.

For safety and tolerability, the main assessment items in the trial, the selected design is judged to have the possibility to stringently evaluate both early and late toxicity, of importance for an immunization approach, via the demand of thorough assessments of related Grade 3/4 AEs for all patients in all cohorts throughout all study treatments (see general safety rules in Section 4.2). Also, beside the active safety oversight of the trial by the Investigators (and their teams) in collaboration with the Sponsor via the Medical Monitor (with associated team), an IDMC will support the safety monitoring and give recommendations for possible actions in relation to their assessments of safety events.

[redacted] a key parameter for evaluation in the trial is to analyze EO2401-induced immunity and the tests for such analyzes [redacted] demand [redacted] blood for adequate tests to be run [redacted] The future development of EO2401 will be directed by the outcome of the analyses of induced immunity in the early development trials.

Preliminary efficacy is also to be assessed in the trial and as indicated RECIST 1.1 [36] and iRECIST [37] criteria will be used for response assessments (local evaluations of response parameters are going to be utilized considering the early development nature of the trial). The basis for this decision is that the novel mechanism of action of the compounds used in the current trial, EO2401 in combination with PD-1 blockade, i.e. a treatment combination aiming at immune and T cell activation, is postulated to lead to unusual patterns of response that might resemble tumor flare [36]. In early trials of immune-based therapeutics in melanoma, investigators described unique response patterns, termed pseudoprogression. Some patients whose disease met the criteria for disease progression based on traditional response criteria such as RECIST (an increase in the sum of measures of target lesions, unequivocal increase in non-target disease, or the appearance of new lesions) were noted to have late but deep and durable responses [36]. Therefore, response and progression in this trial will be evaluated using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee [36] as well as the modified iRECIST guidelines [37].

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 a randomized phase 2 portion of the trial for patients with ACC, by extension of Cohort 2A (patients who had prior systemic therapy for established locally advanced or metastatic disease) with an additional 65 patients which becomes the main phase 2 part of the trial (see Section 1.3.3 and Section 4.1). The randomized extension of Cohort 2A is intended to confirm that the retrospectively defined inclusion/exclusion criteria developed based on data from the initial part of the trial, [redacted] Patients will be randomized in a ratio of 4:1:1 to EO2401/nivolumab, EO2401 monotherapy, and nivolumab monotherapy, respectively. Patients treated with EO2401 monotherapy will constitute an internal concurrent experimental control. Patients treated with nivolumab monotherapy constitutes an internal concurrent control to the combination therapy to ensure assay sensitivity in the randomized extension, since there is information available from other trials.

Considering the size of population which can be considered for recruitment to a further assessment of EO2401/nivolumab based on findings in the initial part of the trial, [redacted] design must be very pragmatic to make any assessment possible. A design which has been used, and accepted in the medical community, to support a changed standard of care in the other adrenal tumor indication, i.e. MPP, has, after adaptation to the specifics of trial EOADR1-19, been applied in the global amendment 2 [68; see also Section 9.4]. The use of the individual components of the combination of EO2401/nivolumab as internal concurrent controls makes it possible to also extend the safety assessment of the combination, and the utilization of nivolumab as an anti-PD1 blocking agent gives an opportunity to use literature information in establishing assumptions for basic parameters in the statistical design (see Section 1.3.3 and Section 9.4). Considering that all treatment strategies applied, i.e. EO2401/nivolumab, EO2401 monotherapy, and nivolumab monotherapy, can be considered interesting by both patients and investigators, it is assumed that an open-label approach is still adequate considering assumed limited bias in any direction of the treatment groups; an approach which of course also supports a logistical setup which is considered relevant for the early development nature of the trial.

5 POPULATION

5.1 Inclusion criteria

1. For inclusion in **Cohort 1** patients should have adrenocortical carcinoma, or malignant pheochromocytoma/paraganglioma, as defined below for Cohorts 2A and 3A.

[redacted]

2. For inclusion in **Cohorts 2A and 2B** patients should have histologically confirmed (at primary diagnosis) unresectable locally advanced or metastatic (ENSAT/AJCC [38] stage 3 = tumor has spread into nearby tissues or lymph nodes, or stage 4 = metastatic disease) adrenocortical carcinoma.

    a. In addition, for inclusion in Cohort 2 A patients should also have received treatment with at least one line, but not more than two prior lines, of systemic therapy for established locally advanced or metastatic disease (i.e. non-adjuvant therapy), and should within these lines of therapy for advanced/metastatic disease, or as neoadjuvant/adjuvant therapy, have received mitotane therapy delivered at an adequate dose per below (if not impossible due to toxicity; situation which should be documented in the patient files).

[redacted]

    b. In addition, for inclusion in Cohort 2B patients should not have received prior systemic therapy for established locally advanced or metastatic disease (i.e. non-adjuvant therapy).

[redacted]

[redacted]

3. For inclusion in **Cohorts 3A and 3B** patients should have histologically confirmed (at primary diagnosis) unresectable malignant (defined as metastatic disease, i.e. presence of chromaffin tissue in non-chromaffin organs) pheochromocytoma/paraganglioma, and RECIST defined progression should have been documented during a maximum of an 18-months period.
    a. In addition, for inclusion in Cohort 3A patients should also have received treatment with at least two prior lines of systemic therapy if the patients are eligible for radionuclide therapy, and at least one prior line of systemic therapy if the patients are not eligible for radionuclide therapy.

[redacted]

    b. In addition, for inclusion in Cohort 3B patients should not have received prior systemic therapy for their malignant pheochromocytoma/paraganglioma.

[redacted]

4. Patients with an age ≥ 18 years old.
5. Patients who are human leukocyte antigen (HLA)-A2 positive.
6. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 with the specific meaning of ECOG 1 being "restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house-work, office work" (see Section 12.2 [39]).

[redacted]

[redacted]

7. Patients with a life expectancy > 4 months as judged by their treating physician.
8. Patients with at least one measurable lesion according to RECIST 1.1 (see Section 12.1; [36]).
9. Males or non-pregnant, non-lactating, females who are:
   a) female, post-menopausal (serum follicle-stimulating hormone (FSH) level > 40 mIU/mL),
   b) female and male, surgically sterile (e.g. bilaterally blocked or removed fallopian tubes, vas deferens),
   c) female of childbearing potential with a negative highly sensitive serum pregnancy test within 72 hours prior to first administration of study treatment and use of a highly effective contraception from signing the Informed Consent Form (ICF) through 5 months after the last study treatment dose administered; note, the male partner should in addition to the use of highly effective contraception by the female patient also use condoms,
   d) male patient with female partners of childbearing potential must use condoms from signing the ICF through 5 months after the last study treatment dose administered; in addition, male patients must ensure that their partners of childbearing potential also use highly effective contraception.

   Highly effective contraception includes:

   i) combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal,

   ii) progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable, intrauterine device, and

   iii) sexual abstinence when in line with the preferred and usual lifestyle of the patient (e.g. periodic abstinence is not considered a highly effective method).
10. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.
11. Patients having received the information sheet and who have provided written informed consent prior to any study-related procedures. [redacted]

5.2 Exclusion criteria

1. Patients treated with dexamethasone > 2 mg/day or equivalent (i.e. 13 mg/day of prednisone, or 53 mg/day of hydrocortisone) within 14 days before the first EO2401 administration, unless required to treat an adverse event. [redacted]
2. Patients with prior treatment with compounds targeting PD-1, PD-L1, CTLA-4, or similar compounds where general resistance against therapeutic vaccination approaches might have developed (e.g. defects to the cellular antigen processing/presentation

machinery, including mutations in Janus kinas [JAK] 1, JAK2, and β-2-microglobulin [B2M]) allowing tumor cells to avoid recognition and attack by immune cells.

3. Patients with prior exposure to EO2401, e.g. patients treated in Cohorts 2B or 3B of the current trial cannot be re-enrolled for treatment also in Cohorts 2A or 3A.
4. Patients treated with immunotherapy (meaning immunostimulatory or immunosuppressive therapy; beside excluded, or allowed, compounds per other inclusion/exclusion criteria specifications), radionuclide therapy, radiotherapy, cytoreductive therapy, or received treatment with any other investigational agent within 28 days before the first EO2401 administration.

[redacted]

5. Patients with an initial diagnosis of ACC less than 9 months from start of screening part 2.
6. Patients with ACC and any individual lesion according to RECIST 1.1 [36] having a maximum diameter of more than 125 mm; irrespective if the lesion is proposed as a target lesion, or not, according to RECIST 1.1 (see Section 12.1; [36]).
7. Patients with ACC with more than three organs involved by disease.

[redacted]

8. Patients with ACC and uncontrolled hormonal secretion (according to the judgement of the treating physician).

[redacted]

9. Patients with MPP and uncontrolled blood pressure (according to the judgement of the treating physician).
10. Patients with abnormal laboratory values according to the following li [redacted]

[redacted]

[redacted]

11. Patients with persistent Grade 3 or 4 toxicities (according to NCI-CTCAE v5.0 [60]) after prior treatments; toxicities must be resolved since at least 2 weeks before study treatment start to Grade 1 or less [redacted]
12. Uncontrolled central nervous system (CNS) metastasis [redacted]
13. Other malignancy or prior malignancy with a disease-free interval of less than 3 years prior to ICF signing [redacted]
14. Patients with clinically significant active infection, cardiac disease, significant medical or psychiatric disease/condition that, in the opinion of the Investigator, would interfere with the evaluation of study results, interpretation of patient safety, or prohibit patient understanding of the informed consent procedure (i.e. only consent able patients can be enrolled in the study) or compliance with the requirements of the protocol – including (but not limited to):

a. bacterial sepsis or similarly severe infections,
b. uncontrolled or significant cardiovascular disease, including:
    i. New York Heart Association > Grade 2 congestive heart failure within 6 months prior to ICF signing (see Section 12.3),
    ii. myocardial infarction within 6 months prior to ICF signing,
    iii. uncontrolled/unstable angina within 6 months prior to ICF signing,
    iv. diagnosed or suspected congenital long QT syndrome,
    v. any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes),
c. stroke within 6 months prior to ICF signing,
d. concurrent neurodegenerative disease, and
e. dementia or significantly altered mental status.

15. Patients with suspected autoimmune or active autoimmune disorder or known history of an autoimmune neurologic condition (e.g. Guillain-Barré syndrome) [redacted]
16. Patients with history of solid organ transplantation or hematopoietic stem cell transplantation.
17. Patients with history or known presence of tuberculosis.
18. Pregnant and breastfeeding patients.
19. Patients with history or presence of human immunodeficiency virus and/or potentially active hepatitis B virus/hepatitis C virus infection.
20. Patients who have received live or attenuated vaccine therapy used for prevention of infectious diseases including seasonal (influenza) vaccinations within 4 weeks of the first dose of study drug.
21. Patients with a history of hypersensitivity to any excipient present in the pharmaceutical forms of the study treatments.
22. Patients treated with herbal remedies with immunostimulating properties or known to potentially interfere with major organ function.
23. Patients with known ongoing drug and alcohol abuse.
24. Patients with known or underlying medical or psychiatric condition that, in the Investigator's opinion, would make the administration of study drug hazardous to the patient or obscure the interpretation of toxicity determination or AEs.
25. Patients deprived of their liberty, under protective custody, or guardship. [redacted]

5.3 Removal of patients from therapy or study

5.3.1 Patient withdrawal of consent

Patients may voluntarily withdraw from the study treatment, or the study as such, including procedures, at any time at his/her request for any reason. In instances where patient consent is withdrawn, the Investigator must clarify to which degree the patient consent is withdrawn, i.e. whether the patient still is willing to continue to participate in some study specific procedures, or not. The degree of consent withdrawal should be carefully documented in patient files and in study documents.

5.3.2 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently included in the analysis population due to failure of the eligibility criteria. A minimal set of information is required to be captured (via the eCRF) for such patients to ensure transparent reporting to meet the standards of reporting clinical trials and to respond to queries from regulatory authorities. Minimal information includes age and gender, screen failure details (including failed eligibility criteria), and any SAEs.

5.3.3 Criteria for treatment discontinuation

Patients should be removed from study treatment for any of the following reasons:

- intolerable toxicity in relation to study treatment and adverse events requiring treatment discontinuation according to this protocol (see Section 4.2),
- pregnancy,
- confirmed tumor progression according to iRECIST criteria (see Section 12.1),
- any medical condition which may jeopardize the patient's safety if he/she continues trial treatment,
- major protocol violation (including non-compliance to study schedule by the patient) judged to impact safety of the patient or interpretability of the trial,
- decision by the Investigator, Sponsor, or any regulatory authority, that treatment discontinuation is in the best interest of the patient,
- patient withdrawal of consent to receive further study treatment, and
- planned or early termination of the study (see Section 4.3).

5.3.4 Lost to follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether, or not, the patient wishes to and/or should continue in the study.

In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls, and if necessary, a certified letter to the patient's last known mailing address, or local equivalent method). These contact attempts should be documented in the patient's medical records.

5.3.5 Criteria for study participation termination

Reasons for patient withdrawal from the study may include, but are not limited to:

- patient withdrawal of consent for any further trial procedures (see also Section 5.3.1),
- patient lost to follow-up,
- major protocol violation (including non-compliance to study schedule by the patient) judged to impact safety of the patient or interpretability of the trial,
- decision by the Investigator, Sponsor, or any regulatory authority, that study participation discontinuation is in the best interest of the patient,
- planned or early termination of the study (see Section 4.3).

5.3.6 Follow-up of patients discontinued from study treatment or withdrawn from study

The primary reason for study treatment discontinuation should be documented in the eCRF. In case of treatment discontinuation, patients will complete follow-up visits according to Section 7.5. The first follow-up visit is to be completed 30 days after completion of last dose of study treatment.

In cases of withdrawal from the study, every effort should be made to obtain adequate information. The primary reason for withdrawal from the study should be documented in the eCRF. If possible, patients will complete a follow-up visit according to Section 7.5.1.

In cases with complete informed consent withdrawal (see also Section 5.3.1), patients will not be followed for any reason, although date of death will be recorded, where applicable and possible to retrieve.

5.3.7 Procedures for handling incorrectly enrolled patients

If a patient is found to have been incorrectly enrolled in the study, the Sponsor must be notified as soon as the error is discovered. The Sponsor will decide on the appropriate action to take regarding study treatment and continuation of the patient in the study.

5.3.8 Patient replacement

Patients who have not received any dose of EO2401 and thereby are not evaluable for safety, will be replaced (reasons for non-evaluability and pre-treatment safety will be reported).

Note, the replacement strategy per above is also applied for the randomized extension of Cohort 2A. Thus, if a patient is randomized and then withdrawn from treatment (for any reason) before a first dose of study medication has been delivered, the patient should be replaced.

In addition, in Cohort 1, if for reasons other than safety a patient does not receive 2 doses of EO2401 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).

6 TREATMENT OF PATIENTS

6.1 Description of EO2401

6.1.1 Pharmaceutical form

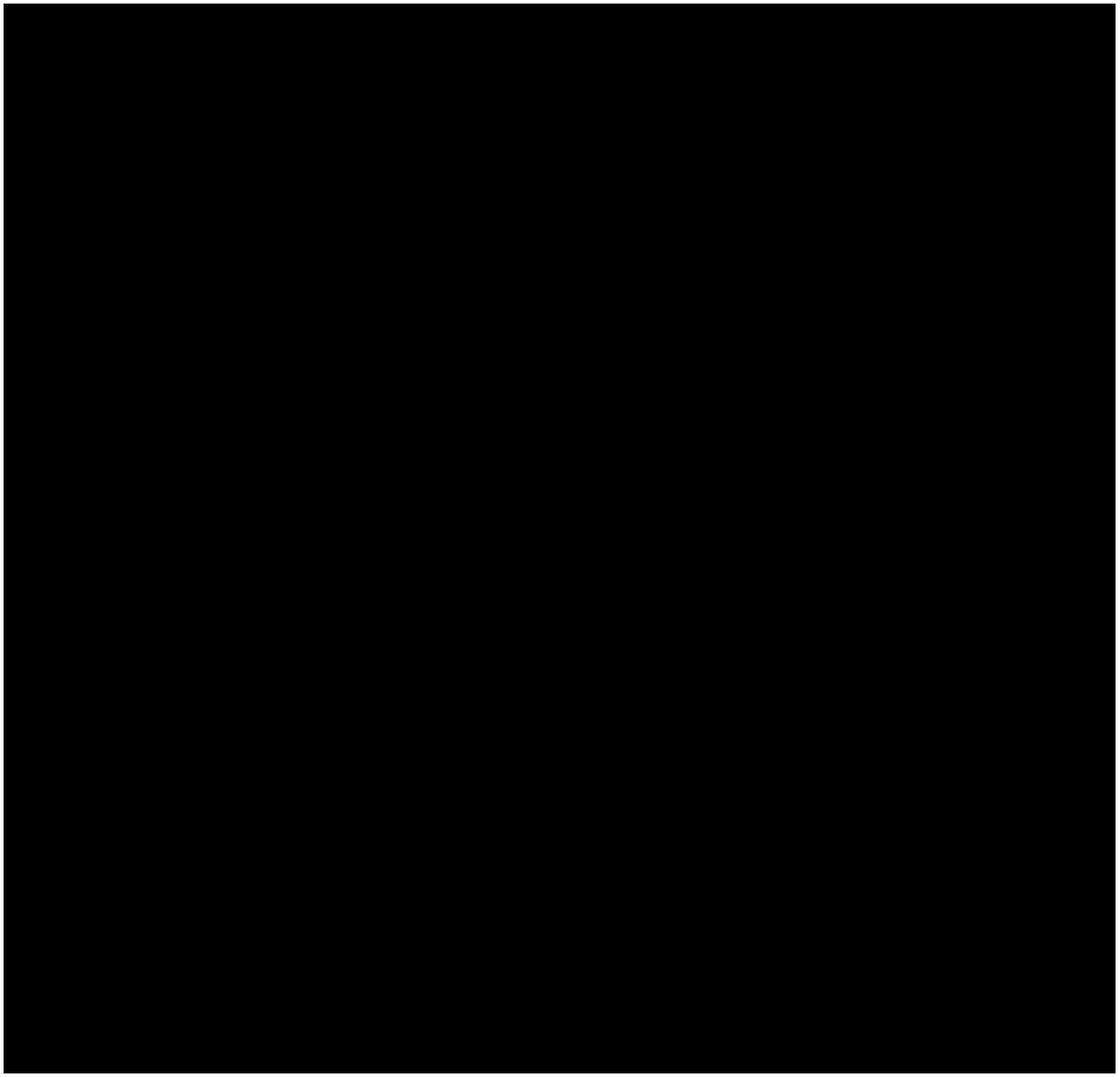
The Investigational Medicinal Product (IMP) of the study, EO2401, consists of a water/DMSO solution (67/33 v/v) containing 4 peptide drug substances [redacted] The final concentration of each peptide is 300 µg/mL.

Further details regarding the components of EO2401 can be found in Section 1.3, and in the current version of the EO2401 IB.

6.1.2 Preparation of the formulation

The IMP is provided to the clinical sites [redacted] The Investigator or pharmacist at the investigational site will undertake specific training on handling and preparing study treatment and will ensure that Good Pharmacy Practices are followed during the preparation and reconstitution process of EO2401.

[redacted]



[redacted]

6.1.3 Packaging and labeling

EO2401 will be manufactured as per Good Manufacturing Practice (GMP) [redacted]

A detailed process for ordering the IMP, handling and administration, packaging, and labeling the IMP will be specified in the Pharmacy Manual.

6.1.4 Storage and stability

The study treatment must be stored in a secure limited access area according to local regulations. [redacted]

6.2 Description of nivolumab

6.2.1 Pharmaceutical form

Nivolumab is sterile concentrate solution for infusion administration. The solution is clear to opalescent, colorless to pale yellow liquid that may contain a few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg.

List of excipients include; sodium citrate dehydrate, sodium chloride, mannitol (E421), pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

Further details regarding nivolumab can be found in the European SmPC or the US PI for nivolumab [42, 43].

6.2.2 Preparation of the formulation

Instructions for preparation of nivolumab for infusion can be found in the European SmPC or the US PI for nivolumab [42, 43].

6.2.3 Packaging and labeling

Nivolumab will be obtained from commercial sources by the Sponsor and clearly labeled for use within the trial.

Adequate supplies of nivolumab in 24 mL glass vials will be provided to each investigational site for preparation and infusion. The vial stopper will be a coated butyl rubber with a grey aluminum flip-off seal.

6.2.4 Storage and stability

Nivolumab should be stored in the refrigerator at 2°C to 8°C in its original package in order to protect from light. Once opened, the medicinal product should be infused or diluted, and infused immediately [42, 43].

If not used immediately, chemical and physical in-use stability of nivolumab has been demonstrated for 24 hours at 2°C to 8°C protected from light and a maximum of 8 hours at 20°C to 25°C with room light (this 8-hour period of the total 24 hours should be inclusive of the product administration period).

6.2.5 Expected safety profile of nivolumab

The following summary is based on the European SmPC [42].

In the pooled dataset of nivolumab as monotherapy across tumour types (n = 4646) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (44%), musculoskeletal pain (28%), diarrhoea (26%), rash (24%),cough (22%), nausea (22%), pruritus (19%), decreased appetite (17%), arthralgia (17%), constipation (16%), dyspnoea (16%), abdominal pain (15%), upper respiratory tract infection (15%), pyrexia (13%), headache (13%), anaemia (13%) and vomiting (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 44%, with 0.3% fatal adverse reactions attributed to study drug.

In addition, nivolumab is associated with immune–related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Table 2 presents the percentage for immune-related adverse reactions leading to permanent discontinuation of nivolumab and the percentages requiring high-dose corticosteroid dosing.

For the laboratory abnormalities observed with nivolumab monotherapy, please refer to the European SmPC or to the US PI [42, 43].

Of the 3529 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti-product-antibodies, 328 patients (9.3%) tested positive for treatment-emergent anti-product-antibodies with 21 patients (0.6%) testing positive for neutralising antibodies.

Generally, no overall differences in safety regarding nivolumab were reported between elderly (≥ 65 years) and younger patients (< 65 years). In the nivolumab non-squamous non-small cell lung cancer study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups.

[redacted]

Table 2 : Nivolumab immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids

	Nivolumab 3 mg/kg or 240 mg monotherapy %
Immune-related adverse reaction leading to permanent discontinuation	
Pneumonitis	1.4
Colitis	1.2
Hepatitis	1.1
Nephritis and renal dysfunction	0.3
Endocrinopathies	0.5
Skin	0.8
Hypersensitivity/Infusion reaction	0.1
Immune-related adverse reaction requiring high-dose corticosteroids[a,b]	
Pneumonitis	65
Colitis	14
Hepatitis	21
Nephritis and renal dysfunction	22
Endocrinopathies	5
Skin	3.3
Hypersensitivity/Infusion reaction	18

a: At least 40-mg daily prednisone equivalents.

b: Frequency is based on the number of patients who experienced the immune-related adverse reaction.

6.3 Administration of EO2401 and nivolumab

[redacted]

EO2401 will be administered by 4 priming injections SC at 2-weekly intervals, followed by boosting injections starting at 4 weeks after the fourth priming injection; continued boosting injections will be given on a 4-weekly interval.

The full dose of EO2401 [redacted] will be administered in sub-cohort 1a (and 1b if applicable), and if implemented, the sub-cohorts 1c and 1d will include half the dose of EO2401 [redacted]

The trial IDMC has recommended use of the full dose of EO2401 after assessment of the safety-lead in part of the trial (Cohort 1) and a further assessment of the initial patients in Cohorts 2A and 3A (see Section 1.3.3).

The dose and schedule of EO2401 is the same whether, or not, the treatment is given in combination with nivolumab, or as monotherapy (latter in the randomized extension of Cohort 2A for patients randomized to Cohort 2A-II).

The location of EO2401 injections will be in a rotating way by injection (so an injection site will be used every fourth time), [redacted]

In Cohort 1, non-randomized part of Cohort 2A, randomized extension of Cohort 2A for patients randomized to treatment schedule Cohort 2A-I, Cohort 3A, and Cohort 3B, EO2401 will be administered in combination with nivolumab. EO2401 will be administered first followed by nivolumab, [redacted]

Nivolumab will, when administered in combination with EO2401, be administered as an IV infusion starting from the first priming injection of EO2401. The nivolumab infusion is to start [redacted] after the EO2401 administration. The dose of nivolumab should be 240 mg every 2 weeks for the first 3 administrations, and from the fourth administration (2 weeks after the 3rd administration), and onwards, a nivolumab dose of 480 mg every 4 weeks is to be applied. The maximum duration of nivolumab treatment is 24 months.

For patients in the randomized extension of Cohort 2A randomized to nivolumab monotherapy (Cohort 2A-III), nivolumab will be administered as an IV infusion starting from study day 1. The dose of nivolumab should be 240 mg every 2 weeks for the first 3 administrations, and from the fourth administration (2 weeks after the 3rd administration), and onwards, a nivolumab dose of 480 mg every 4 weeks is to be applied. The maximum duration of nivolumab treatment is 24 months.

Local standard practice regarding nivolumab administration will be followed. [redacted]

[redacted]

For further information regarding administration of nivolumab, see also the European SmPC or the US PI for nivolumab [42, 43].

Note, administration-related reactions and guidelines on how to handle such reactions are outlined in Section 6.5.

6.4 Treatment modifications

The only adjustments regarding dose for nivolumab are withholding of one or several doses, or discontinuation of treatment; such measures should be taken in accordance with the labeled recommendations in the European SmPC or the US PI [42, 43].

The dose modifications for EO2401 follow the same principles as for nivolumab, i.e. possible dose modifications include withholding of doses, and treatment discontinuation, except in the potential transition from sub-cohort 1b to sub-cohort 1c in relation to safety events (when a dose decrease is planned; see Section 4.2.1).

For all cohorts, and all patients during the whole trial treatment, the safety rules are outlined in Section 4.2, including instructions on when to discontinue study treatments.

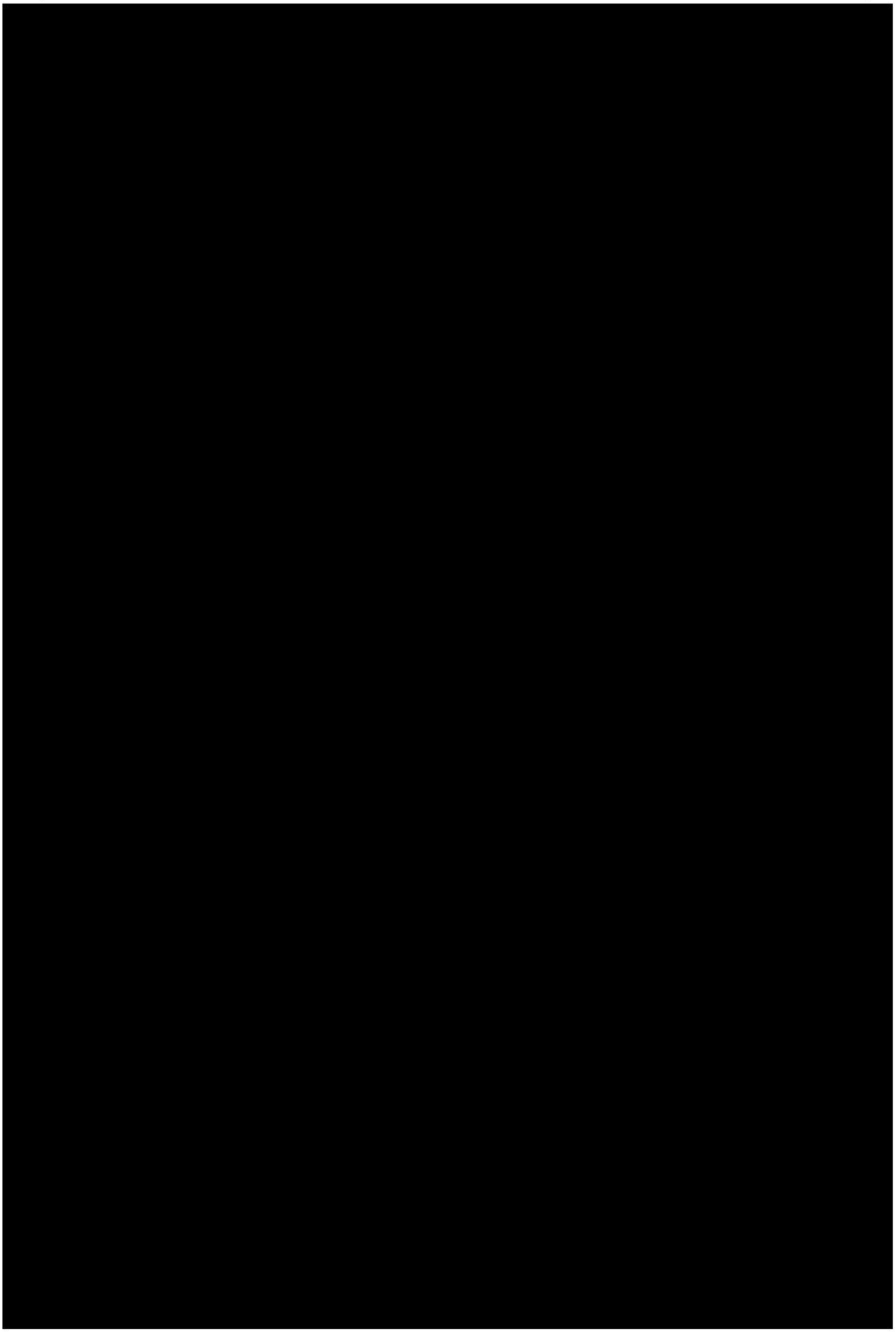
Guidelines for withholding doses or permanent discontinuation of EO2401 and nivolumab in case of immune-related adverse reactions are outlined below in Section 6.4.1. Also, dose adjustments are necessary to consider in the case of administration-related reactions (see Section 6.5).

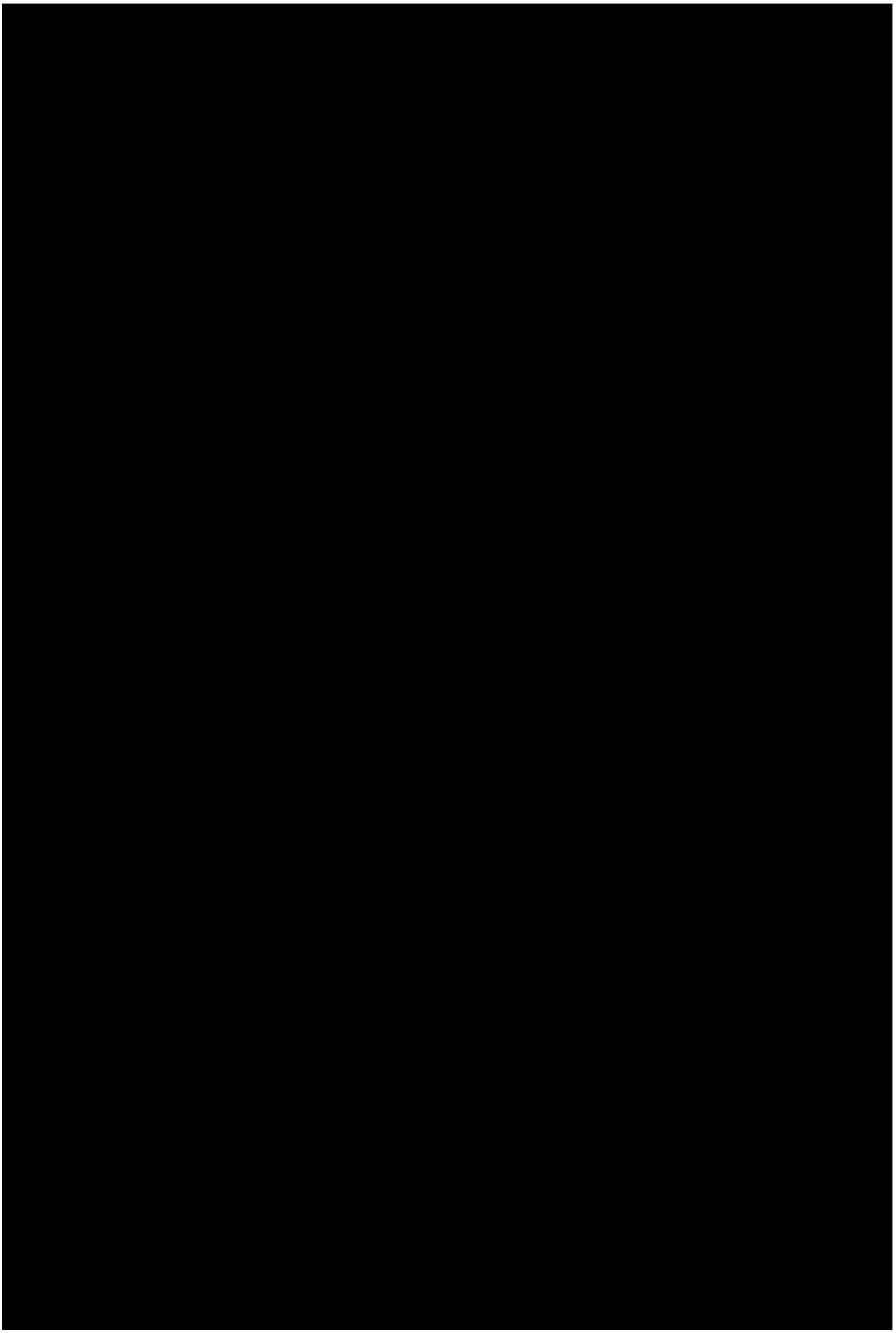
In instances where the label for nivolumab prescribe that the drug should be withheld or discontinued due to safety events, there is, in patients with EO2401/nivolumab combination treatment, an option to continue EO2401 alone provided such a continuation would be recommended by the IDMC and supported by the Sponsor.

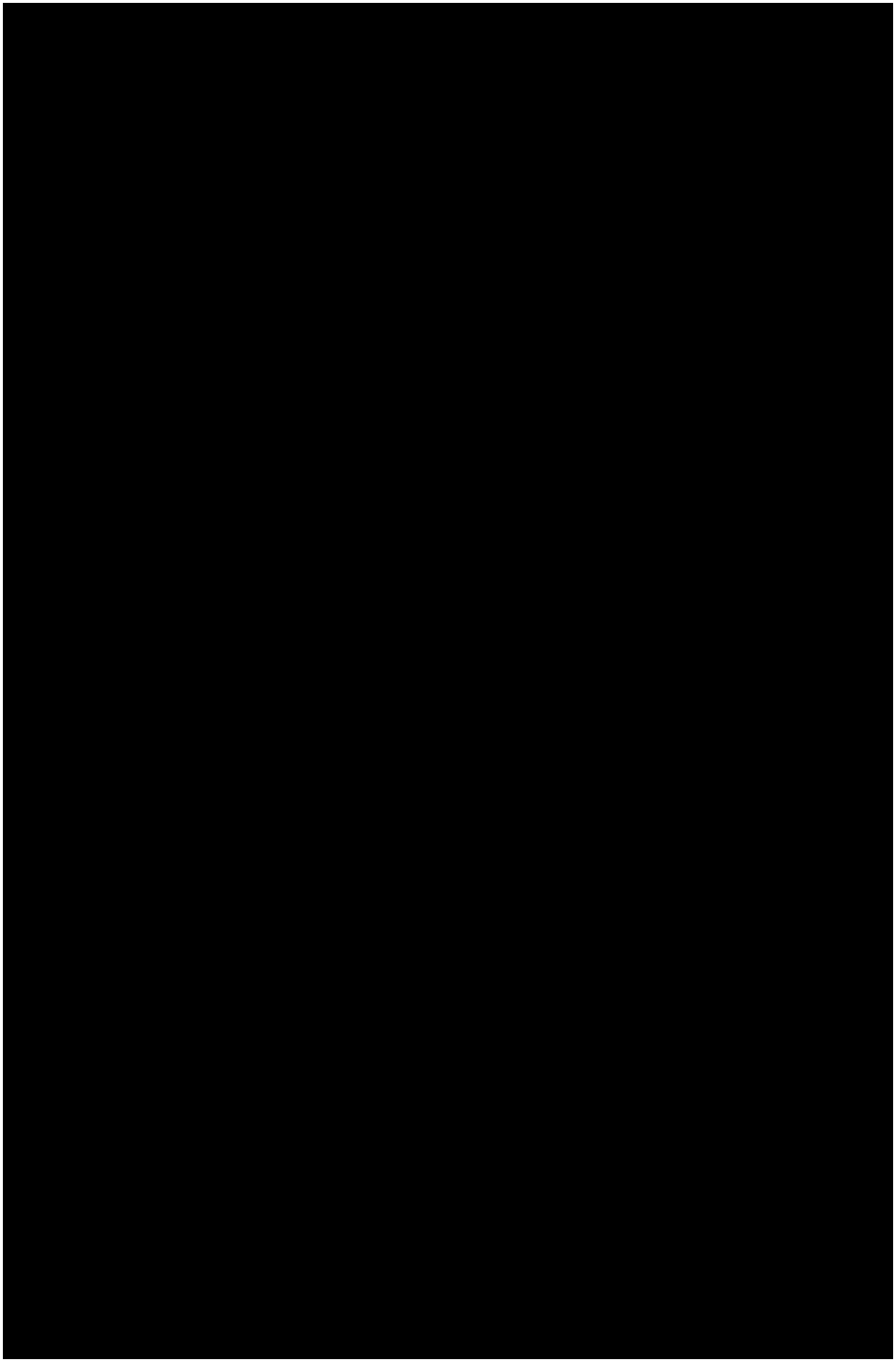
If EO2401 would be stopped, nivolumab will also be stopped in the context of being trial treatment for patients with EO2401/nivolumab combination treatment. In such cases, the Investigator responsible for the patient in question will advise on adequate further treatment options.

Criteria for treatment discontinuation and study participation termination are outlined in Section 5.3.3 and Section 5.3.5.

[redacted]







[redacted]

6.5 Administration-related reactions

The NCI-CTCAE distinguishes between hypersensitivity reactions and acute infusion reactions induced by cytokine release. Despite the different possible mechanisms underlying

hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap.

Immediate systemic reactions, infusion-related reactions (e.g. via cytokine release) and hypersensitivity reactions, at administration of nivolumab are not uncommon (European SmPC and US PI for nivolumab [42, 43]).

Severe infusion reactions have been reported in clinical trials of nivolumab. In case of a severe or life-threatening infusion reaction, the nivolumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring and use of premedication (and/or slowed rate of infusion) according to local treatment guidelines for prophylaxis of infusion reactions [42, 43].

Systemic reaction at administration of EO2401 cannot be excluded either and since this is an early development trial it is advisable to take precautions to be able to ameliorate symptoms if such would occur.

In the current trial, the nivolumab infusion is to start [redacted] after the EO2401 administration.

[redacted]

[redacted]

6.5.2 Late-occurring hypersensitivity symptoms

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids).

[redacted]

[redacted]

[redacted]

[redacted]

6.7 Study treatment accountability, reconciliation, and return

The Sponsor will be responsible for ensuring that the quality of the study treatment is adequate for the duration of the study.

It is the responsibility of the Investigator or designee to ensure that the study treatment is only dispensed to the adequate patient. The study treatment must be dispensed from official study sites by authorized personnel according to local regulations. The Investigator or designee must maintain accurate records of the study treatment receipt, dispensing information, and disposition.

Upon completion and termination of the study, all unused and/or partially used study treatment must be returned to the Sponsor or other authorized party, if not authorized by the Sponsor to be destroyed at the site.

If study treatment is to be destroyed at the site, it is the Investigator's or designee's responsibility to ensure that arrangements have been made for disposal, drug accountability has been completed by the site monitor, procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures, and appropriate records of the disposal have been documented and provided to the Sponsor or designee.

All study treatments returned to the Sponsor or other authorized party must be accompanied by the appropriate documentation and be clearly identified. Study treatment may only be returned after drug accountability is completed. Returned supplies should be in their original containers (component vials that have clinical labels attached).

Empty vials should not be returned to the Sponsor. Empty vials may not be destroyed until drug accountability is completed. It is the Investigator's responsibility to arrange disposal of all empty vials according to the institutional regulations.

The return or destruction of unused study treatment should be arranged by the site monitor. Further guidance and information for the final disposition of unused study treatment are provided in the pharmacy binder.

6.8 Method of treatment assignment

This is an open-label non-randomized trial for Cohort 1, non-randomized part of Cohort 2A, Cohort 2B, Cohort 3A, and Cohort 3B, and each newly enrolled patient (upon signing the ICF) will be assigned a unique patient identification number assigned to the treatment after approval of eligibility, where applicable. Slot assignments will be managed by the Medical Monitor as described in the Charter for cohort management.

[redacted]

[redacted]

User access and permissions:

The IWRS system for randomization will be clearly separated, by programming, from all other trial related computer systems; the randomization system can be programmed to directly release data regarding treatment assignment for a specific patient to other systems (e.g. systems handling drug shipments etc.).

To use the IWRS each user must connect to an https address, enter a personal username, and a password. This feature guarantees the security of the system and creates an automatic audit trail of which person performed what actions. In accordance with 21 CFR part 11, user access codes are unique and never reassigned. For added security, the first time a user connects into the IWRS, he/she is asked to select a new password.

The Sponsor will provide the vendor for the IWRS with a list of IWRS users; the IWRS vendor will keep this list up to date. Codes can be provided to users at the start of the study and throughout the study in case of additions to or changes in staff. User accounts would be deactivated for all users who are no longer participating in the study.

Randomization design:

Randomization to allocate patients in a ratio of 4:1:1 (Cohort 2A-1 EO2401/nivolumab : Cohort 2A-II EO2401 monotherapy : Cohort 2A-III nivolumab monotherapy) and to ensure that sites with low recruitment do not have only control patients among the initially recruited, will be achieved by using an IWRS system and randomization lists with fixed blocks including some flexibility.

For the first 50 patients, the randomization will be stratified by site.

6.9 Ancillary treatments

6.9.1 Prior and concomitant treatments and procedures

Prohibited treatments prior to trial enrollment are outlined in the exclusion criteria (see Section 5.2).

The Investigator must record the use of all prior and concomitant medications or vaccines taken during 28 days prior to signing informed consent. Likewise, for the duration of the study both prescribed and "over-the-counter" medications, including herbal remedies, should be recorded in the source documents and eCRF along with:

- reasons for use,
- dates of administration including start and end dates, and
- dosage information, including dose, frequency, and route of administration.

In case of surgical procedures, or other relevant non-drug medical interventions and procedures, all details must be collected in the eCRF in a similar manner as for medications per above.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Patients should be discouraged from starting any new medication, both prescribed and over-the-counter, including herbal remedies, without consulting the Investigator unless the new medication is required for emergency.

6.9.2 Permitted concomitant medications

All non-cancer therapies that the responsible physician feels appropriate are allowed in this study, except for the medications outlined in Section 6.9.3. Thus, patients should receive full supportive care during participation in the trial and standard of care treatment per local practice and according to the judgment of the Investigator or treating physician.

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

[redacted]

Recommendations regarding vaccination against SARS-CoV-2/COVID-19

- The Sponsor recommends strongly that patients, if possible, are vaccinated against SARS-CoV- 2/COVID-19 before inclusion into the study. The recommended time interval between a COVID-19 vaccine administration and the initial study drug administration is 2 weeks, however, other trial exclusion criteria should also be taken into account (e.g. regarding patients with persistent Grade 3 or 4 toxicities) when assessing possible timing of start of study treatment in relation to COVID-19 vaccine administration.
- For patients who are offered a third (or potential further) dose during the trial, or for patients who have not been vaccinated against SARS-CoV-2/COVID-19 before study inclusion, but want to be vaccinated during their study participation, the Sponsor also strongly recommends vaccination. For such patients the Sponsor recommends administration of the dose of the COVID-19 vaccine during the boosting phase (EO2401 administered every 4 weeks), or 2 weeks after the latest EO2401 administration (and thereby 2 weeks before the next EO2401 administration), and in a different location *[Note, if this time schedule would lead to unnecessarily long waiting time for COVID-19 vaccination, alternative administration time points should be discussed with*

Enterome via the Medical Monitor]. Should you also plan to administer a vaccine against influenza, we would propose the same approach with the same time intervals.

- At screening for inclusion of patients into trial EOADR1-19, Enterome would like to draw your attention to ***Exclusion Criterion #12 (copied below)*** which is valid also for COVID-19 infections, meaning that the PI/co-PI when assessing patients for study inclusion should consider patient history/symptoms and the local pan/endemic situation, and when judged appropriate also test patients regarding SARS-CoV-2 before stating that the individual patient does not fulfill the exclusion criterion (in such cases documentation of testing, including outcome, should be made in the eCRF as an unscheduled test during screening):

  Exclusion criterion #12: Patients with clinically significant active infection, cardiac disease, significant medical or psychiatric disease/condition that, in the opinion of the Investigator, would interfere with the evaluation of study results, interpretation of patient safety, or prohibit patient understanding of the informed consent procedure (i.e. only consent able patients can be enrolled in the study) or compliance with the requirements of the protocol including (but not limited to):

  a. bacterial sepsis or similarly severe infections,

  b. …

  The below by FDA and EMA approved COVID-19 vaccines are acceptable for use in the trial (local restrictions per country specific authority of course takes precedence; also, new approvals by FDA and EMA should be taken into account when selecting vaccine type):

Name	**COVID-19 Vaccine developer/ manufacturer**	**Vaccine platform**	**Type of candidate vaccine**	**Number of doses**	**Timing between doses**	**Route of administration**
Vaxzevria	University of Oxford/AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	2	28 days	IM
Spikevax	Moderna/NIAID	RNA	LNP-encapsulated mRNA	2	28 days	IM
Comirnaty	BioNTech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	2	21 days	IM
COVID-19 vaccine Janssen	Johnson & Johnson/ Janssen	Non-Replicating Viral Vector	Ad26.COV2-S	1	NA	IM
** Local country/site timing between doses might be different from what is stated in the table.*						

6.9.3 Prohibited medications and other therapies

The use of systemic corticosteroids and other immunosuppressants should be avoided because of their potential interference with the pharmacodynamics activity of the study treatment. However, in some cases, systemic corticosteroids cannot be avoided; guidance

regarding steroid use for patients participating in the trial is therefore outlined in Section 6.9.2.

The use of live or attenuated vaccine therapy for prevention of infectious diseases during trial participation should be avoided if possible. However, if such vaccinations would be considered as important for the normal care of the patient, the treating physician should discuss the situation with the Medical Monitor of the Sponsor and an adequate solution regarding timing should be found.

Patient should be discouraged from taking medications, including herbal remedies, with immunostimulatory properties, or known to potentially interfere with major organ function, during trial participation. If needed, any such possible therapy should be discussed between the treating physician and the Medical Monitor of the Sponsor.

During trial participation patients should not receive any other anti-cancer treatment than the specific trial treatment (EO2401 in combination with nivolumab) and treatments outlined in Section 6.9.2.

If any other anti-cancer treatment, or procedure, would be considered for start in an individual patient, it is the duty of the Investigator to discuss the consideration with the Medical Monitor of the Sponsor for a decision on how to handle continued trial specific treatment and trial participation.

In general, if necessary due to e.g. patient symptoms, local therapies will be promoted; depending on localization of the treatment versus localization of measurable lesions, a decision might be necessary to consider censoring the patient for progression related endpoints at the time of start of the therapy if there would be no measurable lesion left outside of the location of the local treatment (or assessing the patient as having progressive disease if relevant criteria would be fulfilled).

Start of non-trial systemic anti-cancer treatments would lead to censoring of the patient for progression related endpoints at the time of start of the therapy; or assessment of the patient as having progressive disease if relevant criteria would be fulfilled.

6.9.4 Contraception

Potential postmenopausal status for female patients will be confirmed with a screening serum follicle-stimulating hormone (FSH) level > 40 mIU/mL. Rules for contraception during study participation are outlined in the inclusion criteria, see Section 5.1.

6.10 Treatment compliance

Since all treatments are administered at the clinical site by site personnel, the Investigator or designee must maintain accurate records of all study treatments, including dates of study drug receipt, quantities received and dispensed, and batch/lot numbers. In addition, the study treatment must be noted in the patient's medical records and eCRF, with the date and time of administration and dose of each study treatment.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Study schedule

Study assessments and procedures, and their timings (including visit windows) are summarized in the Study Schedule (Error! Reference source not found.). As protocol exemptions are not foreseen in this trial, except in case of immediate safety concerns, any deviation from the planned study schedule should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue, or discontinue, the study treatment. Adherence to the study design requirements, including those specified in the Study Schedule, is essential and required for adequate study conduct.

7.2 Screening period #1

The trial will include a 2-stage consent and screening procedure (see Section 4.2).

The initial minimized consent, and screening period #1, is related to the procedure of HLA-testing, and before testing also establishing based on available information that the patient has eligible ACC or MPP, and an age ≥ 18 years (inclusion criteria #1 to 5; see Section 5.1).

The following will be done during screening period #1:

- study ICF procedure for consent #1, and
- eligibility ascertained for inclusion criteria #1 to 5 (#1 to 3 as applicable depending on stage of trial conduct and patient tumor disease).

HLA-testing can be performed within the scope of the trial, but HLA-information based on testing before the screening period is also acceptable (no time limit is applied; patients with prior hematopoietic stem cell transplantation are not eligible for the trial).

HLA-testing will be performed locally; information regarding the local lab, including methods used will be collected. Low resolution HLA-typing (i.e. genotyping of the HLA-A loci 2 to 2 digits) is considered satisfactory for trial enrolment. However, 4-digit resolution typing is preferred; also, a more complete HLA-typing is preferred.

All information available regarding the individual patient MHC-composition will be collected, i.e. also information beside the HLA-A type. Patients who are not HLA-A2 positive will be assigned a “screen failure”-status and not continue any further trial procedures; such patients will be replaced.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3 Screening period #2

The second stage of the consent procedure, and screening period #2, will be related to all other aspects of the trial, except those outlined in Section 7.2 (for remaining inclusion/exclusion criteria see Section 5.1 and Section 5.2). All timelines included in the protocol and related to the signature of the ICF are referring to the signature of this second part of the ICF. All evaluations must be completed and reviewed within the timeframe defined in the Study Schedule (Error! Reference source not found.) to confirm that potential patients meet all eligibility criteria. The Investigator will record adequate details of all patients screened and to confirm eligibility, or record reasons for screen failure, as applicable (see Section 5.3.2).

Procedures conducted as part of the patient's routine clinical management (e.g. blood count) and obtained before signing the consent form may be utilized for screening purposes, provided the procedure met the protocol-specified criteria. Results obtained also the week before screening started [redacted] can be used for study purposes provided the study Medical Monitor's approval is granted; this also includes an acceptable time window for the screening/baseline CT.

All screening examinations will be performed locally, at the site or an affiliate site due to e.g. the location of the site and the patient.

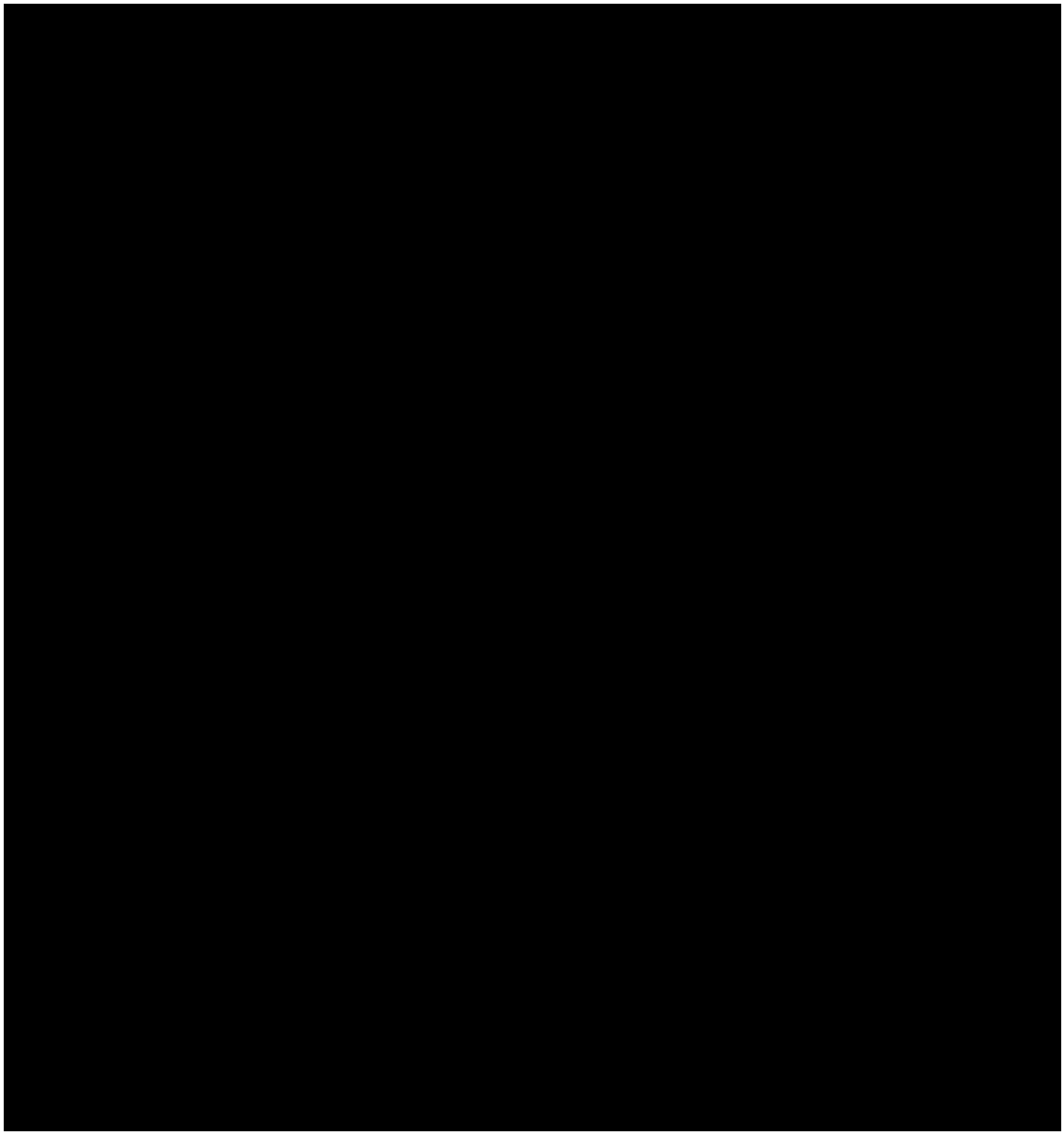
The maximum amount of blood to be taken from each patient at screening, or over the duration of the study, including any extra assessments that may be required, will not exceed volumes as stated by local regulations. Repeat, or unscheduled samples, may be taken for safety reasons, or for technical issues with the samples.

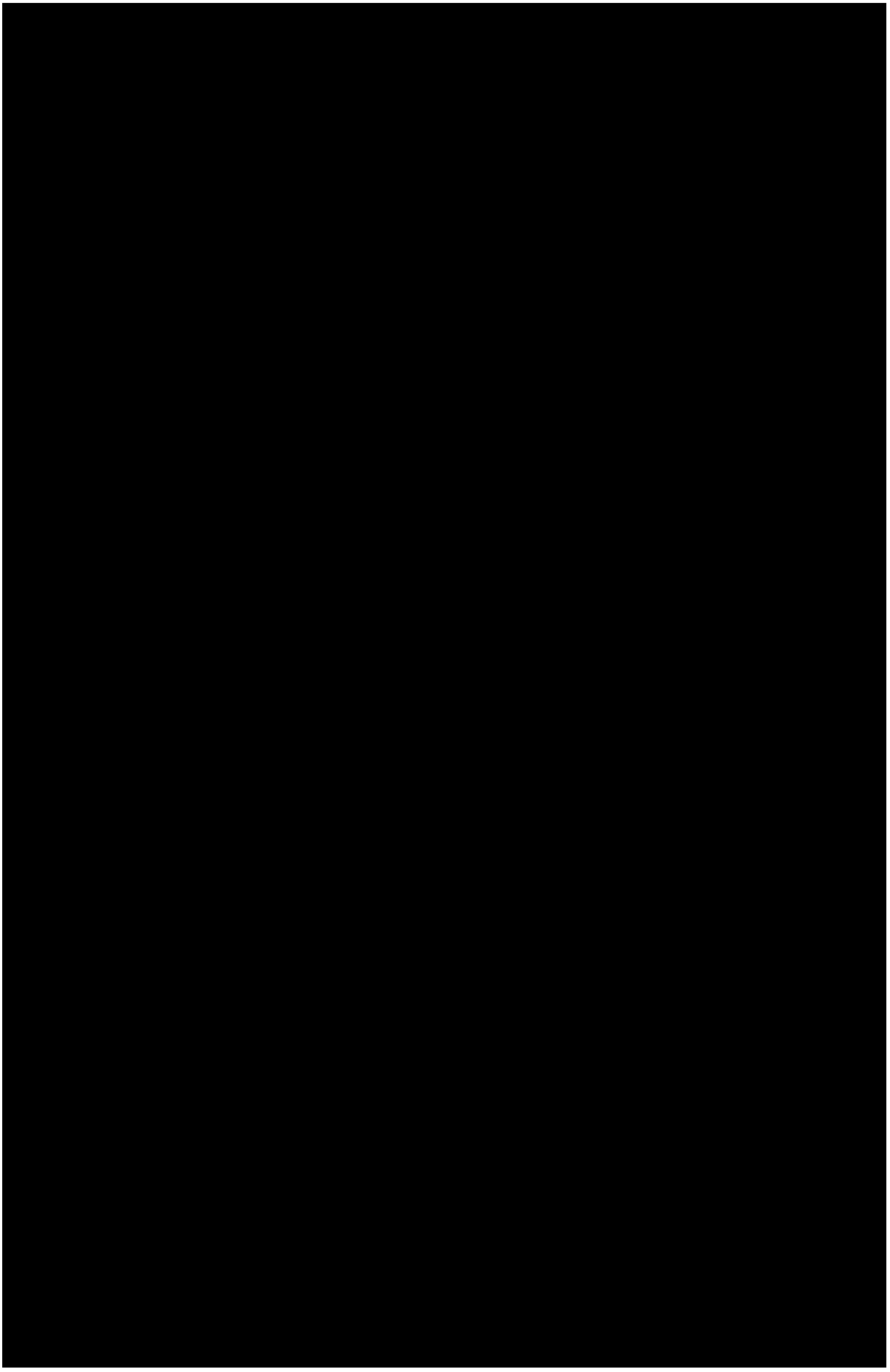
Patients who do not fulfill all eligibility criteria will be assigned a "screen failure"-status and not continue any further trial procedures; such patients will be replaced.

The following will be done during screening period #2:

- study ICF procedure for consent #2,
- eligibility ascertained for inclusion and exclusion criteria (see Section 5.1 and Section 5.2),
- documentation of;
  - patient demographics (age, ethnicity, race),
  - extended history of oncology disease(s), including dates of diagnosis and treatments history,
  - medical history of other (than oncology) disease processes (all prior significant illnesses that are relevant to patient safety or that the patient has experienced prior to screening; especially history of anaphylaxis or other reactions following vaccination, and history of immune deficiencies), and concomitant illness (illnesses present at the time of informed consent are to be regarded as concomitant illnesses; illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF and as SAEs if case seriousness criteria are met),
  - medications, including vaccines, and other relevant treatments (e.g. surgeries) during 28 days prior to signing informed consent; all applicable treatments (systemic and local), also before 28 days prior to informed consent signing, for oncology disease(s) will be collected,
  - concomitant medications/treatments,

- measurement/assessment of;
  - height and weight,
  - ECOG performance status (see Section 12.2),
  - vital signs including temperature, blood pressure (BP), and heart rate (HR) (BP and HR will be measured according to local standard practice); if systolic BP is below 100 mmHg or above 150 mmHg, and/or diastolic BP is below 50 mmHg or above 90 mmHg, the measurement will be repeated; the HR measurement will be repeated when below 50 bpm or above 100 bpm,
  - major body systems via physical examination; general appearance, skin, neck (incl. thyroid), ENT (ears, nose, throat), lungs, heart, abdomen, lymph nodes (all major stations palpable), extremities, neurology, and other sites as applicable (i.e. symptom directed),
- safety blood samples for hematology, coagulation, serum chemistry, urinalysis, hormones, and virus serology to be performed and evaluated locally, detailed as;





- a 12-lead electrocardiogram (ECG) will be recorded according to local site standard procedures, and
- adverse events will be reported according to NCI-CTCAE v5.0; documentation of AEs/SAEs starts after trial consent has been given by the patient.

7.4 Visits during study treatment

Note, measurements/assessments/sampling as outlined below are to be done before administration of study treatments if scheduled for the same day, if no other specific order of events is defined (e.g. for DTH-testing there is a special procedure and timing as outlined in Section 6.6.3).

7.4.1 Visits during EO2401 priming phase; V1, V2, V3, V4, and V5

Visit 1 (V1) must be performed within [redacted] screening/baseline CT.

Visits V1 to V4 are planned to be performed every 2 weeks[redacted] and V5 2 weeks +/-[redacted] after V4.

The following will be done during the visits [redacted]

- at V1, V2, V3, and V4;
  - administration of EO2401 and nivolumab should be done per allocated treatment cohort [redacted]
  - documentation of concomitant medications/treatments,
  - measurement/assessment of;
    - weight, and ECOG performance status (see Section 12.2),
    - vital signs, and major body systems via physical examination, as outlined in Section 7.3,
    - safety blood samples for hematology, coagulation, serum chemistry, and urinalysis, as outlined in Section 7.3,

    [redacted]
  - adverse events will be recorded according to NCI-CTCAE v5.0 (AEs will be monitored for the whole duration of the trial, but assumed recorded at visits for treatments, except in cases where the seriousness demands more immediate reporting, see Section 8),

- at V1, V2, V3, V4, and V5;

  - assessment of serum cortisol, TSH, and free T4, as outlined in Section 7.3
  - for women of childbearing potential, highly sensitive serum pregnancy test,
  - assessment of a 12-lead ECG, as outlined in Section 7.3,
  - a CT for tumor status assessment should be performed and tumor response assessment made, as outlined in Section 7.7.

7.4.2 Visits during EO2401 boost period; from V6 until treatment discontinuation

From visit V6 and onwards,

The following will be done during the visits:

- administration of EO2401 and nivolumab should be done per allocated treatment cohort

[redacted]

- at the visits for study treatment administration the following will also be done;
  - documentation of concomitant medications/treatments,
  - measurement/assessment of;
    - weight, and ECOG performance status (see Section 12.2),
    - vital signs, and major body systems via physical examination, as outlined in Section 7.3,
    - safety blood samples for hematology, coagulation, serum chemistry, and urinalysis, as outlined in Section 7.3,

[redacted]

  - adverse events will be recorded according to NCI-CTCAE v5.0 (AEs will be monitored for the whole duration of the trial, but assumed recorded at visits for treatments, except in cases where the seriousness demands more immediate reporting, see Section 8),

[redacted]

  - for women of childbearing potential, highly sensitive serum pregnancy test,

[redacted]

  - assessment of serum cortisol, TSH, and free T4, as outlined in Section 7.3,

[redacted]

  - a CT for tumor status assessment should be performed and tumor response assessment made, as outlined in Section 7.7.

[redacted]

[redacted]

7.5 Visits during post-treatment follow-up

7.5.1 Post-treatment visit for safety assessment; Vn+1

A post-treatment safety assessment visit should be performed 30 days [redacted] after the last study treatment has been administered.

The following will be done during the visits:

- documentation of concomitant medications/treatments,
- measurement/assessment of;
  - weight, and ECOG performance status (see Section 12.2),
  - vital signs, and major body systems via physical examination, as outlined in Section 7.3,
  - safety blood samples [redacted]
  - for women of childbearing potential, highly sensitive serum pregnancy test,
  - assessment of a 12-lead ECG,

    [redacted]
- adverse events will be recorded according to NCI-CTCAE v5.0 (AEs will be monitored for the whole duration of the trial, but assumed recorded at visits for treatments, except in cases where the seriousness demands more immediate reporting, see Section 8), and

[redacted]

7.5.2 Post-treatment follow-up before assessed progressive disease; Vnn

Patients who are discontinuing all study treatment without having had confirmation of progressive disease according to iRECIST criteria will be followed [redacted] after the latest performed CT assessment during the time period they received study treatment.

At these [redacted] timepoints the following will be done:

- a CT for tumor status assessment should be performed and tumor response assessment made, as outlined in Section 7.7,

[redacted]

- documentation of safety; after the post-treatment visit for safety assessment (see Section 7.5.1) has been made, only SAEs with plausible causal relationship with trial treatment will be documented (in addition, in case of death, an as precise cause of death as possible is going to be documented), and
- if applicable, collection of information regarding further anti-cancer treatments.

7.5.3 Post-treatment follow-up; Vnnn

Patients will be followed [redacted]

At these [redacted] timepoints, which if the patient is unable to attend a site visit can be a telephone contact, the following will be done:

- survival status documentation (in case of death, an as precise as possible cause of death is going to be documented),
- documentation of safety; after the post-treatment visit for safety assessment (see Section 7.5.1) has been made, only SAEs with plausible causal relationship with trial treatment will be documented, and
- if applicable, collection of information regarding further anti-cancer treatments.

7.6 Safety assessments

Safety and tolerability of EO2401 in combination with nivolumab, the primary endpoint for the phase 1 part of the trial, will be assessed by a descriptive medical assessment of the combined profile of incidences of AEs, TEAEs, SAEs, deaths, reasons for treatment discontinuation/delays, and laboratory abnormalities. Adverse events will be categorized by their system organ class (SOC) and preferred term (PT) using the current MedDRA version and graded according to NCI-CTCAE v5.0 [60].

In addition, in the randomized extension of Cohort 2A safety and tolerability of EO2401/nivolumab will be assessed versus internal concurrent controls (groups of patients treated with EO2401 monotherapy and nivolumab monotherapy, respectively), by incidences of adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs); AEs will be analyzed irrespective of relationship, and as related events.

The safety monitoring procedures of the trial are described in Section 8, the specific parameters to monitor/assess are outlined in Section 7.3, Section 7.4, and Section 7.5, and the timing of assessments also described in Table 5.

Clinical laboratory analyses as described in Section 7 will be performed by a local laboratory. More frequent evaluations may be performed at the Investigator's discretion if medically indicated; results of such evaluations should also be recorded in (e)CRFs. Normal ranges for all utilized local laboratories should be provided by the sites to the Sponsor.

7.7 Efficacy assessments

Computed tomography scans will be performed according to the Study Schedule [redacted] for assessments of tumor status; when adequate due to e.g. location of new metastatic disease, other examinations than CTs might be necessary for documentation of tumor status - such assessments are going to be done, and recorded in the trial documentation, on an individual patient basis based on the judgment of the Investigator. Tumor response and progression in this trial will primarily be evaluated by the investigators/local sites using the revised international criteria (1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) committee [36] as well as the modified iRECIST guidelines [37]; see Section 12.1 for a further description of the criteria.

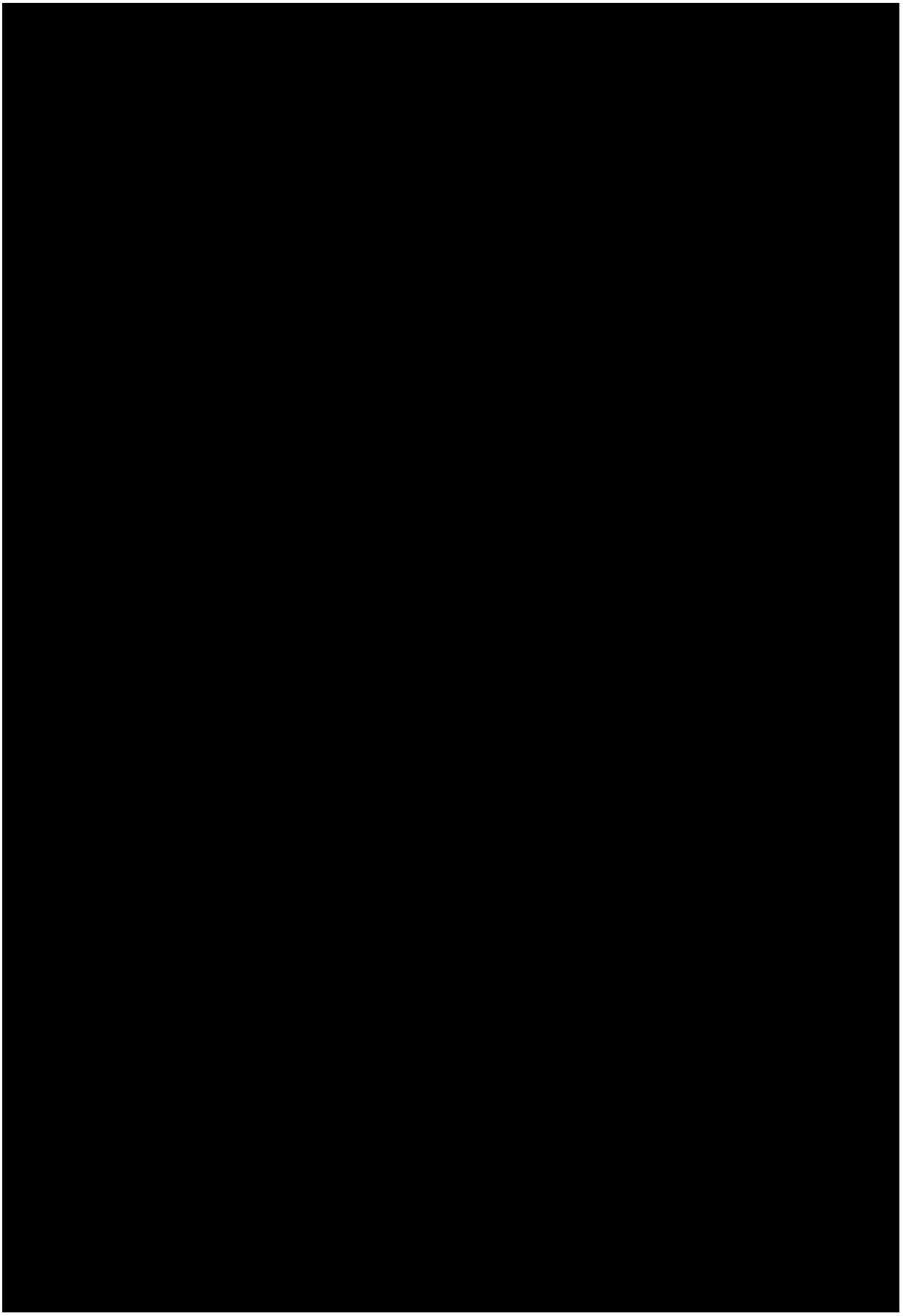
Investigators should especially note the different requirements for confirmatory scans as well as follow-up for the two criteria.

Of particular importance, in the context of confirmation of PD per iRECIST, and the given timeline of confirmatory scans to be performed at least 4 weeks, but no longer than 8 weeks after iUPD, is that in case of any signs of rapidly progressing disease establishment of PD and a following therapy switch should be made also earlier than 4-8 weeks after iUPD when necessary.

The main efficacy assessments will include ORR, DOR, PFS, and OS as outlined in Section 3.2.2.

The primary endpoint of the phase 2 part of the trial is the rate of patients without progression (according to iRECIST criteria [37]) or death due to any cause at 6 months after the first dose of randomized treatment. 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.

[redacted]



[redacted]

7.9 Assessments for other exploratory endpoints

[redacted]

8 SAFETY MONITORING

8.1 Safety monitoring definitions

8.1.1 Adverse events

International Council for Harmonization (ICH) guideline E2A defines an AE as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment".

According to the FDA (21CFR312.32), an AE means any untoward medical occurrence associated with the use of a drug in humans, whether, or not, considered drug related.

An AE can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver), symptom (e.g., nausea, chest pain), abnormal result of an investigation (e.g., laboratory finding), or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.1.2 Serious Adverse events

An SAE is any untoward medical occurrence that at any dose fulfills one or more of the following criteria:

- results in death,
- is immediately life-threatening,

  The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- results in persistent or significant disability/incapacity,

  Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (i.e. the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's bodily function/structure, physical activities, or quality of life).

- is a congenital anomaly/birth defect,
- requires inpatient hospitalization or prolongation of existing hospitalization, and

  A hospitalization is defined as an inpatient overnight stay, but this can be shorter than 24 hours.

- is another medically significant event defined as an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent any of the above listed outcomes.

8.1.2.1 Excluded events

Hospitalization for the following reasons will not be regarded as serious (i.e. will not be immediately reportable):

- routine treatment or monitoring of the disease under study, including hospitalization due to trial-related procedures, not associated with any deterioration of the patient's status,

- elective or pre-planned treatment (before signing the ICF) for a pre-existing condition that is unrelated to the disease under study and has not worsened since signing the ICF,
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions for an SAE and not resulting in hospital admission,
- underlying disease progression (the adrenal malignancy which is the basis for the patient enrollment in the trial) and events which are unequivocally (without doubt) related to the disease progression, and
- social reasons, respite care, and in the absence of a medical condition.

8.1.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs are serious events that are not listed in the Reference Safety Information section of the EO2401 Investigator Brochure. Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. In Europe, SUSARs will be reported as established in the EU Regulation No 536/2014.

When EO2401 is administered in combination with nivolumab, SUSARs are serious adverse events related to EO2401 that are not listed in the Reference Safety Information section of the EO2401 Investigator Brochure (i.e. all events, except local administration site reactions as described in the Investigator Brochure) and/or serious adverse events related to nivolumab that are not listed in the nivolumab European SmPC.

When nivolumab is administered alone, SUSARs are serious adverse events related to nivolumab that are not listed in the nivolumab European SmPC.

8.1.4 Severity/intensity versus seriousness

ICH E2A: The term "severe" is often used to describe the intensity (severity) of a specific event (as mild, moderate, or severe myocardial infarction); the event itself, however, may be of a relatively minor medical significance (such as a severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.2 Pregnancies

Patients who are fertile must use adequate birth control methods during the trial, from signing the ICF through 5 months after the last study treatment dose administered (see Section 6.9.4).

Pregnancy is not considered an AE unless it meets any criteria for becoming serious (see Section 8.1.2). However, it is the responsibility of the Investigator or their designee to report any pregnancy in a patient or the patient's sexual partner that occurs during the study. All patients who become pregnant must immediately discontinue the study drug and be withdrawn from study treatment.

The Investigator should make every effort to follow the patient until completion of the pregnancy and provide the corresponding information by the mean of a SAE/Pregnancy form within 2 weeks from awareness (see Section 8.5.3). The Sponsor Safety Group will periodically request from the investigator targeted follow-up information using specific pregnancy follow-up forms. If the events during pregnancy and/or outcome of pregnancy

(i.e. complications regarding mother/baby) meet the criteria for classification of an SAE, the Investigator must follow the procedures for SAE reporting.

8.3 Safety monitoring periods

8.3.1 Reporting

In patients exposed to study treatment, the following must be reported from the date of the patient's signing the ICF until 30 days after the final administration of study treatment:

- AEs regardless of their causal relationship to study treatment,
- SAEs without a plausible causal relationship to study treatment, and
- pregnancy of the patient.

SAEs with a plausible causal relationship to study treatment must be reported from the date of the patient's signing the ICF until indefinitely (regardless of the time elapsed from the final study treatment administration).

In addition, for consistency with nivolumab clinical trial protocols as advised by Bristol-Myers Squibb (marketing authorization holder for nivolumab), collect all non-serious adverse events (not only those deemed to be treatment-related) continuously during nivolumab treatment periods and for a minimum of 100 days following discontinuation of nivolumab treatment. The most conservative approach (longest follow-up) emanating from the two principles (30 days and specifics per above paragraph versus 100 days following discontinuation of nivolumab treatment) should be followed for nivolumab.

In patients not exposed to study treatment, the reporting period for AEs (including SAEs regardless of causal relationship) starts with signature of the ICF and ends:

- the date of the Investigators assessment of "screen failure"-status (see Section 5.3.2), or
- the date of the patient's consent withdrawal.

8.3.2 Follow-up

The Investigator assesses at each visit (or more frequently, if necessary) if there are any changes in AE diagnosis, severity, suspected causal relationship to clinical trial medication/procedure, interventions required to treat the event, and AE outcome.

An AE causally not related to study treatment is monitored (followed-up) until resolution, stabilization (becoming a permanent condition), or end of the clinical trial. Clinically relevant laboratory abnormalities will be followed up until they return to normal or become stabilized (permanent condition).

Any AE with a plausible causal relationship to study treatment as well as all SAEs (regardless of their causal relationship) will be followed up until the event has resolved or stabilized (permanent condition).

Pregnancies will be monitored by the Investigator to determine the outcome, including spontaneous abortion or voluntary termination, birth details, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications. Every infant should be followed up for 2 months after delivery.

8.4 Assessing adverse events

Information about adverse reactions (causally related events) already known for EO2401 monotherapy, or EO2401 in combination with nivolumab, can be found in the current

version of the EO2401 IB or will be communicated between IB updates in the form of "Dear-Investigator Letter".

8.4.1 Causality

The Investigator needs to assess the causal relationship of any AE in relation to the study treatment (see Section 6). In context of the intended study treatment, as composed of EO2401 [redacted] 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).

In the rare instances an AE would appear [redacted] between the first injection of EO2401, and the first infusion of nivolumab, there might be the possibility to assess causality for some types of AEs in relation to EO240 [redacted] without the nivolumab component. In addition, there might also be a possibility to assess causality for some types of AEs in relation to EO2401 [redacted], without the nivolumab component, in cases where nivolumab administrations have been terminated but treatment continues with EO2401 [redacted] There will be a possibility in the eCRF to record AEs taking these specific circumstances into account. Otherwise, it is assumed that the causality assessment is in relation to the complete study treatment.

The causality assessment is based on the Investigator's clinical judgment taking into consideration all relevant information available at the time of AE reporting including:

- temporal association of the event onset with administration of the medication,
- known type of reaction for the administered compounds,
- disappearance or abating of symptoms when the compound(s) is discontinued, or withheld,
- reappearance of symptoms when the compound is re-administered,
- event may or may not be caused by the patient's health condition,
- presence of risks or factors not related to trial intervention that are known to be associated with the occurrence of the event.

Causal relationship of all AEs will be classified as follows:

- **Not suspected**: it is not plausible that the AE is caused by the medication(s) and a likely alternative explanation exists. *There is no reasonable possibility of a causal relationship.*
- **Suspected**: it is plausible that the AE is caused by the medication(s). *There is a reasonable possibility of a causal relationship.*

  For the purposes of safety reporting, ***'reasonable possibility'*** *means there is evidence to suggest a causal relationship between the medication(s) and the AE.*

8.4.2 Severity/intensity

Severity or intensity of an AE should be assessed according to the NCI CTCAE v5.0 [60]; a grading scale is provided for AE terms displaying grades 1 through 5 with unique clinical descriptions of severity for each AE.

8.5 Reporting by the investigational site

8.5.1 Adverse events

Any AE (including SAEs), whether, or not considered to be causally related to the trial medication and regardless of its seriousness, must be reported (described and recorded) in the AE section of the patient's eCRF on an ongoing basis.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the ICF and that is documented as part of the patient's medical history; any clinically significant worsening of a pre-existing condition constitutes an AE. Also, any recurrence of a pre-existing condition is an AE.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a TEAE. 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 100 days after the last study drug administration [redacted]

A standardized question such as "Have you had any health problems since your last visit or since you were last questioned?" will be given by the Investigator or the investigational site personnel at each contact with the patient.

Progression of the underlying disease or an AE unequivocally (without doubt) related to the progression of the underlying disease, regardless of its outcome or seriousness criteria, does not need to be reported as an AE/SAE. However, the medical conditions and underlying diseases associated with disease progression needs to be captured on the AE eCRF page (as a non-serious AE). An SAE must be reported only if there are clinical symptoms/signs that cannot be without doubt associated with the progression of the underlying disease.

Whenever possible, a diagnosis rather than symptoms should be provided (e.g. anemia instead of low Hb).

Abnormal laboratory and other abnormal examinations (e.g. at physical examination) should not be reported as AEs, unless they are associated with clinical signs/symptoms, require medical intervention/therapy (e.g. transfusion due to low Hb), require a change in trial medication (e.g. temporary interruption of treatment, or definitive treatment discontinuation), or are otherwise considered clinically relevant by the Investigator. Clinically relevant laboratory, or examination abnormalities will be followed up until they return to normal or become stabilized (permanent condition).

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g. ALP and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e. cholecystitis) should be recorded on the AE eCRF page.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF page, along with a descriptor indicating if the test result is above or below the normal range (e.g. "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Physical examination findings will be compared with the baseline status and any clinically significant change, as assessed by the Investigator, should be documented as an AE.

A surgical procedure is not an AE but a therapeutic measure for a condition that necessitates surgery. Therefore, the condition for which the surgery is required should be reported as an AE.

Any pre-planned surgery (i.e. planned before signature of the ICF) or other intervention permitted by the protocol and the condition leading to that measure are not AEs. In such cases, the underlying condition needs to be documented in the patient's medical history.

Death itself is an outcome of an event, which needs to be described and reported using medical terminology. Information about death will be captured on the respective eCRF page along with relevant details (date of death, immediate and underlying causes of death).

8.5.2 Documenting in the eCRF

The reported term should be a medical diagnosis or sign/symptom of the event, not a procedure. Each symptom in a constellation of symptoms should be listed separately if the Investigator has not made a preliminary/tentative summary diagnosis.

Fluctuations or re-occurrences of a condition, which are considered normal for the patient and are recorded in patient's eCRF medical history, do not need to be reported as an AE. However, if the condition deteriorates during the trial it needs to be captured as an AE.

If the same AE occurs repeatedly it must be assessed and documented separately each time, if there are "AE-free" time periods between the AEs.

If possible, each AE should be evaluated to determine:

- event term or a description of the AE in medical terms (not as reported by the patient),
- severity grade as assessed by the Investigator (1 - 5 per NCI CTCAE v5.0),
- its causal relationship to study treatment as assessed by the Investigator (suspected; not suspected),
- event duration, including onset date and end date,
- action taken with study treatments due to the reported event (no action taken; interruption of administrations; treatment permanently withdrawn; other),
- other action taken (no action taken; medication required; surgical intervention required; other),
- event seriousness (non-serious or serious AE),
- event outcome (resolved without sequelae, resolved with sequelae, not resolved, fatal, unknown), and
- disease progression-related event (yes, no).

8.5.3 Immediately reportable events - Serious Adverse Events

The Investigator or designated investigational site staff must immediately (within 24 hours [redacted]) notify/report to pharmacovigilance at the Sponsor, [redacted] any initial or medically relevant follow-up information about SAEs, or pregnancies (see Section 8.2).

All immediate reports from the investigational site to the Safety Group (i.e. SAEs and pregnancy reports) must also be recorded in the site's source documentation.

The primary mode of reporting a SAE is based on entering the appropriate and complete information into the clinical database via the SAE reporting form and submitting the SAE form [redacted] to the trial Safety Group within 24 hours of obtaining knowledge of the event.

The SAE Form [redacted] is to collect data surrounding the event (e.g. the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether, or not therapy was interrupted or discontinued). The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic test reports, and procedures as well as all pertinent medical information related to the event will also be collected. Once the AE page has been updated in the eCRF for an SAE by the site, the site will submit it to the safety group within the system. Then an alert from the clinical database will be initiated and sent to the Safety Group. The Safety Group will generate the SAE report, a PDF extracted from the clinical database, and send to the Sponsor.

The Safety Group will generate SAE queries requesting missing information, correction of implausible, etc., and add the queries directly in the clinical database. It is the Investigator's responsibility to be diligent in providing the answer as soon as it is available by entry of the corrections in the eCRF and submission of the follow-up SAE report to the Safety Group.

In case of technical or any other reason the SAE reporting cannot be carried out via the EDC system per above, the Investigator (or designated investigational site staff) will complete a paper SAE form and send to the Safety Group as outlined below. The paper SAE form will be provided to the sites prior to start of the study.

[redacted]

When a paper form is completed, follow-up information should not be reported on the same form that was used for the initial reporting, but using a new form filled in only with the new information. Changes/completions need to be done in a Good Clinical Practice (GCP)-compliant manner (i.e. dated and initialized). Originals of the report forms must be kept in the site study file.

Initial reports of SAEs should never be left on telephone voicemails. In case of using the paper SAE form, please always fax or e-mail the SAE report, and follow-up with a telephone call if needed.

Serious AEs to be reported to th [redacted] Safety Group:

Facsimile: [redacted]

E-mail:

In case of urgent questions regarding SAE reporting please call:

Enterome Medical Monitor [redacted]

[redacted]

The initial Pregnancy Data Collection form should be handled in the same way as an initial SAE report, i.e. via the EDC system, or via the specific paper form.

Follow-up information is to be sent within the same timelines using the same modes of reporting as outlined above.

All sites will follow their institutional requirements for submission of SAEs to their IRBs/IECs.

The processing and reporting of all relevant SAEs to authorities will be done by the Sponsor or Sponsor's designee according to all applicable rules/regulations. The Sponsor or designee will inform all investigational sites about reported relevant events according to applicable regulations.

8.5.3.1 Minimum notification/reporting requirements

The following information must be provided for a valid notification/report:

- identification of the notifying/reporting person (e.g. name of the reporter),
- identification of the patient (e.g. patient trial identification number),
- concerned IMP and/or clinical trial (e.g. EO2401, trial EOADR1-19),
- reason for notification/reporting (i.e. SAE, or pregnancy), and
- event term.

*In addition, providing the **assessment of the causal relationship** is necessary for comprehensive evaluation by the Sponsor.*

[redacted]

8.6 Independent Data Monitoring Committee (IDMC)

The IDMC will serve as an external monitoring group for the study. The primary role of the IDMC will be to examine the safety and tolerability of study participates throughout the duration of the study. The IDMC will be created to further protect the rights, safety, and well-being of patients who will be participating in the trial by monitoring their progress and results. 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 in relation to the recruitment start of Cohort 2A/B and Cohort 3A/B.

The major tasks for the IDMC are outlined in relation to the description of the design of the trial (see Section 4.2).

[redacted]

The frequency of IDMC meetings will be based on the development of the safety profile of the study treatments and necessity to assess safety events and progression steps in the trial (e.g. transitions between cohorts).

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.

The IDMC members are to be international oncology/immune-oncology experts who are not in other ways than via the IDMC involved in the current trial. The IDMC will be described in detail in an IDMC Charter.

9 STATISTICAL EVALUATION

9.1 Analysis populations

The following analysis populations will be included:

- The All Patient Population 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 Per-Protocol (PP) Population will consist of patients who received at leas [redacted] of EO2401, for whom no important protocol deviations occurred, and who have at least one evaluable post-screening tumor assessment. Patients who are not considered evaluable for this population will not be replaced.
- The Safety Population 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] 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 EO2401 he/she should be evaluated in the Safety Population.

Efficacy will be analyzed using both the FAS and PP populations. Safety will be analyzed using the Safety Population, and Cohort 1 will be analyzed based on patients evaluable for the 3-by-3 design.

9.2 Statistical methods

All data collected in this trial will be reported by patient data listings, summary tables, and figures for all demographic and baseline characteristics, medical history, efficacy, and safety variables. Proportions and the denominators will be provided to summarize response, toxicity, and other categorical variables. Objective response rate by the RECIST 1.1/iRECIST criteria will be estimated with two-sided exact 95% confidence intervals. Duration of response, PFS, and overall survival will be analyzed using the method of Kaplan and Meier and Cox proportional hazards model. The PFS rate at 6 months after the first dose of randomized treatment, the primary endpoint for the randomized study part, will be calculated based on all patients in the analysis set and stratified by randomized treatment.

For baseline parameters, safety and efficacy analyses, patients enrolled in Cohort 1 will be added to the respective Cohorts 2A, and 3A, as appropriate. Baseline and safety data will additionally be presented for sub-cohorts 1a+1b and 1c+1d separately.

Statistical assessments of correlations between e.g. immunogenicity parameters (see Section 3.2.3, Section 7.8.4, and Section 7.9) and tumor progression/response and safety outcome parameters will be conducted as described in the SAP.

For the initial study part (Cohorts 1, non-randomized 2A, 2B, 3A, and 3B) statistical tests may be planned in the SAP or performed as needed. The importance of the tests does not reside in making conclusions on statistical relevance of differences, but rather identification of possible results that could be worth further exploration.

The randomized extension of Cohort 2A is from a statistical perspective described in Section 9.4.2, and the statistical methods to be used will be further outlined in the SAP.

The primary analysis of the study will be performed when the last patient included in the study will reach 6 months of study treatment; additional data will be generated:

- when all patients will have stopped the study treatment and have been followed for safety [redacted].
- when overall survival information will have been collected for all patients who received the study treatment or when the sponsor decides.

9.3 Interim analysis

The nature of the study, i.e. 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.

Above is not applicable for efficacy analyses related to the randomized extension of Cohort 2A, where information only will be utilized for scientific discussions/presentations at the timepoint of verification of passing (or not) to the second stage of the Simon-design, and at the final analysis of the Simon-design.

9.4 Determination of sample size

9.4.1 Considerations regarding 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 (see Section 1.1.1 and Section 1.1.2). 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; also taking into account the assumption that for efficiency the recruitment time should not be longer than approximately 18 months with a reasonable number of highly specialized trial sites. Based on these factors, the trial was initially 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 (see Section 4.2 regarding adjusted patient numbers).

[redacted]

[redacted]

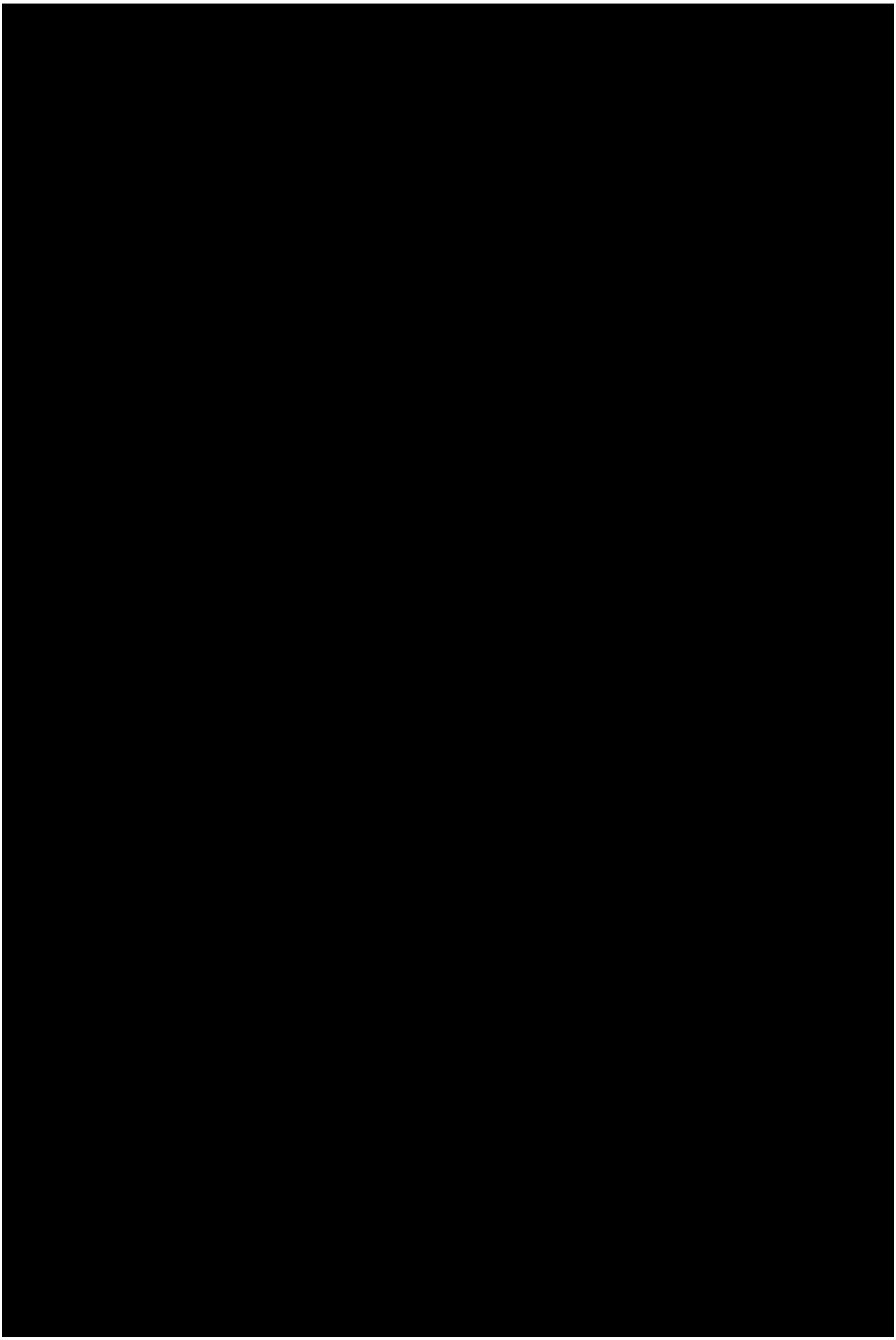
The 3-by-3 approach for Cohort 1 include predefined stopping rules if concerning safety events would be encountered; in short 0 (zero) concerning safety event in 3 patients, or 1 concerning safety event in 6 patients, are considered acceptable (see further Section 4.2.1).

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.

[redacted]

9.4.2 Considerations regarding the randomized extension of Cohort 2A

[redacted]



10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines,
- applicable International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and
- applicable laws and regulations; approval will be obtained from the appropriate regulatory authorities before any site is initiated in a country.

Before study start, each Site Principal Investigator is required to sign a protocol signature page confirming his agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to clinical research associates (CRAs), auditors, the Sponsors quality assurance representatives, designated agents of the Sponsor, ECs, and regulatory authorities as required.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

The Investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
- notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures, and
- providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

A signed and dated statement that the protocol and ICF have been approved by the ECs must be given to the Sponsor (or designee) before study initiation.

10.2 Finances and insurances

Financing and insurance will be addressed in separate site agreements.

For each participating patient, the Sponsor has taken out insurance covering the amount determined by respective national laws. All participating patients will be informed about the existence of the insurance in the patient informed consent. They have the right to review the terms and conditions of the insurance.

[redacted]

10.3 Informed consent

Written informed consent for the study will be obtained from all patients before any protocol-specific procedures are conducted. The ICF generated by the Sponsor or designee will be approved (along with the protocol) by the IRB/IEC.

Information about the study will be given to the patient both verbally and in writing. The written patient information sheet will explain the objectives of the study and its potential risk and benefits. The patient should have adequate time to read the information sheet and to ask the Investigator any questions. The Investigator must be satisfied that the patient has understood the information provided before written consent is obtained. If there is any doubt as to whether the patient has understood the written and verbal information, the patient should not enter the study.

If a patient agrees to participate, he/she will be asked to sign and date the study ICF, which will be retained by the Investigator. A copy of the signed ICF will be given to the patient. The informed consent process must be documented in the patient's source documents. The original ICF must be retained by the Investigator and made available for inspection by the Study Monitor.

Following the stage 1 analysis results and the IDMC recommendations and considerations (please refer to section 1.3.7), the patients with currently ongoing treatment in the randomized Cohort 2A should be given the possibility to continue study treatment per protocol, provided they are informed about the outcome of the stage-1 assessment of the Cohort 2A-I Simon 2-stage design. Oral consent and written addendum to ICF will be collected as per applicable regulations.

> For patients who are unable to visit the site, and in accordance with applicable laws, the consent form may be sent to them by post. After sufficient time for reflection and a possible telephone call to clarify any question the patient may have with the investigator or delegate, they will be asked to return the signed and dated consent form by post to the investigator site. All correspondence as well as a copy of the consent form received from the patient, must be retained, and filed in the participant's medical file.

10.4 Future use of patient samples; sample traceability

Following the completion of all study testing, the remaining tissue and blood/blood components may be used for future biomedical research (e.g. additional analysis on PBMC). This research will help to understand response against other tumor-associated antigens not included in the current peptide mix and possibly DNA sequencing. If a patient requests destruction of his/her tissue and blood samples and the samples have not yet been de-identified, the Sponsor will destroy the samples under specific regulations and notify the Investigator in writing that the samples have been destroyed. Patients will be asked whether, or not they consent to the (optional) future use of patient samples. This consent will be documented separately, and patients will not be excluded from study participation if they do not consent to this future use of residual samples.

Blood samples being collected and stored for research purposes within this study should be traceable as required by local regulations, or the clinical trial authorization, as applicable. The Sponsor and Investigator institutions should keep their parts of the traceability records accordingly.

[redacted]

10.5 Patient data protection

Patients will be assigned a unique identifier and will not be identified by name in eCRFs (data pseudonymization), study-related forms, study reports, or any related publications. Patient and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or Investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her medical records may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, and by inspectors from regulatory authorities.

10.6 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, Sponsor personnel (or a designated contract research organization [CRO]) will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of filling of the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that the study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each patient in the study recruited at the relevant site, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF filling. The Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.7 Handling of data and data collection

Data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679 and other national legislations as applicable.

All individual, patient-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

At an organizational level, to meet European requirements, the sponsor has appointed a certified Data Protection Officer (DPO) in charge of ensuring compliance with data protection regulations. The DPO oversees the conduct of the required Data Protection Impact Assessment (DPIA) to assess and protect rights and freedoms of data subjects regarding processing operations. All data processors (e.g. sites and vendors) are bound by a data protection agreement (DPA). If personal data are transferred

to a third country within the meaning of the GDPR, the DPA contains the Standard Contractual Clauses established by the European Commission. The DPO is also in charge of any data subject request and can be contacted directly by the data subject through the email provided in the information sheet.

At a technical level, personal data are stored in a secured environment, encrypted, and partitioned from other data. The Sponsor, or designee, will supply the investigational site with access to a web-based EDC computer system. The designated Investigator site staff will not be given access to the EDC system until they have been trained.

Access to the EDC system at the site, for vendors, at the Sponsor, and at the CRO is password protected. Study access is granted to site personnel only after they have been trained in the use of the EDC system by web-based training at the investigational site.

The EDC system contains a system generated audit trail that captures any changes made to a data field, including who made the change, and the date and time it was made. This information is available at the Investigator's site, and at the Sponsor (and CRO when applicable).

Data will be entered into the study database by the Investigator/Study Coordinator at each site. Entries made in the EDC screens should be completed within 5 days of the patient's study visit and must be supported by source documents maintained for all patients enrolled in the study.

All data generated from external sources (e.g. central laboratory) and transmitted to the Sponsor or designee electronically will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each patient who signs an ICF and undergoes any pre-screening or screening procedures, according to the eCRF completion instructions. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the Investigator staff before transfer of data to the Sponsor (or a designated CRO).

Sponsor personnel (or a designated CRO) will review the eCRFs entered by site staff for completeness and accuracy (verification against source documents) and instruct the site personnel to make any required corrections or additions. System or manually generated queries are raised to the investigational site using the study EDC system. Designated Investigator/site staff is required to respond to the queries and make any necessary changes to the data.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

At the conclusion of the study, the occurrence of any protocol deviations will be determined (guidance can be found in Section 12.4).

After these actions have been completed and the database has been declared to be complete and accurate, it will be locked.

After database lock, the Investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

A specific EDC tool will be used after the database lock planned at the last safety visit of the last treated patient, to collect the survival data of all patients who will be followed until death or until sponsor decides to stop the study.

Following the final safety visit of the last treated patient and the subsequent database lock, the sponsor will internally utilize an EDC tool compliant with 21 CFR Part 11 to collect survival data. Survival data will be transmitted directly from the investigational sites to the sponsor, who will then integrate these data into the EDC system.

10.8 Collection and storage of biological samples

The details on the collection and storage of biological samples can be found in the laboratory manual.

10.9 Protocol amendments

Any substantial amendments in the research protocol during the period, for which the IEC/IRB approval had already been given, will not be initiated without submission of an amendment for IEC/IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the Investigator in the interest of preserving the safety of all patients included in the trial.

10.10 Protocol deviations

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 IEC/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.

Important protocol deviations, such as significant non-compliance or other serious unforeseen deviations deemed to invalidate the data collected in lieu of the purpose of the study will lead to exclusion of data from analysis.

All decisions regarding the type of deviations will be made prior to commencing the final analysis on the finally locked database. A listing of patients with protocol deviations will be maintained by the Sponsor (or designee) and a listing of protocol deviations (see Section 12.4) will be presented in the final study report.

Investigators shall apply due diligence to avoid protocol deviations. If the Investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the EC and concerned regulatory authorities, it cannot be implemented.

The Investigator will report protocol deviations to their IEC/IRB per institutional reporting requirements.

10.11 Change in investigator

If any Investigator retires, relocates, or otherwise withdraws from conducting the study, the responsibility for maintaining records may be transferred to the Sponsor or designee, IRB, or another Investigator. The Sponsor or designee must be notified of and agree to the change. Regulatory agencies will be notified with the appropriate documentation.

10.12 Clinical study report

A clinical study report will be prepared following the primary analysis of the study. Addenda to this report will be prepared when new data will have been generated. The Global

Coordinating Investigator should if required by local law/regulations be the Investigator who should review and sign the study report.

10.13 Confidentiality/disclosure

All information provided regarding the study, as well as all information collected and/or documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

10.14 Record retention

Essential documents must be retained for longer than 5 years after completion of the study, 2 years after the final marketing authorization in an ICH region or until at least 2 years have elapsed since the discontinuation of clinical development of the study drug. If it becomes necessary for the Sponsor or a relevant competent authority to review any documentation relating to the study, the Investigator must permit access to such records.

Study files may be discarded upon written notification by the Sponsor. To avoid error, the Investigator must contact the Sponsor before destroying any records or reports pertaining to the study, to ensure that retention is no longer required. Other source documents, such as patient's medical records, must be retained for the maximum time permitted by the hospital or institution and until such time when the Investigator is informed by the Sponsor that there is no further need to do so.

In addition, in accordance with the Investigator agreement, the Sponsor should be contacted if the Site Principal Investigator plans to leave the investigational site so that appropriate arrangements can be made.

Archiving of the clinical trial master file

Unless other law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

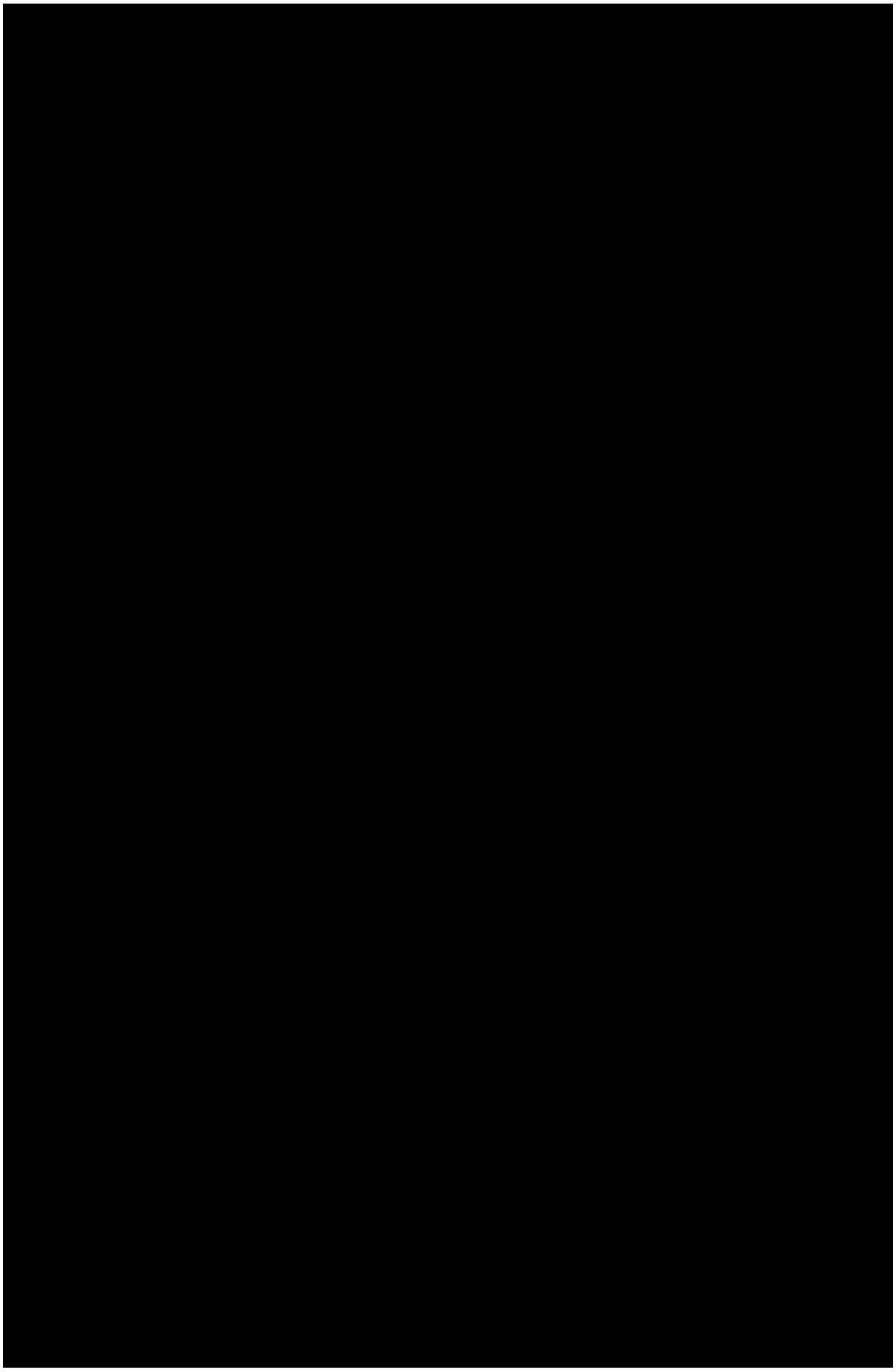
10.15 Publications

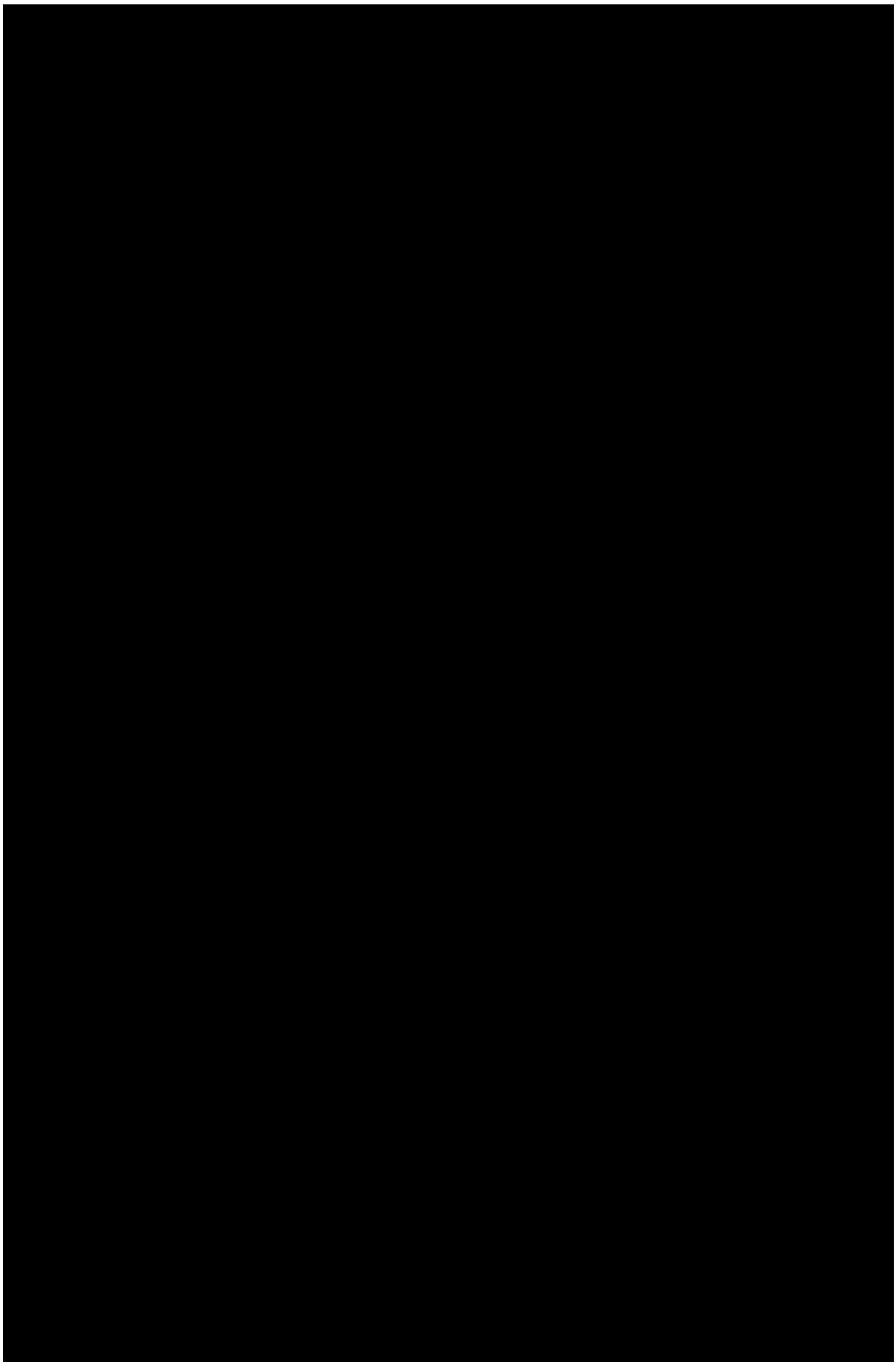
If based on preliminary data, or on completion of the study, the data warrant publication/presentation according to a judgement by the Global Coordinating Investigator after collaborative discussions with other involved Investigators (meaning such Investigators who have recruited patients to the trial or have had a significant participation in the trial by other means), the results may be published/presented, under the auspice of the Global Coordinating Investigator, in a recognized scientific journal, or at a scientific conference, subject to the provisions of the following process:

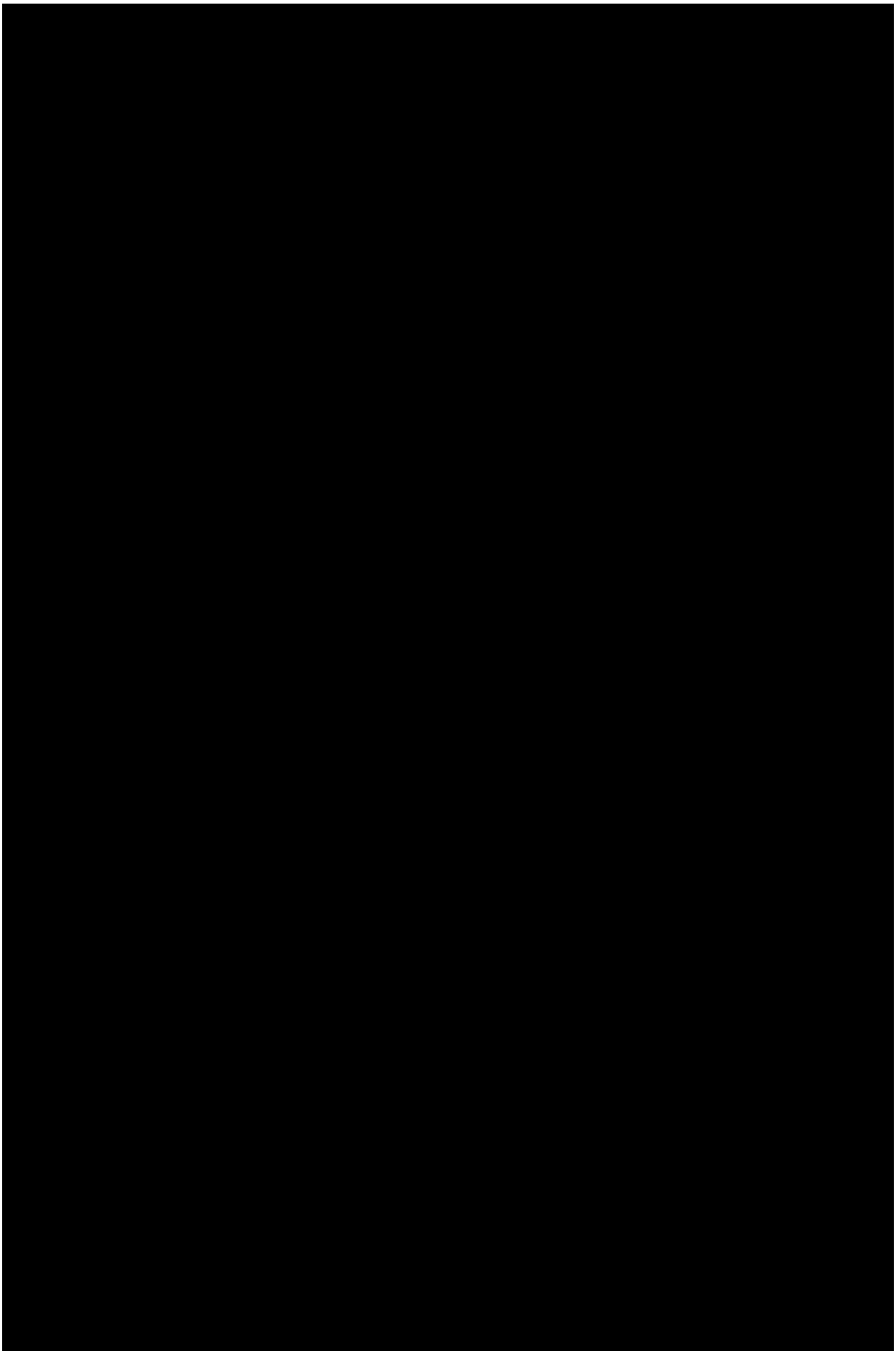
- no publication based on the results obtained at an individual trial site (or group of sites) shall be made before the first multicenter publication or presentation unless otherwise agreed in writing. Notwithstanding the foregoing, if a multicenter publication is not published within twelve (12) months after completion of the clinical trial and final lock of the clinical trial database at all research sites that are part of the multicenter clinical trial or any earlier termination or abandonment of the clinical trial, or if the Sponsor informs the Principal Investigator that such multicenter publication will not take place, or if publication has been agreed otherwise, the Principal Investigator shall have the right to publish or present the methods and results of the clinical trial,

- in case a publication/presentation is proposed the Global Coordinating Investigator shall discuss the proposed publication/presentation with the Sponsor, and give the Sponsor a relevant time (depending on the planned publication situation; e.g. referred journal, or scientific conference abstract, submission) to support with data collection and analyses which could be the basis for a publication,
- the Sponsor should have adequate time for review of proposed abstracts, manuscripts, and/or other presentation materials before submissions (time is dependent on the planned publication situation; adequate time for review before submission of a complete manuscripts to a referred journals can be considered as 30 days, to respond with any requested revisions, including the deletion of confidential information which must be done).

11 LITERATURE







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12 APPENDICES

12.1 Appendix 1: Criteria for measurement of tumor response and progression; RECIST and iRECIST

Response and progression in this trial will be evaluated using the revised international criteria (1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) committee [36] as well as the modified iRECIST guidelines [37]. Investigators should especially note the different requirements for confirmatory scans as well as follow-up for the two criteria.

RECIST 1.1 Response and Evaluation Endpoints

Measurable Disease

Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-target Lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

Response

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology, specialized imaging, or other techniques as appropriate for individual cases) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Confirmatory measurement/duration of response

Confirmation: In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease. Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

[redacted]

Table 7 : Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table 2.

iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

In the context of confirmation of PD per iRECIST, and the timeline of confirmatory scans to be performed at least 4 weeks, but no longer than 8 weeks after iUPD, it should be specifically noted that in case of any signs of rapidly progressing disease establishment of PD and a following therapy switch should be made also earlier than 4-8 weeks after iUPD when necessary.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in Table 8 and Table 9, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

[redacted]

Table 8 : Time-point iRESPONSE

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: ○ further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: ○ previously identified T lesion iUPD SOM ≥5 mm and / or ○ NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: ○ previously identified T lesion iUPD ≥5 mm and / or ○ previously identified NT lesion iUPD (need not be unequivocal) and /or ○ size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on ○ increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

[redacted]

Table 9 : iRECIST best overall response

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based

on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case.4 For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

Cytology, Histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

12.2 Appendix 2: ECOG performance status

The performance status grading as outlined below was developed by the Eastern Cooperative Oncology Group (ECOG) [39].

Table 10 : ECOG performance status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

12.3 Appendix 3: New York Heart Association Functional Classification

Table 11 : New York Hear Association functional classification

Class	Patient Symptoms
Class I (None)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

12.4 Appendix 4: Protocol deviations

Notes:

- *the term "subject" has been switched to "patient" by the Sponsor in the below text, and*
- *in trial EOADR1-19 the terminology only includes the word "Deviation", which is subdivided into "Major Deviations" (corresponding to the "Protocol Violation" term as defined by NIH below, when the definition for "Minor Deviation" is not fulfilled), and "Minor Deviations" (corresponding to "Minor Protocol Deviation" as defined by NIH below).*

http://www.genome.gov/Pages/Research/Intramural/IRB/Deviation_Violation_examples8-07.pdf

National Institute of Health (NIH) Institutional Review Board Professional Administrators Committee Version 5.1

Regulatory Process Workgroup 11/18/2005

Protocol Deviations and Violations

Protocol Deviation - A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and that has not been approved by the EC. Upon discovery, the Principal Investigator is responsible for reporting protocol deviations to the EC using the standard reporting form.

Any change, divergence, or departure from the study design or procedures of a 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 protocol violation.

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.

Protocol Violation - A protocol violation is a deviation from the EC approved protocol that may affect the patient's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

If the deviation meets any of the following criteria, it is considered a protocol violation.

Example list is not exhaustive.

I. The deviation has harmed or posed a significant or substantive risk of harm to the patient.

Examples:

- a patient received the wrong treatment or incorrect dose,
- a patient met withdrawal criteria during the study but was not withdrawn, and
- a patient received an excluded concomitant medication.

II. The deviation compromises the scientific integrity of the data collected for the study.

Examples:

- a patient was enrolled but does not meet the protocol's eligibility criteria,
- failure to treat patient per protocol procedures that specifically relate to primary efficacy outcomes (if it involves patient safety it meets the first category above),
- changing the protocol without prior EC approval, and
- inadvertent loss of samples or data.

III. The deviation is a willful or knowing breach of human patient protection regulations, policies, or procedures on the part of the Investigator(s).

Examples:

- failure to obtain informed consent before initiation of study-related procedures,
- falsifying research or medical records, and
- performing tests or procedures beyond the individual's professional scope or privilege status (credentialing).

IV. The deviation involves a serious or continuing noncompliance with federal, state, local, or institutional human patient protection regulations, policies, or procedures.

Examples:

- working under an expired professional license or certification,
- failure to follow federal and/or local regulations, and intramural research or clinical center policies, and
- repeated minor deviations.

V. The deviation is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles.

Examples:

- a breach of confidentiality, and
- inadequate or improper informed consent procedure.

Minor Protocol Deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the EC and which DOES NOT have a major impact on the patient's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

[redacted]

12.5 Appendix 5: The CKD-EPI equation for estimating glomerular filtration rate [63]

The CKD-EPI Equation for Estimating GFR on the Natural Scale*

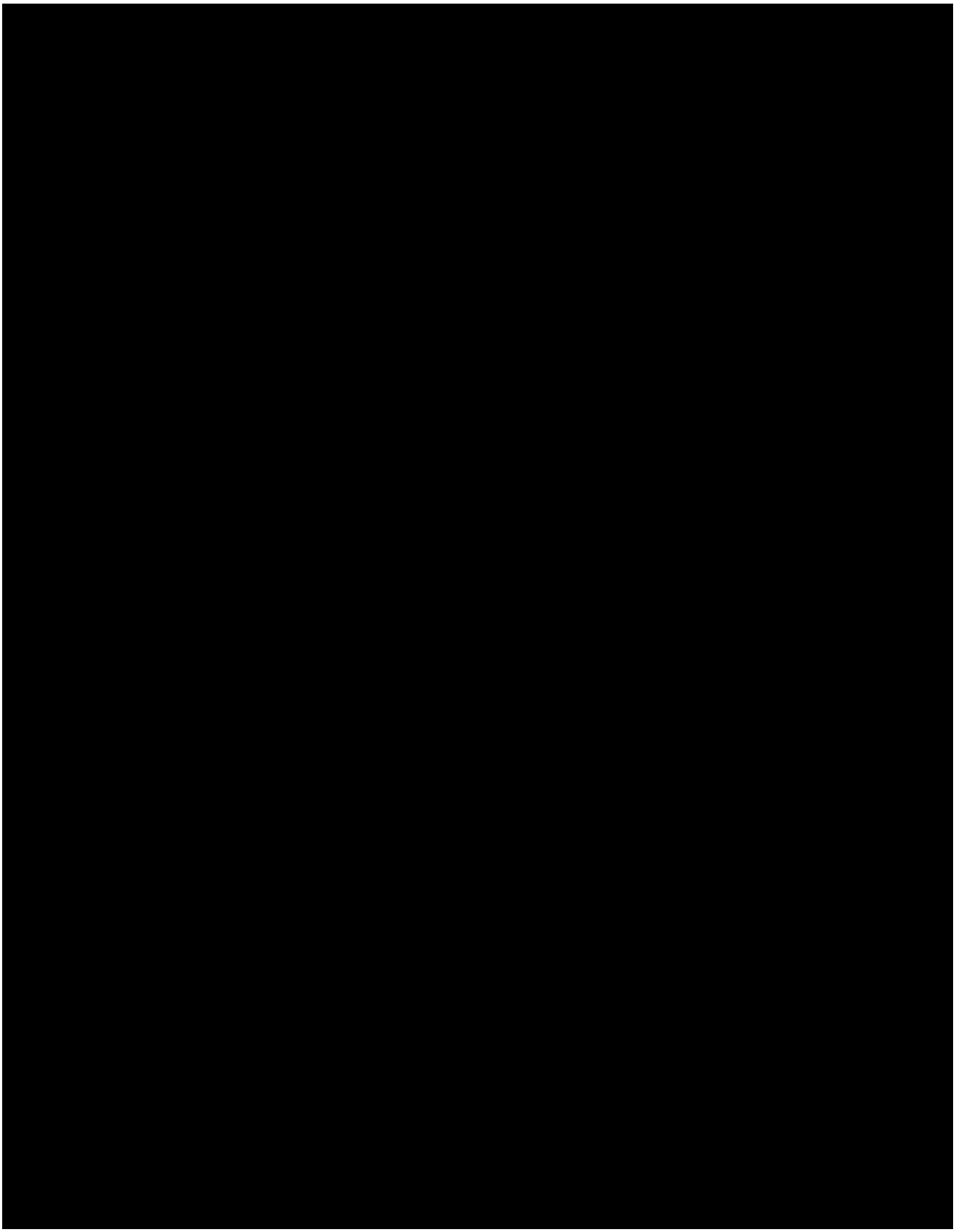
Race and Sex	Serum Creatinine µmol/L (mg/ dL)	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

*Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min per 1.73 m2 to mL/s per 1.73 m2, multiply by 0.0167. We derived equation coefficients from pooled development and internal validation data sets.

The CKD-EPI equation, expressed as a single equation, is $GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

[redacted]



[redacted]

12.7 Appendix 7: Management algorithms regarding nivolumab for studies under CTCAE version 5.0

These general guidelines are standard nivolumab protocol safety algorithms (28-Sep-2020) and recommended for inclusion also in protocol EOADR1-19 by Bristol-Myers Squibb (marketing authorization holder for nivolumab).

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy.
Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; Limiting instrumental ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recurs: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Diarrhea (G3): ≥ 7 stools per day over baseline; IV fluids ≥24 hrs; limiting self care ADL Colitis (G3): severe abdominal pain, peritoneal signs G4: life-threatening, perforation	• Discontinue or delay I-O therapy per protocol* • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication) or other immunosuppressants. • Consider testing CMV for steroid refractory colitis Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
* Discontinue for Grade 4 diarrhea or colitis. For Grade 3 diarrhea or colitis, 1) Nivolumab monotherapy: Nivolumab can be delayed. 2) Nivolumab+ Ipilimumab combination: Ipilimumab should be discontinued while nivolumab can be delayed. Nivolumab monotherapy can be resumed when symptoms improve to Grade 1. Please refer to protocol for dose delay and discontinue criteria for other combinations.

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v5)	Management	Follow-up
Grade 1 Creatinine > ULN to ≤ 1.5x ULN	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline:</u> •Resume routine creatinine monitoring per protocol <u>If worsens:</u> • Treat as Grade 2 to Grade 4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1-2 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u>: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections <u>If no improvement or worsening</u>, add additional immunosuppression.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v5)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	If improves to Grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider imaging for obstruction.

Liver Function Test	Management	Follow-up
AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol • Consider increasing frequency of monitoring	• Continue LFT monitoring per protocol If worsens: • Treat as below
AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen: • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when and AST ALT returns to <3X ULN and bili <1.5X ULN, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
AST or ALT > 5 x ULN or T.bili >3 x ULN	• Delay or Discontinue I-O therapy per protocol^ • Increase frequency of monitoring to every 1-2 days • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist or hepatologist	If AST and ALT returns to <5X ULN and bili <3X ULN, • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens, or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider tacrolimus or other immunosuppressants per local guidelines Note: Avoid infliximab due to potential risk of liver failure

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
^ Please refer to protocol dose delay and discontinue criteria for specific details.
*The recommended starting dose for AST or ALT > 20 x ULN or bilirubin >10 x ULN is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

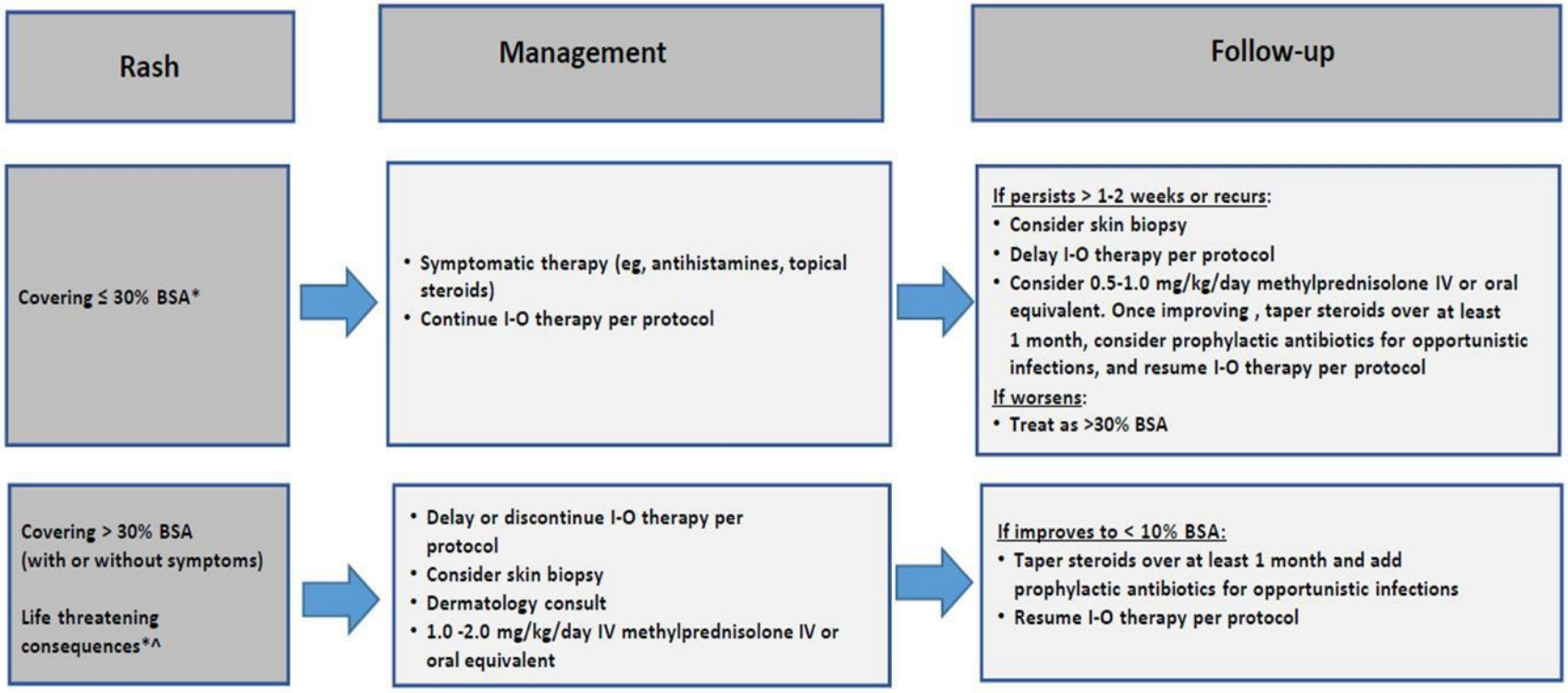
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.
Consider visual field testing, endocrinology consultation, and imaging.

Endocrinopathy	Management	Follow-up
Asymptomatic TSH abnormality or Hyperglycemia requiring no medical intervention	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: o include fT4 at subsequent cycles as clinically indicated; o consider endocrinology consult	• Monitor TSH as per protocol • Monitor blood sugar • If symptomatic or blood sugar requiring initiation of treatment or change in management, manage as below
Symptomatic endocrinopathy or hyperglycemia requiring initiation of treatment or change in daily management or work up	• Evaluate endocrine function; consider endocrinology consult • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent for hypophysitis • Initiate appropriate hormone/medical therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Continue IO therapy. Repeat labs in 1-3 weeks /MRI in 1 month Hyperglycemia: Screen for Diabetic Ketoacidosis (DKA). If negative, continue IO and treat diabetes. If DKA hold IO, admit, manage DKA. Steroids not recommended for DKA/hyperglycemia	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist	• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component • If adrenal crisis resolves and patient is adequately controlled with physiologic hormone replacement, patient can resume IO therapy per protocol.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v5 for term-specific grading criteria.

^If Steven-Johnson Syndrome (SJS),toxic epidermal necrosis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS, TEN, or DRESS is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v5)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol • Discontinue I-O for select AEs^	• Continue to monitor per protocol. If worsens: • Treat as Grade 2 or Grade 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Discontinue I-O for select AEs^ • Consider neurology consult • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent	If returns to baseline: • Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg. prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

^Discontinue for any grade myasthenia gravis, Guillain-Barre syndrome, treatment-related myelitis, or encephalitis.

Myocarditis Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Myocarditis	Management	Follow-up

Symptoms with mild to moderate activity or exertion	• Delay I-O therapy; hospitalization with cardiac monitoring
	• Urgent cardiology consultation for evaluation and management
	  ○ Troponin and BNP
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	• Prompt initiation of 2 mg/kg/day methylprednisolone IV or equivalent
		• If worsens, intensify treatment according to grade
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP. as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessment and cardiology follow-up
		• Retreatment may be considered after recovery and completion of steroid taper

Severe with symptoms at rest or with minimal activity or exertion; intervention indicated
 	
Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)
	• Permanently discontinue I-O therapy
	• Hospitalize to intensive cardiac monitoring
	• Cardiac evaluation to include:
	  ○ Troponin and B-type natriuretic peptide monitoring
	  ○ ECG ± continuous cardiac monitoring
	  ○ Echocardiogram
	  ○ Cardiac MRI
	  ○ Myocardial biopsy if feasible
	• Immediate initiation of 2 mg/kg/day methylprednisolone IV or 1 g IV bolus
	• Consider adding a second immunosuppressive agent
	Additionally, for life threatening myocarditis:
	• Hospitalize/transfer to institution with expertise in intensive cardiac monitoring
	• Consider anti-thymocyte globulin as second agent given its immediate effect
		• If no improvement, consider additional immunosuppression
		• Upon recovery, taper steroids over at least 1 month with close monitoring of troponin and BNP as well as for new symptoms
		• Repeat cardiac MRI for post treatment assessments and cardiology follow-up

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, after sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

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